STUDIES OF THE SYNTHESIS AND REACTIVITY OF BRIDGEHEAD-FUSED 1,2,3-TRIAZOLES

by

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DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh under the supervision of Dr. G. Tennant between October 1973 and September 1976.

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ABSTRACT

Studies of the synthesis, structure and reactivity of bridgehead-fused 1,2,3-triazoles provide the subject material for the following thesis.

Further synthetic routes to 1,2,3-triazolo[1,5-a]pyrimidines have been investigated and the effect of substituents on their diazoalkylideneamine-1,2,3-triazole ring-chain tautomerism has also been studied. Synthetic routes to the hitherto unknown 1,2,3-triazolo-[5,1-c]pyrimidine ring system have been explored with the finding, in the cases studied, that the diazoalkylideneamine tautomer appears to be the stable structure in this ring system.

A synthesis of 1,2,3-triazolo[5,1-c]-1,2,4-triazines has been extended to compounds bearing electron-withdrawing substituents on both the triazole and triazine rings. Despite the expectation that such molecules would exist in the diazoalkylideneamine form no evidence for this, either in the solid state or in solution at elevated temperature, could be obtained. However, tentative evidence for the existence of diazoalkylideneamine-1,2,3-triazole tautomerism in the 1,2,3-triazolo-[5,1-c]-1,2,4-triazine ring system has been provided by the demonstration of the apparent rearrangement of a 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative into the corresponding 1,2,3-triazolo[5,1-c]-1,2,4-triazine isomer. New examples of the Dimroth rearrangements of vinylamino-1,2,3-triazoles have also been discussed and their scope investigated.

Synthetic routes to the as yet unknown 1,2,3-triazolo[1,5-d]-1,2,4-triazine and 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring systems have also been investigated. Methods for the preparation of suitable substrates for such synthesis have been devised but attempts to convert these substrates into simple 1,2,3-triazolo[1,5-d]-1,2,4-triazine and 1,2,3-triazolo[5,1-f]-1,2,4-triazine derivatives were largely unsuccessful.

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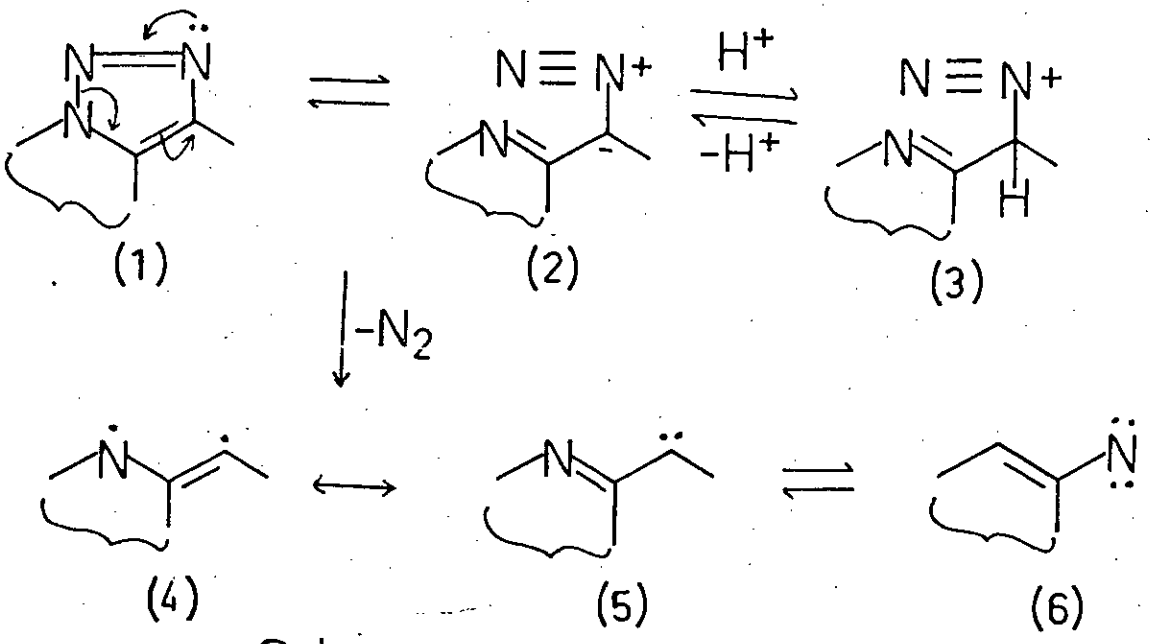
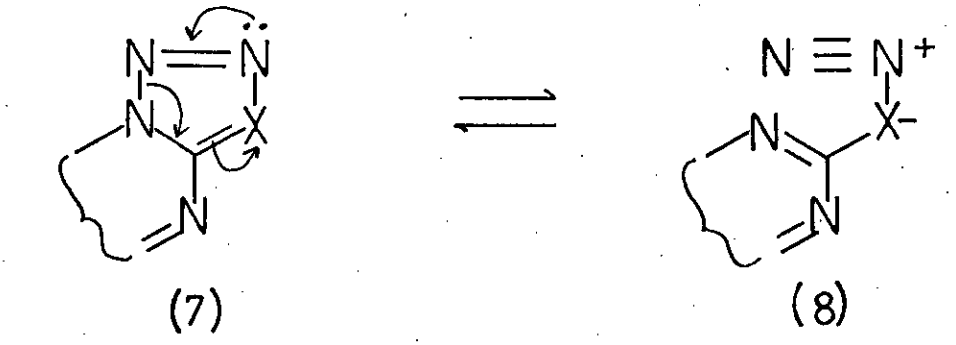
General Introduction

Molecules containing bridghead-fused 1,2,3-triazole rings are of interest as substrates for the generation and study of a variety of energetic species which include carbenes[1,3], nitrenes[1,3] and diazonium cations.[4] Thus, homolytic scission induced thermally



Scheme 1

or photochemically can result in the loss of molecular nitrogen (Scheme 1) to afford a diradical (4) capable of electronic rearrangement to a heterocyclic carbene (5) and thence by molecular rearrangement.[1-3,6,7] to a nitrene (6). Alternatively, stepwise heterolytic scission may lead to a heterocyclic diazo-compound (2), loss of nitrogen from which provides an alternative route to the carbene (5). Conversely, protonation of the diazo-intermediate (2) may give rise to a heterocyclic diazonium species (3). The further implication of stepwise heterolytic scission



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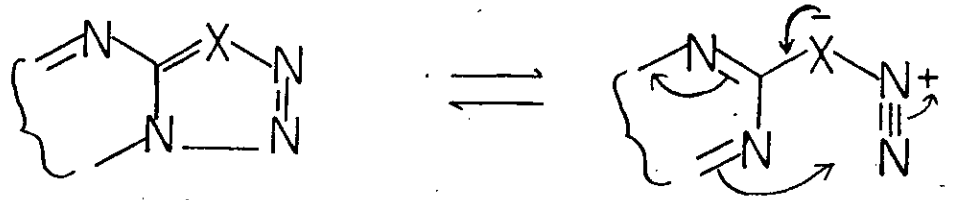

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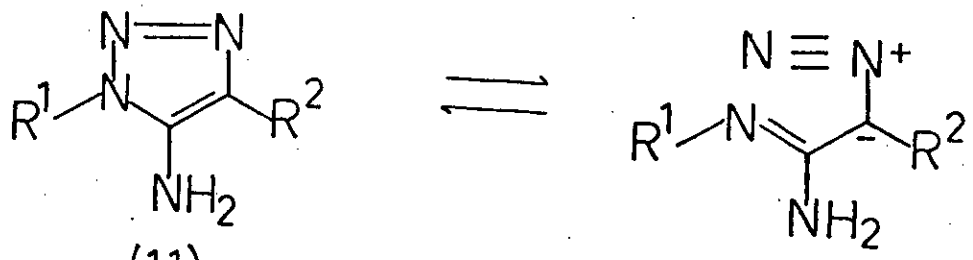
Scheme 2



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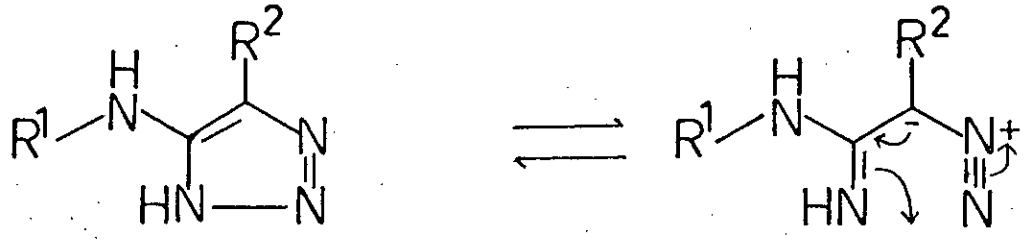


(14) (13)

Scheme 3

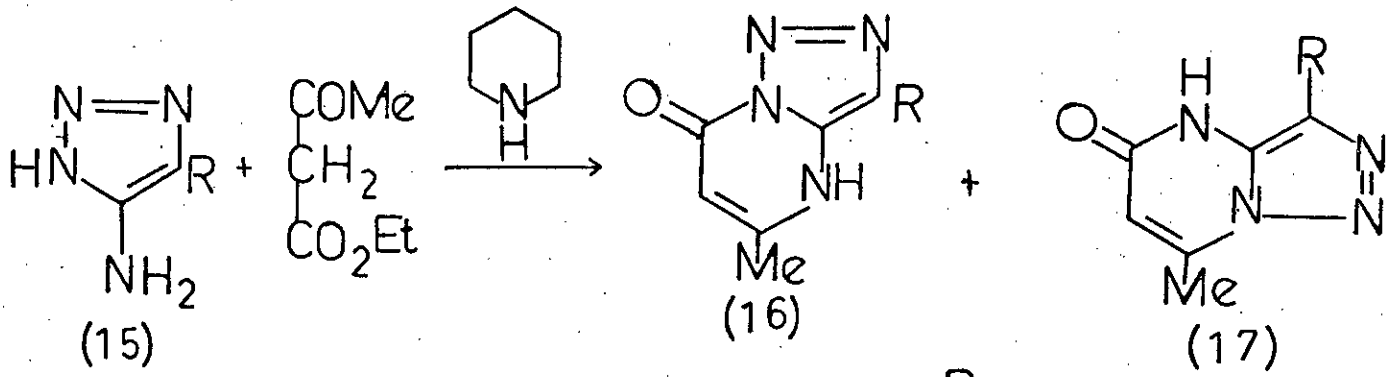
is that bridgehead-fused 1,2,3-triazoles may behave chemically like masked heterocyclic diazo-compounds[1] and indeed that the 1,2,3-triazole and diazo-structures may coexist in equilibrium [(1) ⇌ (2)].[2,5,8] The resulting diazoalkylideneamine-triazole ring-chain tautomerism [(1) ⇌ (2)] would then be the carbon analogue of tetrazole-azide tautomerism [(7) ⇌ (8); X = N] whose existence is now well established.

Tetrazole-azide tautomerism [(7) ⇌ (8); X = N] is also an integral component of the Dimroth rearrangement[9,10] [(7) ⇌ (8) ⇌ (9) ⇌ (10); X = N] undergone by bridghead-fused tetrazoles. Analgous Dimroth rearrangement [(11) ⇌ (12) ⇌ (13) ⇌ (14)] [9,10] is observed for simple amino-1,2,3-triazoles, thus providing indirect evidence for the existence of diazoalkylideneamine-triazole tautomerism [Scheme 3; (11) ⇌ (12) and (13) ⇌ (14)] which is a necessary component of such rearrangement. In contrast to the situation with bridgehead-fused tetrazoles, however, the first examples of diazoalkylideneamine-triazole tautomerism [Scheme 2; (7) ⇌ (8); X = CR] and the attendant Dimroth rearrangemnt [Scheme 2; (7) ⇌ (8) ⇌ (9) ⇌ (10); X = CR] in fused 1,2,3-triazoles have only recently been demonstrated.[9,10]

The following thesis describes the results of studies whose objectives have been, on the one hand, to devise synthetic routes to new ring systems containing bridgehead-fused 1,2,3-triazole rings and, on the other hand, to study the reactivity of such structures in terms of their triazole scission, diazoalkylideneamine-triazole tautomerism, and related Dimroth rearrangement. The discussion of the results obtained is preceded by a short review of the methods for the synthesis of bridgehead-fused 1,2,3-triazoles already in the literature and also aspects of the reactivity of such structures.

Chapter 1

A Review of the Synthesis and Reactivity of Bridgehead-Fused 1,2,3-Triazoles



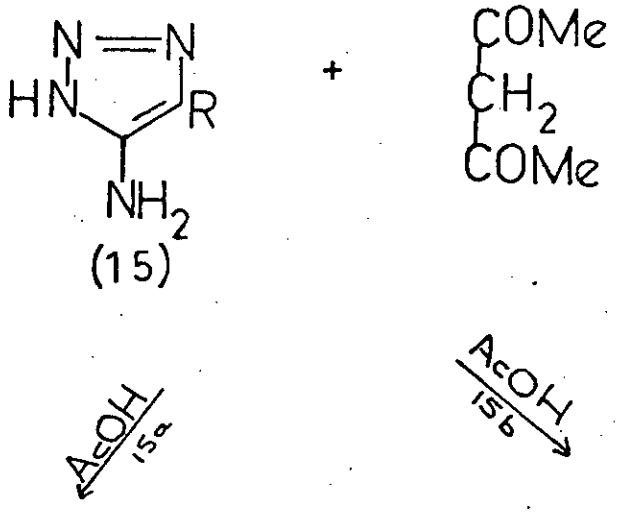
(15) (16) (17)

R

a; Ph

b; $CONH_2$

Scheme 4



(15)

(18) (19)

R

a; Ph

b; $CONH_2$

Scheme 5

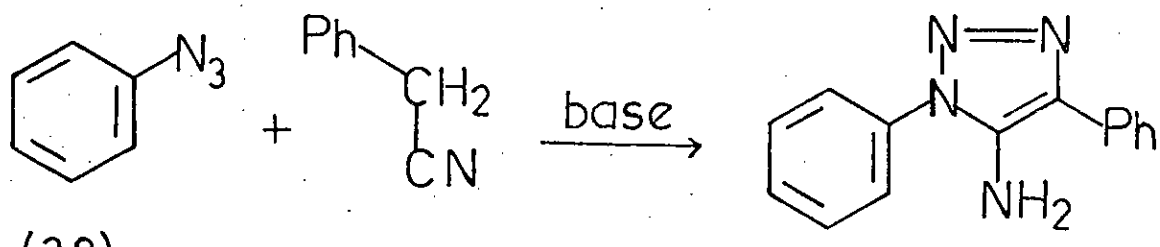
1.1 Synthetic Routes to Bridgehead-Fused 1,2,3-Triazoles

(i) From Preformed 1,2,3-Triazole Derivatives

Condensation of 4-substituted 5-amino-1H-1,2,3-triazoles with β-dicarbonyl compounds in the presence of piperidine has been shown[5b,8] to provide a moderately general route to 1,2,3-triazolo-[1,5-a]pyrimidines. Thus, when 5-amino-4-phenyl-1H-1,2,3-triazole (15a) and ethyl acetoacetate are heated with piperidine in ethanol mainly 5-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidin-7(4H)-one (16a) is formed together with some of the isomer [Scheme 4; (17a)]. However, similar condensation of the amino-triazole (15b) with ethyl acetoacetate affords a roughly 1:1 mixture of the isomeric 1,2,3-triazolo[1,5-a]pyrimidines (16b) and (17b) which cannot be separated.

When the aminotriazole (15b) is heated with acetylacetone in glacial acetic acid, the triazolopyrimidine (19) is obtained while a similar condensation of the aminotriazole (15a) with acetylacetone affords (Scheme 5) the acetoxybenzylpyrimidine (18) which is a triazole ring-scission product (see later).

Lieber and his group[11,27] have shown that azidobenzene derivatives react with phenylacetonitrile under basic conditions to give the expected 5-amino-1-aryl-4-phenyl-1,2,3-triazole. Thus, when azidobenzene (20) reacts with phenylacetonitrile, 5-amino-1,5-diphenyl-1,2,3-triazole (21) is obtained. However, o-nitrophenyl azide (22) behaves anomalously, giving 3-phenyl-1,2,3-triazolo[1,5-c]benzo-1,2,4-triazine 5-oxide (24).



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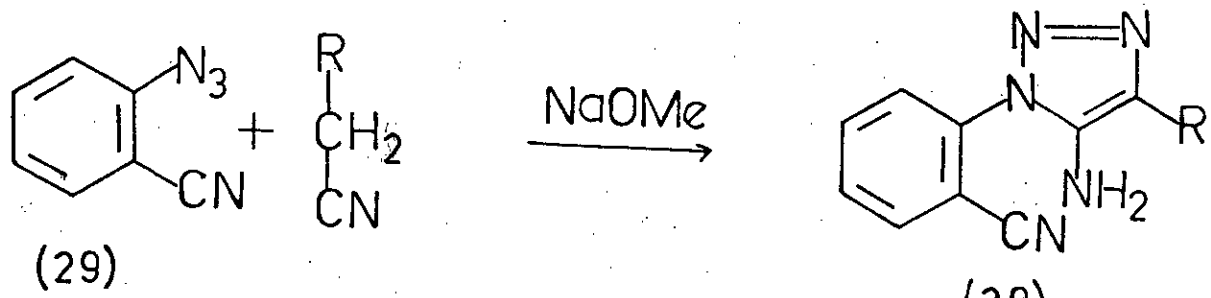
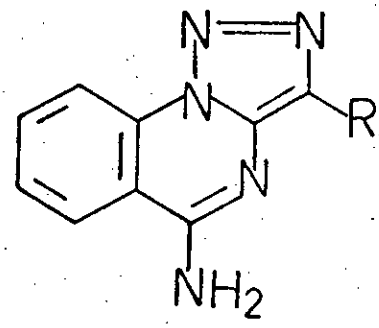


(29)

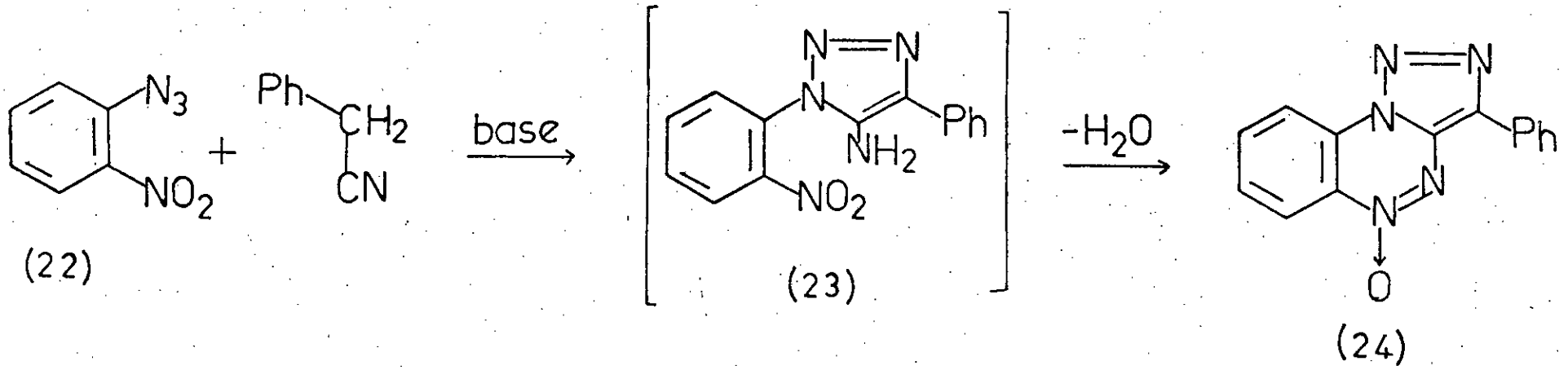
(30)

	R
a;	Ph
b;	$CONH_2$
c;	CN
d;	CO_2H
e;	CO_2Et



(31)

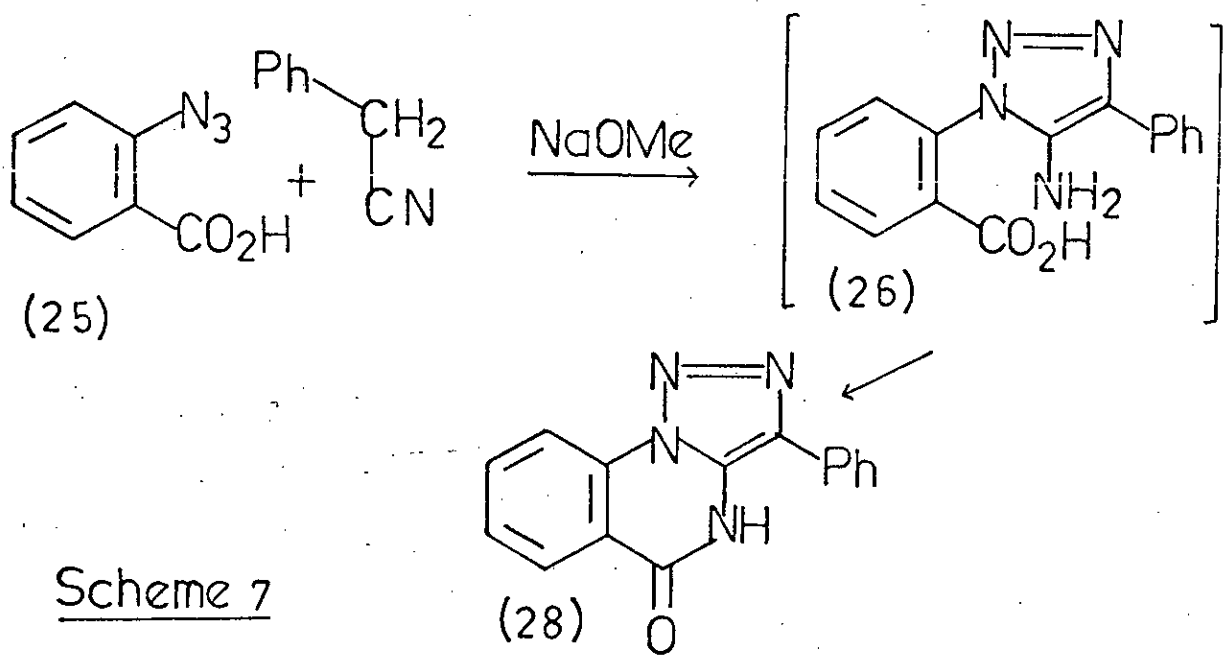
Scheme 8



(22) (23) (24)

Scheme 6

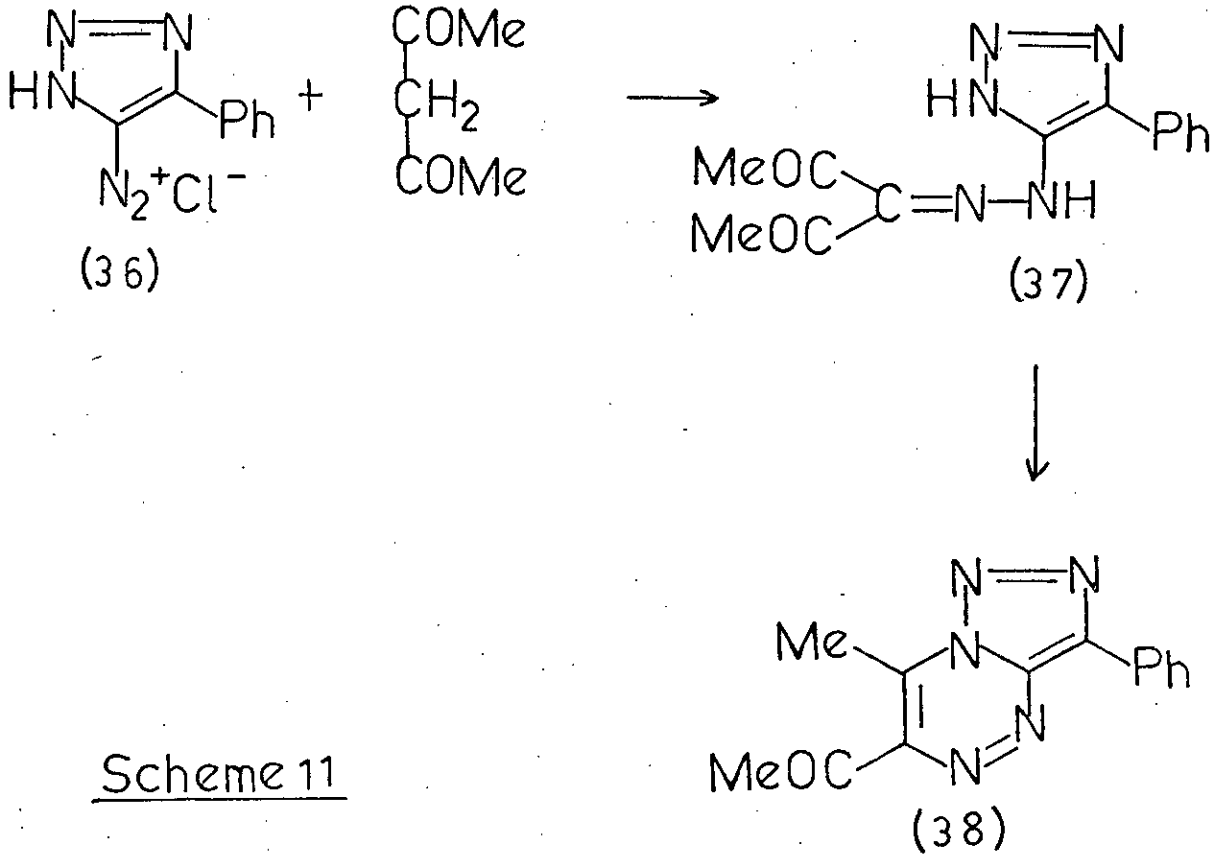
This reaction sequence, presumably, goes through an aldol-type condensation [(23) → (24)] between the nitro- and amino- groups in the intermediate 1,2,3-triazole (23). This work has been extended by Tennant et al[2a] using other azidobenzene derivatives. Ortho-azidobenzoic acid reacts with phenylacetonitrile in the presence of sodium methoxide to afford[2a] 3-phenyl-1,2,3-triazolo-[1,5-a]quinazol-5(4H)-one (28) in high yield (Scheme 7). The



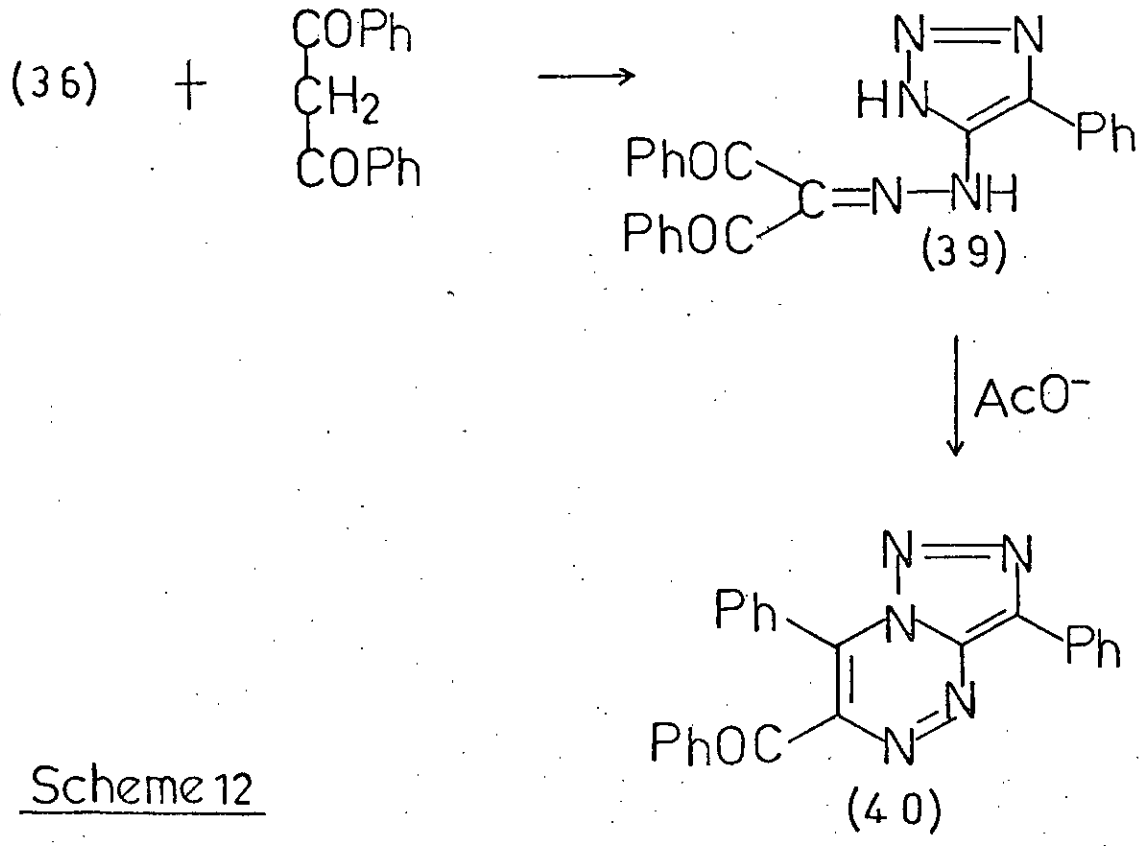
Scheme 7

readily available[12] ortho-azidobenzonitrile (29) reacts similarly[13] with active methylene compounds containing cyano groups in the presence of sodium methoxide to afford high yields of 5-amino-1,2,3-triazolo[1,5-a]quinazolines [Scheme 8; (31a-e)].

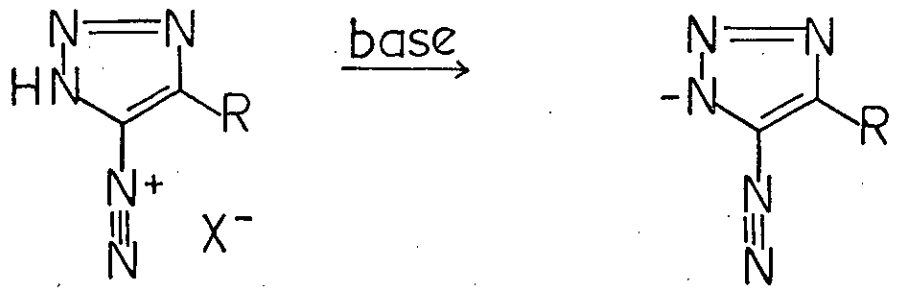
Diazonium salts of the type (32) in the presence of base are known to generate betaines (33) which couple with active methylene compounds to provide the basis for a general route to bridgehead-fused 1,2,3-triazoles according to the general route



Scheme 11



Scheme 12

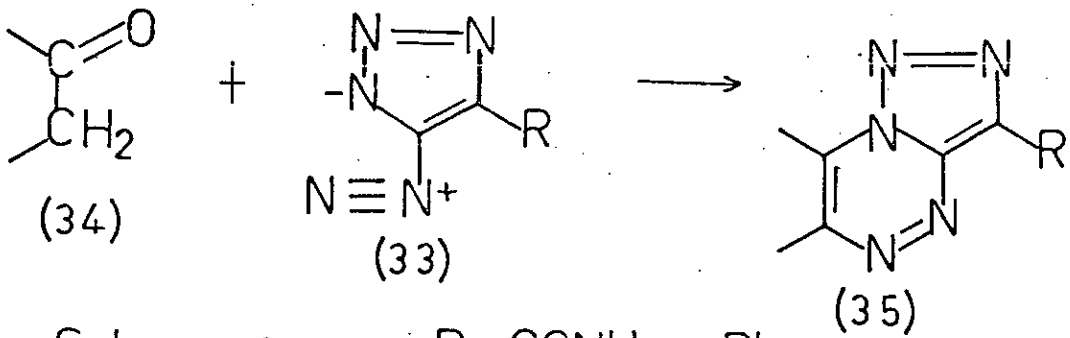


(32) R= $CONH_2$, Ph (33)

X= Cl^-, NO_3^-

Scheme 9

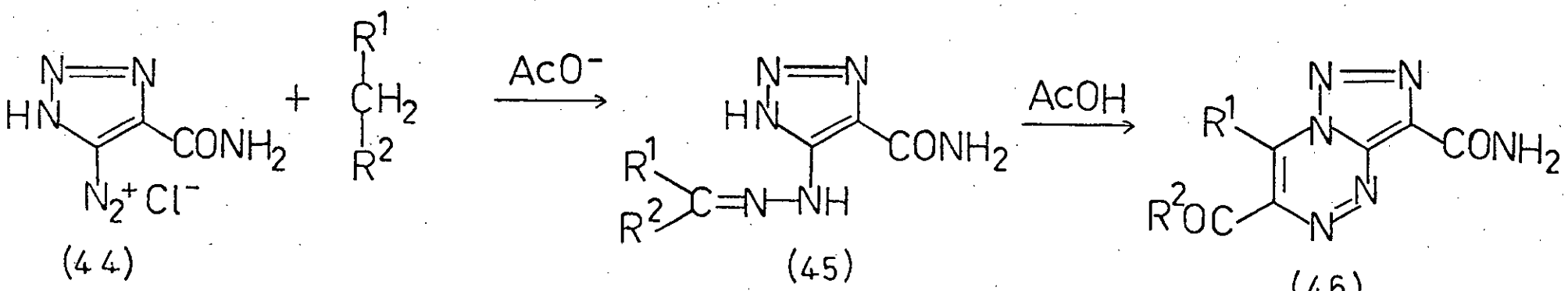
[Scheme 10; (34 + 33) → (35)].[14] Thus, when acetylacetone



(34) (33) (35)

Scheme 10 R=$CONH_2$, Ph

is coupled with 4-phenyl-1H-1,2,3-triazole-5-diazonium chloride[15] (36) in aqueous ethanol at room temperature in the presence of sodium acetate, 6-acetyl-7-methyl-4-phenyl-1,2,3-triazolo[5,1-c]--1,2,4-triazine (38)is obtained in excellent yield (Scheme 11). Both benzoylacetone and ethyl acetoacetate react similarly to afford triazolotriazines. That this coupling reaction goes through the intermediate triazolylhydrazone stage (37) has been demonstrated by the fact that when the diazonium salt (36) couples with dibenzoylmethane, only the hydrazone (39) is obtained and this readily cyclises to the corresponding triazolotriazine (40) when it is



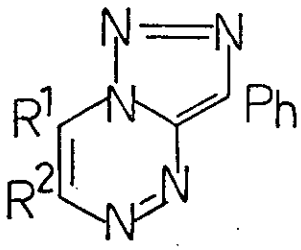
(44) (45) (46)

	R^1	R^2
a;	Ac	Ac
b;	Ac	CO_2Et
c;	Ac	COPh
d;	$CONH_2$	CN
e;	COPh	COPh

	R^1	R^2
a;	Me	Me
b;	Me	OEt
c;	Me	Ph
d;	NH_2	NH_2
e;	Ph	Ph

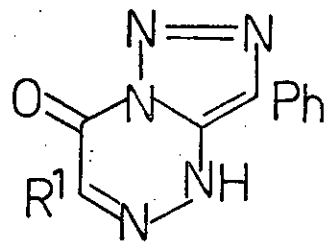
Scheme 13

heated with sodium acetate or glacial acetic acid. Both ethyl benzoylacetate and benzoylacetonitrile couple similarly[15] to give hydrazones, whereas diethyl malonate, ethyl cyanoacetate and cyanoacetamide give mixtures of triazolotriazines (41a and b) and (42), and the triazolylhydrazones (43a-c). This type of coupling[16]



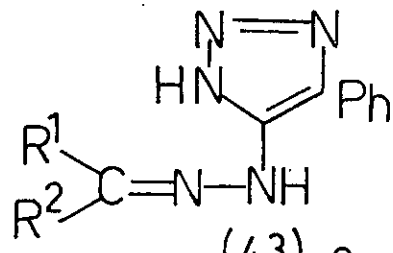
(41)

	R^1	R^2
a;	NH_2	CO_2Et
b;	NH_2	$CONH_2$



(42)

R^1
CO_2Et



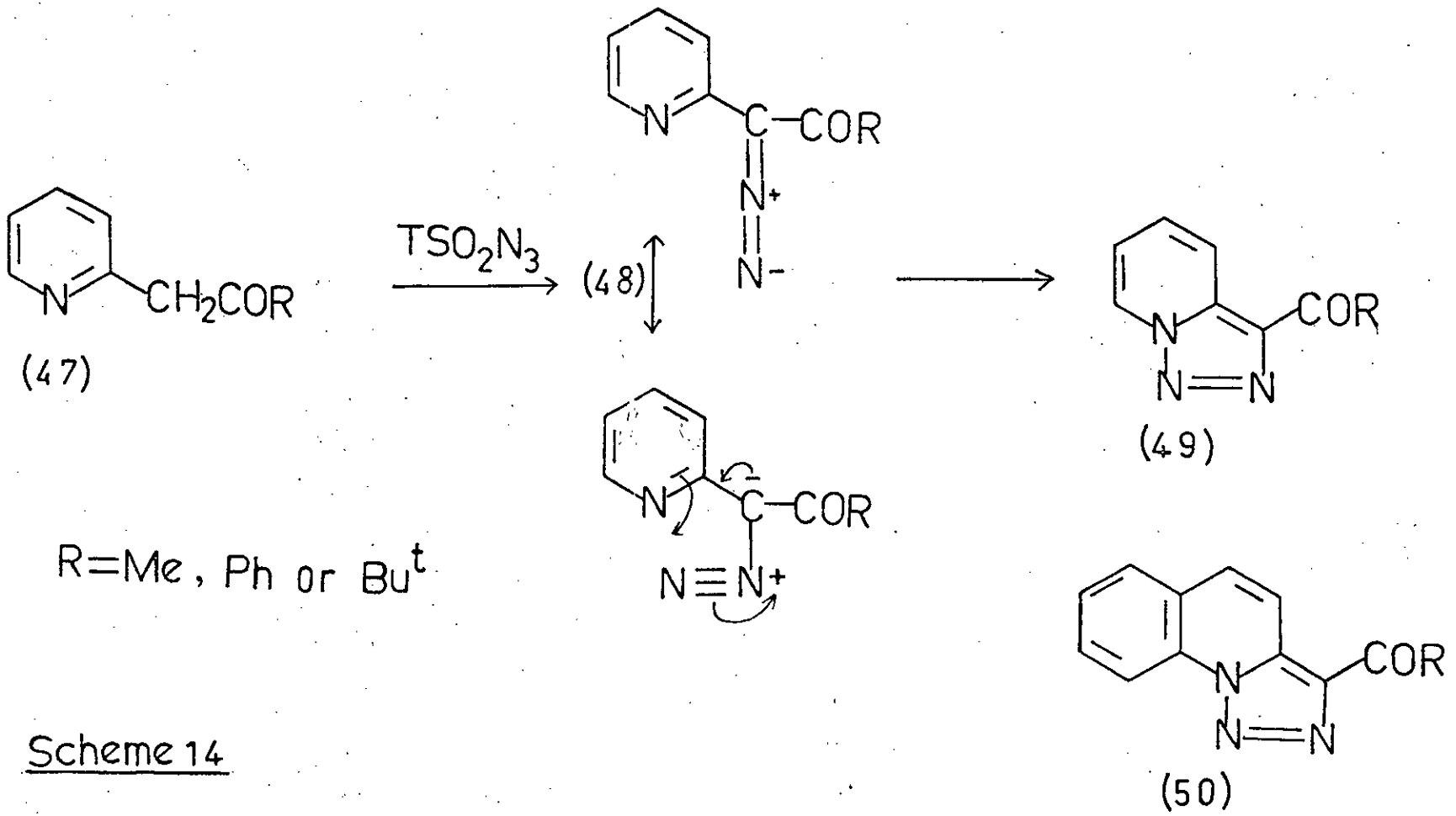
(43)

	R^1	R^2
a;	CO_2Et	CO_2Et
b;	CN	CO_2Et
c;	CN	$CONH_2$

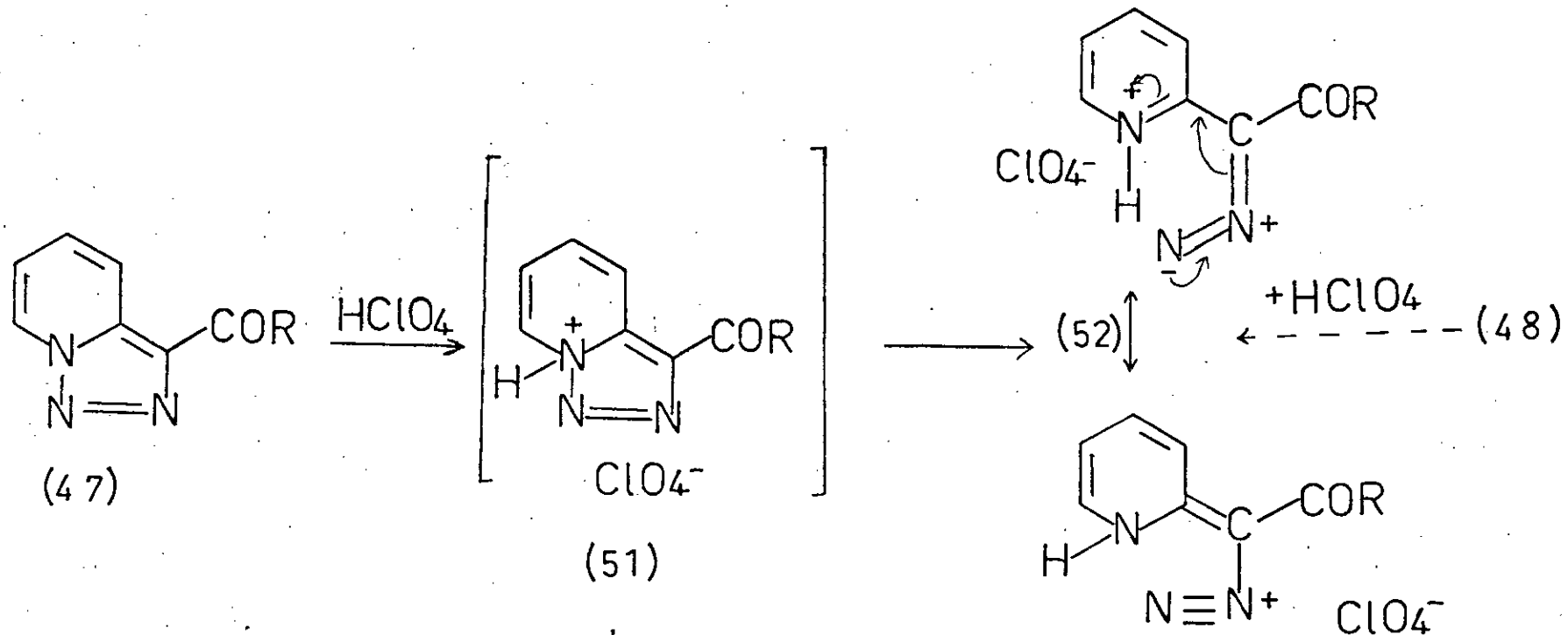
has been extended to 4-carbamoyl-1H-1,2,3-triazole-5-diazonium chloride. Thus, when the diazonium salt (44) is coupled with a range of active methylene compounds in the presence of base, the main products are the hydrazones [Scheme 13; (45a-e)] and not the corresponding triazolotriazines as was observed in the coupling reactions of the phenyldiazonium salt (36). However, the hydrazones (45a-e) on heating with glacial acetic acid cyclise to the corresponding triazolotriazines (46a-e).

(ii) The Reaction of Heterocyclic Methylene Derivatives with Toluene-p-sulphonyl Azide: Diazo-Transfer Reactions

The transfer of an existing diazo group from a donor



Scheme 14

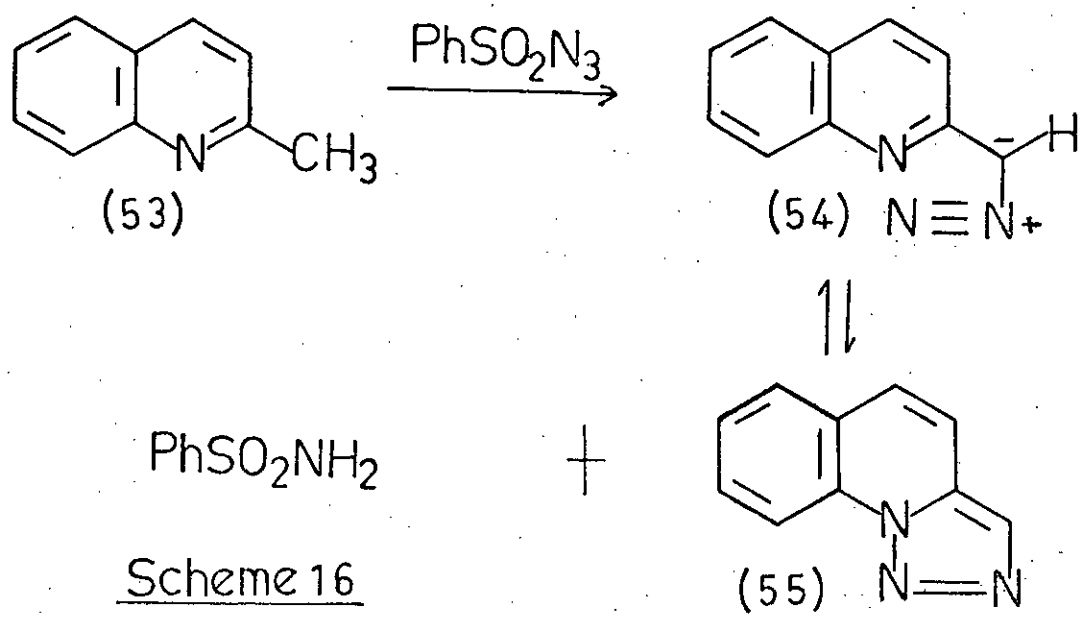


R=Me, Ph or Bu^t

Scheme 15

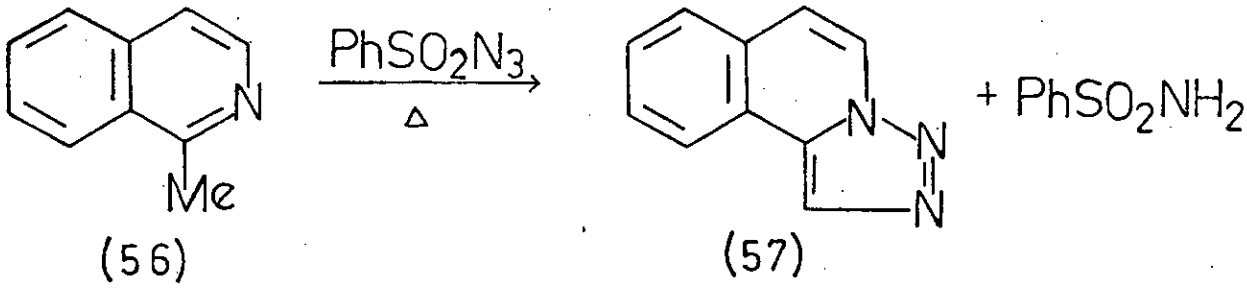
molecule, usually toluene-p-sulphonyl azide, to an acceptor molecule - usually an active methylene centre- has been used in the synthesis of bridgehead-fused 1,2,3-triazoles.[4,17] Thus, when (2-pyridylmethyl) ketones (47) are treated with ethanolic potassium ethoxide followed by toluene-p-sulphonyl azide, they afford high yields of the corresponding 3-acyl-1,2,3-triazolo-[1,5-a]pyridines [Scheme 14; (49)]. High yields of 3-acyl-1,2,3-triazolo [1,5-a]quinolines (50) are obtained by the similar reaction of aryl (quinolin-2-yl) methyl ketones with toluene-p-sulphonyl azide.[4,17] The diazo stage (48) in none of these reactions could be isolated. However, treatment of 1-acyl-1,2,3-triazolo-[1,5-a] pyridines with perchloric acid[4] in dioxan gives [probably via the fused perchlorate (51)] the yellow-orange diazonium perchlorates (52), derivatives of the hypothetical diazo- intermediates (48).

Further examples of the 'Diazo Transfer' route to bridgehead-fused 1,2,3-triazoles have been furnished by the work of Abramovitch and his co-workers.[18] They found that heating quinaldine (53) with benzenesulphonyl azide gave benzensulphonamide

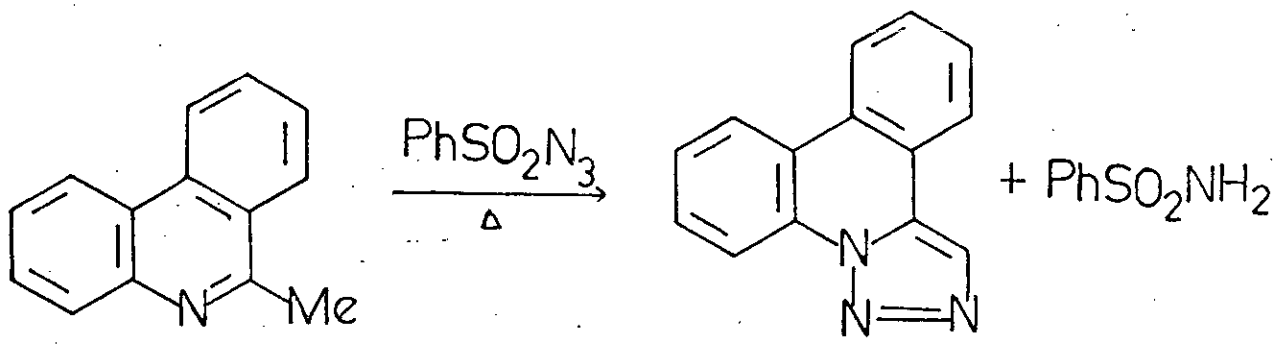


Scheme 16

and 1,2,3-triazolo[1,5-a]quinoline (55) instead of the expected 2-diazomethylquinoline [Scheme 16; (54)]. Formation of the fused triazole (55) was explained as resulting from the ring-chain tautomerism [(54)⇌(55)] of 2-diazomethylquinoline (54). The general applicability of this synthetic route is demonstrated by the reaction of benzenesulphonyl azide with 1-methylisoquinoline (56)



(56) (57)

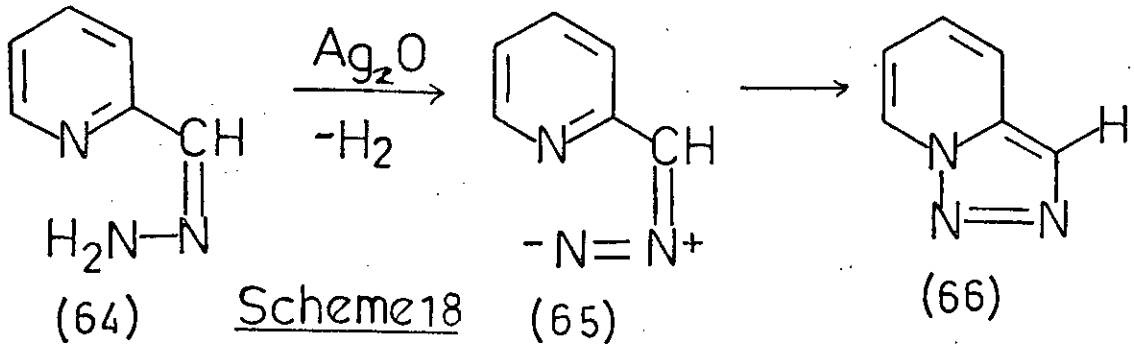


(58) (59)

and 6-methylphenanthridine (58). In each case, the 1,2,3-triazolo heterocycles (57) and (59) were produced in excellent yields.[18]

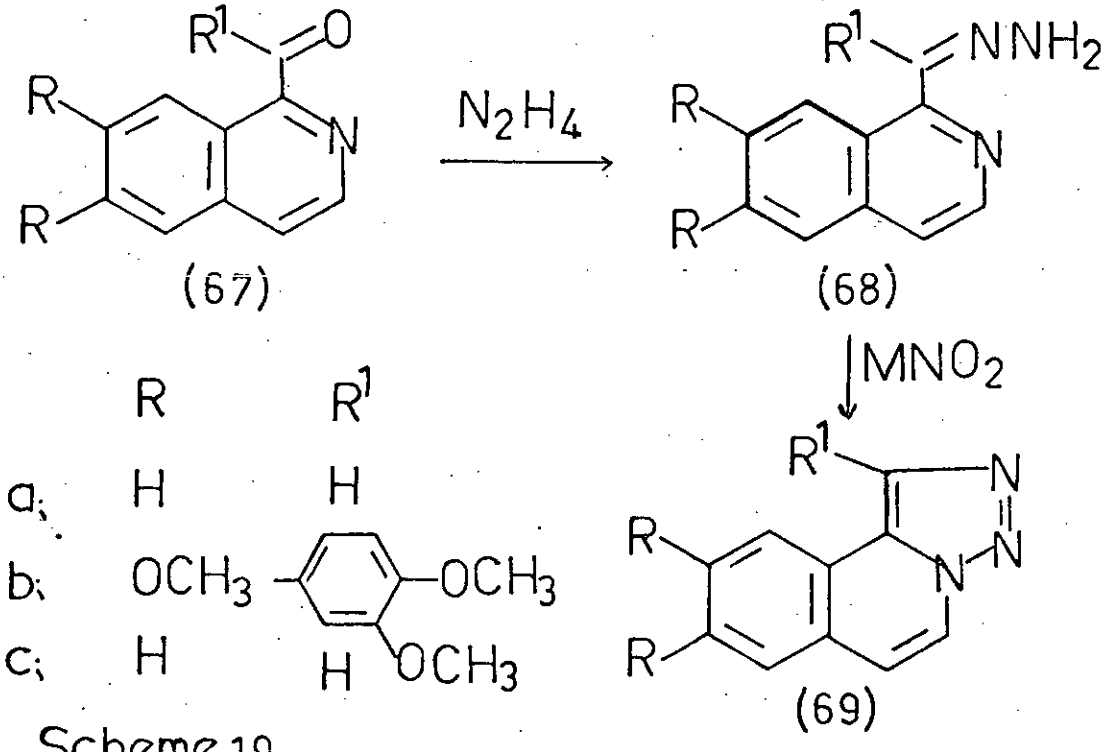
(iii) The Oxidative Cyclisation of Heterocyclic Ketone Hydrazones

Heterocyclic ketone hydrazones (61) can be oxidised to give bridgehead-fused 1,2,3-triazoles (63) via cyclisation of the diazoalkyl intermediates (62) according to the general Scheme 17. Thus dehydrogenation of pyridine-2-carboxaldehyde hydrazone[19,20] (64) using silver oxide or potassium ferricyanide in alkali yielded not the expected 2-diazomethylpyridine (65) but the cyclic 1,2,3-triazolo[1,5-a]-



Scheme 18

pyridine [Scheme 18; (66)]. Reimlinger et al[21] prepared 1,2,3-triazolo[5,1-a]isoquinoline (69a) and its derivatives (69b and c) by

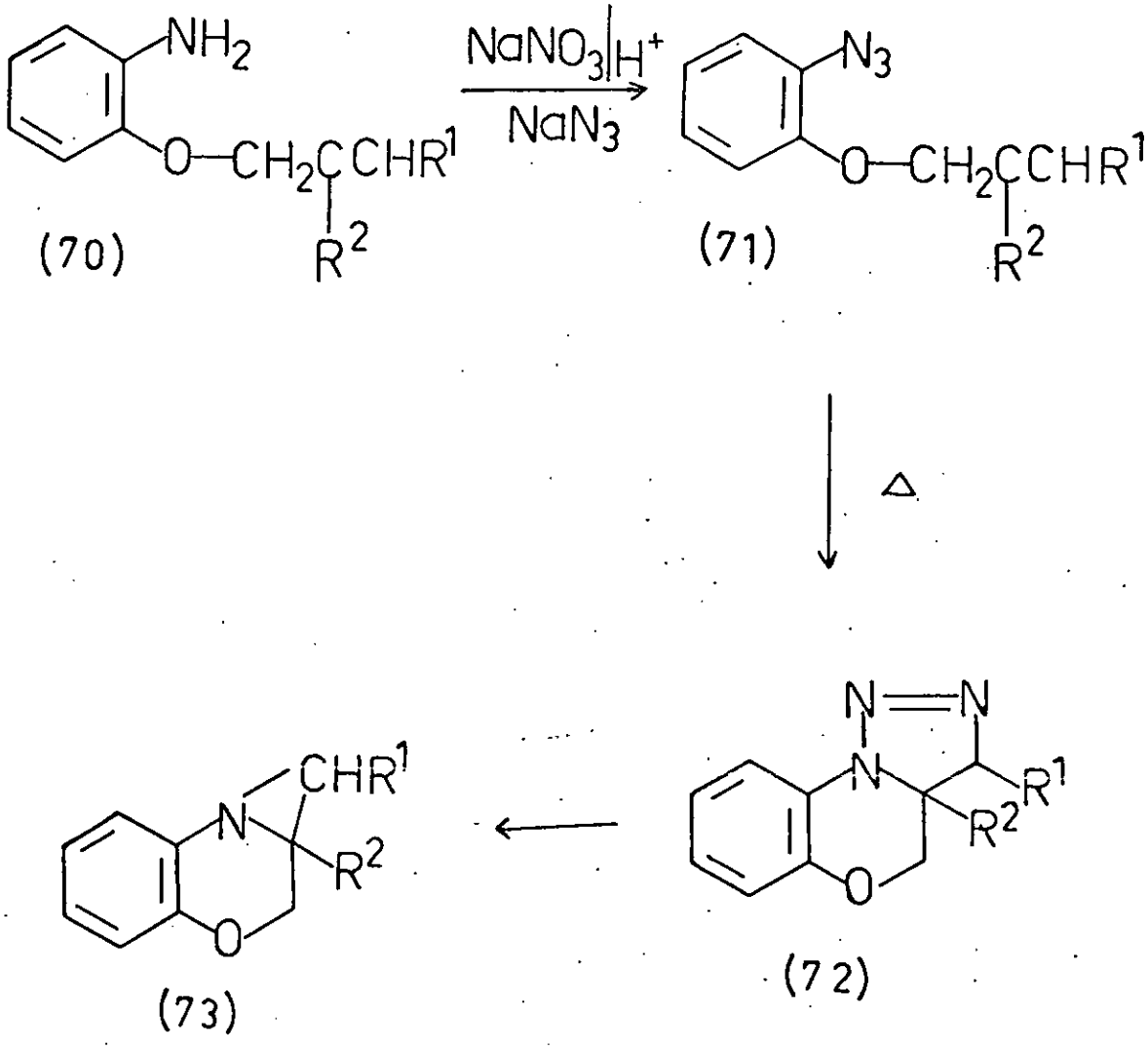


Scheme 19

the oxidation of the corresponding 1-acylisoquinoline hydrazones (67) with manganese dioxide.

(iv) The Formation of Bridgehead-Fused 1,2,3-Triazoles by Intramolecular Cycloaddition Reactions of Azides.

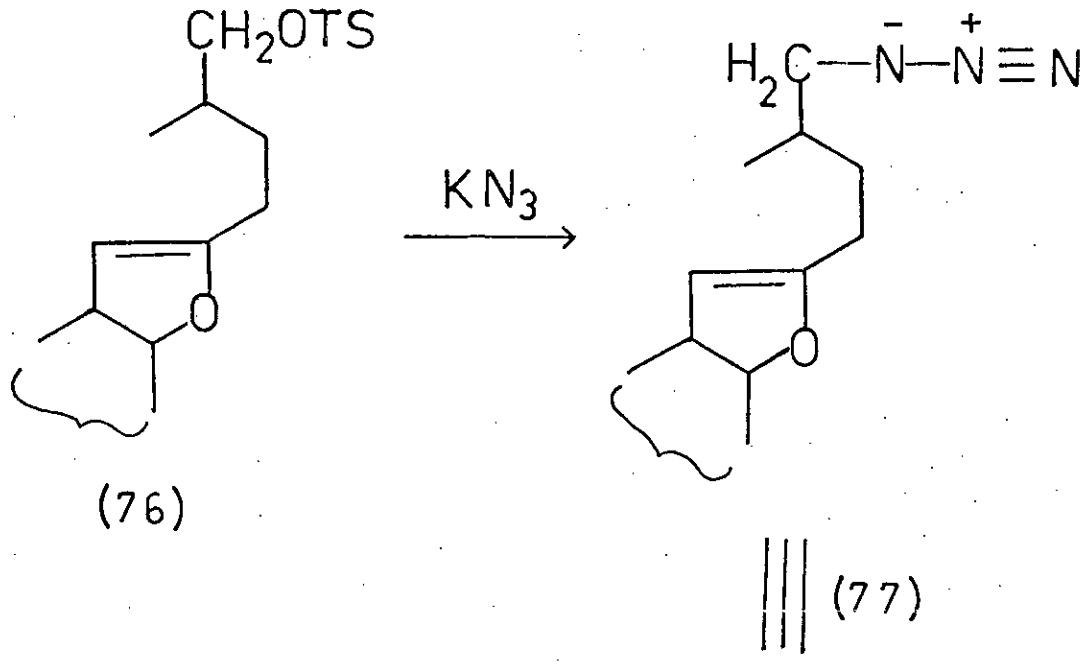
Bridgehead-fused 1,2,3-triazoles are also accessible by the intramolecular 1,3-dipolar cycloaddition of many azides. Thus, the intramolecular cycloaddition of aryl azides bearing ortho-alkenyl and alkynyl side-chains has been reported by Fusco et al.[22] Heating the



R^1 = H or Ph

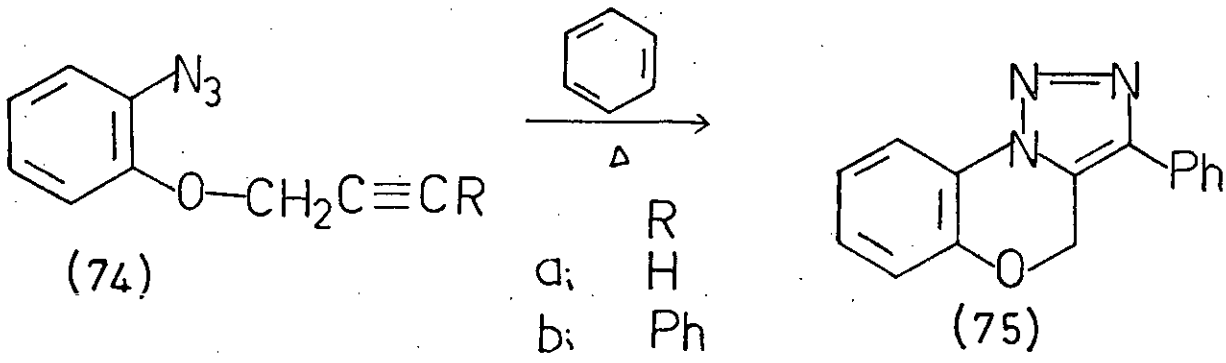
R^2 = H or Me

Scheme 20



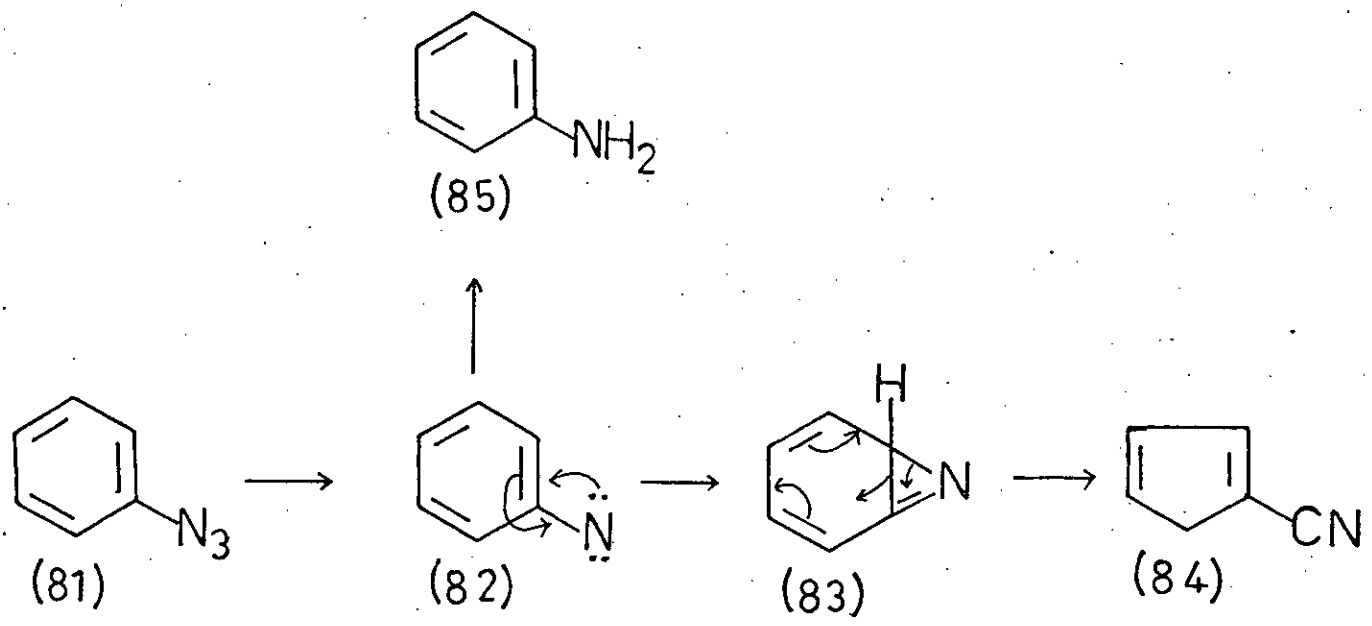
Scheme 21

ortho-azidophenyl alkenyl ethers [Scheme 20; (71)] under reflux in benzene gave aziridines (73) via the unstable triazoline intermediates (72). The involvement of such intermediates in these reactions was established[22] by carrying out the decomposition of (71) at room temperature in hexadeuteriobenzene and monitoring the progress of the reaction by ^{1}H n.m.r. In addition to the signals due to the starting azide (71) and the final aziridine product (73), the spectrum showed a set of signals due to the corresponding triazoline (72).

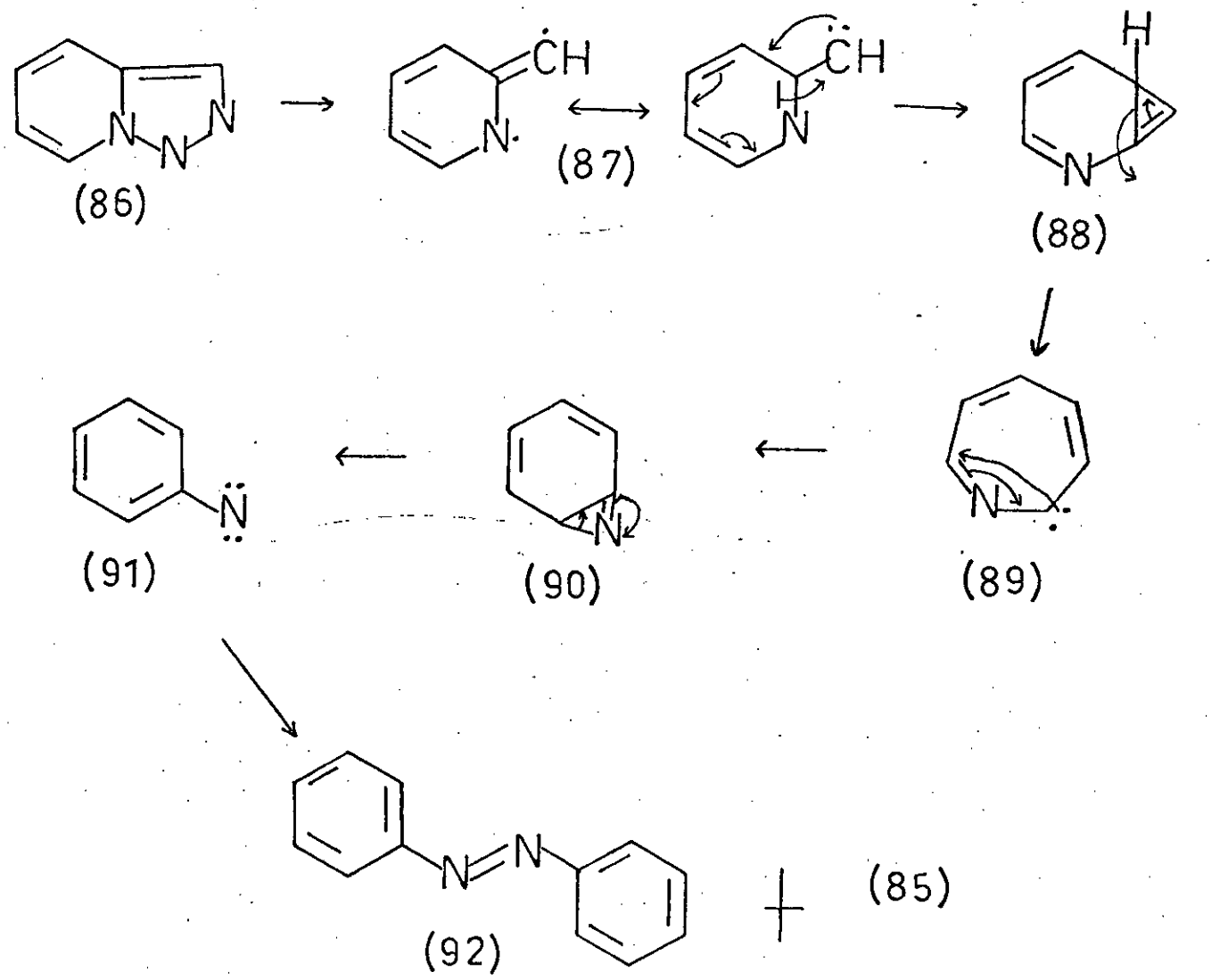


Heating the corresponding alkynes (74) in benzene for 0.5h gave the fused 1,2,3-triazoles (75). It was found that the reaction was faster in the case of the terminal alkyne (74a) as compared with the phenyl derivative (74b). This kinetic effect was attributed[22] to increased steric hindrance to cycloaddition due to the phenyl group in (74b).

A further example of 1,3-dipolar cycloaddition leading to a bridgehead-fused 1,2,3-triazole is furnished by the work of Uhle.[23] He reports that when the pseudodiosgenin derivative (76) is treated with potassium azide in dimethylformamide, the toluene-p-sulphonyl group is displaced (Scheme 21) and this is followed by intramolecular dipolar cycloaddition of the azide group in the intermediate (77) to the enol ether olefinic bond to furnish the triazoline derivatives (78).



Scheme 22



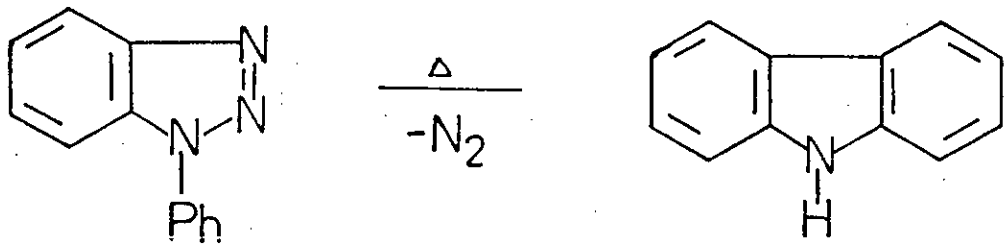
Scheme 23

1.2 Aspects of the Reactivity of Bridgehead-Fused 1,2,3-Triazoles

(i) Reactions Involving the Loss of Molecular Nitrogen (Triazole Scission).

(a) Homolytic (Thermal or Photochemical) Scission

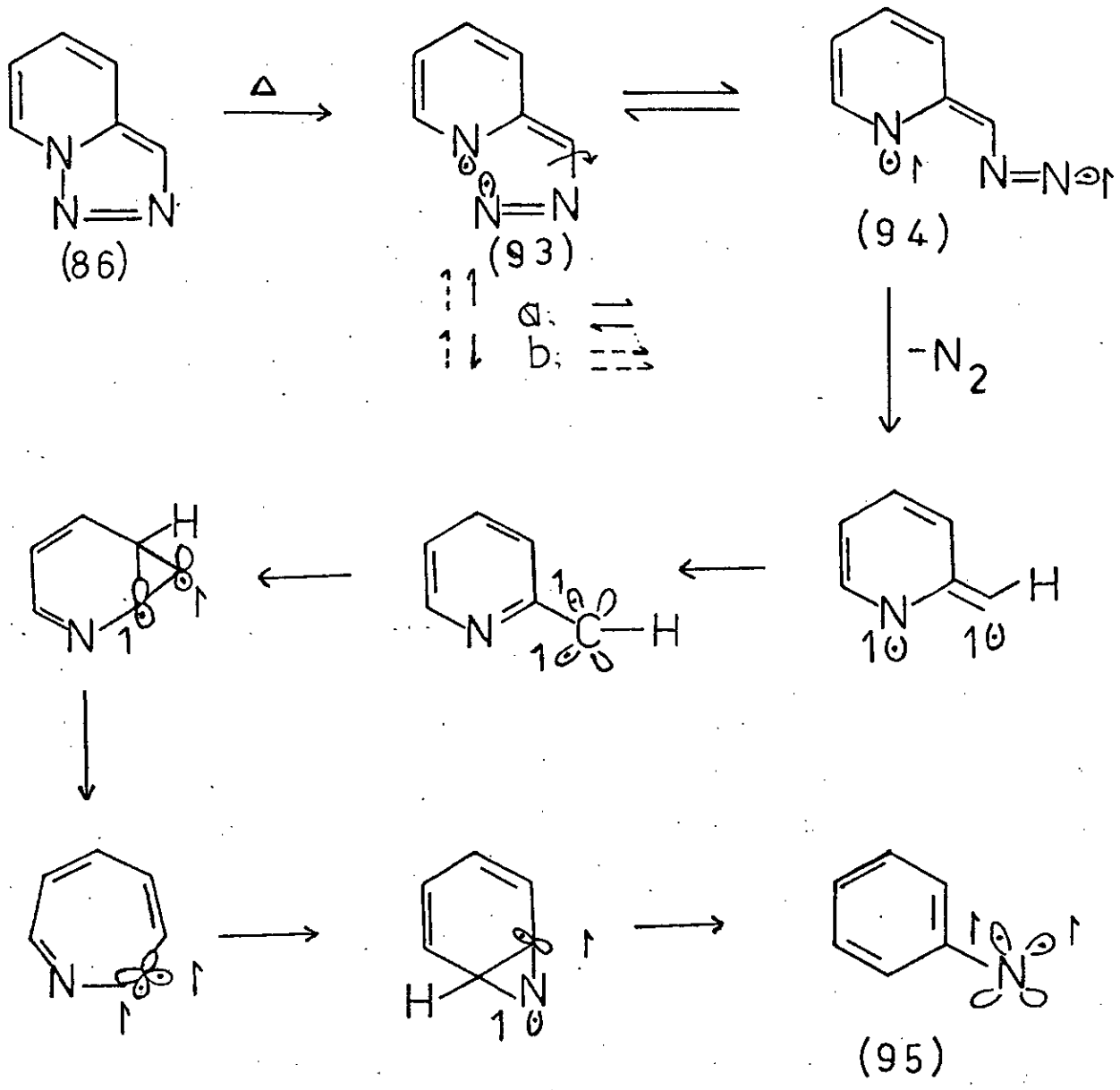
The first reported example of the loss of molecular nitrogen from a 1,2,3-triazole was that described by Graebe and Ullmann in 1896.[7] They showed that when 1-phenylbenzo-1,2,3-triazole (79) was heated, it eliminated nitrogen to give carbazole (80). This type



(79) (80)

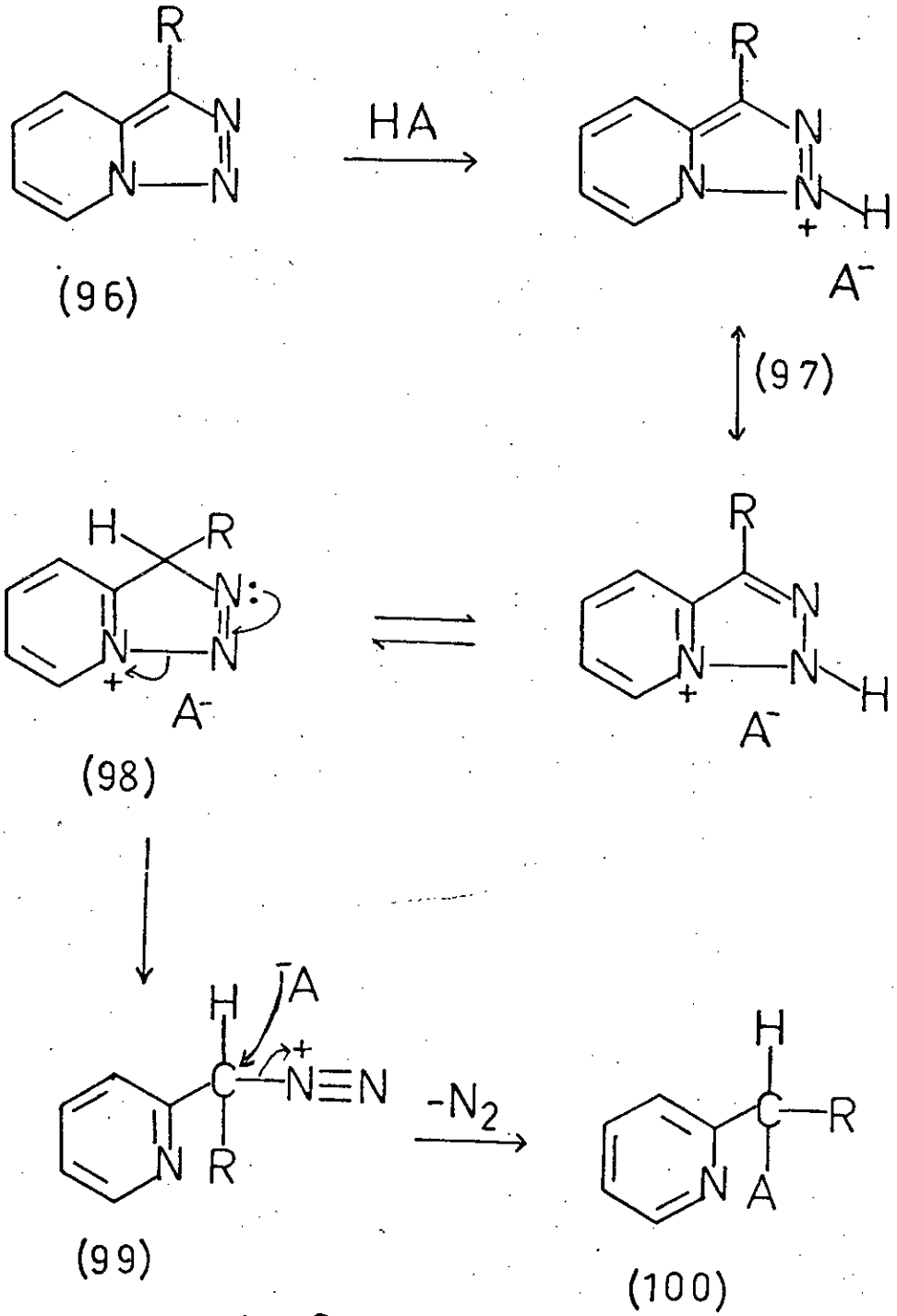
of reaction has been explained by a number of workers[1,8,24] as probably occurring by a radical mechanism involving the homolytic scission of the triazole ring.

Crow and Wentrup[24,25] have shown that the pyrolysis of phenylazide (81) under vigorous thermal conditions results in ring contraction to give 1-cyanocyclopentadiene (84) and thermal rearrangement to give aniline [Scheme 22; (85)]. In contrast, they found that pyrolysis of 1,2,3-triazolo[1,5-a]pyridine (86) gave mainly azobenzene [Scheme 23; (92)] plus some aniline (85) but no 1-cyanocyclopentadiene (84). The different product mixtures observed despite the apparent common intermediacy of phenylnitrene in both thermal processes is explained in terms of generation of the phenylnitrene in different electronic states. Thus, it is proposed[24,25]



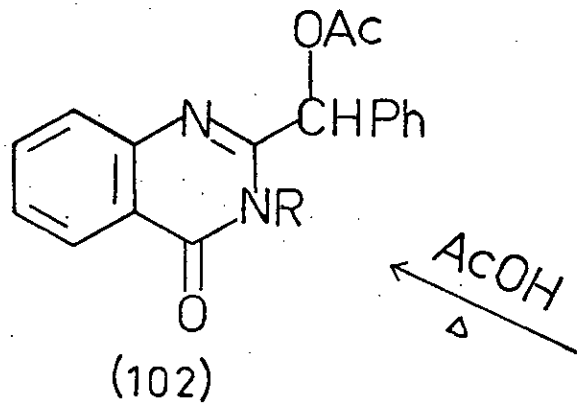
Scheme 24

that the pyrolysis of phenyl azide generates the phenylnitrene in the singlet state which then undergoes preferential ring contraction to yield (84). Conversely, the 2-pyridylcarbene (87) produced by the pyrolysis of 1,2,3-triazolo[1,5-a]pyridine (86) is suggested[24] to rearrange to phenylnitrene in the triplet state which preferentially dimerises to azobenzene (92). Pyrolysis is assumed to involve initial homolytic cleavage of the N-N-bond shown in [Scheme 24;(86)] and to occur with spin conservation to give the singlet biradical (93a). Subsequent rotation about the N(2)-C(3) bond [(93)⇌(94)] would then produce a species in which the separation of the radical lobes may be sufficiently large to render the distinction between singlet and triplet states meaningless. Subsequently, loss of nitrogen from the ground state (93b) or (94) (more likely now to be in the triplet state) would give the triplet nitrene (95) which then dimerises to azobenzene (92) or hydrogen abstracts to give aniline (85). To test the validity of these assertions, Crow and his workers[24,25] studied other generators of 2-pyridylcarbene to compare their thermal behaviour with that of 1,2,3-triazolo[1,5-a]pyridine. They found that in the pyrolysis of tosylhydrazones of pyridine 3- and 4-aldehydes and of 5-pyridyltetrazoles the major products were 1-cyanocyclopentadiene (84) (20-60%), aniline (85) (2-10%), benzene (1-10%) and benzonitrile (0.5-5%) and that detectable amounts of azobenzene (92) were not produced. The logical conclusion from these observations seems to be that of all the generators of phenylnitrene, only 1,2,3-triazolo[1,5-a] pyridine (86) has the unique ability of producing the triplet species which is capable of dimerisation to azobenzene (92).



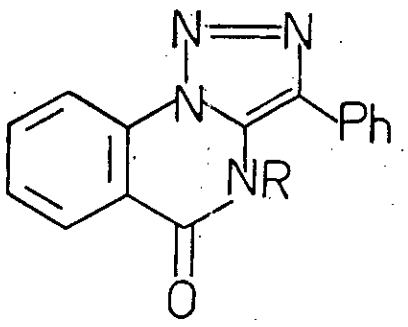
A= OCOR or OPh

Scheme 25



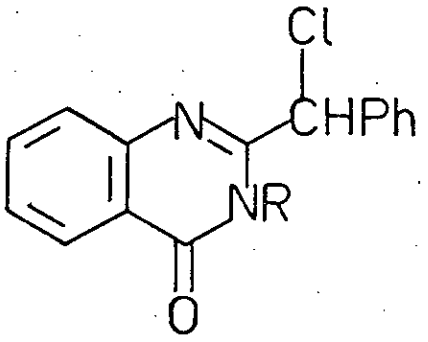
(102)

AcOH
Δ



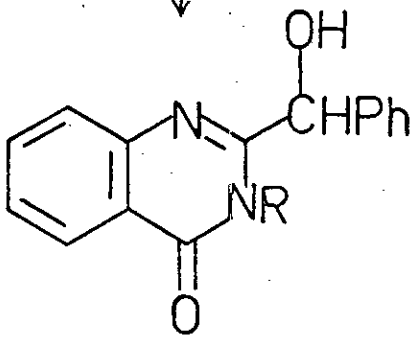
(101)

CH_3COCl
AcOH



(103)

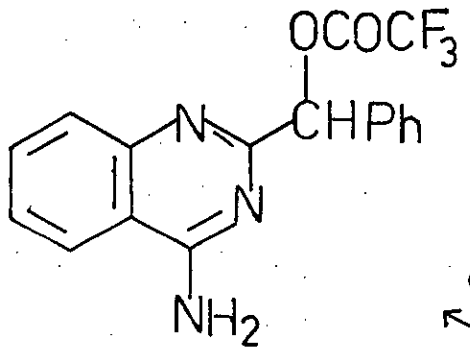
EtOH | H^+



(104)

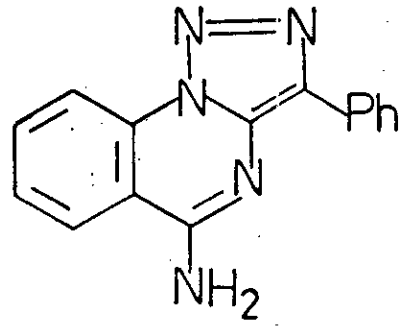
R = H or Me

Scheme 26



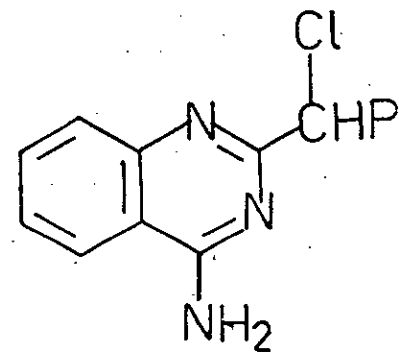
(106)

CF_3CO_2H



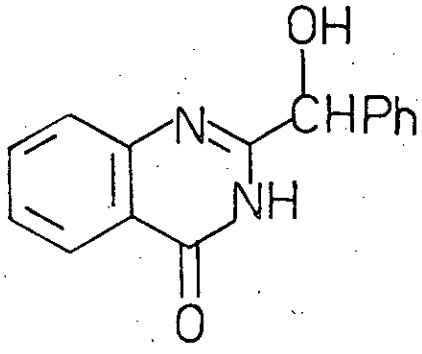
(105)

CH_3COCl / AcOH



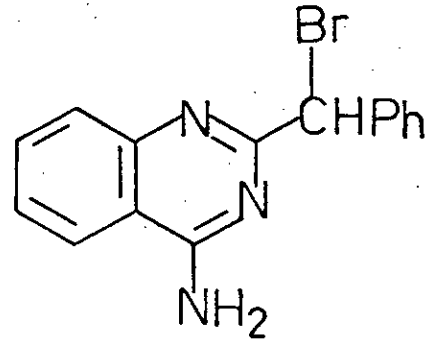
(107)

EtOH / H^+



(108)

CH_3COBr / AcOH



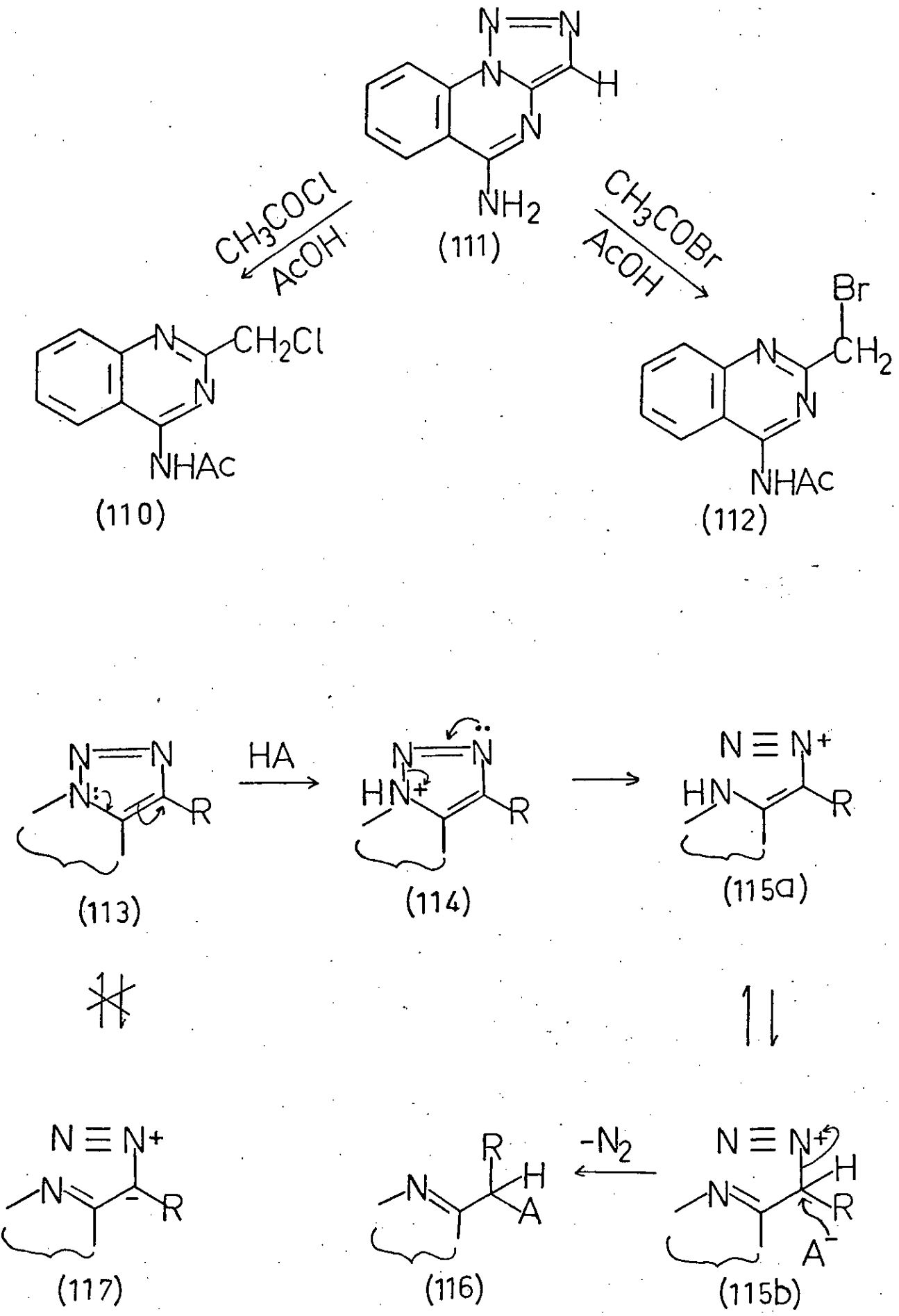
(109)

Scheme 27

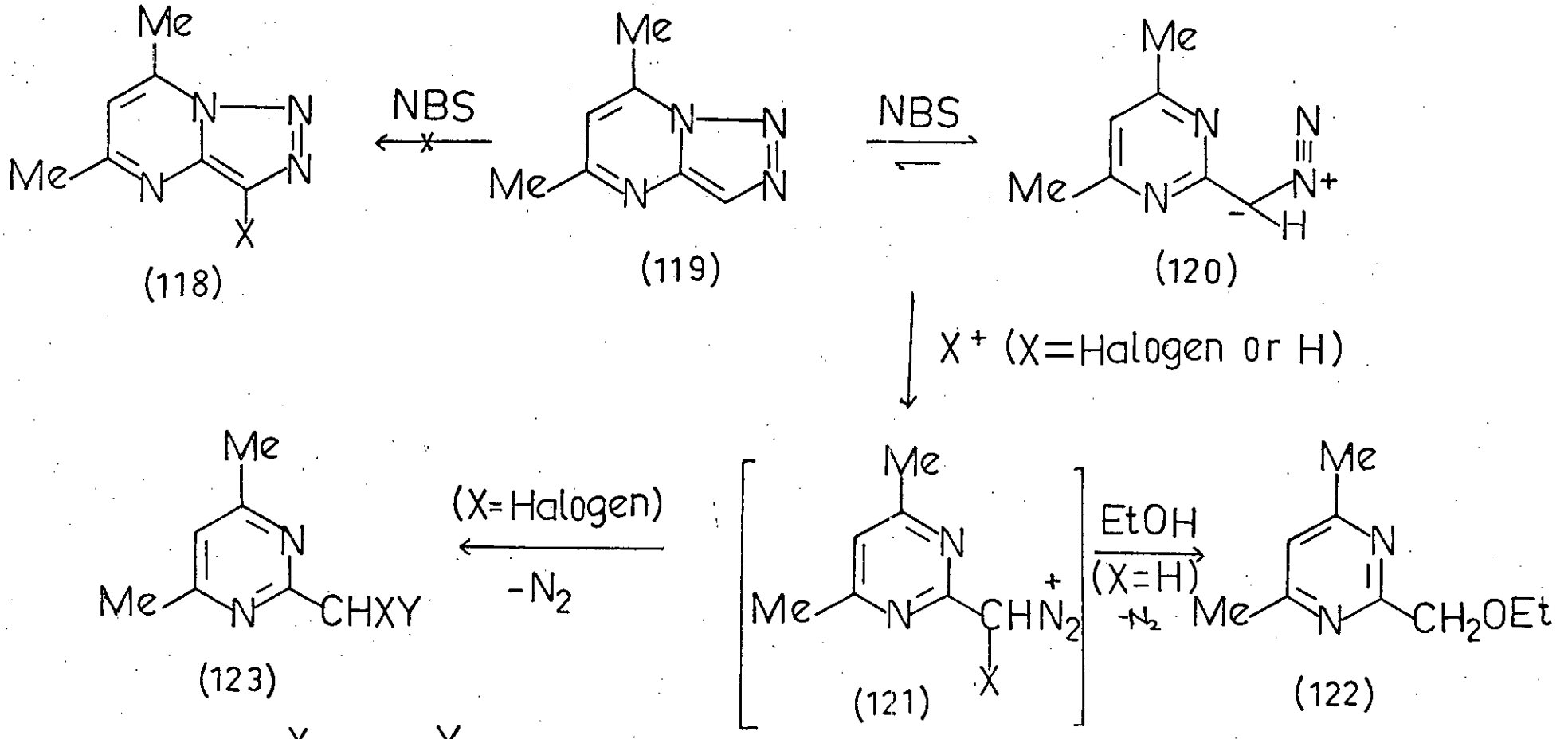
(b) Acid Catalysed Heterolytic Fission

Acid-catalysed scission of bridgehead-fused 1,2,3-triazoles has been studied by a number of workers.[2a,5b,8,26] Thus from the studies of the ultraviolet absorption of 1,2,3-triazolo-[1,5-a]pyridine in acidic solution, Boyer and his group[26] concluded that the species present was the corresponding cation [Scheme 25; (97)] The stability of these cations was shown by the fact their solutions in 1.2M aqueous hydrochloric acid showed no change in wavelength or intensity of ultraviolet absorption after standing at room temperature for two weeks. At higher temperatures, however, rearrangement of (97) occurred with loss of nitrogen to give the product of acid-catalysed triazole scission (100).

Tennant and his group[2a,5b,8] have described a number of examples of acid-catalysed triazole scission. Thus, when the triazoloquinazolone (101) is heated under reflux in acetic acid, it affords the acetoxyquinazolone [Scheme 26; (102)] while warming with both aqueous dilute sulphuric acid in ethanol and acetyl chloride in glacial acetic acid, gives the hydroxy- and chloro- derivatives (104) and (103) respectively.[2a] When the triazoloquinazoline (105) is treated with trifluoroacetic acid at room temperature for 24h, triazole scission[5b] occurred, giving the trifluoroacetate [Scheme 27; (106)]. A similar breakdown of the triazoloquinazoline (105) also occurs in acid halides to give the bromo- and chloro- derivatives (109) and (107) but scission in ethanolic sulphuric acid is accompanied by hydrolysis to give the quinazolone (108). Likewise, heating the parent triazoloquinazoline (111) with both acetyl chloride and bromide in glacial acetic acid gives the halogen derivatives (110) and (112) in which the amino group has been


CH3COCl
AcOH
CH3COBr
AcOH
(111)
(110)
(112)
HA
(113)
(114)
(115a)
(115b)
(116)
(117)
-N2
(A=OH, Cl, Br, OAc, or OCOCF3)

Scheme 28



	X	Y
a;	Br	Br
b;	OEt	OEt
c;	Cl	I
d;	Cl	Cl

Scheme 29

acetylated.

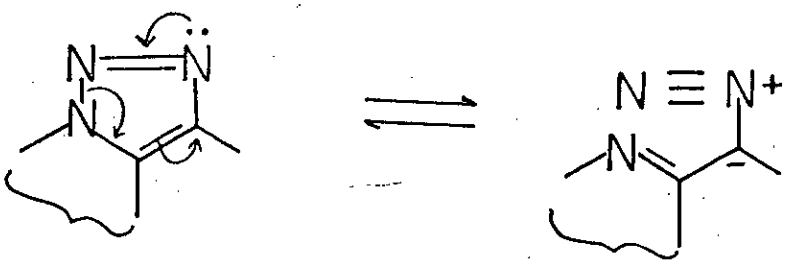
Acid-catalysed triazole scission is not successful with bridgehead-fused 1,2,3-triazoles bearing electron-withdrawing groups at C-3[5b,8]. This inertness is suggested to be due to the reduced basicity of the triazole ring and hence inhibition of the protonation which is postulated as the initial step in the mechanism (Scheme 28) proposed for acid-catalysed triazole scission. Thus, treatment of the bridgehead-fused 1,2,3-triazole with acid leads to a protonated species (114) which ring opens to the tautomeric forms (115a and b). Loss of nitrogen from (115a and b) gives the product. The alternative route in which the triazole ring first opens to a diazo species (117) prior to protonation is not thought to happen because with electron-withdrawing groups at C-3 this species (117) will be stabilised and hence scission should be favoured. However, it has been shown[5b,8] that with electron-withdrawing groups at C-3, triazole scission does not occur. (See later).

A recent report[28] describes the ring opening of 5,7-dimethyl-1,2,3-triazolo[1,5-a]pyrimidine by halogenating agents. Thus when 5,7-dimethyl-1,2,3-triazolo[1,5-a]pyrimidine [Scheme 29; (119)] is treated with N-bromosuccinimide in chloroform, it gives 2-(α,α-dibromomethyl)-4,6-dimethylpyrimidine (123a) as the major product (90%) with minor amounts of 4,6-dimethylpyrimidine-2-carboxaldehyde dimethyl acetal (123b) and 4,6-dimethyl-2-ethoxy-methylpyrimidine (122) and not the expected product 3-bromo-5,7-dimethyl-1,2,3-triazolo[1,5-a]-pyrimidine (118). Formation of the dibromo-product (123a) is proposed[28] to occur (Scheme 29)by initial ring-opening of the triazolopyrimidine (119) to the diazo-tautomer (120) followed by reaction with bromonium cation to give a diazonium intermediate (121) which affords the product (123a) by reaction with

bromide ion and loss of nitrogen. The diethyl acetal (123b) is suggested[28] to originate from trace amounts of ethanol in the chloroform while the ether (122) is postulated to arise by ethanolysis of the intermediate [(121);X=H]. Reaction of the triazolopyrimidine (119) with N-chlorosuccinimide gives the expected product (123d) while the analogous reaction with iodine monochloride affords 4,6-dimethyl-2-(α-iodo-α-chloromethyl)pyridine(123c).

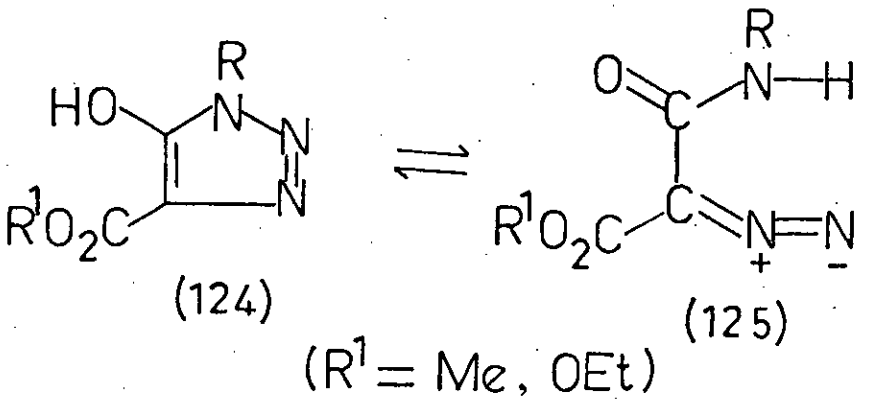
(ii) Rearrangement Processes

As already discussed, acid-catalysed triazole scission is probably not preceeded by ring opening to a diazo-form [that is by diazoalkylideneamine-1,2,3-triazole ring-chain tautomerism



(1) (2)

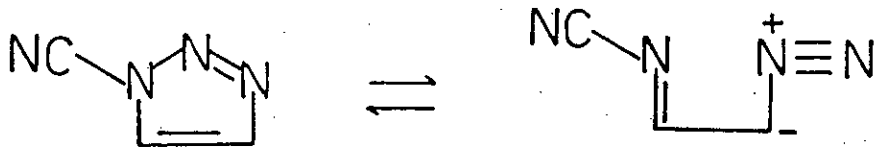
(1)⇌(2)]. However, this type of tautomerism is well documented for simple 1,2,3-triazole derivatives, the earliest example being that reported by Dimroth[29] in the early 1900's when he interpreted the kinetics of the reaction sequence [(124)⇌(125)] as taking place in the unionised enol molecule. Later on, however, a reconsideration of this reaction by Brown and Hammick[30] indicated that the mechanism of the ring-chain tautomerism[(124)⇌(125)]was probably bimolecular in



(124) (125)

(R^1 = Me, OEt)

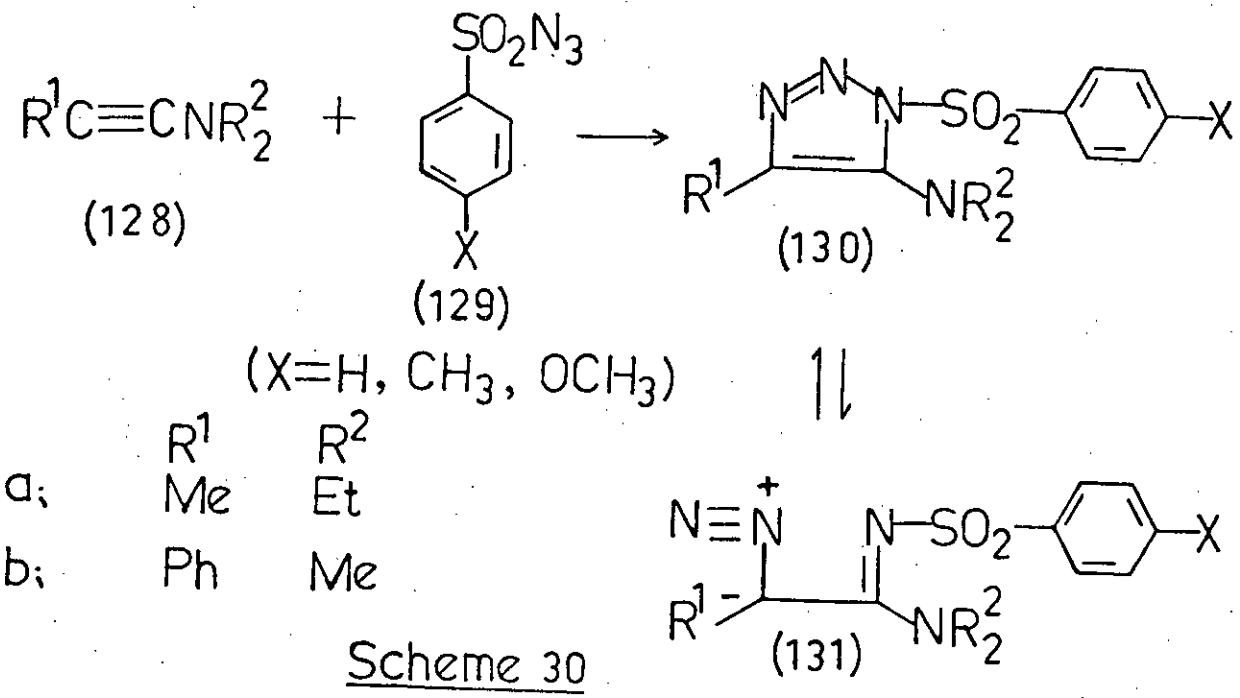
character and involved initial ionisation to the enolate anion of (124). Hermes and Marsh[32] observed the same type of ring-chain tautomerism between 1-cyano-1,2,3-triazole (126) and the α-diazo-



(126) (127)

N-cyanoethylideneneimine (127). The evidence for the co-existence of both tautomers (126) and (127) is based on the temperature dependence of the i.r. spectrum. Thus the i.r. spectrum at -10^{o} shows only cyano absorption at 2250cm^{-1} while at 35^{o}, it exhibits additional strong absorptions at 2160, 2130 and 1560cm^{-1}, indicating the presence of the C=N-CN group.

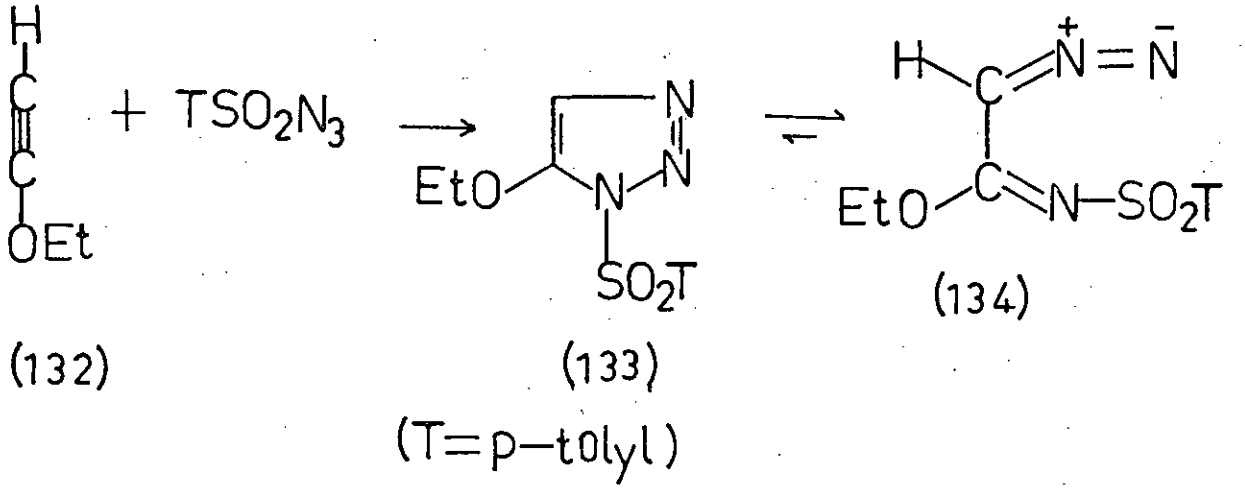
Cycloaddition reactions[33] of arenesulphonyl azides with ynamines affords 1-arenesulphonyl-1,2,3-triazoles which also exhibit



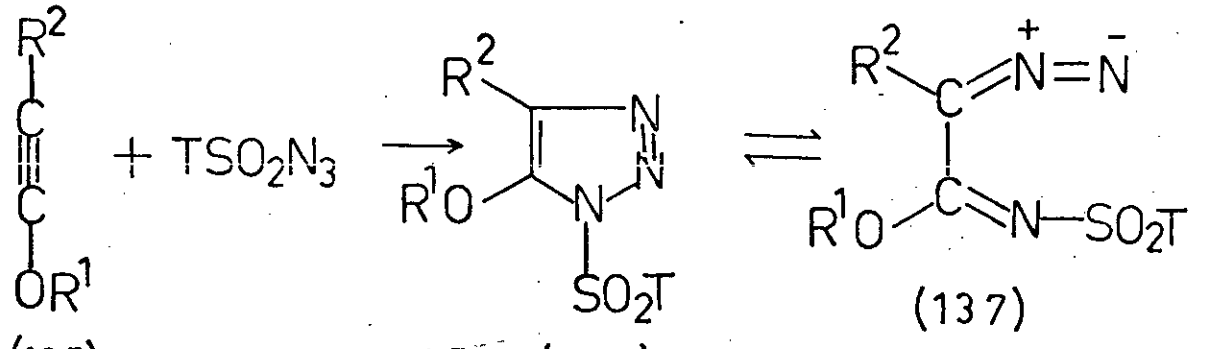
Scheme 30

diazoalkylideneamine-1,2,3-triazole ring-chain tautomerism. Thus, the cycloaddition of the arenesulphonyl azides (129) to 1-(N,N-diethylamino)prop-1-yne (128a) and 2-(N,N-dimethylamino)phenylacetylene (128b) yields the crystalline N,N-dialkylamino-1,2,3-triazoles (130 a and b) whose i.r. spectra in chloroform contain peaks at about 2000cm^{-1} characteristic of diazo-absorption and attributable to the presence of the diazo- tautomers [Scheme 30;(131a and b)]. On the other hand, the solid phase i.r. spectra of (130 a and b) lack absorption at about 2000cm^{-1} demonstrating the absence of the diazo-tautomers (131a and b) in the solid state.

More recently,[31] it has been shown that this type of ring-chain tautomerism also takes place in diazo-group transfer reactions with acetylenes. Thus, toluene-p-sulphonyl azide reacts with 2-ethoxyacetylene (132) to give the diazoacetimidate (134). β-Alkynyl ethers (135a-d) react similarly to afford the alkyl α-diazocarboximidates



(137a-d) or the isomeric 5-alkoxyl-1(arylsulphonyl)-4-alkyl-1,2,3-

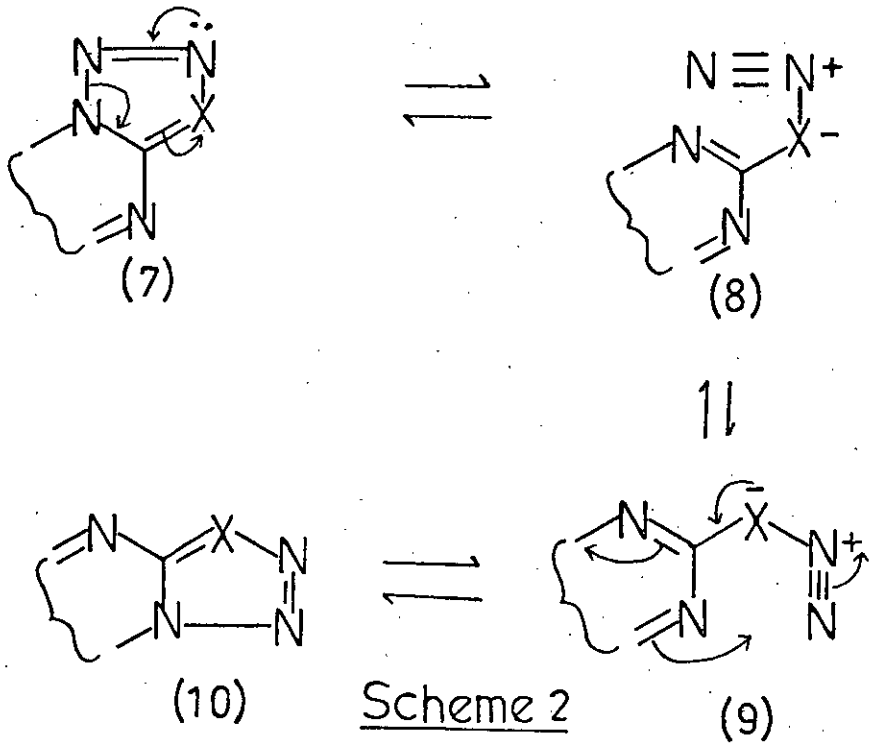


	R^1	R^2
a;	C_2H_5	CH_3
b;	CH_3	C_2H_5
c;	CH_3	CH_3
d;	C_2H_5	C_2H_5

Scheme 31

triazoles (136a-d), which exist in equilibrium in deuterochloroform. In these systems, the diazo- forms (134) and (137) can be isolated and characterised.

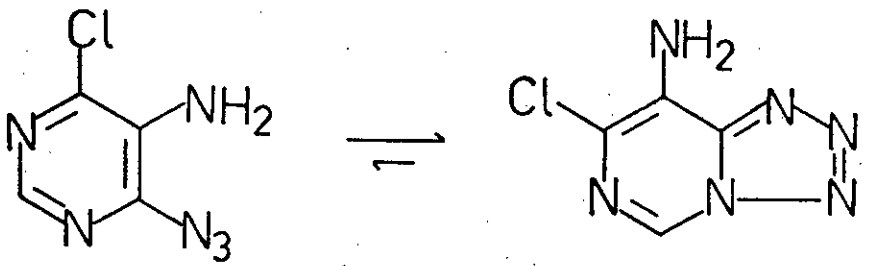
As has been said earlier, both the azide -tetrazole tautomerism



(7) (8) (10) (9)

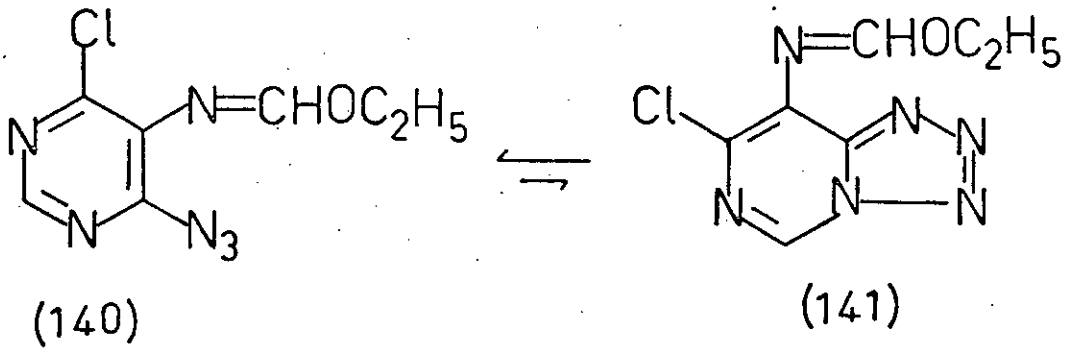
Scheme 2

[(7)⇌(8); X = N] and the attendant Dimroth rearrangement[9,10,34,36] [(7)⇌(8)⇌(9)⇌(10); X = N] have been well documented for bridgehead-fused tetrazoles. Temple and his group[9,10,34] report that the azide



(138) (139)

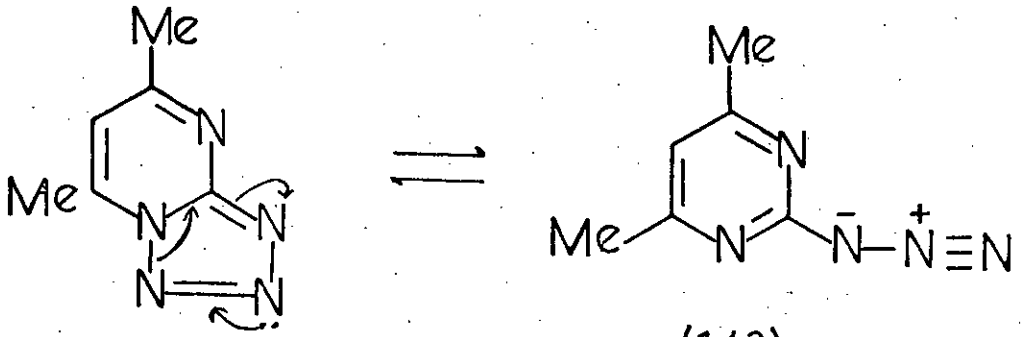
exists (138) mainly as the 4-amino-5-chlorotetrazolo[1,5-c]pyrimidine (139) while (140) exists mainly as 4-azido-6-chloro-5-ethoxymethyleneaminopyrimidine (140). The structures of these compounds have been established from their i.r. spectra. In (138)



(140) (141)

the i.r. spectrum shows a peak at 1100 - 1000cm^{-1} which is characteristic of tetrazoles while in the i.r. spectrum of (140), there is an absorption at 2200 - 2100cm^{-1} - the azide region. Temple et al studied other fused tetrazoles[10] and came to the conclusion that the tetrazole tautomer is stabilised by electron-donating groups while the azido-tautomer is stabilised by electron-withdrawing groups.

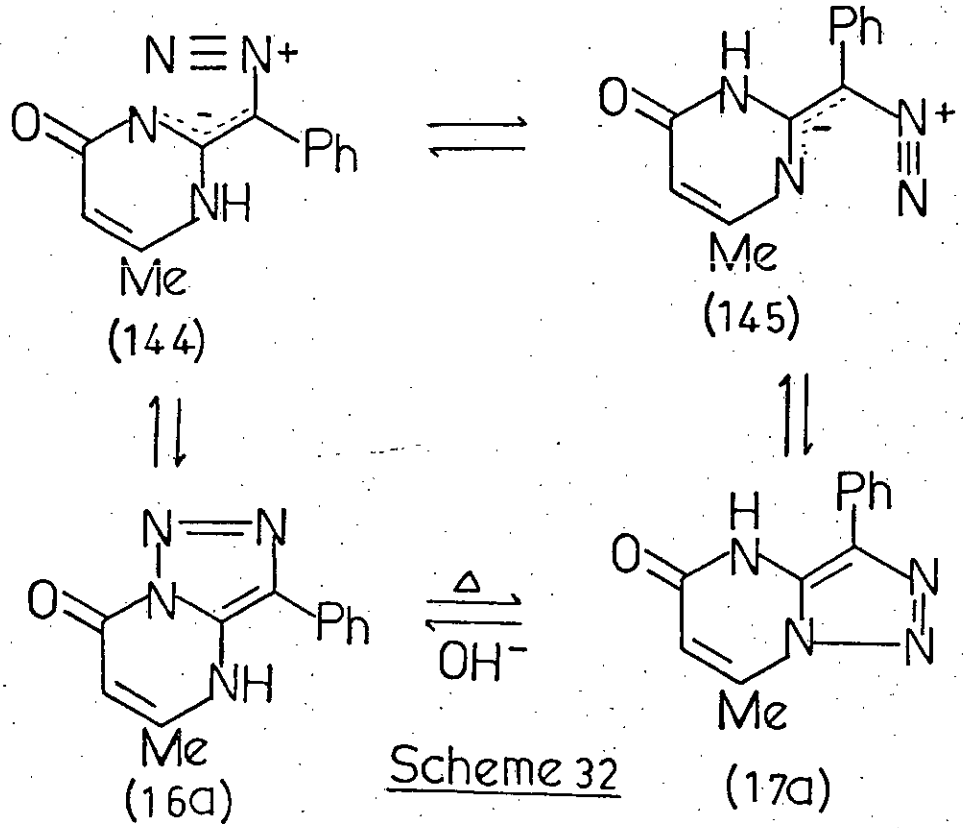
Another example of azide-tetrazole tautomerism is that demonstrated by Huisgen and his group[35] who have shown that there is an equilibrium between 5,7-dimethyltetrazolo[1,5-a]pyrimidine



(142) (143)

(142) and 2-azido-4,6-dimethylpyrimidine (143), which has been isolated as the cycloadduct with dimethyl acetylenedicarboxylate.

In contrast to bridgehead-fused tetrazoles, however, only one rearrangement of a bridghead-fused 1,2,3-triazole [(7) ⇌ (8) ⇌ (9) ⇌ (10); X = CR] has been reported.[8] As was mentioned earlier, it has been shown[8] that the condensation of 5-amino-4-phenyl-1H-1,2,3-triazole (15a) with ethyl acetoacetate in the presence of piperidine gave two isomers, mainly 5-methyl-3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidin-7 (4H)-one (16a) as the base stable isomer, which during crystallisation or drying out elevated temperatures reverted



Scheme 32

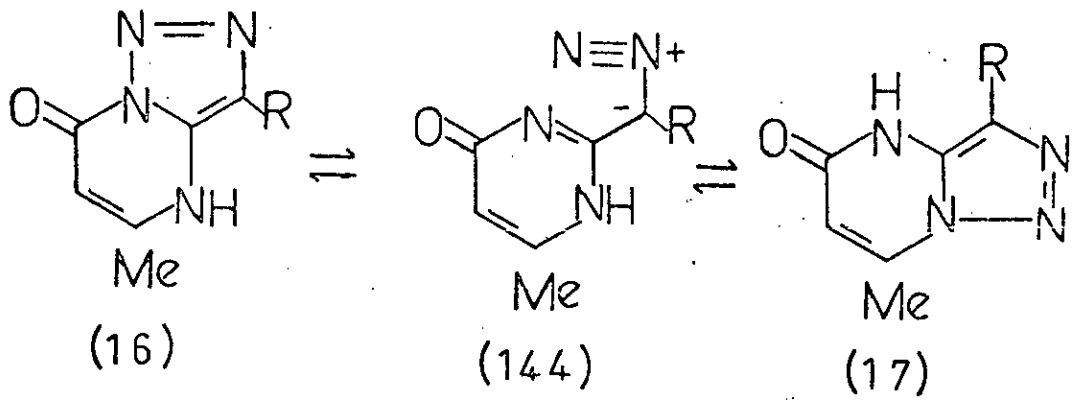
to the thermally stable isomer (17a). Reconversion of the isomer (17a) into (16a) was achieved[8] by warming in ethanolic piperidine. The proposed mechanism for this rearrangement (Scheme 32) involves the open chain forms [(144) ⇌ (145)] which could not, however, be detected by i.r. and ^{1}H n.m.r. studies of the products.

Chapter 2

Syntheses and Variable Temperature ^{1}H N.m.r. Studies of 1,2,3-Triazolo[1,5-a]pyrimidines

2.1 Introduction

As was discussed in Chapter 1, bridgehead-fused 1,2,3-triazoles of the 1,2,3-triazolo [1,5-a]pyrimidine type (16) have been shown[13] to undergo the new type of reversible Dimroth rearrangement [(16)⇌(144)⇌(17)] which embodies the hitherto unknown diazoalkylideneamine -1,2,3-triazole ring-chain tautomerism [(16a)⇌(144a) and



R

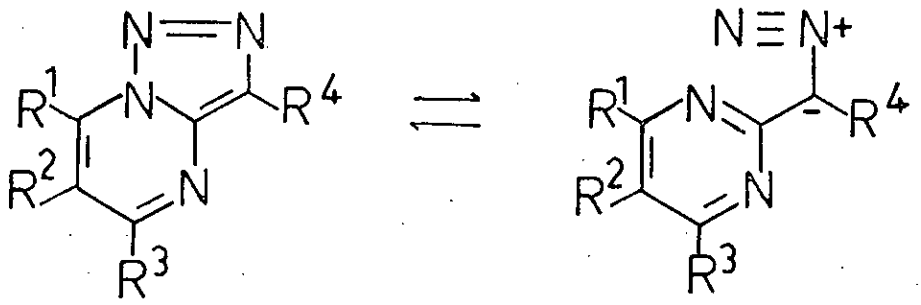
a; Ph

b; $CONH_2$

Scheme 33

(144a)⇌(17a)] . Despite the fact that electron-withdrawing groups on the pyrimidine and 1,2,3-triazole rings should stabilise the presumed diazo-intermediate (144) in such rearrangements (see Chapter 1), i.r. and ^1H n.m.r. studies of the phenyl compounds (16a) and (17a) and the corresponding amides (16b) and (17b) failed to provide any evidence for the corresponding diazo- intermediates (144a) and (144b). On the other hand, variable temperature ^1H n.m.r. studies[38] have shown that the ^1H n.m.r. absorption of the triazolopyrimidines (145) exhibits temperature dependence which can

be attributed to the rapid ring-chain tautomerism [Scheme 34; (145)⇌(146)] and that the activation energy for the process is

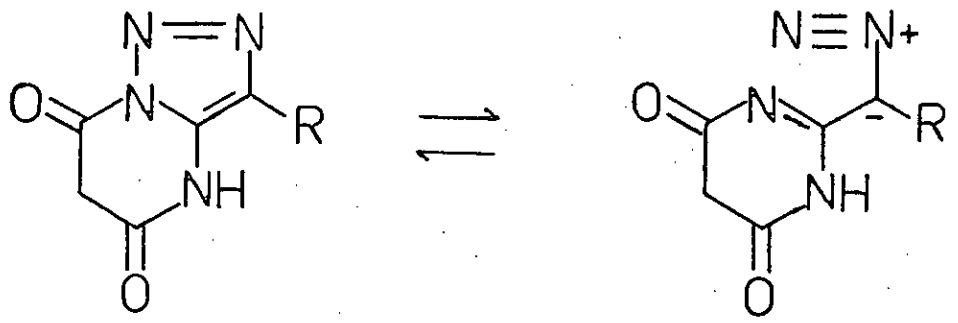


(145) (146)

	R^1	R^2	R^3	R^4
a;	Me	H	Me	Ph
b;	H	Ac	Me	Ph
c;	H	H	H	Ph
d;	Me	H	Me	$CONH_2$
e;	H	Ac	Me	$CONH_2$
f;	H	H	H	$CONH_2$

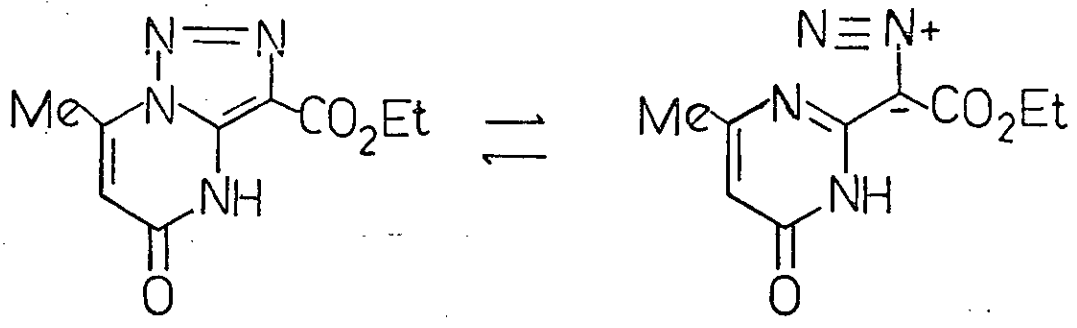
Scheme 34

lower in the case of the amide series (145d-f) compared with the phenyl series (145a-c) indicating the stabilising effect on the diazo-tautomer (146) of electron-withdrawal in the 1,2,3-triazole ring. Consequently, it was of interest to investigate the effect of increased electron-withdrawal in the pyrimidine and 1,2,3-triazole rings in 1,2,3-triazolo [1,5-a] pyrimidines on the stability of the diazo- form (146) in the hope that the latter might become the stable tautomer and hence be more readily observable. With this aim in mind it was decided to investigate synthetic routes to the substrates (147), (149) and (151), in which electron-withdrawal in either or both the pyrimidine and triazole rings is enchanced hence allowing the possibility that the molecules might exist largely or to a significant

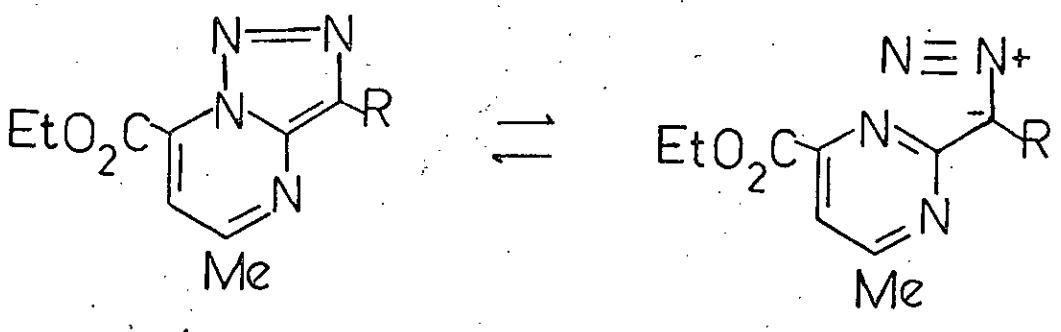


(147) (148)

extent in the corresponding diazo- forms (148),(150) and (152).

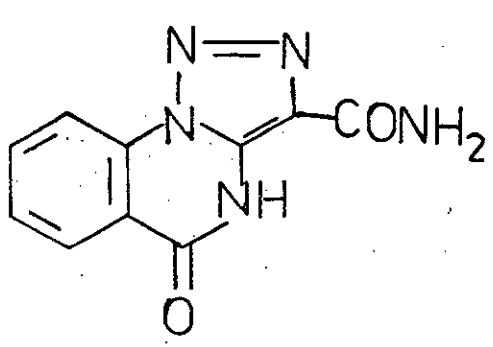


(149) (150)



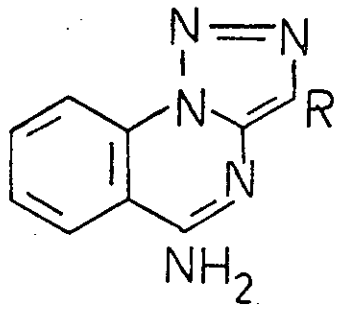
(151) (152)

	R
a;	Ph
b;	$CONH_2$



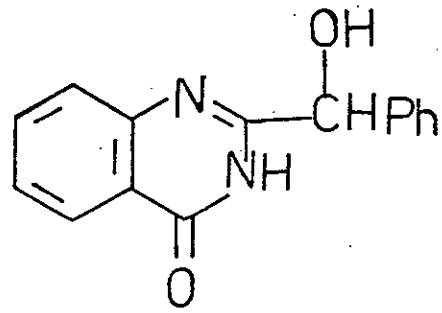
(156)

$\xleftarrow[(155b)]{OH^-}$



(155)

$\xrightarrow[(155a)]{H^+}$



(157)

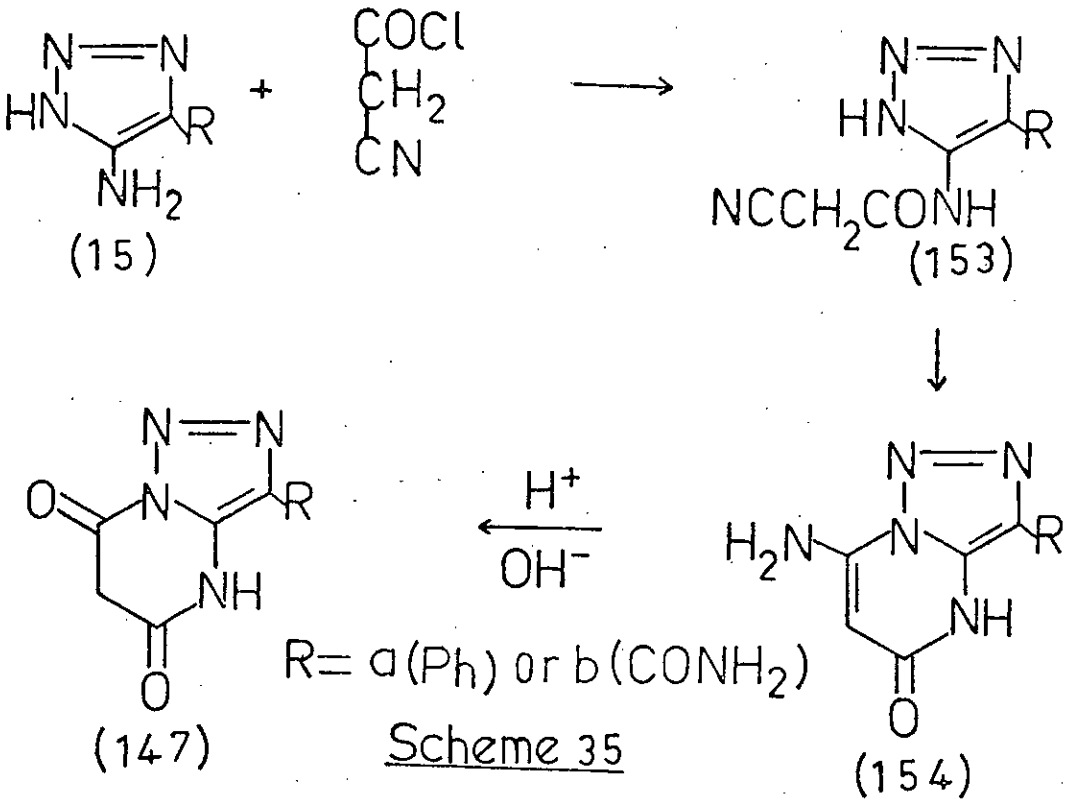
R

a; Ph

b; $CONH_2$

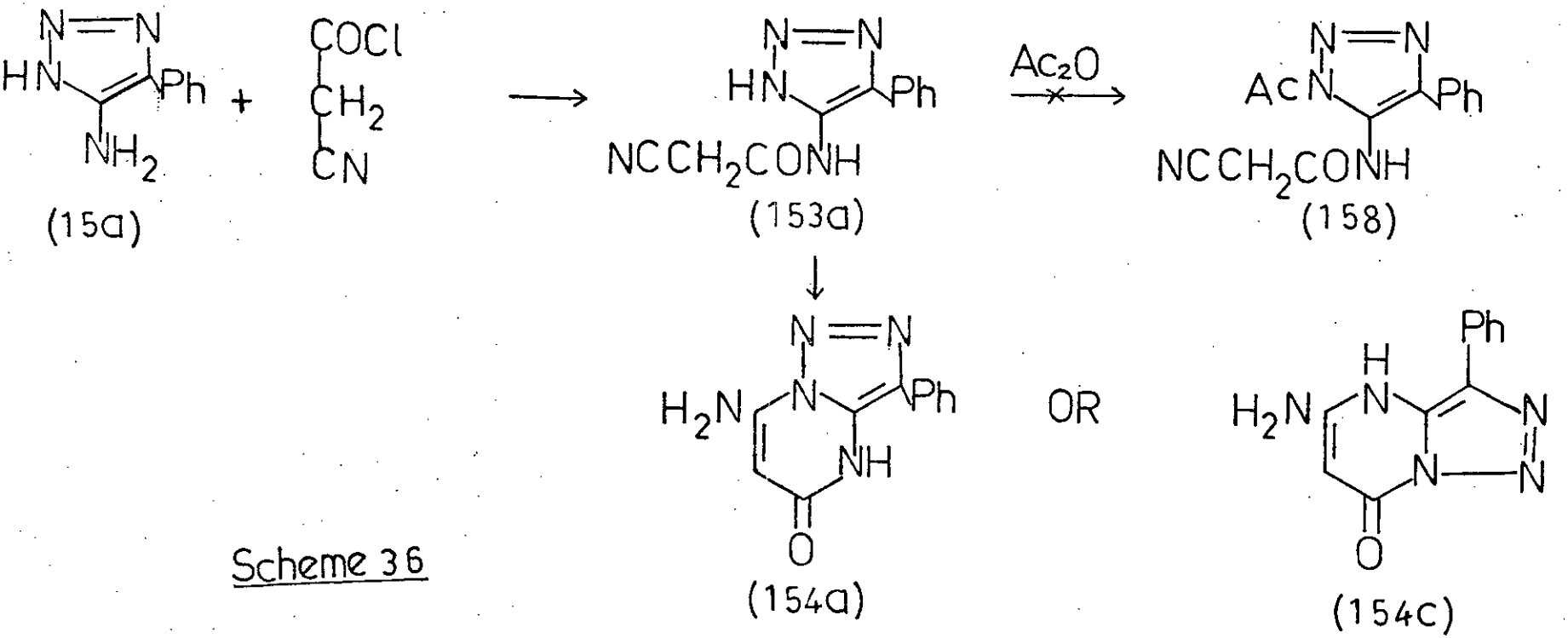
2.2 The Attempted Synthesis of 3-Substituted-1,2,3-Triazolo-[1,5-a]pyrimidine-5,7(4H, 6H) - diones (147)

The route envisaged for the synthesis of the 1,2,3-triazolo-pyrimidinediones (147) involved the condensation of the aminotriazoles (15) with cyanoacetyl chloride to afford the aminotriazolopyrimidinones (154) either directly or via the cyanoacetamidotriazoles (153). It was then hoped that acid- or base-

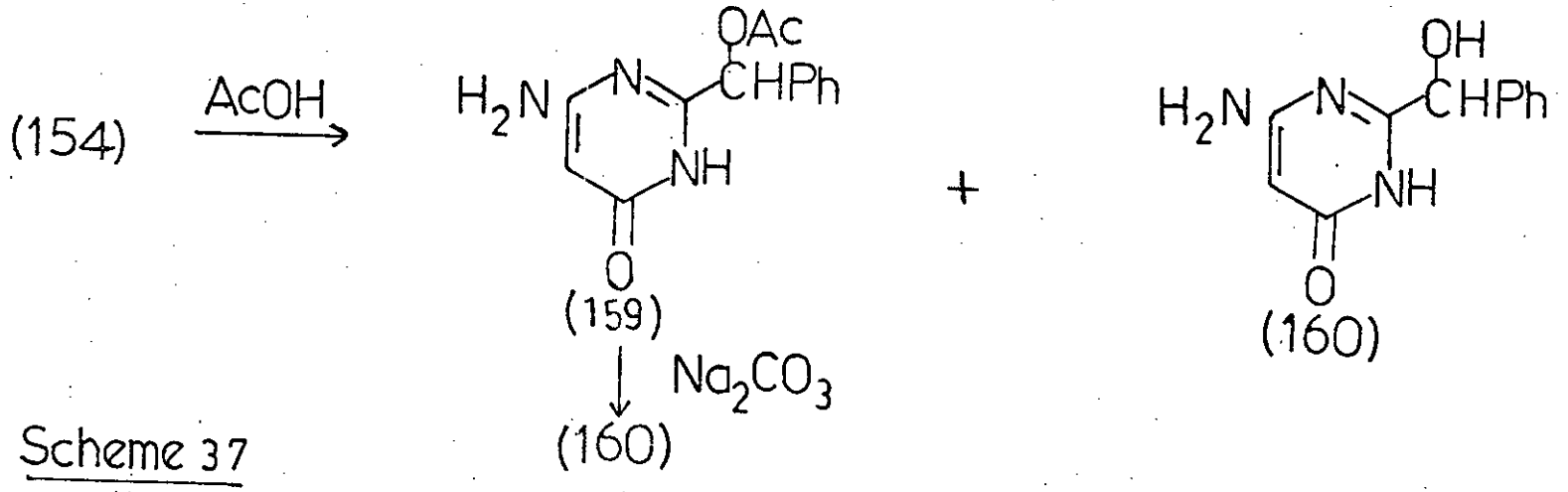


Scheme 35

catalysed hydrolysis of the amino-group in the amines (154) would give the required diones (147). This type of hydrolysis is observed[13] in the acidic or alkaline hydrolysis of aminotriazoloquinazolines (155) to give triazoloquinazolones (156) or quinazolones (157) and in the well known[37] hydrolysis of 4-aminoquinazolines to quinazolin-4(34)-ones.



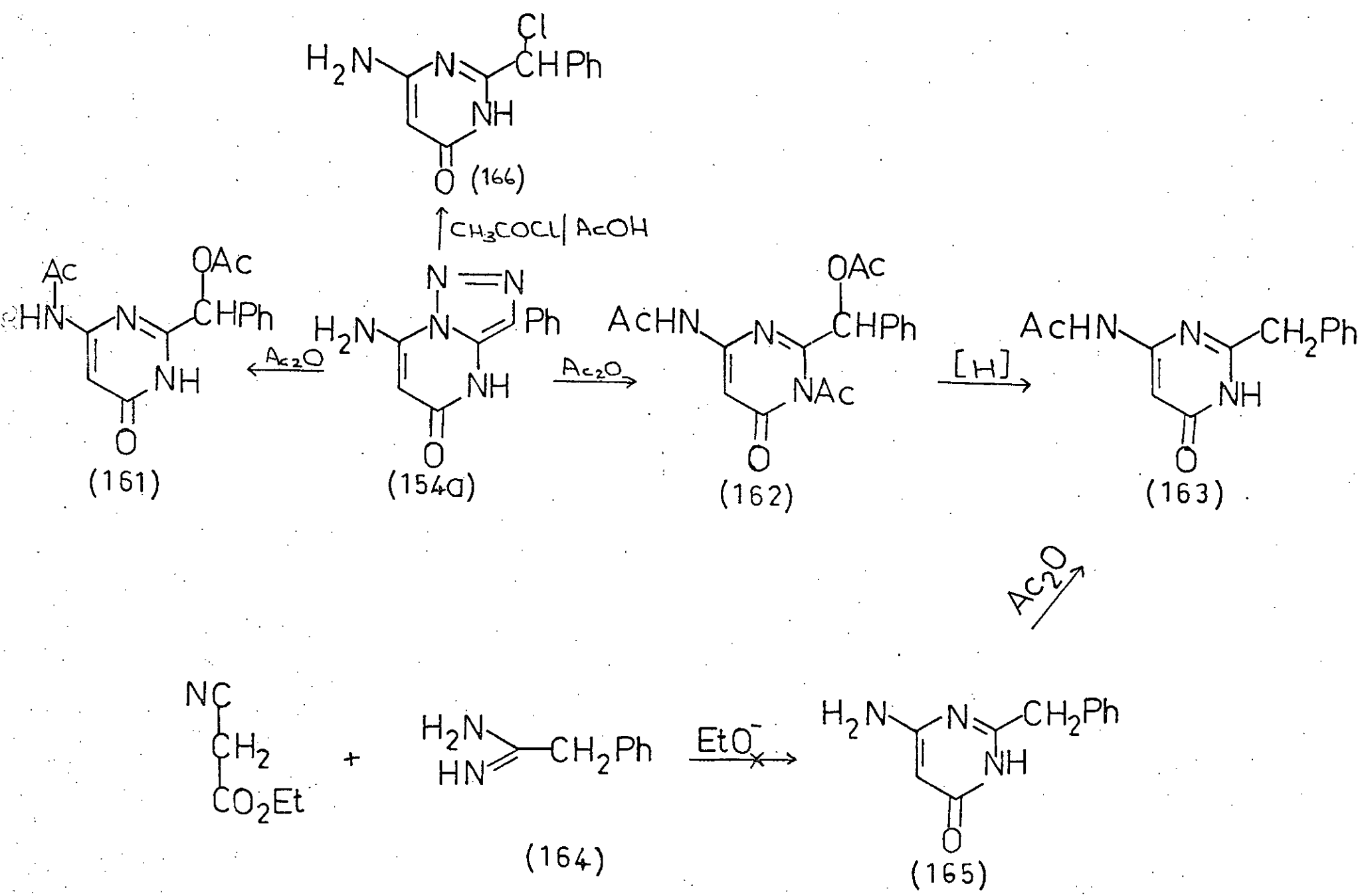
Scheme 36



Scheme 37

In practice, 4-phenyl-1H-1,2,3-triazole (15a) condensed readily with cyanoacetyl chloride in refluxing benzene to afford the cyanoacetamidotriazole (153a). The structure assigned to this product is fully consistent with its properties and transformations. Its i.r. spectrum contained cyano- absorption at 2250cm^{-1} and also carbonyl and NH bands and its ^{1}H n.m.r. spectrum showed methylene absorption at τ 6.28. By way of further establishing the structure of the triazole derivative (153a) an attempt was made to convert it by acetylation into an N-acetyl derivative (158) which would show characteristic[5a] spectral properties for the acetyl group. However, the attempted acetylation of (153a) was unsuccessful.

An initial attempt to effect cyclisation of the amide (153a) by heating in glacial acetic acid was unsuccessful. In contrast, the conversion of (153a) into the desired amine (154a) or (154c) was smoothly achieved in high yield by heating under reflux with piperidine in ethanol. The analytical, mass spectral and i.r. data of the product obtained are consistent with the structure of (154a) or (154c). Its i.r. spectrum contains primary amino- and carbonyl absorptions but no ^{1}H n.m.r. spectrum could be obtained because of its insolubility in [$^{2}H_{6}$]-dimethylsulphoxide. It was not possible to determine which isomer (154a) or (154c) was formed and so for the purpose of discussion the product will be assumed to be (154a). The attempted characterisation of the aminotriazolopyrimidine (154a) by methylation was unsuccessful. Thus, the compound (154a) was largely unaffected by treatment with dimethyl sulphate in the presence of alkali or methyl iodide in the presence of sodium hydroxide. The use of methyl iodide in the presence of potassium carbonate gave a very low yield of a product whose mass spectrum showed a parent ion


Cl
H2N
N
CHPh
NH
O
(166)
CH3COCl/ AcOH
Ac
OAc
HN
N
CHPh
NH
O
(161)
Ac2O
N=N
H2N
N
Ph
NH
O
(154a)
Ac2O
OAc
AcHN
N
CHPh
NAc
O
(162)
[H]
AcHN
N
CH2Ph
NH
O
(163)
Ac2O
NC
CH2
CO2Et
+
H2N
HN
CH2Ph
(164)
EtO⁻
H2N
N
CH2Ph
NH
O
(165)

Scheme 38

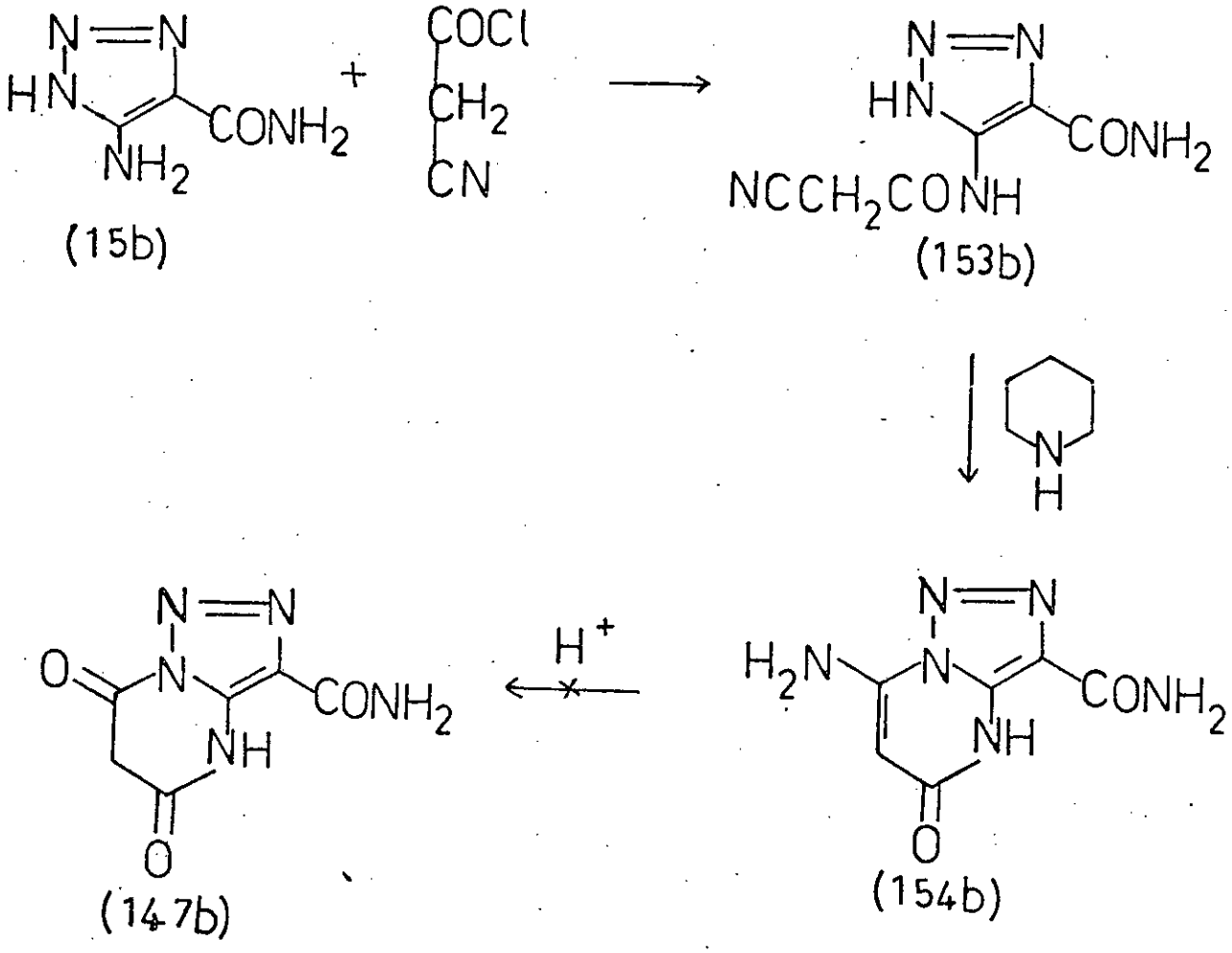
at m/e 255 indicating it to be a dimethyl derivative but, unfortunately, there was insufficient of this material for characterisation.

However, the structure of the amine (154a) was readily verified by its behaviour towards acid-catalysed triazole scission.[8,24] Thus, when (154a) was heated with glacial acetic acid, it gave a product whose spectral properties indicated it to be a mixture of the acetoxybenzyl and hydroxybenzyl pyrimidinones (159) and (160). In particular, the i.r. spectrum of the product contained bands at 3200 and 1720 cm^{-1} attributable to hydroxyl and acetoxy- groups respectively and its mass spectrum showed parent ions at m/e 216 and 259. Since the mixture defied all attempts at separation it was converted by hydrolysis completely into the alcohol [Scheme 37; (160)]. The structure of the alcohol (160) is fully consistent with its properties. Its i.r. spectrum shows hydroxyl, carbonyl, and NH absorption and its ^1H n.m.r. spectrum contains pyrimidine and benzylic hydrogens at τ 4.66 and 5.08 respectively. The analytical and mass spectral data are also consistent with the structure (160).

Triazole scission also occurred when the amine (154a) was heated under reflux in acetic anhydride. On a relatively small scale, this reaction afforded a diacetyl derivative which is assigned the structure (161) on the basis of the following evidence. The i.r. spectrum of the diacetyl derivative contained NH, acetoxy and acetyl absorption and its mass spectrum showed a parent ion at m/e 301 which is expected for the diacetyl derivative (161) but there was insufficient of it for its ^1H n.m.r. spectrum to be obtained. However, when the reaction of the amine (154a) with acetic anhydride was repeated on a larger scale the product was a triacetyl derivative. The structure (162) assigned

to this product is based on its properties and transformations. The i.r. spectrum of (162) shows characteristic[5a] high carbonyl bands at 1780 and 1740 cm^{-1} while its ^1H n.m.r. spectrum contains proton absorption at τ 7.70, 7.88 and 7.80 typical of a ring N-acetyl group, NHAc and an acetoxy group respectively. The mass spectrum of (162) shows the expected parent ion at m/e 343 and it gave a correct elemental analysis. The structure of the triacetyl derivative (162) is further supported by its ~~hydrolysis~~ hydrogenolysis to a product whose properties are consistent with its being the benzylpyrimidine (163). Thus, its i.r. spectrum contains both carbonyl and NH bands while the mass spectral and analytical data agree with the expected values but there was insufficient material to measure its ^1H n.m.r. spectrum.

In an effort to establish rigorously the structure of (163) and hence that of the aminotriazolopyrimidine (154a) an attempt was made to synthesise the benzylpyrimidine unambiguously by the standard condensation of phenylacetamidine (164) with ethyl cyanoacetate to give the amine (165) followed by acetylation. In practice, the attempted condensation of ethyl cyanoacetate with phenylacetamidine (164) failed to yield the desired pyrimidine (165), the only identifiable product isolated being phenylacetamide which is presumably formed by the hydrolysis of phenylacetamidine in the reaction mixture. However, the structure (154a) for the aminotriazolopyrimidine was further substantiated by its triazole scission[8] in a hot mixture of acetyl chloride and acetic acid to give the chlorobenzylpyrimidine (166). The i.r. spectrum of (166) contains primary amino- and carbonyl absorption while its mass spectrum shows a parent ion at m/e 279 instead of the expected value of 277, indicating the presence of the heavier isotope of chlorine.


(15b)
(153b)
(147b)
(154b)
(167)
Scheme 39

In an attempt to obtain the dione (147a) an ethanolic solution of the triazolopyrimidinone (154a) was heated under reflux with aqueous dilute sulphuric acid but this reaction gave only a small quantity of an unidentified solid. The attempted base-catalysed hydrolysis of (154a) was also unsuccessful, giving instead a product whose i.r. spectrum showed NH and hydroxyl absorption while its mass spectrum gave no ion pressure. However, the combustion analysis was almost consistent with its being the monohydrate of the hydroxyl derivative (160).

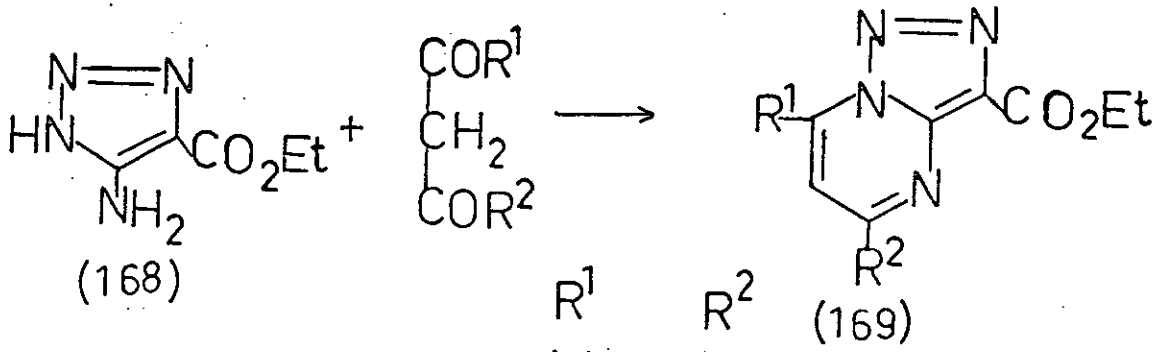
The failure of the attempted base-catalysed conversion of the amine (154a) into the dione (147a) prompted an attempt to synthesise the amide (154b) or its isomer (167). In these compounds the triazole ring should be stable to acid-catalysed scission[5b], thus allowing the possibility of their acid-catalysed conversion into the dione (147b). Consequently, the cyanoacetamidotriazole (153b) was synthesised by condensing the triazole amide (15b) with cyanoacetyl chloride. The product (153b) was isolated as a monohydrate and its structure is fully consistent with its i.r. spectrum which shows amino and carbonyl absorption and a band at 2280 cm^{-1} characteristic of the cyano-group. In accord with the assigned structure, the cyanoacetamidotriazole (153b) underwent smooth cyclisation on heating with piperidine in ethanol, to afford the desired triazolopyrimidine amide (154b) in high yield. This product was again isolated as a monohydrate and attempts to obtain the anhydrous compound were unsuccessful. However, its structure is fully consistent with its i.r. spectrum which lacked cyano-absorption but showed bands assignable to a primary amino-group and a cyclic amide group respectively. Also its mass spectrum contained a peak due to the parent ion at m/e 194. The attempted acid

hydrolysis of the amino-amide (154b) to the dione (147b) gave only unreacted starting material. Base-catalysed solvolysis of (154b) was not attempted due to the lack of success with the phenyl compound (154a) (see before).

2.3 The Synthesis of 3-Ethoxycarbonyl-1,2,3-Triazolo [1,5-a] pyrimidine Derivatives

As has been discussed earlier, replacing the phenyl group by a carboxamide group at the 3-position in a 1,2,3-triazolo [1,5-a] pyrimidine lowers the ^{1}H n.m.r. coalescence temperature for diazoalkylideneamine-1,2,3-triazole tautomerism in these molecules presumably due to stabilisation of the diazo-tautomer by the electron-withdrawing groups at C(3). Since an ester function is significantly more electron-withdrawing than a carboxamide group, the coalescence temperature for tautomerism should be even lower in 1,2,3-triazolo-[1,5-a] pyrimidines substituted with a 3-ethoxycarbonyl group. Conversely, the demonstration of such a substituent effect would lend further support to diazoalkylidene$_{amine}$-triazole tautomerism as the origin of the temperature dependence of ^{1}H n.m.r. spectra of triazolo [1,5-a] pyrimidines.[38] To test the validity of these assertions, it was decided to attempt the synthesis of a series of 3-ethoxycarbonyl-1,2,3-triazolo [1,5-a] pyrimidines and to study the temperature dependence of their ^{1}H n.m.r. spectra.

The synthetic route to suitable 1,2,3-triazolo [1,5-a] pyrimidines with an ethoxycarbonyl substituent at C(3) was modelled on previous work[5b] and involved the condensation of β-dicarbonyl compounds with

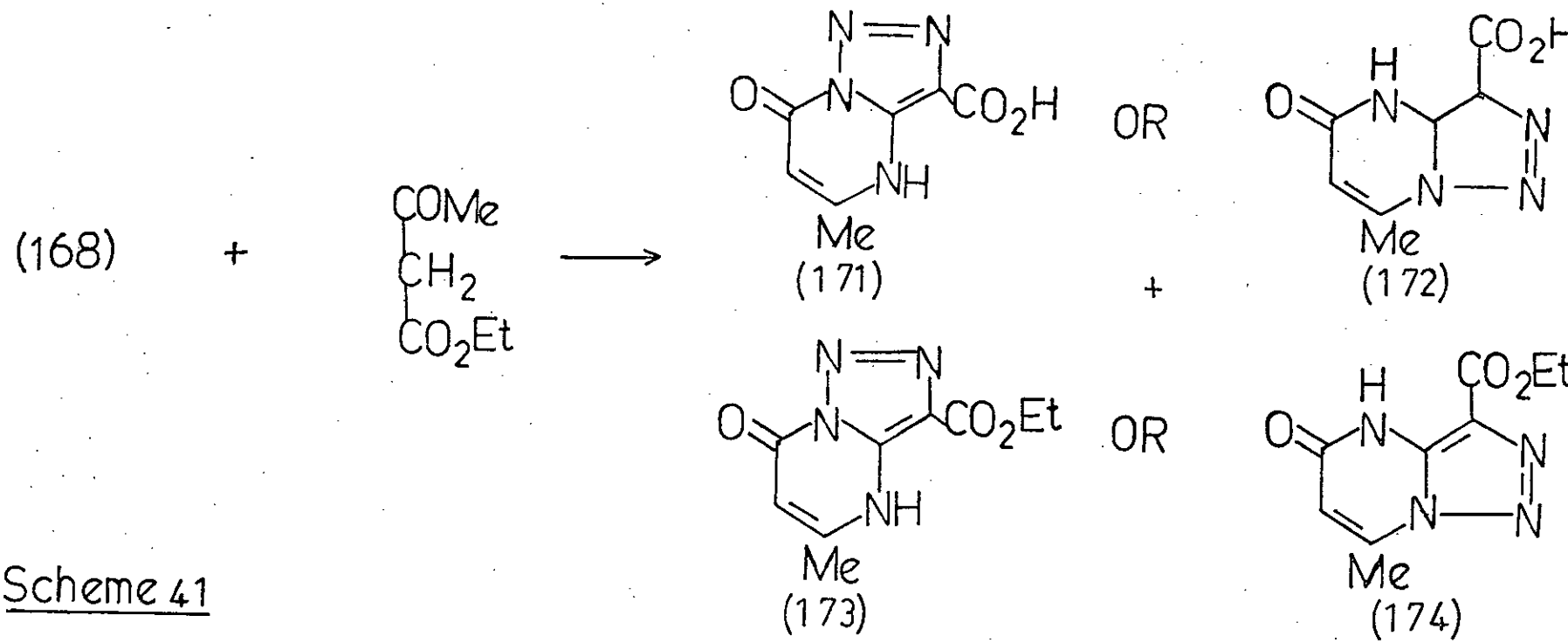


(168)

	R^1	R^2
a;	Me	Me
b;	Ph	Me
c;	Me	Ph

(169)

Scheme 40



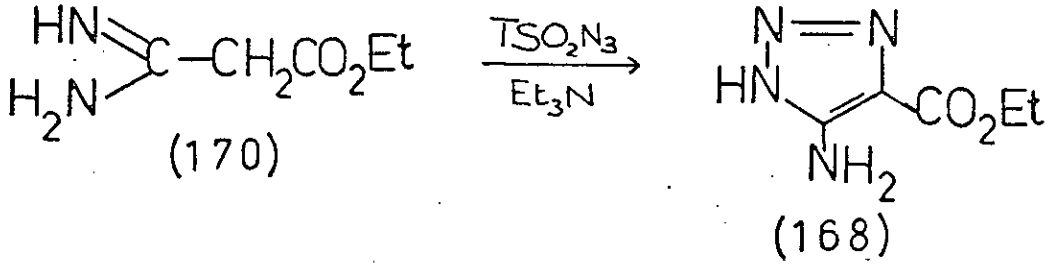
(168)

(171) OR (172)

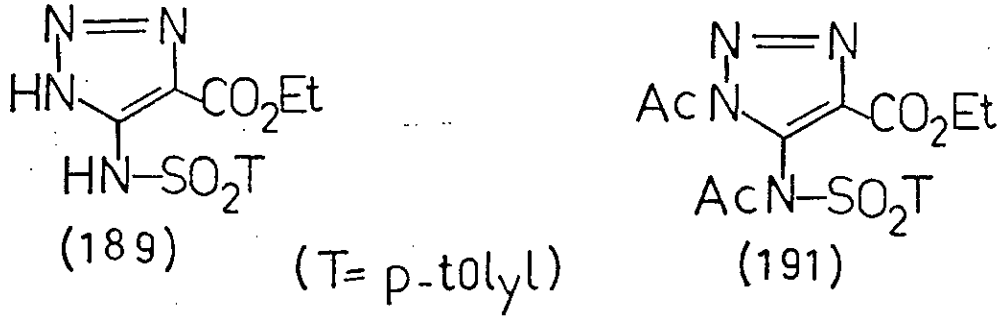
(173) OR (174)

Scheme 41

ethyl 5-amino-1,2,3-triazole-4-carboxylate (168). This previously unknown triazole derivative was readily synthesised by the diazo-transfer reaction[17] of toluene-p-sulphonyl azide with the known amidine (170). This reaction also gave toluene-p-sulphonamidotriazole (189) identified by its conversion to the diacetyl derivative (191). The amine (168) reacted smoothly with acetylacetone in the presence of



(170) (168)

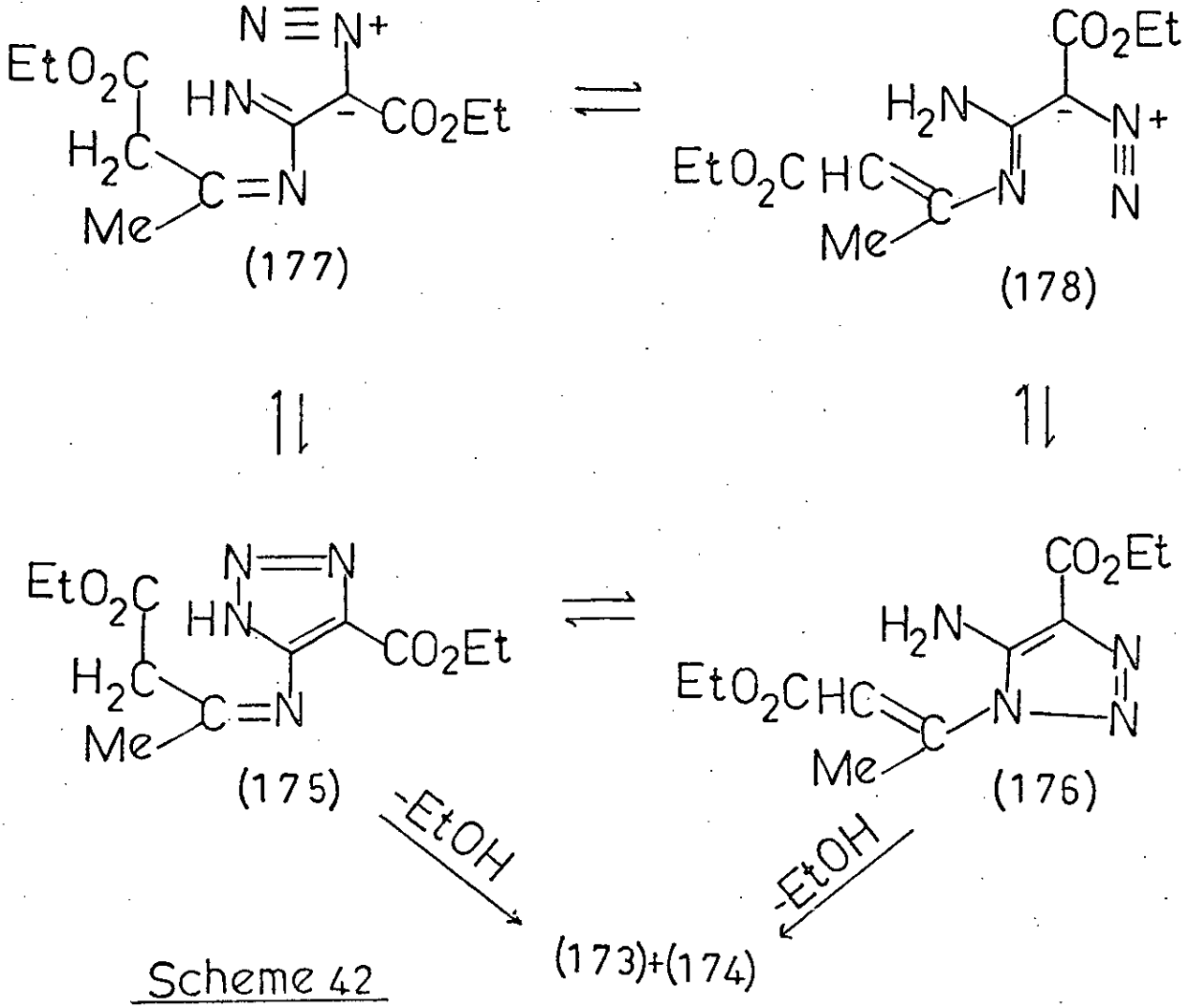


(189) (T= p-tolyl) (191)

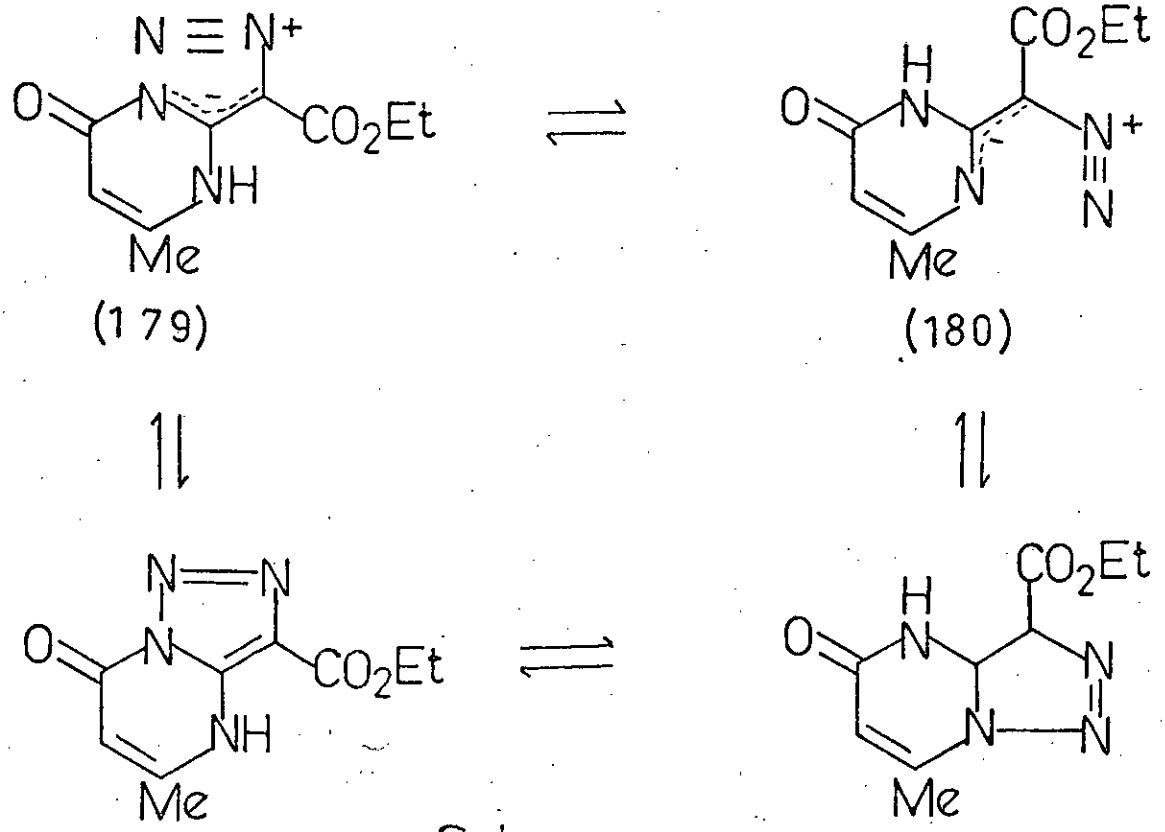
piperidine to afford the triazolopyrimidine ester (169a) in good yield. The structure of this product follows from its combustion analysis and its spectral properties. In particular, its ^{1}H n.m.r. absorption is similar to structurally closely related triazolopyrimidines.[5b] Thus, its ^{1}H n.m.r. spectrum shows a singlet at τ 2.76 due to the C(6) proton and absorption at τ 7.38 and 7.16 attributable to the C(5) and C(7) methyl groups respectively. The amino-triazole (168) also condensed smoothly with benzoylacetone in the presence of piperidine to afford

a single triazolopyrimidine product. This is assigned the structure (169b) as opposed to the alternative possibility (169c) on the basis of its ^{1}H n.m.r. spectrum. This shows unsplit methyl absorption at τ 7.06 and a singlet at τ 2.03 due to the C(6) proton whereas the methyl band in ^{1}H n.m.r. spectrum of (169c) would be split due to the C(6) - C(7) double bond. The preferential formation of (169b) is in accord with initial condensation between the amino-group in (168) with the more reactive acetyl group.

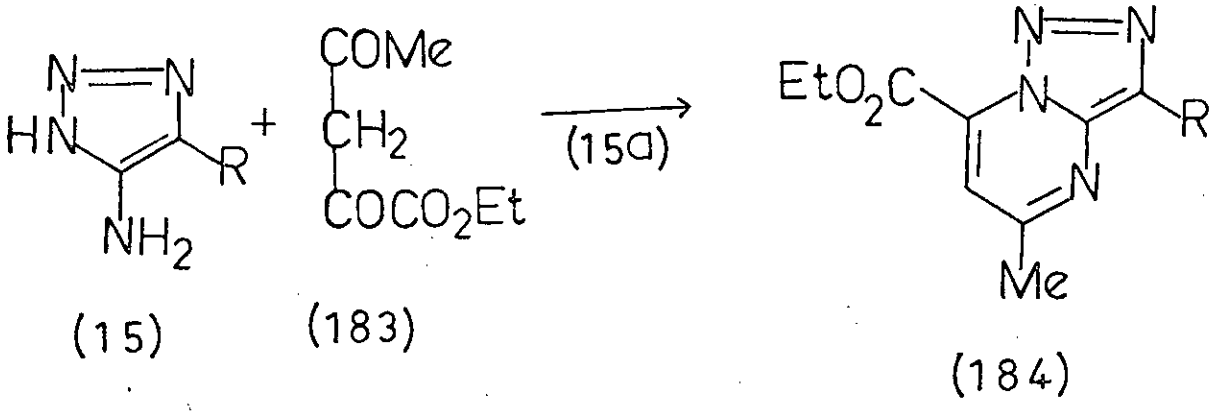
Unexpectedly, the aminotriazole (168) failed to condense with ethyl acetoacetate in the presence of piperidine. This behaviour is unexpected in view of the success with similar condensations[5b], and may reflect the lower basicity of the primary amino-group in the ester (168), compared with the corresponding amide which does condense satisfactorily with ethyl acetoacetate.[5b] However, the amine (168) did react with ethyl acetoacetate in the presence of glacial acetic acid. Two products were obtained one of which was high melting and gave analytical and i.r. spectral data corresponding to the carboxylic acid (171) or (172) though it did not liberate carbon dioxide from sodium hydrogen carbonate solution. The second lower melting product was formed in major amount and gave analytical and i.r. spectral data consistent with its formulation as either the triazolopyrimidinone (173) or its isomer (174). However, its ^{1}H n.m.r. spectrum showed clearly it was a 50:50 mixture of the two isomers (173) and (174). Thus, the ^{1}H n.m.r. spectrum contains two pyrimidine hydrogens at τ 3.68 and 4.04, the first one being split into a doublet with a coupling constant of 2Hz. There are also two ester peaks and two methyl signals at τ 7.33 and 7.54 due to the isomers (173) and (174) respectively. The first methyl signal is also split into a doublet this time with a coupling



Scheme 42



Scheme 43

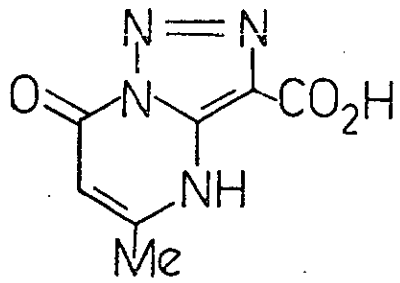


(15) (183) (184)

	R
a;	Ph
b;	$CONH_2$

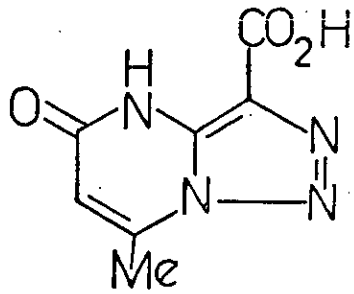
Scheme 44

constant of 1Hz. Repeated crystallisation of the mixture failed to change the proportions of the two isomers. The formation of the isomeric mixture of (173) and (174) may be due to condensation of the aminotriazole with the ethyl acetoacetate in both possible ways. However, it is more likely in view of previous work[16] that the formation of (173) and (174) is the result of Dimroth rearrangement either before (Scheme 42) or after (Scheme 43) cyclisation of the vinylaminotriazole [(175) ⇌ (176)] which is the probable[16] intermediate in the condensation of the aminotriazole with ethyl acetoacetate. The attempted alkaline or acidic hydrolysis of the isomer mixture (173)/(174) to the corresponding mixture of acids (181)/(182) was unsuccessful.



(181)

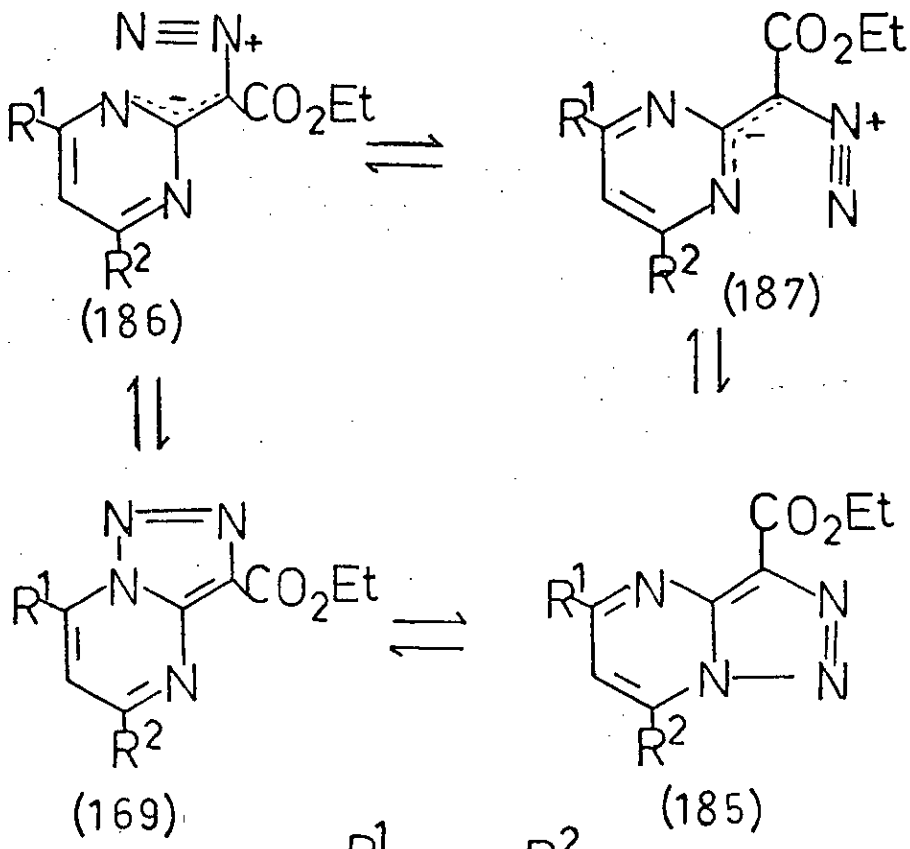
OR



(182)

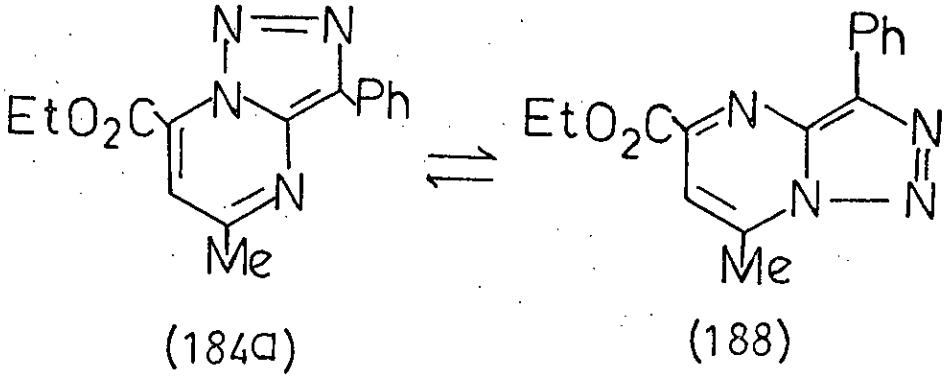
2.4 The Synthesis of 7-Ethoxycarbonyl 1,2,3-Triazolo [1,5-a] pyrimidine Derivatives

With a view to obtaining 1,2,3-triazolo [1,5-a] pyrimidine derivatives bearing an ethoxycarbonyl substituent at C(7) for variable temperature ^{1}H n.m.r. studies, the condensation of the aminotriazoles (15a and b) with ethyl acetopyruvate (183) was investigated. Thus, the aminotriazole [Scheme 44; (15a)] condensed readily with the



	R^1	R^2
a:	Me	Me
b:	Ph	Me

Scheme 45



diketo-ester (183) in the presence of piperidine to afford the ester (184a). The i.r. spectrum of (184a) contains carbonyl absorption at 1710 cm^{-1} and the analytical and mass spectral data agree with the expected values for the structure (184a). However, the attempted condensation of the aminotriazole (15b) with the diketo-ester (183) in the presence of piperidine was unsuccessful.

It will be recalled (see before) that 1,2,3-triazolo[1,5-a]-pyrimidines of type (16) are now known[13] to exhibit diazoalkylideneamine-triazole ring-chain tautomerism [(16a) ⇌ (144a)]. Further convincing evidence for this equilibrium (Scheme 45) was obtained in the present work when the ^1H n.m.r. spectrum of the triazolopyrimidine (169a) was measured in dimethylsulphoxide at various temperatures. Thus, when the ^1H n.m.r. spectrum of (169a) was run at suitably elevated temperatures, the Me(5) and Me(7) signals coalesced. Further elevation of the temperature resulted in the appearance of a single singlet due to coalesced Me(5) and Me(7). Two interpretations can be made about these variable temperature effects. The first is that the structures (169a) and (185a) are undergoing rapid interconversion and consequently only an averaged spectrum of (169a) and (185a) is being observed. Secondly, at elevated temperature, the open chain form [(186a) ⇌ (187a)] is preferred. Each interpretation, however, involves the existence of diazoalkylideneamine-triazole tautomerism. Unfortunately, the ^1H n.m.r. resonance of the C(5) methyl group in the compounds (169b) and (184a) showed no splitting, thus providing no basis for the study of the temperature dependence of the ^1H n.m.r. spectra of the compounds (169b) and (184a) and hence for the detection of the expected equilibria [(169b) ⇌ (185b)] and [(184a) ⇌ (188)].

The free energy of activation, $\Delta G^* = 16.7$ kcal mol^{-1}, for the process [(169a)/(185a) ⇌ (186a)/(187a)], was obtained from the coalescence temperature, Tc, and the chemical shift δ (in Hertz) being averaged, by using

the equation:[42]

$$\Delta G^{*} = 4.59Tc \left[9.97 + \log_{10} Tc/\delta \right] \quad (1)$$

It has been mentioned earlier that the activation energy for diazoalkylideneamine-1,2,3-triazole tautomerism in 1,2,3-triazolo[1,5-a]-pyrimidines is lower for amide substituted triazolo[1,5-a]pyrimidines (ΔG^{*} = 18kcal mol^{-1}) compared with phenyl substituted triazolo[1,5-a]-pyrimidines (ΔG^{*} = 22kcal mol^{-1}). Thus, in the ester series [cf. Scheme 45; (169a) / (185a) $\rightleftharpoons$ (186a) / (187a)], the activation energy (ΔG^{*} = 16.7kcal mol^{-1}) is even lower than in the amide series. This evidence supports the theory that a more electron-withdrawing substituent at C(3) in 1,2,3-triazolo[1,5-a]pyrimidine helps to destabilise the structures (169a) and (185a) relative to (186a) and (187a).

2.5 Experimental (For general experimental procedures, see Appendix)

5-Amino-4-phenyl-1H-1,2,3-triazole (15a) and 5-Amino-1H-1,2,3-triazole-4-carboxamide (15b)

The aminotriazoles (15a) (86%) m.p. 218° (lit.,[41] 219°) and (15b) (93%) m.p. 118° (lit.,[41] 120°)were prepared as described by Vevers.[16]

Ethoxycarbonylacetamidine Hydrochloride (170)

The amidine hydrochloride[46] (170) (63%) m.p. 102° (lit.,[46] 104°) was prepared as described by Collins.[46]

Ethyl 5-Amino-1H-1,2,3-triazole-4-carboxylate (168)

A solution of the amidine hydrochloride (170) (13.32g, 0.08 mol) in absolute ethanol (300 ml) was cooled to 0° (ice-salt bath), stirred and treated dropwise with piperdine (11.2g, 0.17g). The mixture was then treated dropwise with stirring with a solution of toluene-p-sulphonyl azide (34.8g, 0.17 mol) and the mixture was stirred in the melting ice bath for 2h. The mixture was evaporated and the oil formed was triturated with water to give the impure triazole (168) (8.85g) m.p. 100° which crystallised from ethanol as a pale yellow solid (4.28)m.p. 170°, $\nu_{max.}$ 3450, 3300 and 3160 (NH) and 1690 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 4.98(2H, s, NH), 5.76(2H, q J 7Hz CH_2) and 8.74(3H, t J 7Hz, CH_3).

Found: 38.1; H, 5.2, N, 35.4%; M^+ 156.

$C_5H_8N_4O_2$ requires: 38.5; H, 5.2; N, 35.9%; M, 156.

The aqueous mother liquor on standing deposited the impure toluene-p-sulphonyl triazole (189) (2.18g) m.p. 170° which crystallised from ethanol as colourless prisms (1.5g) m.p. 193°, $\nu_{max.}$ 3260, and 3300w (NH) and 2520, and 2510 (NH, OH) and 1680 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.28 (2H, d J 8Hz, Ar-H), 2.60 (2H, d J 8Hz, Ar-H), 5.82(2H, q J 7Hz, CH_2), 7.68(3H, s, CH_3), and 8.74(3H, t J 7Hz, CH_3).

Found: N, 17.9%; M^+ 310 .

$C_{12}H_{14}N_4O_4S$ requires: N, 18.0%; M, 310 .

The aqueous mother liquor was evaporated to give an oil which was triturated with ether to yield a solid (8.96g) m.p. 105° which was extracted with hot light petroleum (b.p. 100 - 120°) to leave toluene-p-sulphonamide as an insoluble solid (4.5g) m.p. 140° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The light petroleum extract on cooling formed colourless crystals of toluene-p-sulphonyl piperidide[44] (190) (1.8g) m.p. 100° (lit.,[44] 103°).

Acetylation of the Toluene-p-sulphonamidotriazole (189)

The toluene-p-sulphonamidotriazole (189) (0.62g, 0.002mol) was heated under reflux in acetic anhydride (5.0 ml) for 0.5h. The solution was evaporated under reduced pressure and the oil obtained was triturated with ether to afford the colourless diacetyl derivative (191) (0.35g) m.p. 156° (from ethanol), $\nu_{max.}$ 1780 and 1720 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.14(2H, q J 8Hz, Ar-H), 2.52(2H, q J 8Hz, Ar-H), 5.74(2H, q J 7Hz, CH_2), 8.10(3H, s, CH_3) 8.13(3H, s, CH_3) and 8.85(3H, t J 7Hz, CH_3).

Found: C, 48.8, H, 4.8; N, 14.3%; M^+ 394 .

$C_{16}H_{18}N_4O_6S$ requires: C, 48.8; H, 4.6; N, 14.4%; M, 394.

5-(2-Cyanoacetamido)-4-phenyl-1H-1,2,3-triazole (153a)

A solution of cyanoacetic acid (8.5g, 0.1 mol) in dry ether (100 ml) was treated in one portion with phosphorus pentachloride (22.0g, 0.1mol) and stirred at room temperature for 15min. The ether and phosphoryl chloride were distilled off at low temperature under reduced pressure and the cyanoacetyl chloride left as a pale yellow oil was dissolved in dry benzene (100 ml) and the solution added dropwise with stirring to a suspension of the aminotriazole (15a) (16.0g, 0.1 mol) in dry benzene (400ml). The mixture was heated under reflux on the steam bath for 2h and then evaporated and the solid residue was triturated successively with portions of ethanol to give cyanoacetamido-triazole (153a) as a pink solid (total 10.21g; 46%) m.p. 222° (from ethanol), $\nu_{max.}$ 3200, 2250 (C≡N) and 1680 (CO) cm^{-1} τ[$CDCl_3$ - $(CD_3)_2SO$] 2.28 - 2.37 (2H, m, Ar-H), 2.60 - 2.68(3H, m, Ar-H) and 6.28 (2H, s, CH_2).

Found: C, 58.1; H, 4.0; N, 30.7%; M^+, 227.

$C_{11}H_9N_5O$ requires: C, 58.2; H, 4.0; N, 30.8%; M 227.

The Attempted Acetylation of 5-(2-Cyanoacetamido)-4-phenyl-1H-1,2,3-triazole (153a)

The cyano-compound (153a) (0.45g, 0.002mol) was heated under reflux in acetic anhydride (5.0ml) for 0.5h. The solution was evaporated under reduced pressure and the oil left was repeatedly triturated with ethanol-ether to give a solid (total 0.18g) m.p. 160°. Crystallisation of this solid from ethanol gave the unreacted cyano-compound (153a) (0.1g) m.p. 215°, identical (m.p. and i.r. spectrum) with an authentic sample.

Cyclisation of 5-(2-Cyanoacetamido)-4-phenyl-1H-1,2,3-triazole (153a) Using Piperidine in Ethanol.

A solution of the cyano-compound (153a) (9.1g, 0.04mol) in ethanol (60.0 ml) was heated under reflux with piperidine (4.0ml) for 24h. Evaporation of the solution left an oil which was dissolved in water and acidified with aqueous dilute acetic acid to give an impure solid which was washed with ethanol to give the pure triazolopyrimidinone (154a) as brown crystals (9.0g; 99%) m.p. > 290 (decomp.) (from dimethylformamide - water), $\nu_{max.}$ 3350w and 3200w (NH) and 1665 (CO) cm^{-1}.

Found: C, 56.7; H, 5.1; N, 29.3%; M^+, 227 .

$C_{11}H_9N_5O$ requires: C, 58.2; H, 4.0; N, 30.8%; M, 227 .

The Attempted Cyclisation of 5-(2-Cyanoacetamido)-4-phenyl-1H-1,2,3-triazole (153a) using Glacial Acetic Acid

The cyano-compound (153a) (0.40g) was heated under reflux in glacial acetic acid (10.0ml) for 6h. The solution was evaporated under reduced pressure and the residue was treated with ethanol-ether to give the unreacted cyano-compound (153a) more of which was obtained when the ethanol-ether mother liquour was evaporated and the resulting oily solid was triturated with ether (total 0.28g) m.p. 208°, identical (i.r. spectrum)with an authentic sample.

The Attempted Methylation of the Triazolopyrimidinone (154a)

(a) Using Methyl Iodide in the Presence of Potassium Carbonate

A solution of the triazolopyrimidinone (154a) (0.91, 0.004mol) in anhydrous acetone (150ml) was heated under reflux with anhydrous potassium carbonate (0.8g) and methyl iodide (0.8ml) for 3h. The mixture was not filtered and the inorganic residue was washed with acetone, dissolved in water and acidified with aqueous dilute sulphuric acid but gave no solid material.

The combined acetone filtrate and washings were evaporated to give a solid (1.46g) m.p. 105° which had a poorly resolved i.r. spectrum. This was suspended in water and extracted with chloroform to give an oil which on trituration with ether-ethanol gave a solid (0.08g) m.p. 184°. This crystallised from ethanol-water to afford another solid (0.02g) m.p. 186°, $\nu_{max.}$ 3450, 3350 and 3200 (NH) and 1665 (CO) cm^{-1}, which was found ($M,^{+}$ 255) to be the dimethyl derivative.

Acidification of the aqueous mother liquor with aqueous dilute sulphuric acid gave the unreacted triazolopyrimidinone (154a) (0.27g) m.p. 220°, identical (m.p. and i.r. spectrum) with an authentic sample.

(b) Using Methyl Iodide in the Presence of Sodium Hydride

A solution of the triazolopyrimidinone (154a) (0.45g, 0.002mol) in dry dimethylformamide (10.0ml) was added dropwise with stirring over 15min at room temperature to a suspension of sodium hydride (0.06g) in dry dimethylformamide (1.0ml). The mixture was stirred for a further 15min, treated in one portion with methyl iodide (0.32g) and stirred at room temperature for 1h. The mixture was diluted with water and extracted

with chloroform to give a negligible amount of an unidentified oil.

The aqueous extract was acidified with aqueous dilute sulphuric acid to give an impure solid (0.14g) m.p. 240° which was crystallised from dimethylformamide-water to give the unreacted triazolopyrimidinone (154a) (0.14g) m.p. >250 (decomp.), identical (m.p. and i.r. spectrum) with an authentic sample.

(c) Using Dimethylsulphate in the Presence of Alkali

A solution of the triazolopyrimidinone (154a) (0.45g,0.003 mol) in aqueous 2M sodium hydroxide solution (5.0ml) was shaken at room temperature with dimethylsulphate (0.4ml) for 1h. The solution was acidified with aqueous dilute sulphuric acid to give impure unreacted triazolopyrimidinone (154a) (0.40g) m.p. 220° which crystallised from dimethylformamide-water to give the pure starting material (154a) (0.24g) m.p. >250 (decomp.), identical (m.p. and i.r. spectrum) with an authentic sample.

6-Amino-2(α-hydroxybenzyl)pyrimidin-4(3H)-one (160)

The triazolopyrimidinone (154a) (0.45g, 0.002mol) was heated under reflux in glacial acetic acid (15.0ml) for 3h. The solution was evaporated under reduced pressure and the resulting oil was cooled and triturated with ether to give a solid (0.36g) m.p. 213° whose i.r. spectrum, $\nu_{max.}$ 3460, 3350 and 3200 (NH, OH) and 1720 and 1640br (CO, OH), and ^{1}H n.m.r. spectrum τ[$CDCl_3$ - $(CD_3)_2SO$] 2.50 - 2.56 (2H, M, Ar-H), 2.66 - 2.73 (3H, m, Ar-H), 3.77 (3H, d, NH_2, CH), 5.00(1H, s, CHOAc), and 7.86(3H, s, $OOCCH_3$), and mass spectrum, m/e 259 and 216 showed it to be a mixture of the acetoxy (159) (M^+, 259) and

the hydroxy (160) (M^+, 216) derivatives.

A solution of this mixture (0.40g) in ethanol (15.0ml) was heated under reflux with aqueous 0.5M sodium carbonate solution (10.0ml) for 20min. The mixture was concentrated to remove the ethanol and filtered to afford the hydroxy derivative (160) as a colourless solid (0.23g) m.p. 228° (from ethanol-water), νmax. 3400, 3350w, and 3250br (NH, OH) and 1640 br (CO) cm^{-1}, τ[$CDCl_3$ - $(CD_3)_2$ SO] 2.50 - 2.61 (2H, m, Ar-H), 2.72 - 2.79 (3H, m, Ar-H), 3.65(2H, s, NH_2), 4.66(1H, s, CH) and 5.08(1H, s, CH).

Found: C, 60.8; H, 5.1; N, 19.0%; M,$^+$ 217 .

$C_{11}H_{11}N_3O_2$ requires: C, 60.8; H, 5.1; N, 19.4%; M, 217 .

The Attempted Hydrolysis of the Triazolopyrimidinone (154a) with Aqueous Ethanolic Sulphuric Acid.

The triazolopyrimidinone (154a) (0.45g, 0.002mol) was heated under reflux in ethanol (10.0ml) with aqueous 2M dilute sulphuric acid (4.0ml) for 0.5h. The mixture was concentrated to remove the ethanol and extracted with chloroform to give a negligible amount of an unidentified solid.

Neutralisation of the aqueous extract with saturated aqueous sodium hydrogen carbonate gave an unidentified solid (0.06g) m.p. 225°, νmax. 3350 and 3200 br (NH) and 1640 - 1620br (CO) cm^{-1}. The aqueous mother liquor was acidified with aqueous dilute acetic acid, evaporated and the inorganic residue was extracted with hot ethyl acetate to give a negligible amount of an unidentified oil.

The Attempted Hydrolysis of the Triazolopyrimidinone (154a) with Potassium Hydroxide

A solution of the triazolopyrimidinone (154a) (0.45g, 0.002mol) in 2-ethoxy-ethanol (20.0ml) was heated under reflux with 20% $w/_v$ aqueous potassium hydroxide (10.0ml) for 3h. The solution was acidified with aqueous dilute hydrochloric acid to give an unidentified solid (0.22g) which showed a poorly resolved i.r. spectrum and did not burn.

Evaporation of the acidic mother liquour left a solid which was dissolved in water and extracted with chloroform to afford an oil (0.16g) whose t.l.c. in ethyl acetate over silica showed one component which streaked on the plate. Attempts to solidify the oil failed.

The aqueous extract on standing yielded a cream solid (0.06g) m.p. 170° (from dimethylformamide-water), $\nu_{max.}$ 3320br, 3160br (NH,OH) cm^{-1}.

Found: C, 55.9, H, 4.5; N, 17.5%; $M,^{+}$ No Ion Pressure.

2-(α-Acetoxybenzyl)-6-acetamidopyrimidin-4(3H)-one (161)

The triazolopyrimidinone (154a) (0.45g, 0.002mol) was heated under reflux in acetic anhydride (5.0ml) for 0.5h. The solution was evaporated under reduced pressure and the resulting dark oil was suspended in water and extracted with chloroform to give an oil which was triturated with ethanol to give the cream acetoxy compound (161) more of which was obtained by evaporating the ethanol mother liquor and triturating the resulting oil with ether (total 0.12g) m.p. 236° (from ethanol-water), $\nu_{max.}$ 3360(NH) and 1720 and 1660 (CO) cm^{-1}.

Found: C, 59.3; H, 5.0; N, 13.7%; M^+ 301 ;

$C_{15}H_{15}N_3O_4$ requires: C, 59.8; H, 4.9; N, 13.9%; M, 301 .

2-(α -Acetoxybenzyl)-6-acetamido-3-N-acetylpyrimidin-4(3H)-one (162)

The procedure described in the previous experiment was repeated on a larger scale using the pyrimidinone (154a) (1.36g, 0.006mol), and acetic anhydride (30.0ml). Following exactly the same work up, the cream triacetyl derivative (162) was obtained (total 0.97g) m.p. 121° (from ethanol-water), ν max. 3300 (NH) and 1780, 1740 and 1700 (CO) cm^{-1}, τ($CDCl_3$) 2.20(1H, s , CH), 2.49 - 2.60(2H, m, Ar-H), 2.65 - 2.75(3H, m, Ar-H) 3.42(1H, s , CH), 7.70(3H, s , CH_3), 7.80(3H, s, CH_3) and 7.88(3H, s, CH_3).

Found: C, 59.4; H, 4.9; N, 12.1%; M^+ 343 .

$C_{17}H_{17}N_3O_5$ requires: C, 59.5; H, 5.0; N; 12.2%; M, 343 .

6-Acetamido-2-benzylpyrimidin-4(3H)-one (163)

The triacetyl derivative (162) (0.68g, 0.0015mol) was hydrogenated in ethanol (50.0ml) over 10% palladium-charcoal (0.15g). Evaporation of the filtered solution gave 6-acetamido-2-benzypyrimidin-4(3H)-one (163) as colourless shiny crystals (0.20g) m.p. 279° (from dimethylformamide-water), ν max. 3200br (NH), and 1710(CO) cm^{-1}.

Found: C, 64.1; H, 5.3; N, 17.3%; M^+ 243 .

$C_{13}H_{13}N_3O_2$ requires: C, 64.3; H, 5.4; N, 17.3%; M, 243.

The Attempted Synthesis of 6-Amino-2-benzylpyrimidin-4(3H)-one (165)

A solution of ethyl cyanoacetate (1.16g, 0.014mol) and phenylacetamidine (164) (1.96g, 0.014mol) in absolute ethanol (20.0ml) was heated under reflux with 5.0ml of a solution of sodium (0.22g) in absolute ethanol (25.0ml) for 1h. The mixture was evaporated and the solid residue was dissolved in water and extracted with chloroform to give impure phenylacetamide (0.64g)m.p. 130°. Crystallisation from water gave the pure phenylacetamide (0.21g) m.p. 148°, identical (m.p. and i.r. spectrum) with an authentic sample.

The aqueous extract was evaporated and the residue was suspended in water and the insoluble part was filtered off to give an unidentified solid (0.17g) m.p. 182 (from ethanol), νmax. 3260w, 3200w, and 3100 (NH) and 1710 (CO) cm^{-1}.

Found: C, 56.7; H, 5.4; N, 9.4%; M^+, 158.

6-Acetamido-2-(α -chlorobenzyl)pyrimidin-4(3H)-one (166)

The triazolopyrimidinone (154a) (0.45g, 0.002 mol) was heated under reflux with acetyl chloride (5.0ml) in glacial acetic acid (8.0ml) for 1h. The solution was evaporated under reduced pressure and the resulting oil was cooled and triturated with ether to afford the chloro-compound (166) as a pale yellow solid (0.24g) m.p. 166° (from ethanol-water), νmax. 3300w and 3150w (NH), 1700 (CO), and 1660(NH) cm^{-1}.

Found: C, 55.6; H, 4.6; N, 15.8%; M^+, 279/277 .

$C_{13}H_{12}N_3O_2$ requires: C, 55.9; H, 4.4; N, 15.0%; M, 277.

5-(2-cyanoacetamido)-1H-1,2,3-triazole-4-carboxamide (153b)

A solution of cyanoacetic acid (1.7g, 0.02mol) in dry ether (25.0ml) was treated in one portion with phosphorus pentachloride (4.4g, 0.02mol) and stirred at room temperature for 15min. The ether and phosphoryl chloride were distilled off at low temperature under reduced pressure to give the cyanoacetyl chloride as a pale yellow oil which was dissolved in dry benzene (25.0ml) and the solution added dropwise to a stirred suspension of the triazole amide (15b) (2.54g, 0.02mol) in dry benzene (300ml). The mixture was then heated under reflux on a steam bath for 2h, and evaporated to give the cyanoacetamidotriazole (153b) as a pale yellow solid (4.67g) m.p. 222° (decomp.) (from ethanol-water), νmax. 3600, 3500, 3400, and 3250 (NH), and 1760 and 1680 (CO) cm^{-1}.

Found: C, 34.3; H, 3.6; N, 39.7%; M^+ 194 .

$C_6H_6N_6O_2H_2O$ requires: C, 34.0; H, 3.8; N, 39.6%; M, 194 .

7-Amino-1,2,3-triazolo[1,5-a]pyrimidin-5(4H)-one-3-carboxamide (154b)

The cyanoacetamidotriazole (153b) (3.8g, 0.02 mol) was heated under reflux with piperidine (2.0ml) in ethanol (150ml) for 24h. The mixture was hot filtered to give the piperidine salt of the product which was suspended in water and acidified with aqueous dilute acetic acid to give the impure triazolopyrimidinone (154b) more of which was obtained by evaporating the ethanol filtrate and triturating the solid residue with water (total 1.34g) m.p. 280° (decomp.). Crystallisation from dimethylformamide-water afforded the pure brownish-yellow triazolopyrimidinone (154b) (0.82g) m.p. 240° (decomp.), νmax. 3350

and 3200 (NH) and 1700br(CO) cm^{-1}.

Found: C, 34.2; H, 3.6; N, 39.0%; $M,^{+}$ 194 .

$C_6H_6N_6O_2H_2O$ requires: C, 34.0; H, 3.8; N, 39.6%; M, 194 .

The Attempted Hydrolysis of the Triazolopyrimidone (154b)with Aqueous Ethanolic Sulphuric Acid.

The triazolopyrimidinone (154b) (0.38g, 0.002mol) in ethanol (10.0ml) was heated under reflux with aqueous 4M dilute sulphuric acid (4.0ml) for 0.5h. The mixture was filtered hot to afford the unreacted triazolopyrimidinone (154b) (0.27g; 71%)m.p. 270°, identical (m.p. and i.r spectrum) with an authentic sample.

The acidic aqueous filtrate was diluted with more water and extracted with chloroform but gave no material.

Synthesis of Ethyl 1,2,3-triazolo[1,5-a] pyrimidine-3-carboxylates (169a and b)

A solution of the aminotriazole ester (168) (0.62g, 0.004mol) and the active methylene compounds (0.004 mol) in ethanol (20.0ml) containing piperidine (0.2ml) was heated under reflux for 24h. The reaction mixtures were worked up as described for the individual reactions.

(a) Ethyl 5,7-Dimethyl-1,2,3-triazolo[1,5-a] pyrimidine-3-carboxylate (169a)

The triazolopyrimidine (169a) crystallised from the cooled reaction mixture from acetylacetone and was combined with a second crop obtained by evaporating the ethanolic filtrate and triturating the residue with

ethanol (67%). Crystallisation from dimethylformamide-water afforded the pure colourless product (169a) m.p. 176°, $\nu_{max.}$ 1700(CO) cm^{-1}, $\lambda_{max.}$ 222, 272, 281, and 304nm (log ε 4.26, 3.60, 3.63 and 3.58). τ [$(CD_3)_2SO$] 2.76(1H, s, pyrimidine H), 5.64(2H, q J 7Hz, CH_2) 7.16(3H, s, CH_3), 7.38(3H, s, CH_3), and 8.66(3H, t J 7Hz, CH_3).

Found: C, 55.0; H, 5.5; N, 25.8%; $M,^+$ 220 .

$C_{10}H_{12}N_4O_2$ requires: C, 54.8; H, 5.5; N, 25.7%; M, 220 .

Evaporation of the ethanol mother liquor left a negligible amount of an unidentified solid.

(b) Ethyl 5-Methyl-7-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxylate (169b)

The reaction mixture from benzoylacetone on cooling yielded the impure triazolopyrimidine (169b) which was combined with a second crop obtained by triturating the oil (isolated by evaporating the ethanol filtrate, treatment with water, and extraction with chloroform) with ether (50%). Crystallisation from ethanol gave the pure triazolopyrimidine (169b) as colourless needles (0.39g) m.p. 200°, $\nu_{max.}$ 3020w (NH), and 1700 (CO) cm^{-1}, τ[$(CD_3)_2SO$] 1.68 - 1.78(2H, m, Ar-H), 2.03(1H, s, pyrimidine H), 2.40 - 2.46(3H, m, Ar-H), 5.60(2H, q J 8Hz, CH_2), 7.06(3H, s, CH_3) and 8.62(3H, t J 8Hz, CH_3).

Found: C, 64.0; H, 5.0; N, 19.8%; $M,^+$ 282 .

$C_{15}H_{14}N_4O_2$ requires: C, 63.8; H, 5.0; N, 19.9%; M, 282 .

The ether mother liquor on evaporation left a semi-solid whose t.l.c. in ethyl acetate over silica showed it to contain mainly unreacted benzoylacetone.

The Attempted Reaction of the Aminoester (168) with Ethyl Acetoacetate

A solution of the amino-ester (168) (0.62g, 0.004mol) and ethyl acetoacetate (0.52g, 0.004mol) in ethanol (20.0ml) containing piperidine (0.2ml) was heated under reflux for 24h. The solution was evaporated and the residual oil was triturated with water to give the amino-ester(168) (0.11g) m.p. 158° which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The aqueous filtrate was acidified with aqueous dilute hydrochloric acid but on extraction with chloroform gave no identifiable product.

Ethyl 7-Methyl-1,2,3-triazolo[1,5-a]pyrimidin-5(4H)-one-3-carboxylate (173) and its Isomer (174)

A solution of the amino-ester (168) (0.78g, 0.005mol) and ethyl acetoacetate (0.65g, 0.005mol) in glacial acetic acid (10.0ml) was heated under reflux for 4h. The solution was evaporated under reduced pressure and the residue was triturated with water to give the acid (171) or (172) as a colourless solid (0.1g) m.p. 261° (from dimethylformamide), $\nu_{max.}$ 3320(NH) and 1690(CO) cm^{-1}, $\lambda_{max.}$ 209sh, 239 and 253nm (logε 3.80, 4.02 and 4.03).

	Found:	N, 28.6% .
$C_7H_6N_4O_3$	requires:	N, 28.6% .

The aqueous mother liquor on standing deposited a solid (0.38g) m.p. 152° which was crystallised from ethanol to give a mixture of the triazolopyrimidinone isomers (173) and (174) as a colourless solid (0.32g) m.p. 215°, $\nu_{max.}$ 3500 and 3350(NH) and 1700 - 1660br (CO) cm^{-1},

$\lambda_{max.}$ 214sh, 230, 263inf., 285sh, 303, and 325nm (logε 4.05, 4.26, 3.80, 3.72, 3.76 and 3.64), τ [$(CD_3)_2SO$] 3.68(1H, d J 2Hz, CH), 4.04(1H, s, CH), 5.58(2H, q J 7Hz, CH_2), 5.58(2H, q J 7Hz, CH_2), 7.33(3H, d J 1Hz, CH_3), 7.54(3H, s, CH_3), 8.60(3H, t J 7Hz, CH_3), and 8.66(3H, t J 7Hz, CH_3).

Found: C, 48.8; H, 4.6; N, 25.3%; M^+ 222 .
$C_9H_{10}N_4O_3$ requires: C, 48.7; H, 4.5; N, 25.2%; M^+, 222 .

The Attempted Hydrolysis of the Isomer Mixture of the Triazolopyrimidinone Esters (173) and (174)

(a) Using Hot Ethanolic Sulphuric Acid

A solution of the ester mixture (173) and (174) (0.44g, 0.002mol) in ethanol (5.0ml) was heated under reflux with aqueous 20% w/v sulphuric acid (5.0ml) for 0.5h. The cooled solution on standing afforded the impure unreacted ester mixture (173) and (174) (0.33g; 75%) m.p. 170° which was crystallised from ethanol to give the pure starting triazolopyrimidinone ester mixture (173) and (174) (0.21g) m.p. 206°, identical (m.p. and i.r. spectrum) with an authentic sample.

The ethanol filtrate was concentrated and the aqueous residue was neutralised with solid sodium hydrogen carbonate and extracted with chloroform to give a negligible amount of an unidentified oil.

(b) Using Hot Ethanolic Sodium Carbonate Solution

A solution of the ester mixture (173) and (174) (0.3g, 0.0016mol) in ethanol (10.0ml) was heated under reflux with aqueous M sodium carbonate solution (5.0ml) for 1h. The solution was filtered hot to remove inorganic material and concentrated to remove the ethanol. The

aqueous residue was acidified with aqueous dilute sulphuric acid to afford the impure unreacted ester mixture more of which was obtained on standing (total 0.16g; 54%) m.p. 170°. Crystallisation from ethanol gave the pure unreacted triazolopyrimidinone ester mixture (173) and (174) (0.14g) m.p. 206° which was identical (m.p. and i.r. spectrum)with an authentic sample.

Ethyl 5-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-7-carboxylate (184a)

A solution of the aminotriazole (15a) (0.64g, 0.004 mol) and the keto-diester (183) (0.63g, 0.004 mol) in ethanol (20.0 ml) containing piperidine (0.2 ml) was heated under reflux for 24h. The solution was evaporated and the gummy residue was triturated with ethanol-ether to afford the triazolopyrimidine (184a) (0.30g) m.p. 160° which crystallised from ethanol as yellow prisms (0.25g) m.p. 168°, $\nu_{max.}$ 1710 (CO) cm^{-1}, $\lambda_{max.}$ 213, 247, 308, 319sh, and 388nm (logε 4.26, 4.39, 3.43, 3.38 and 3.76), $\tau[(CD_3)_2SO]$ 1.56-1.64(2H, m, Ar-H), 2.22(1H, s, pyrimidine H), 2.31-2.56(3H, m, Ar-H), 5.51(2H, q J 7Hz, CH_2), 7.01(3H, s, CH_3), 8.56(3H, t J 7Hz, CH_3).

Found: C, 63.5; H, 5.0; N, 20.2%; M^+ 282.
$C_{15}H_{14}N_4O_2$ requires: C, 63.8; H, 5.0; N, 20.0%; M 282.

The ethanol-ether mother liquor on evaporation left an oil whose t.l.c. in ethyl acetate over silica showed it to be a mixture of two components, the bulk of which was unreacted keto-diester (183).

The Attempted Condensation of the Triazole Amide (15b) with the Keto-diester (183)

A solution of the amide (15b) (0.51g, 0.004 mol) and the keto-diester (183) (0.63g, 0.004 mol) in ethanol (30.0 ml) containing piperidine (0.2 mol) was heated under reflux for 24h. The solution was evaporated and the oil left was suspended in water, acidified with dilute aqueous hydrochloric acid and extracted with chloroform. The solid present in the chloroform-water mixture was filtered (0.26g) m.p. 195° and it showed a poorly resolved i.r. spectrum. The solid was suspended in saturated sodium hydrogen carbonate solution to give another solid which decomposed on attempted isolation.

The alkaline mother liquour was acidified with aqueous dilute hydrochloric acid to give a small amount of an unidentified solid (0.02g) m.p. 205° which showed a poorly resolved i.r. spectrum and had m/e 221.

The chloroform extract on evaporation gave no material.

The Variable Temperature Study of the ^{1}H n.m.r. Spectrum of Ethyl 5,7-Dimethyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxylate (169a)

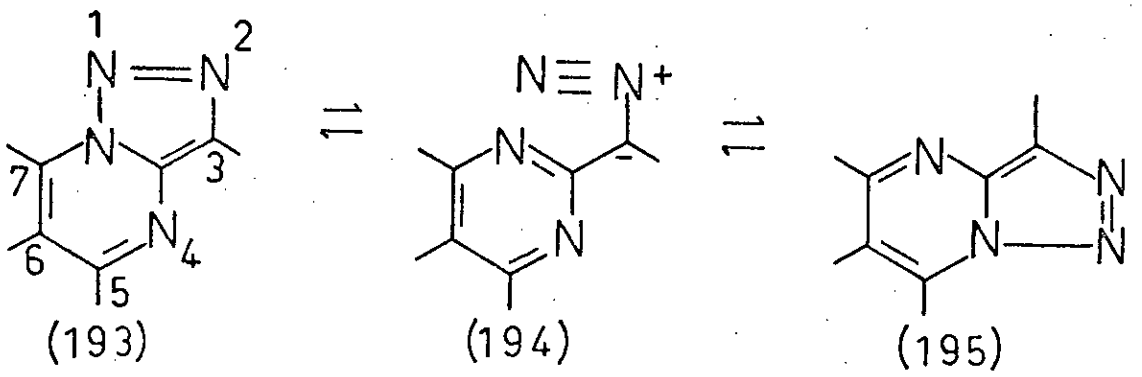
The ^{1}H n.m.r. spectrum of the triazolopyrimidine (169a) in $[^{2}H_{6}]$-dimethylsulphoxide was measured at room temperature (28°) and thereafter at approximately 5° intervals, using a sweep width of 250Hz. The solution was allowed to cool to room temperature (28°) after reaching a temperature of 140° and the resulting spectrum was found to be identical with the original. The coalescence temperature, Tc, was found to be 103° while the average chemical shift (δ) (in Hertz) was 724.7. On insertion of this data into equation (1) (cf. page 37), the free energy of activation, ΔG^{*}, was found to be 16.7kcal mol^{-1}.

Chapter 3

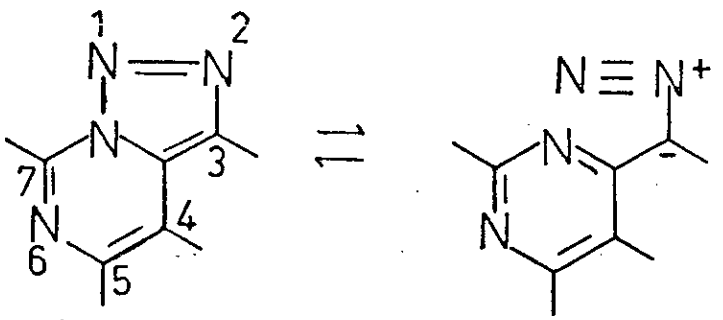
Approaches to the Synthesis of 1,2,3-Triazolo[1,5-c]pyrimidine Derivatives

3.1 Introduction

There are only two possible bridgehead-fused ring systems derived by the fusion of a pyrimidine ring with a 1,2,3-triazole nucleus. These are the 1,2,3-triazolo[1,5-a]pyrimidine ring system (193) dealt with in Chapter 2 and the yet unknown



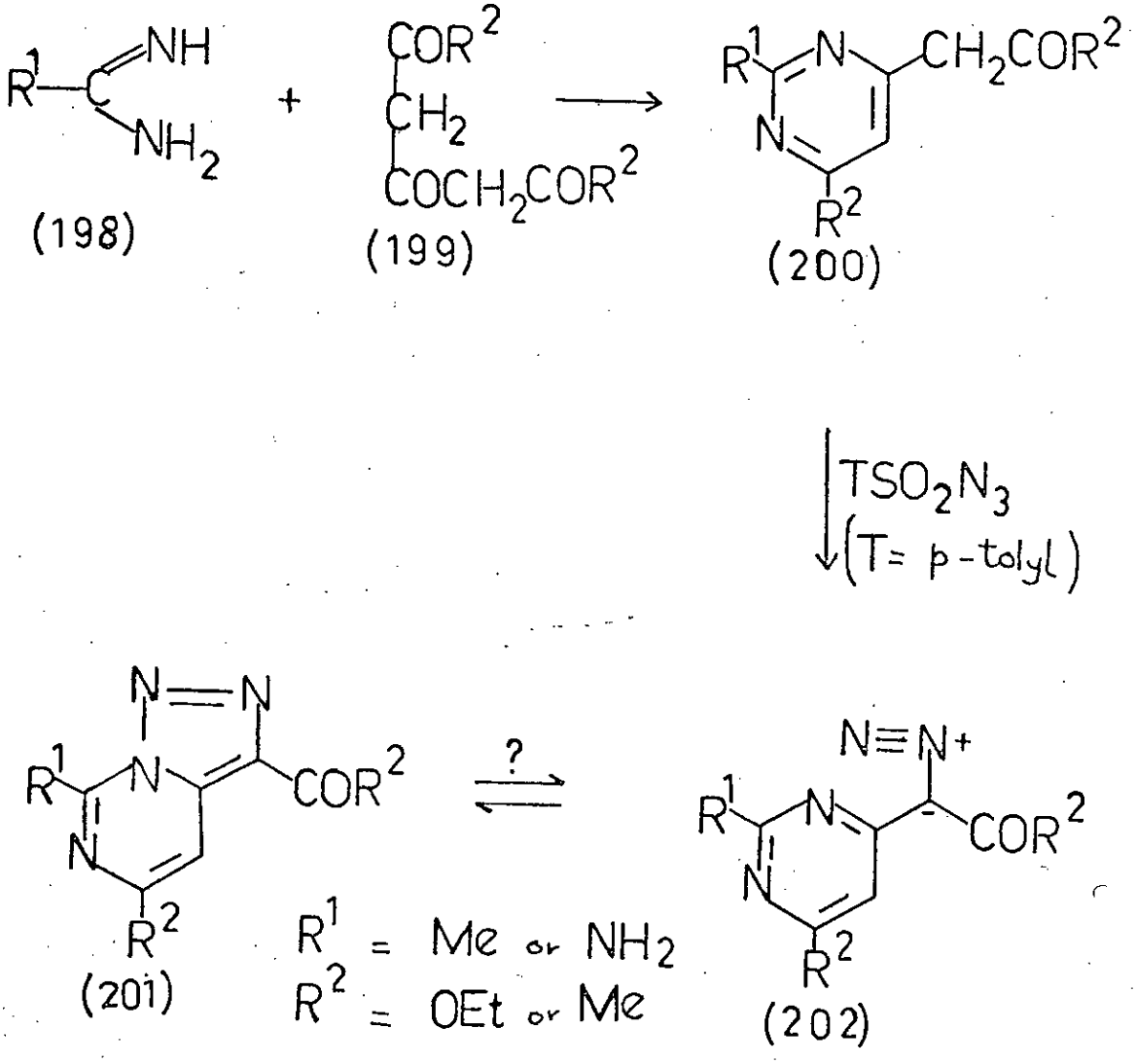
(193) (194) (195)



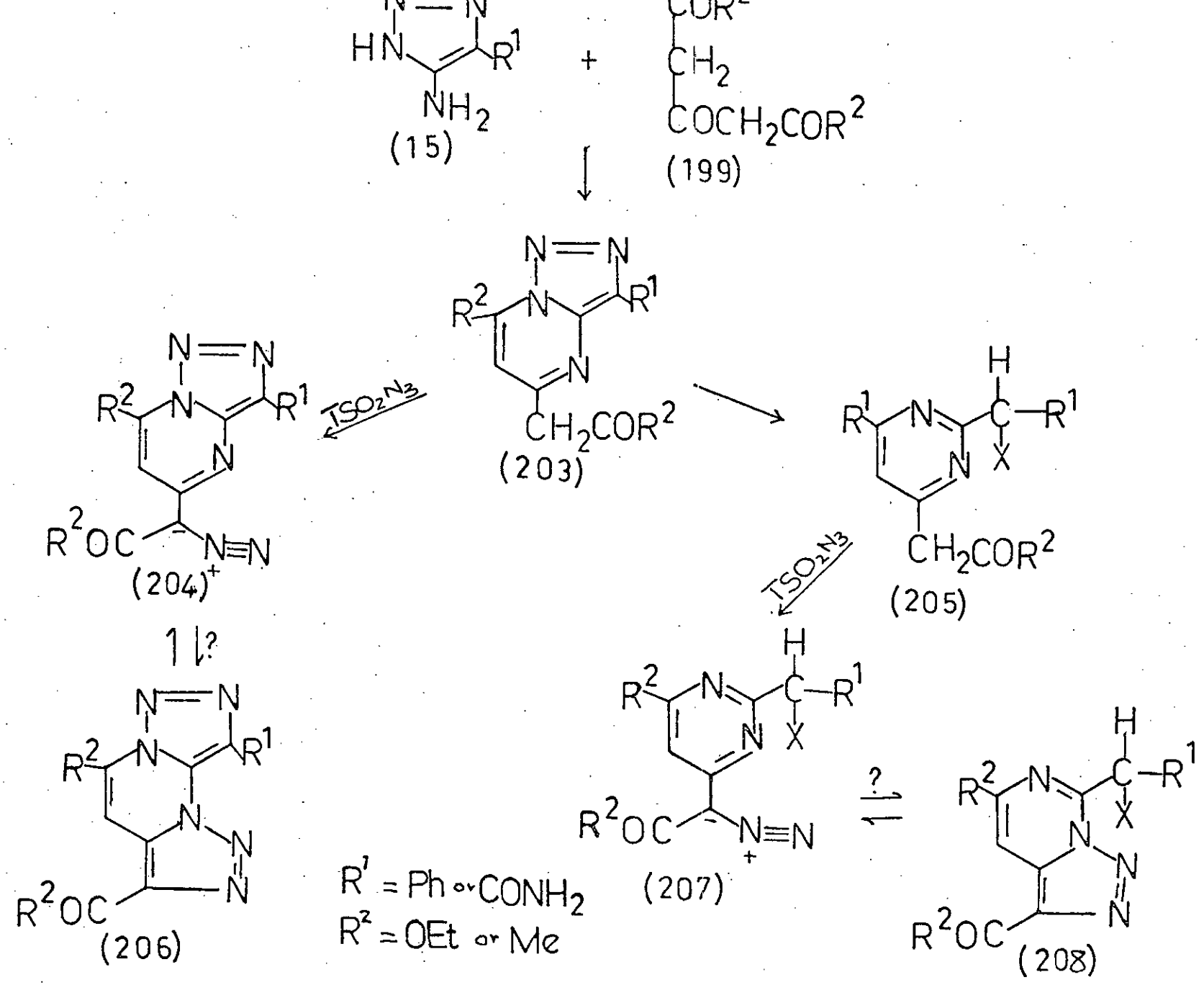
(196) (197)

Scheme 46

1,2,3-triazolo[1,5-c]pyrimidine ring system (196). As has already been discussed at some length in Chapter 2, 1,2,3-triazolo[1,5-a]-pyrimidine derivatives are of interest because of the diazoalkylid-eneamine-1,2,3-triazole tautomerism [Scheme 46; (193) $\rightleftharpoons$ (194)] which they exhibit. Consequently, it was of interest to investigate the possible existence of analogous ring-chain tautomerism [Scheme 46; (196) $\rightleftharpoons$ (197)] in the triazolo[1,5-c]pyrimidine ring system.


NH
NH2
COR2
CH2
COCH2COR2
N
CH2COR2
R2
TSO2N3
(T= p-tolyl)
N=N
COR2
?
N≡N+
R1 = Me or NH2
R2 = OEt or Me
(198)
(199)
(200)
(201)
(202)

Scheme 47

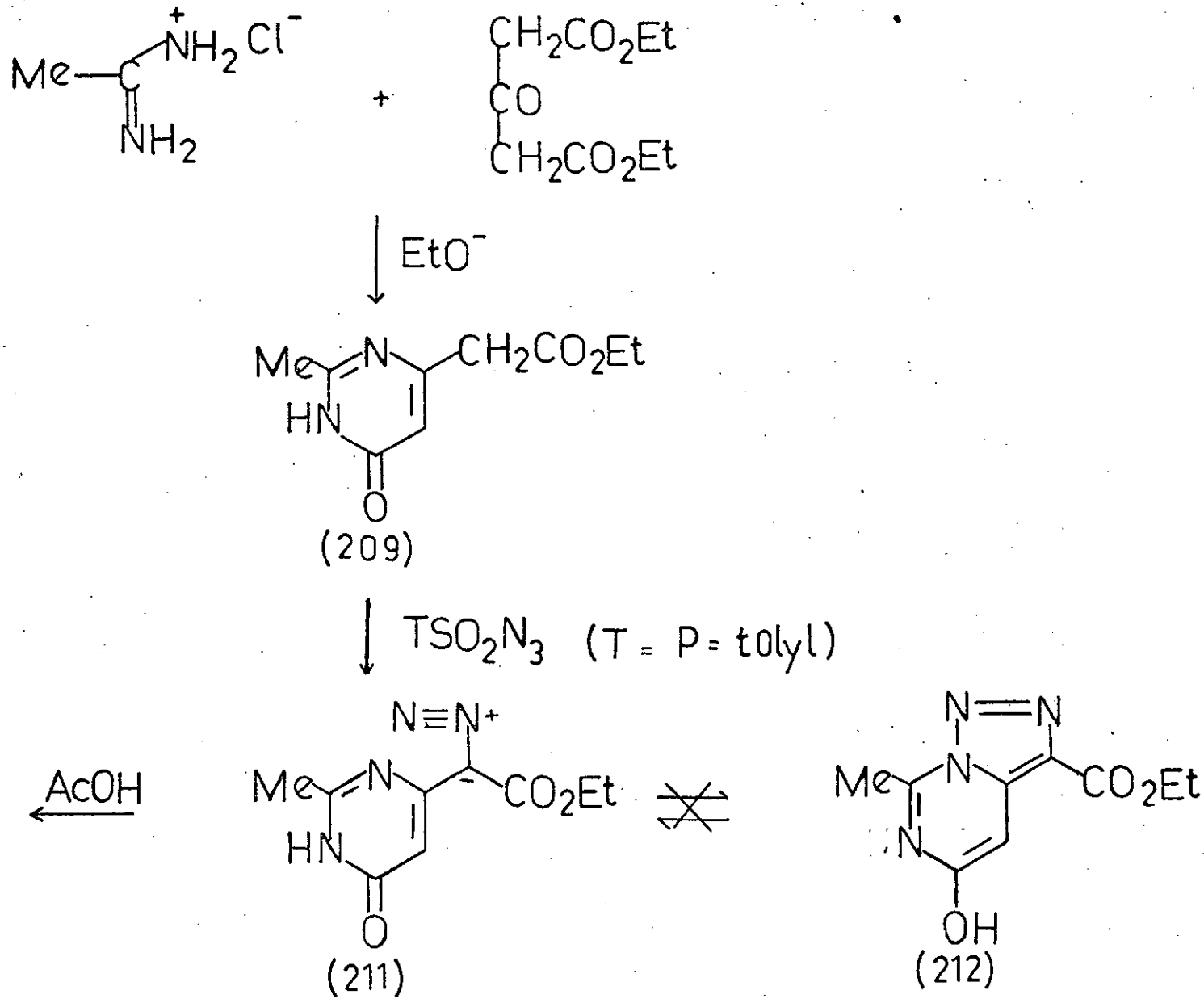

(15)
(199)
(203)
(204)+
(205)
(206)
(207)
(208)
ISO2N3
ISO2N3
1 ⇌ ?
?
R1 = Ph or CONH2
R2 = OEt or Me

Scheme 48

Also, the demonstration of diazoalkylideneamine-1,2,3-triazole tautomerism [Scheme 46; (196) ⇌ (197)] in the latter ring system would not be complicated by the concomitant Dimroth rearrangement [Scheme 46; (193) ⇌ (194) ⇌ (195)] exhibited by 1,2,3-triazolo[1,5-a]-pyrimidine derivatives. However, since, as already mentioned, the 1,2,3-triazolo[1,5-c] pyrimidine ring system was unknown, the initial objective was to devise a suitable synthetic route to 1,2,3-triazolo-[1,5-c] pyrimidine derivatives.

Two potentially general synthetic approaches were investigated. The first approach (Scheme 47) involved the construction (by condensation of an amidine with a tricarbonyl reagent) of a pyrimidine derivative (200) containing an active methylene group at C(4) [Scheme 47; (198) + (199) → (200)] and its diazo-transfer reaction with toluene-p-sulphonyl azide to give a diazo-intermediate (202) convertible by spontaneous ring-closure (or otherwise) into the desired 1,2,3-triazolo[1,5-c] pyrimidine derivative (201).

In the second approach (Sheme 48) a preformed amino-1,2,3-triazole (15) is condensed with a tricarbonyl reagent (199) to afford a 1,2,3-triazolo[1,5-a] pyrimidine (203) bearing an active methylene substituent at C(5) and hence suitable for direct conversion [Scheme 48; (203) → (204) → (206)] into a tricyclic 1,2,3-triazolo-[1,5-c] pyrimidine (206) or after triazole-scission (see Chapter 2) [Scheme 48; (203) → (205)] to a pyrimidine derivative (205) capable of conversion [Scheme 48; (205) → (207) → (208)] by diazo-transfer into a 1,2,3-triazolo[1,5-c] pyrimidine (208).


Me
NH2 Cl
NH2
CH2CO2Et
CO
CH2CO2Et
EtO
Me
N
HN
CH2CO2Et
O
(209)
TSO2N3 (T = P = tolyl)
OAc
Me
N
HN
C
CO2Et
H
O
(210)
AcOH
N≡N+
Me
N
HN
CO2Et
O
(211)
N
N
Me
N
N
CO2Et
OH
(212)

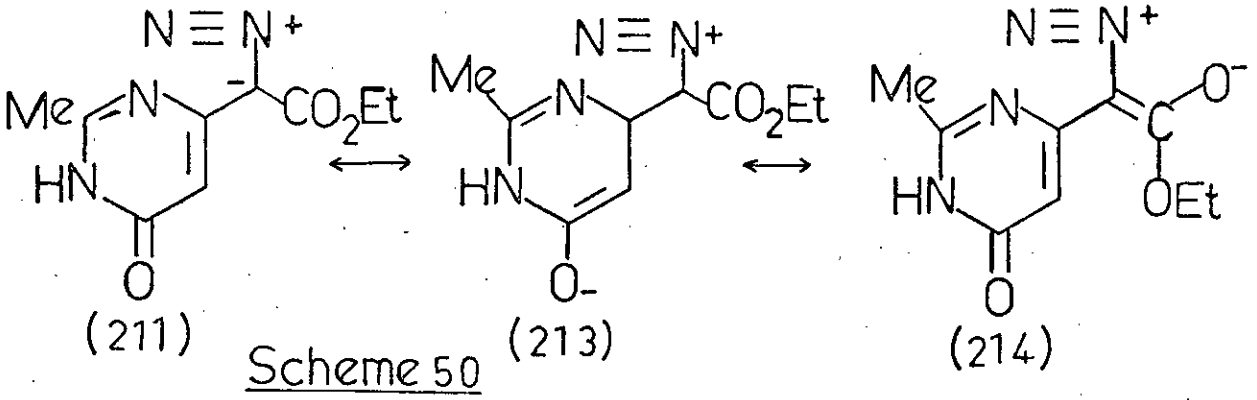
Scheme 49

3.2 The Attempted Synthesis of 1,2,3-Triazolo[1,5-c]pyrimidine Derivatives by Diazo-transfer Reactions of 4-Methylenepyrimidines

Acetamidine hydrochloride reacted readily with diethyl acetonedicarboxylate in the presence of ethanolic sodium ethoxide to afford the pyrimidinone [Scheme 49; (209)] containing an ethoxycarbonylmethylene side-chain at C(4). The spectral properties of this product were consistent with the assigned structure. Thus, its i.r. spectrum showed NH and carbonyl absorption characteristic of a cyclic amide structure and a band at 1730 cm^{-1} demonstrated the presence of an intact ethoxycarbonyl group. This structural feature was also demonstrated by signals typical of the protons of an ethyl group in its ^1H n.m.r. spectrum which also contained a one proton singlet at τ 3.70 due to H(5), a two proton singlet at τ 6.45 due to the protons of the methylene group, and a three proton singlet at τ 7.54 attributable to a methyl group. The pyrimidine derivative (209) reacted with toluene-p-sulphonyl azide in the presence of triethylamine to give an excellent yield of a product assigned the diazo-structure (211) on the basis of the following evidence. It analysed correctly for the molecular formula $C_9H_{10}N_4O_3$ and its mass spectrum showed a parent ion at m/e 222 and a fragment ion at m/e 194 ($M^+ - 28$) due to loss of molecular nitrogen. Its i.r. spectrum in addition to bands due to a cyclic amide group and an ester group contained absorption at 2150 cm^{-1} characteristic of a diazo-group. The ^1H n.m.r. spectrum of (211) showed a one proton singlet at τ 3.86 due to H(5), a three proton singlet at τ 7.22 due to a methyl group and no further methylene protons.

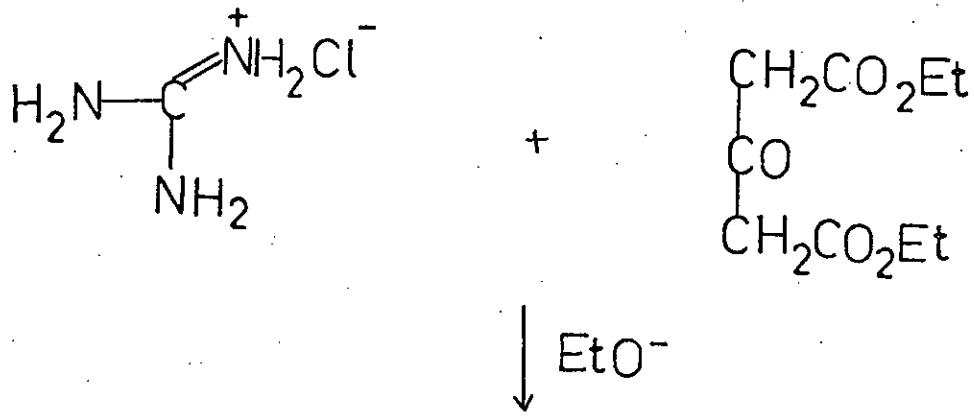
The structure of the diazomethylpyrimidinone (211) was firmly

established by its conversion in hot glacial acetic acid into the acetoxy-product (210) whose i.r. and ^{1}H n.m.r. spectra were fully consistent with the assigned structure. The formation of the acetoxy-compound (210) from the diazo-compound (211) with glacial acetic acid is typical[45] reactivity for a diazo-alkyl species. The diazo-compound (211) was remarkably stable. It was unaffected by attempted pyrolysis in refluxing toluene or xylene and it failed to undergo cycloaddition with either diethyl fumarate or dimethyl acetylenedicarboxylate. The stability of the diazo-compound (211) may be attributed to enchanced delocalisation [Scheme 50; (211)↔(213)↔(214)] of the negative charge on carbon. This enhanced

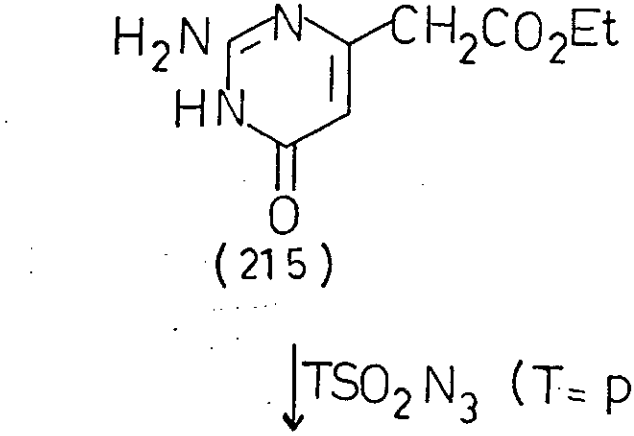


Scheme 50

stability is in marked contrast to the apparent instability of 3-diazomethylpyrimidines relative to their 1,2,3-triazolo[1,5-a]-pyrimidine tautomers (cf. Chapter 2) and accounts in part for the failure of the diazo-compound (211) to ring close to the triazolo[1,5-c] pyrimidine (212). However, formation of the latter is also opposed by the necessity for the pyrimidine ring in the fused structure (212) to exist in an enol form as opposed to a more



(215)



(216)

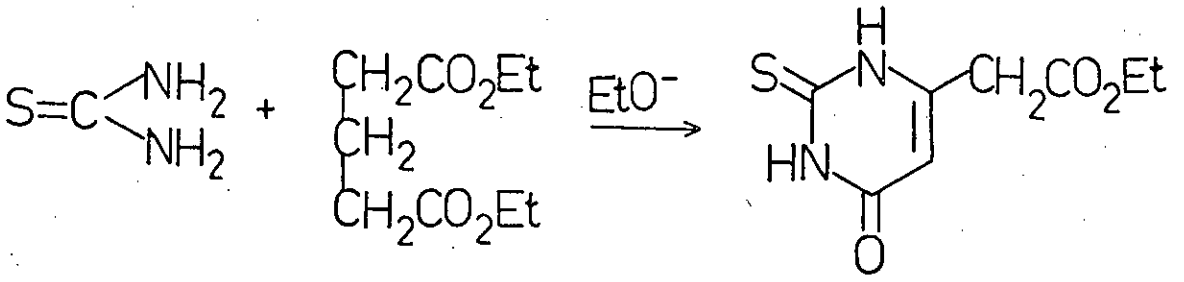
Scheme 51

stable cyclic amide form.

In an attempt to extend the synthesis of ethoxycarbonylmethylene-pyrimidines and hence their diazo-derivatives to other systems, the condensation of diethyl acetonedicarboxylate with other amidine-type reagents was investigated. Thus, guanidine hydrochloride reacted with diethyl acetonedicarboxylate in the presence of ethanolic sodium ethoxide to afford (Scheme 51) a low yield of the ethoxycarbonylmethylenepyrimidinone (215) whose spectral properties were fully in accord with the assigned structure. Reaction of the pyrimidinone (215) with toluene-p-sulphonyl azide in the presence of triethylamine afforded a high yield of a solid whose mass spectrum indicated the molecular weight 249 consistent with its being the azido-diazo compound (216), although it did not give correct combustion analysis for this structure. Its i.r. spectrum contained NH, ester and cyclic amide absorption in addition to a band at 2100 cm^{-1} characteristic of the diazo- group. In an attempt to establish the structure of the product (216), it was heated under reflux in glacial acetic acid but was recovered unchanged in high yield. The attempted cycloaddition of (216) to diethyl fumarate was likewise unsuccessful. The precise nature of the product tentatively assigned the structure (216) must await further experimental investigation.

Urea failed to react with diethyl acetonedicarboxylate in the presence of ethanolic sodium ethoxide as did S-methylisothiourea bisulphate and formamidine acetate. The attempted condensation of thiourea with diethyl acetonedicarboxylate in the presence of ethanolic sodium ethoxide afforded a low yield of a product whose combustion analysis was not consistent with its being the expected

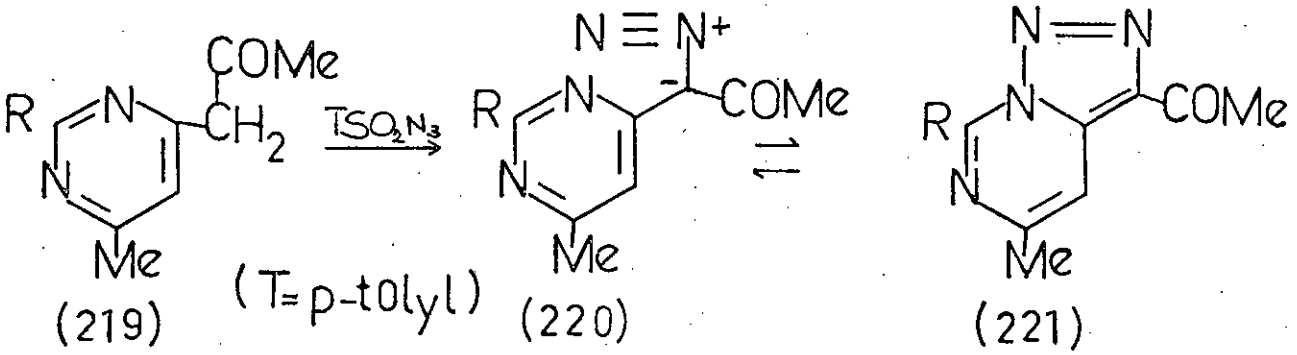
pyrimidinone [Scheme 52; (217)] though it gave the correct



Scheme 52 (217)

molecular formula by exact mass measurement. Unfortunately, there was insufficient material for the further characterisation of the pyrimidinone (217) or for its reaction with toluene-p-sulphonyl azide. Attempts to improve the yield of (217) by carrying out the condensation of thiourea with diethyl acetonedicarboxylate in the presence of a variety of condensation catalysts (potassium carbonate, piperidine or concentrated hydrochloric acid) were unsuccessful.

Since the greater stability of the diazo-tautomer (211) relative to the 1,2,3-triazolo[1,5-c] pyrimidine (212) could be due not only to electronic factors but also to structural reasons (see before) it was of interest to investigate the synthesis of other related pyrimidine systems not subject to such structural restrictions. Consequently, an investigation of the condensation of amidines and related reagents with heptane-2,4,6-trione (218) was undertaken. Not only should this tricarbonyl compound be more reactive than diethyl acetonedicarboxylate in the initial pyrimidine synthesis but the pyrimidines produced would be of the type (219) and hence should give by reaction with toluene-p-sulphonyl azide, diazo-compounds (220) and thence 1,2,3-triazolo[1,5-c] pyrimidines (221) not destabilised

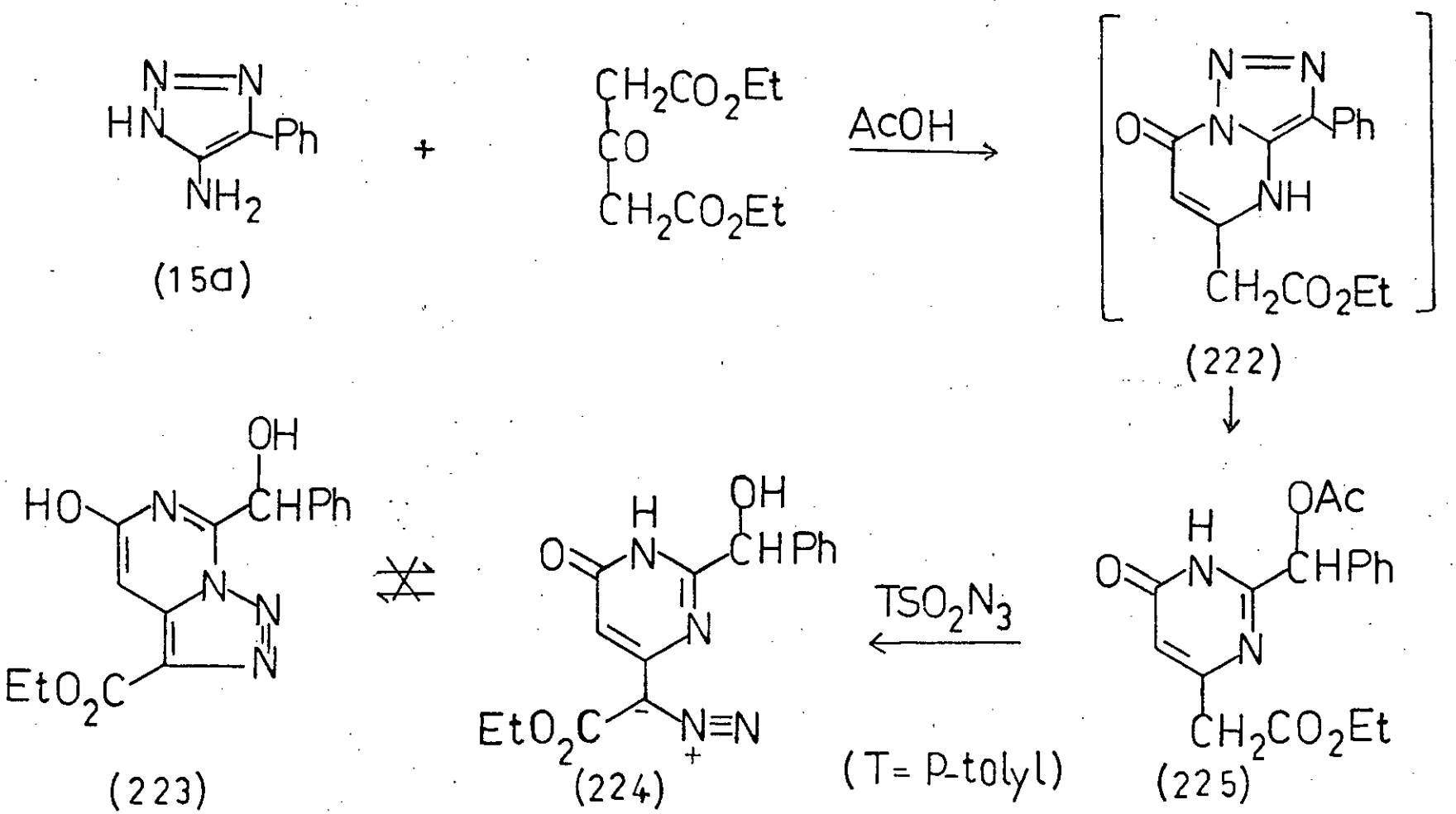


Scheme 53

for structural reasons. The relative stability of the tautomers (220) and (221) would then provide more clear cut information on the effect of electronic factors on the position of diazoalkylideneamine-1,2,3-triazole equilibria. In practice, the triketone (218) failed to react with acetamidine hydrochloride in the presence of both ethanolic sodium ethoxide or potassium carbonate. The attempted condensation of formamidine acetate with the triketone (218) in glacial acetic acid was likewise unsuccessful.

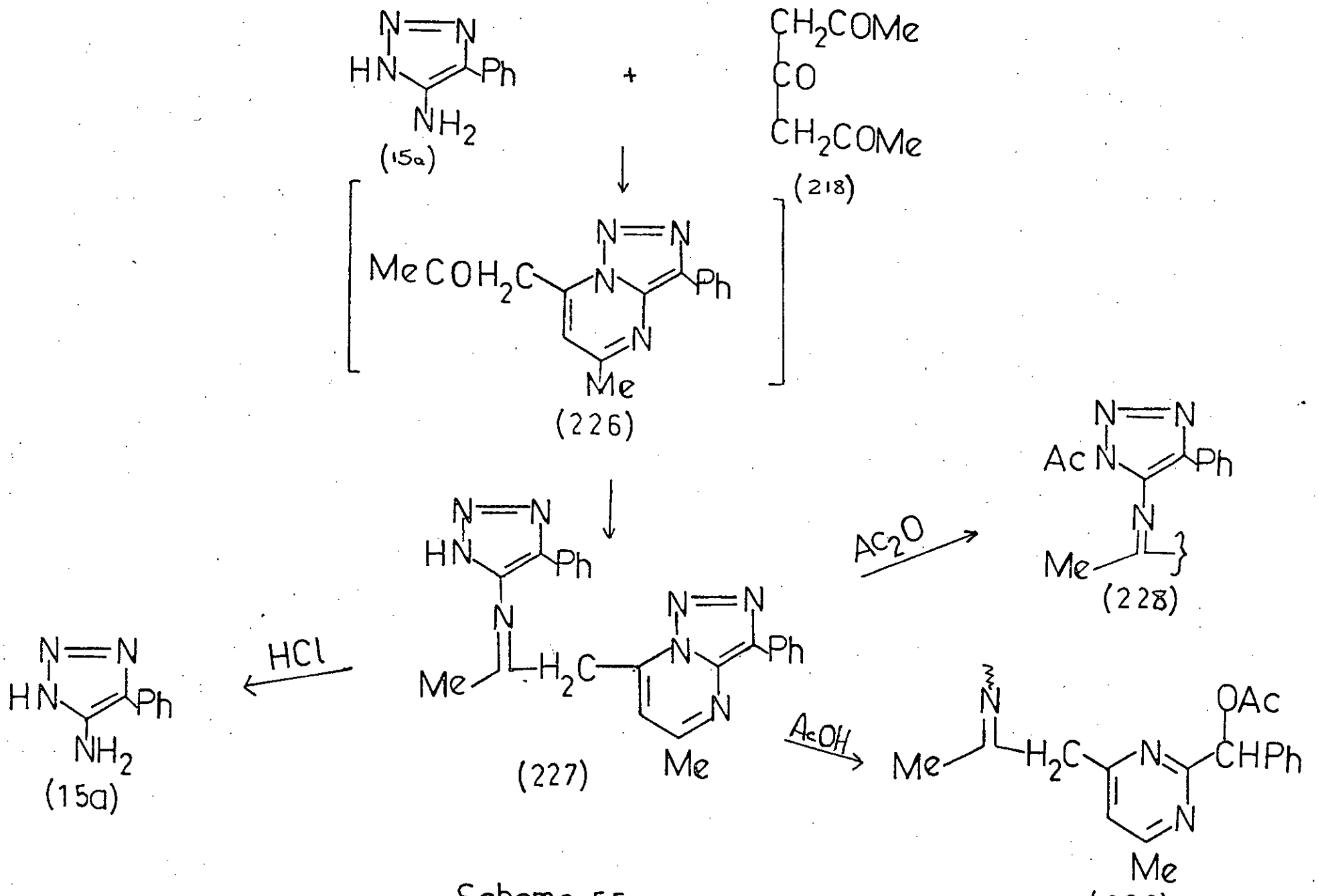
3.3 The Attempted Synthesis of 5-Methylene-1,2,3-triazolo[1,5-a]-pyrimidines and their Conversion into 1,2,3-Triazolo[1,5-c]pyrimidine Derivatives.

As discussed before (Chapter 3, page 58) the second synthetic approach to 1,2,3-triazolo[1,5-c]pyrimidine ring system involved the attempted synthesis of 1,2,3-triazolo[1,5-a]pyrimidines containing an active methylene group at C(5) and their diazo-transfer reaction with toluene-p-sulphonyl azide before or after triazole scission.[2a,5b,8] Thus, an attempt was made to react aminotriazole (15a) with diethyl acetonedicarboxylate in the presence of piperidine for a prolonged



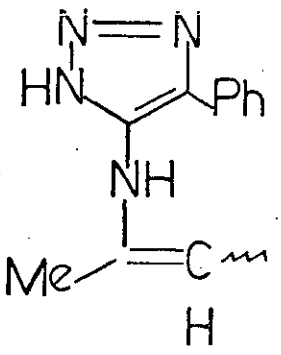
Scheme 54

period. However, the hoped for triazolopyrimidine product (222) was not obtained. In contrast, the amine (15a) condensed with diethyl acetonedicarboxylate in refluxing acetic acid to afford a product whose properties are consistent with the acetoxybenzylpyrimidinone structure (225). The i.r. spectrum of (225) in addition to a band due to NH group contained a high carbonyl band at 1755 cm^{-1} attributable to the acetoxy-group and an ester absorption at 1725 cm^{-1}. Also its ^1H n.m.r. spectrum showed a one proton singlet at τ 3.80 due to H(5), a one proton singlet at τ 3.88 due to the benzylic hydrogen, a two proton singlet at τ 6.50 due to the methylene group, and a three proton singlet at τ 7.91 due to the acetoxy-group in the structure (225). Formation of this product is readily explained (Scheme 54) by the formation of the expected triazolopyrimidine product (222) and its in situ acid-catalysed triazole scission[2a,5b,8] to the acetoxybenzylpyrimidinone (225). The structure of this product was further established by its reaction at 0° with toluene-p-sulphonyl azide in the presence of triethylamine to afford the diazo-compound (224) with concomitant hydrolysis of the acetoxy-group to the corresponding alcohol. The i.r. spectrum of the alcohol (224) in addition to NH and carbonyl absorption showed a diazo-band at 2130 cm^{-1}. Its ^1H n.m.r. spectrum contained one proton singlets at τ 3.45 and 3.70 due to H(5) and the benzylic hydrogen respectively while the absorption due to the acetoxy-group in the precursor (225) had disappeared. The ready isolation and apparent stability of the diazo-compound (224) again demonstrates the reluctance to ring-close to the corresponding 1,2,3-triazolo[1,5-c]pyrimidine (223) as observed before (cf. Chapter 3, page 60).

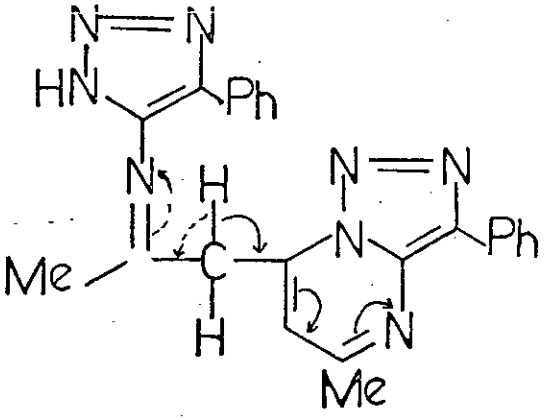


Scheme 55

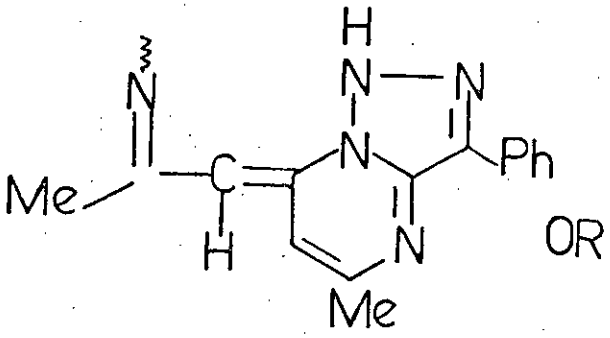
Condensation of the amine (15a) with the triketone (218) in ethanolic piperidine, gave a product which is formulated as the pyrimidylacetonylidenetriazole [Scheme 55; (227)] on the basis of the following evidence. Thus, its i.r. spectrum showed an NH absorption at 3140 cm^{-1} and its ^1H n.m.r. spectrum showed no methylene hydrogens but instead contained two one proton singlets at τ 2.30 and 4.52 due to H(6) and a methine hydrogen respectively, and also two three proton singlets at τ 7.23 and 7.93 due to Me(5) and the methyl group attached to the imino function respectively, indicating that (227) does not exist in the Schiff base form (227) but most likely as the enamine form (230) or as either of the possible



(230)

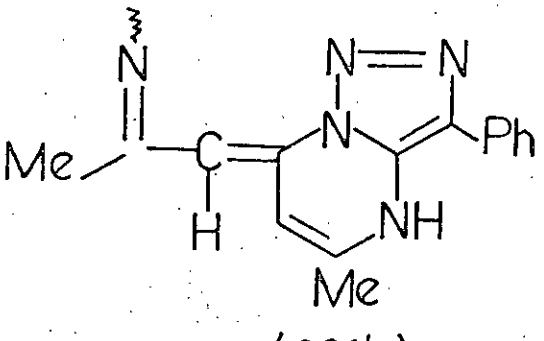


(227)



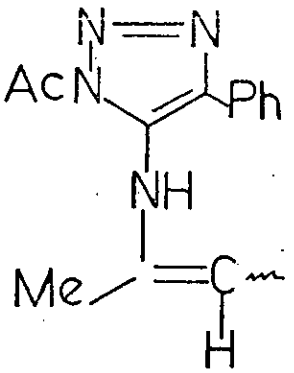
(231a)

OR

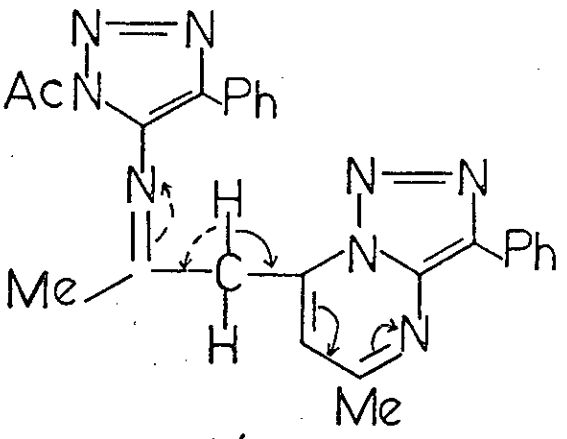


(231b)

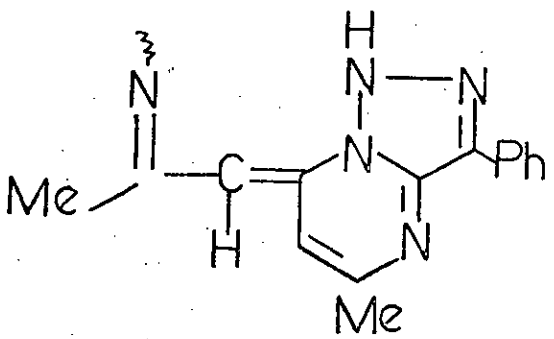
ene-imine structures (231a) or (231b), the latter possibly being preferred due to the greater possibility of conjugation. In further support of the assigned structure, the compound (227) was converted in hot acetic anhydride into an N-acetyl derivative (228) whose i.r. spectrum showed a carbonyl band at 1750 cm^{-1} characteristic of a ring N-acetyl group,[5a] whose presence was further indicated by a three proton singlet at τ 7.20 again characteristic[5a] of a triazole N-acetyl group. The ^1H n.m.r. spectrum of (228) also lacked signals due to a methylene group but contained a one proton singlet at τ 4.58 showing that the N-acetyl compound (228) exists in one or other of the tautomeric forms (232), (233a)or (233b). Further, when



(232)

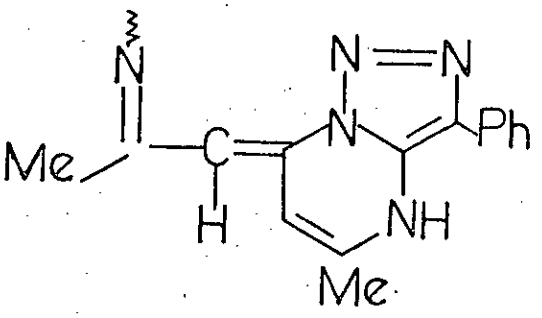


(228)



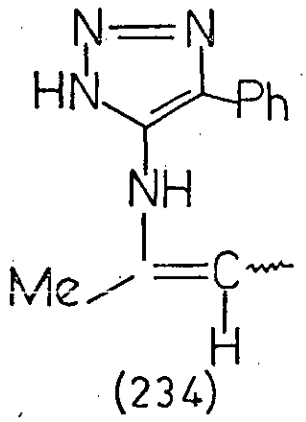
(233a)

OR

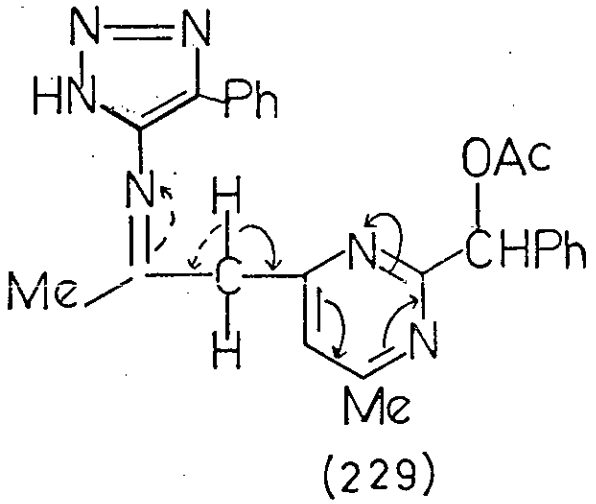


(233b)

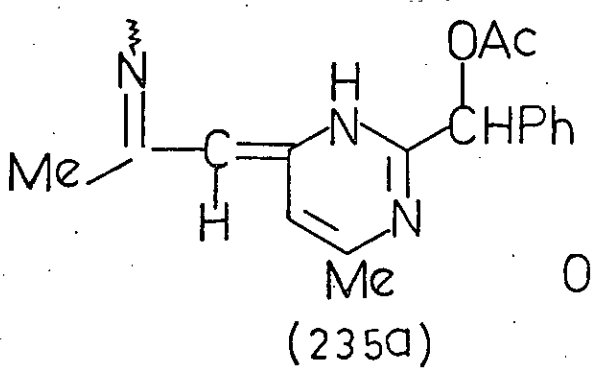
the triazolopyrimidine (227) was heated under reflux in glacial acetic acid, typical acid-catalysed triazole scission[2a,5b,8] occurred to afford the acetoxy derivative (229) whose structure is fully in accord with its i.r. and ^{1}H n.m.r. absorption. Again, the ^{1}H n.m.r. spectrum of (229) lacked methylene absorption but contained a one proton singlet at τ 4.82 indicating that it exists in one of the tautomeric forms (234), (235a) or (235b) rather than in the imine form



(234)

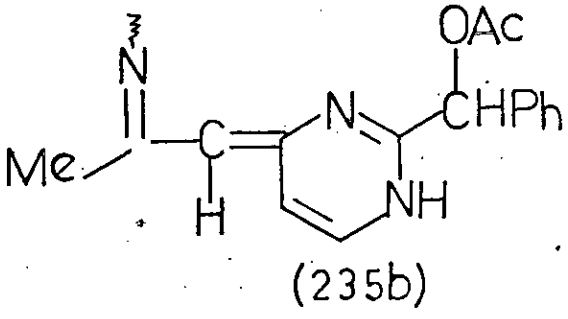


(229)



(235a)

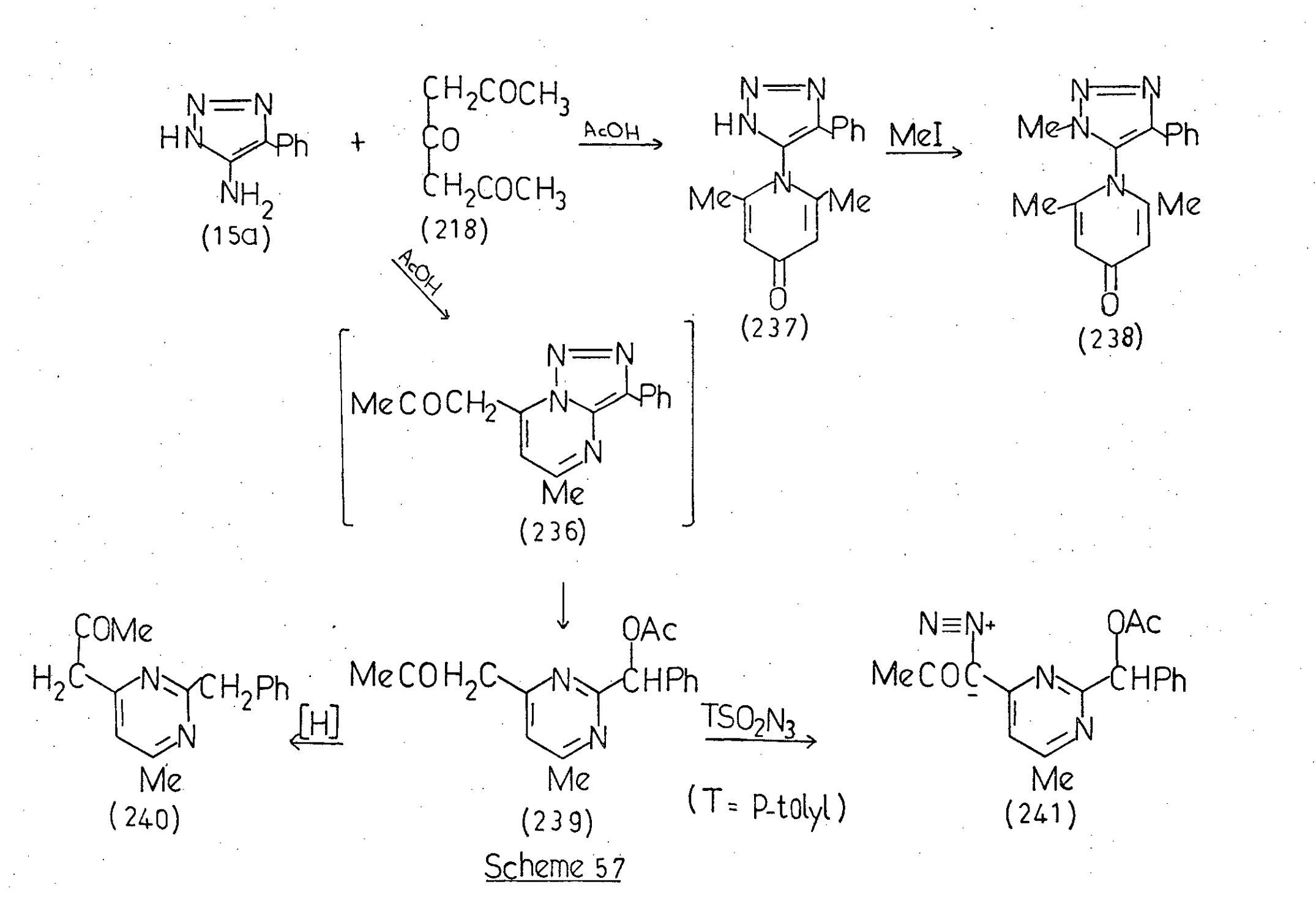
OR



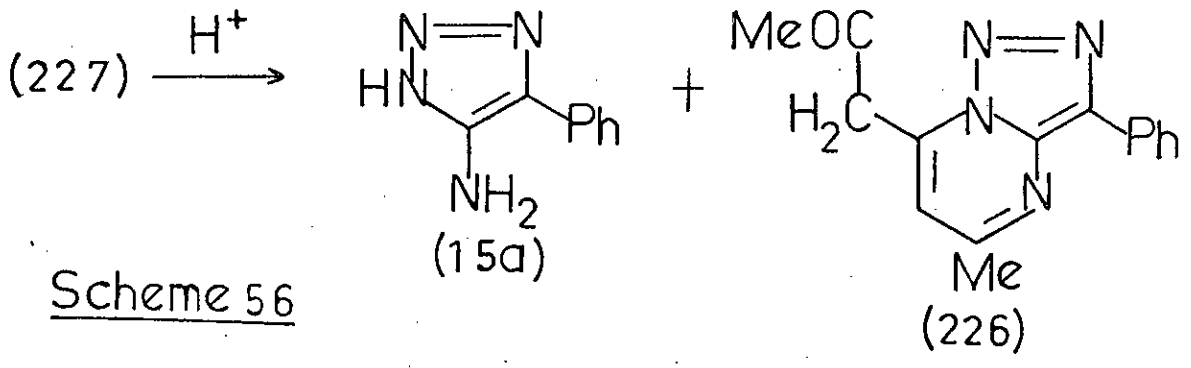
(235b)

(229).

In order to establish the structure of the triazolopyrimidylacetonylideneaminotriazole (227) rigorously an attempt was made to degrade it by acidic hydrolysis to the constituent amine (15a) and triazolopyrimidine [Scheme 56; (226)]. However, when heated with aqueous 2M hydrochloric acid, (227) was only partly converted into the amine (15a) and none of the triazolopyrimidine (226) could be isolated. The relative resistance of (227) to acidic hydrolysis



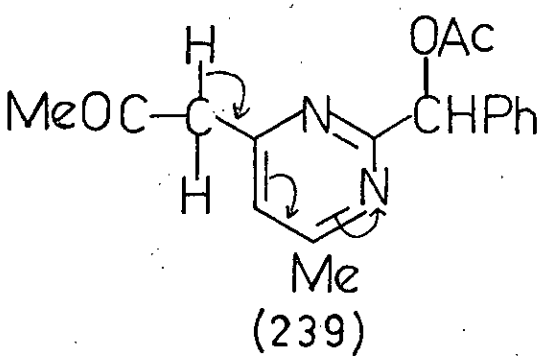
Scheme 57



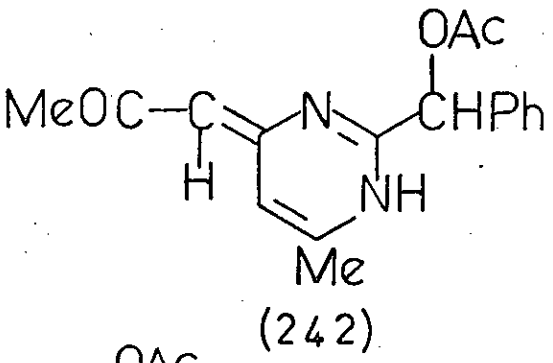
Scheme 56

excludes the Schiff base structures (227), (231a) and (231b) (which would be expected to be labile to acid) and hence indicates that (227) exists mainly in the enamine form (230). The formation of (227) can be explained on the basis of the condensation of the aminotriazole (15a) with a molecule of the triketone (218) to give the intermediate triazolopyrimidine (226) which then condenses with a second molecule of (15a) to afford (227).

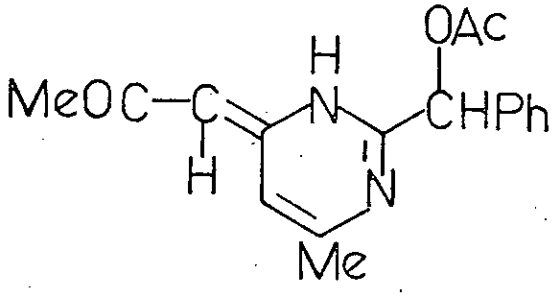
When the aminotriazole (15a) was heated under reflux with the triketone (218) in glacial acetic acid, two products were obtained (Scheme 57) namely, the triazolylpyridone (237) and the acetoxy-pyrimidine (239). The acetoxy derivative (239) is probably a triazole scission product of the expected triazolopyrimidine (236) which could not be detected as a product of the reaction. The ^{1}H n.m.r. spectrum of the acetoxypyrimidine (239) indicated that it was a mixture of the tautomers (239) and (242) or (243). Thus, it contained two one proton singlets at τ 3.09 and 3.30 due to two distinct pyrimidine CH groups and two one proton singlets at τ 3.35 and 3.58 due to two distinct benzylic protons. It also contained a one proton singlet at τ 4.81 due to the acetonylidene CH in (242) or (243) and a two proton singlet at τ 6.22 due to the methylene group in (239). The ^{1}H n.m.r. spectrum also indicated the presence of six distinct



(239)

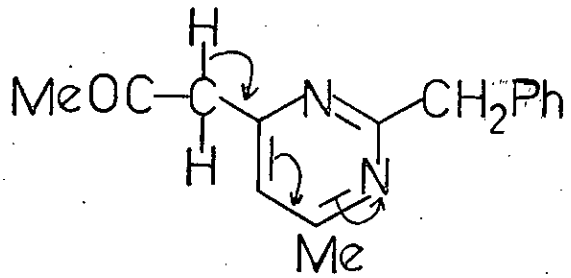


(242)

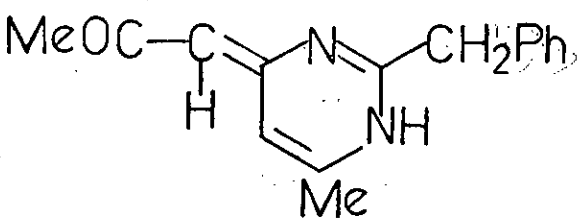


(243)

methyl groups again in accord with the presence of two tautomeric forms (239) and (242) or (243). Hydrogenation of the acetoxy derivative (239) afforded the benzylpyrimidine (240) whose ^{1}H n.m.r. spectrum once again suggested it was a tautomeric mixture of (240) and (244) or (245). Thus, it showed the presence of two pyrimidine hydrogens at τ 3.13 and 3.63, two sets of benzylic hydrogens at

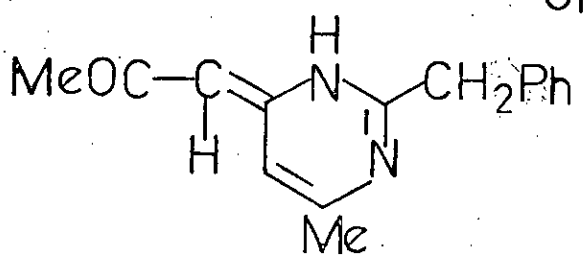


(240)



(244)

OR

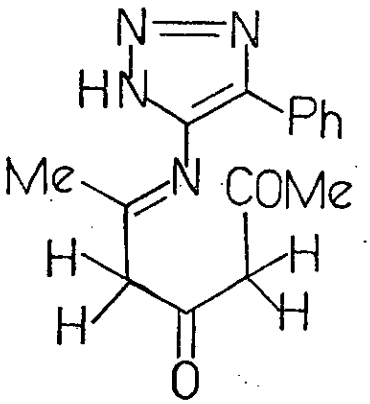


(245)

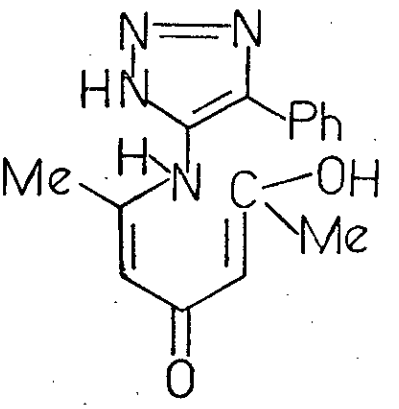
τ 5.79 and 5.89, one methine proton due to (244) or (245) at τ 4.88 and two methylene hydrogens at τ 6.24 due to (240). The ^{1}H n.m.r. spectrum also indicated the presence of absorptions at τ 7.56, 7.64, 7.83, and 8.04 due to two distinct pyrimidine methyl groups respectively. The pyrimidine (240) was further characterised as its hydrochloride. The attempted 'diazo-transfer' reaction of the acetoxy compound (239) with toluene-p-sulphonyl azide (Scheme 57) yielded an oil which could not be solidified but which was shown by t.l.c. to be a single component. Its i.r. spectrum contained characteristic diazo-absorption at 2130 cm^{-1} in accord with its tentative formulation as the diazo-compound (241). However, the attempted characterisation of (241) by acetolysis in glacial acetic acid gave only an intractable oil.

The spectral properties of the triazolylpyridone [Scheme 57; (237)] were consistent with the assigned structure. Thus, its i.r. spectrum showed NH and carbonyl absorption while its ^{1}H n.m.r. spectrum was in accord with the symmetrical nature of the molecule (237). Its ^{1}H n.m.r. spectrum showed a two proton singlet at τ 3.80 due to the pyridone hydrogens and a six proton singlet at τ 8.14 due to the two methyl groups. Further characterisation of the triazolylpyridone (237) was achieved by methylation. Thus, when (237) in acetone was heated under reflux with methyl iodide in the presence of anhydrous potassium carbonate, it yielded the expected N-methyl derivative (238). The i.r. and ^{1}H n.m.r. spectral data of (238) were consistent with the structure assigned to it. Thus, its i.r. spectrum lacked NH absorption while showing low carbonyl absorption at 1640 cm^{-1}. Its ^{1}H n.m.r. spectrum again showed that the molecule was symmetrical

since it contained a two proton singlet at τ 3.63 due to the pyridone hydrogens, a six proton singlet at τ 8.06 attributable to the Me(2) and Me(6), groups and a three proton singlet at τ 5.68 due to the N-methyl protons. An attempt was made to open up the triazole ring in (237) by tosylation and thereby to degrade it to known compounds as a means of further establishing its structure. Unfortunately, the attempted tosylation of the triazolylpyridone (237) with toluene-p-sulphonyl chloride in the presence of triethylamine and sodium hydroxide was unsuccessful. The formation (237) can be explained by the following mechanism. First,the aminotriazole (15a) condenses with a terminal keto-group of the triketone (218) to afford (246) which

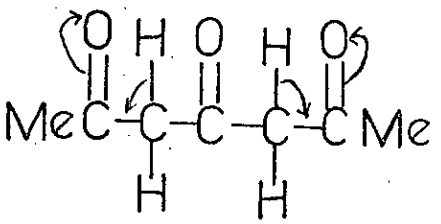


(246)



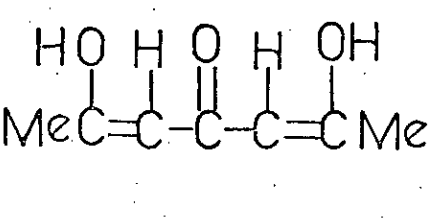
(247)

undergoes two 1,3-hydrogen shifts leading to (247) and loss of water from (247) gives the product (237). It is also possible for the triketone (218) to exhibit keto-enol tautomerism [(218a) $\rightleftharpoons$ (218b)]



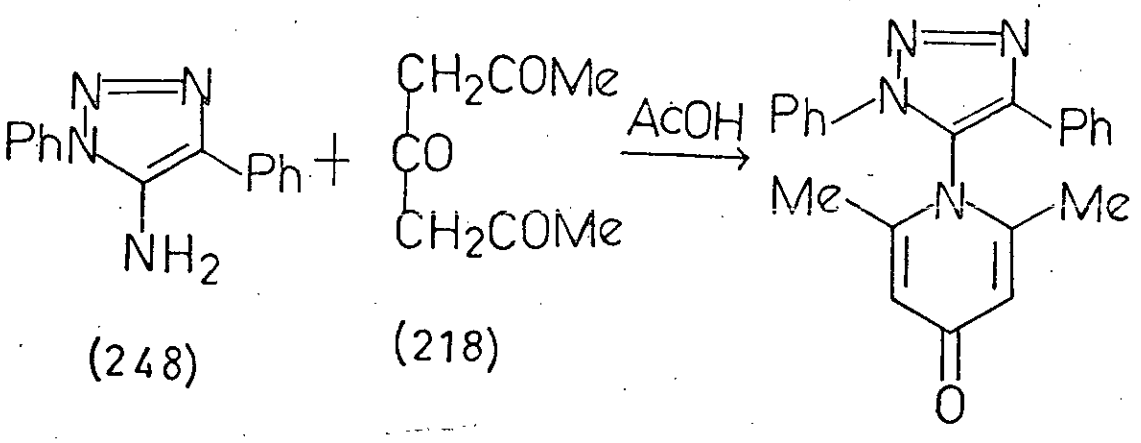
(218a)

$\rightleftharpoons$



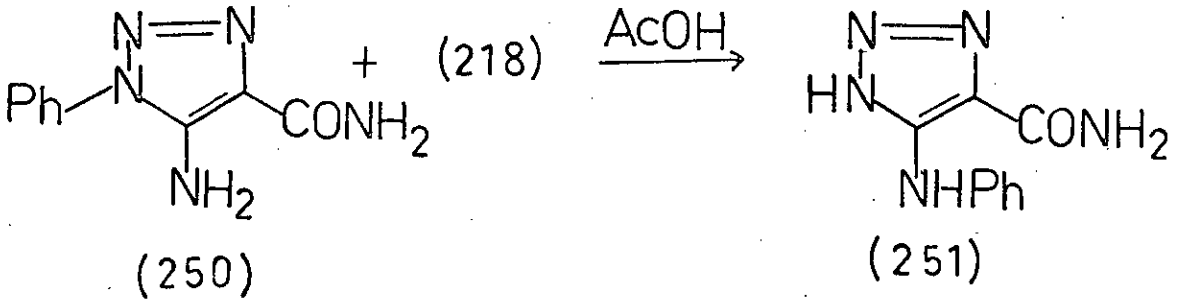
(218b)

in which case, the enol form (218b) will condense with the aminotriazole (15a) to afford (247) directly. Whichever pathway is followed however, the triazole NH is not involved in the formation of (247) as confirmed by the condensation of the diphenyltriazole (248), (which has no triazole NH group) with the triketone (218). This condensed smoothly with the triketone (218) in the presence of glacial acetic acid to afford the triazolylpyridone (249) whose



(248) (218) (249)

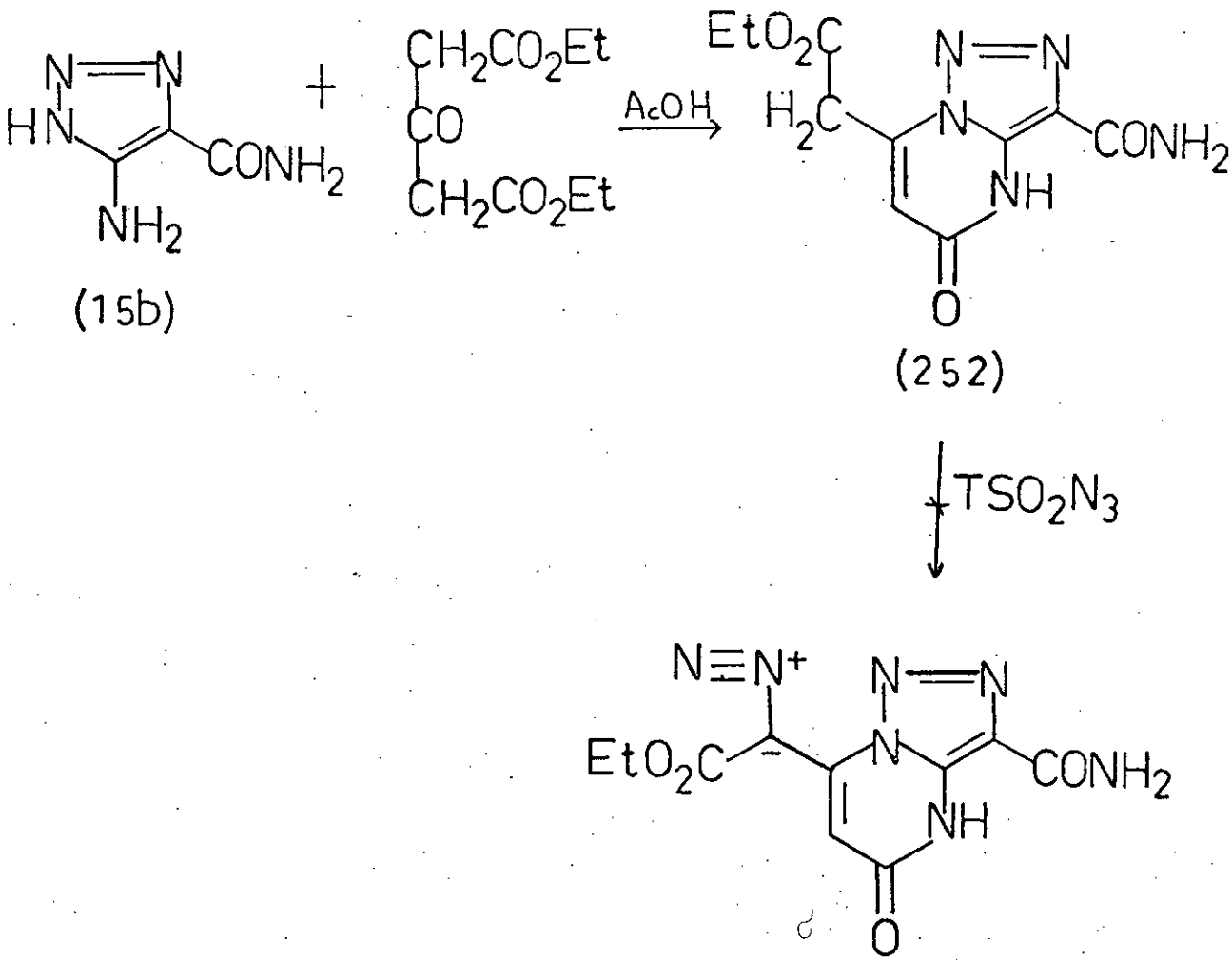
spectral properties were in accord with the assigned structure. Thus, its i.r. spectrum showed a carbonyl band at 1650 cm^{-1} and its ^1H n.m.r. spectrum was in good agreement with the symmetrical structure of (249). Thus, its ^1H n.m.r. spectrum showed a ten proton multiplet at τ 2.32-2.62 due to the two phenyl groups, a two proton singlet at τ 3.66 due to the two pyridone protons and a six proton singlet at τ 8.12 attributable to the two methyl groups. An attempt was also made to condense the aminotriazole (250) with the triketone (218) in glacial acetic acid. However, this reaction merely resulted in the



(250) (251)

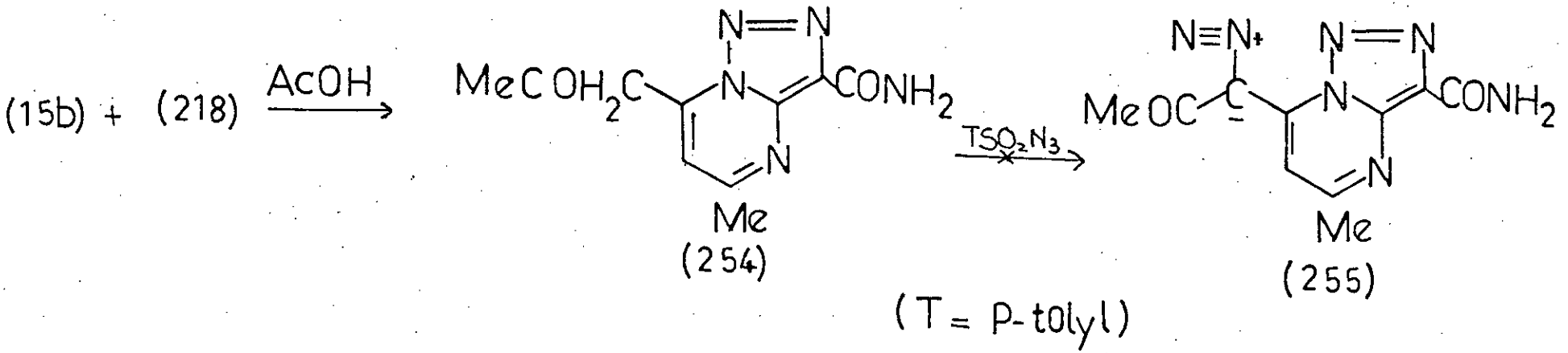
isomerisation[5a] of the amine (250) to the anilino isomer (251).

When the triazole amide (15b) was heated under reflux with diethyl acetonedicarboxylate in glacial acetic acid, the triazolopyrimidinone



(15b) (252) (253)

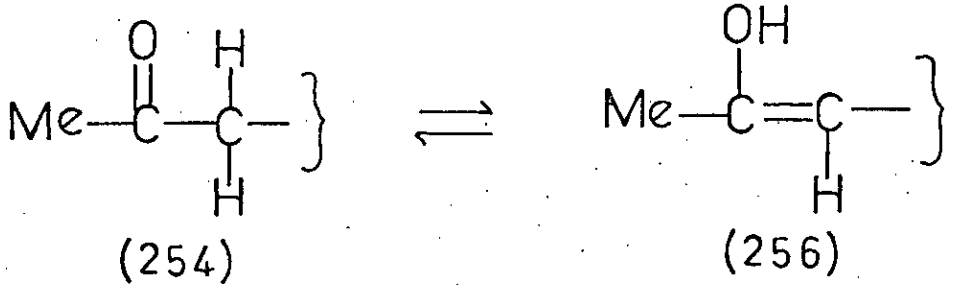
Scheme 58


(15b) + (218)
AcOH
MeCOH2C
CONH2
Me
(254)
TSO2N3
MeOC
CONH2
Me
(255)
(T = p-tolyl)

Scheme 59

[Scheme 58; (252)] bearing an active methylene side chain was produced. In accord with its structure the ^{1}H n.m.r. spectrum of (252) showed a pyrimidine hydrogen at τ 4.06 and methylene protons at τ 6.09. When treated with toluene-p-sulphonyl azide in the presence of triethylamine, the triazolopyrimidinone (252) failed to give the expected diazo-compound (253). Instead only a very high melting unidentified solid was obtained whose mass spectrum showed no ion pressure while its i.r. spectrum exhibited a strong diazo-absorption at 2120 cm^{-1}. In the expectation that this product might be a salt of the diazo-compound (253) it was dissolved in water and acidified with aqueous dilute sulphuric acid but this treatment gave no organic material.

The condensation between the aminotriazole (15b) and the triketone (218) afforded a low yield of the triazolopyrimidine [Scheme 59; (254)] whose i.r. spectrum showed only a single carbonyl absorption at 1680 cm^{-1} indicating that the acetonyl group might be existing in the enol form (256). Because of lack of material the ^{1}H n.m.r. spectrum of (254)



(254) (256)

could not be obtained. The attempted reaction of (254) with toluene-p-sulphonyl azide in the presence of triethylamine was unsuccessful - only the starting material being recovered. One reason for the failure of this diazo-transfer reaction might be the existence of the acetonyl compound (254) in the enol form (256) as this would lower the reactivity of the methylene group to diazo-transfer.

3.4 Experimental (For general experimental procedures, see Appendix)

Heptane-2,4,6-trione (218)

Heptane-2,4,6-trione[41] (218) m.p. 48° (lit.,[41] 49°) was prepared by the method of Bethell and Maitland.[43]

5-Amino-4-phenyl-1H-1,2,3-triazole (15a) and 5-Amino-1H-1,2,3-triazole-4-carboxamide (15b)

For the method of preparing the aminotriazoles (15a) and (15b) see Chapter 2 page 38.

5-Amino-1,4-diphenyl-1,2,3-triazole (248) and 5-Amino-1-phenyl-1,2,3-triazole-4-carboxamide (250)

The aminotriazoles (248) m.p. 180° (lit.,[5a] 173°) and (250) m.p. 168° (lit.,[5a] 170°) were prepared by the method of Sutherland and Tennant.[5a]

6-Ethoxycarbonylmethyl-2-methylpyridin-4(3H)-one (209)

A solution of diethyl acetonedicarboxylate (0.81g, 0.004mol) and acetamidine hydrochloride (0.38g, 0.004 mol) in absolute ethanol (20.0ml) was heated under reflux with a solution of sodium (0.23g; 0.01g atom) in absolute ethanol (10.0ml) for 1h. The mixture was evaporated and the solid residue was dissolved in water and extracted with chloroform. Evaporation of the chloroform extract gave an oil which was triturated with ether to yield the colourless pyrimidinone (209) which was combined with a second crop obtained by acidifying the aqueous extract with aqueous dilute sulphuric acid, neutralising with solid sodium acetate and extracting with chloroform, and the oil

obtained triturated with ether (total 0.37g; 47%) m.p. 133° (from benzene), $\nu_{max.}$ 1730, and 1690 (CO) cm^{-1}, $\tau(CDCl_3)$ 3.70(1H, s, CH), 5.80(2H, q J 7Hz, CH_2), 6.45(2H, s, CH_2), 7.54(3H, s, CH_3) and 8.72(3H, t J 7Hz, CH_3).

Found: C, 54.8; H, 6.0; N, 14.2%; M^+, 196.

$C_9H_{12}N_2O_3$ requires: C, 55.0; H, 6.1; N, 14.3%; M, 196.

Work up of the aqueous extract by evaporation and extraction of the solid obtained with hot benzene gave no further material.

6-(2-Diazoethoxycarbonylmethylene)-2-methylpyrimidin-4(3H)-one(211)

A solution of the pyrimidinone ester (209) (1.57g, 0.008mol) in absolute ethanol (85.0ml) was cooled to 0° (ice-salt bath), stirred, and treated in one portion with triethylamine (3.23g, 0.032mol). The solution was then treated dropwise with stirring with a solution of toluene-p-sulphonyl azide (3.15g, 0.016mol) in absolute ethanol (25.0 ml) and stirred in the melting ice for 2h. The mixture was evaporated and the oily solid obtained was successively triturated with ethanol-ether to give the diazo-ester (211) as yellow needles (total 1.11g) m.p. 211° (from ethanol), $\nu_{max.}$ 2750w (OH, NH), 2150 ($-\overset{+}{N} \equiv N$), and 1700 and 1660br (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 3.86 (1H, s, pyrimidine H), 5.90(2H, q J 7Hz, CH_2), 7.72(3H, s, CH_3) and 8.78(3H, t J 7Hz, CH_3).

Found: C, 48.5; H, 4.5; N, 25.1%; M^+, 222.

$C_9H_{10}N_4O_3$ requires: 48.6; H, 4.5; N, 25.2%; M, 222.

The ether-ethanol mother liquor was evaporated to give an oil which was triturated with ether to afford toluene-p-sulphonamide more of which was obtained by evaporating the ether mother liquor) and triturating the oil obtained with water (total 0.28g) m.p. 118°, identical (m.p. and i.r. spectrum) with an authentic sample.

6-(2-Acetoxyethoxycarbonylmethylene)-2-methylpyrimidin-4(3H)-one (210)

The diazo-ester (211) (0.44g, 0.002mol) was heated under reflux in glacial acetic acid (15.0ml) for 17h. The dark solution was evaporated and the dark oil obtained was successively triturated with ether to give the impure acetoxy compound (210) (total 0.21g) m.p. 115°. Crystallisation from benzene-light petroleum gave the pure product (210) as colourless crystals (0.07g) m.p. 121°, $\nu_{max.}$ 1750 and 1680 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 3.66(1H, s, CH), 4.32(1H, s, CH), 5.86(2H, q J 7Hz, CH_2), 7.72(3H, s, CH_3), 7.86(3H, s, CH_3) and 8.82(3H, t J 7Hz, CH_3).

Found: C, 52.3; H, 5.5; N, 11.5%; M^+, 254.

$C_{11}H_{14}N_5O_4$ requires: C, 52.0; H, 5.5, N, 11.0%; M,254.

The Attempted Pyrolysis of the Diazo-Ester (211)

(a) In Toluene.

The diazo-ester (211) (0.44g, 0.002mol) was heated under reflux in dry toluene (20.0ml) for 1h. The solution was cooled and the unreacted diazo-ester (211) was filtered off and combined with a second crop obtained by evaporating the toluene filtrate and triturating the solid obtained with ethanol-ether (total 0.39g; 88%) m.p. 207° identical (m.p. and i.r. spectrum) with an authentic sample.

(b) In Xylene

The diazo-ester (211) (0.44g, 0.002mol) was heated under reflux in dry xylene (20.0 ml) for 1h. The dark solution was cooled and filtered to give the unreacted diazo-ester (211) which was combined with a second crop obtained by evaporating the xylene filtrate and triturating the solid residue with ethanol-ether (total 0.24g; 54%) m.p. 202°, identical (i.r. spectrum) with an authentic sample.

The Attempted Cycloaddition of the Diazo-Ester (211)

(a) With Diethyl Fumarate

A solution of the diazo-ester (211) (0.34g, 0.0015mol) and diethyl fumarate (0.22g, 0.0015 mol) in chloroform (20.0 ml) was left at room temperature for 24h. The chloroform was evaporated leaving a yellow solid which was triturated with ether to give the unreacted diazo-ester (211) (0.32g; 94%) m.p. 194°, which was identical (i.r. spectrum) with an authentic sample.

The ether mother liquor was evaporated to give unreacted diethyl fumarate (0.2g) m.p. 100°, which was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) With Dimethyl Acetylenedicarboxylate

A solution of the diazo-ester (211) (0.44g, 0.002 mol) and dimethyl acetylenedicarboxylate (0.28g, 0.002 mol) in chloroform (20.0 ml) was left at room temperature for 24h. The solution was evaporated and the solid residue was triturated with ethanol-ether to afford the unreacted diazo-ester (211) (0.34g; 84%) m.p. 206°, identical (m.p. and i.r. spectrum) with an authentic sample.

2-Amino-6-ethoxycarbonylmethyl pyrimidin-4(3H)-one (215)

A solution of guanidine hydrochloride (1.54g, 0.016mol) and diethyl acetonedicarboxylate (3.23g, 0.016mol) in absolute ethanol (80.0ml) was treated with a solution of sodium (0.23g; 0.01 g atom) in absolute ethanol (40.0ml) and the mixture was heated under reflux for 1h. The mixture was evaporated under reduced pressure and the residual oily solid was dissolved in water and extracted with chloroform to give unreacted diethyl acetonedicarboxylate (1.09g), identical (i.r. spectrum) with an authentic sample.

The aqueous extract was acidified with aqueous dilute sulphuric acid, neutralised with solid sodium acetate and extracted with chloroform to give an oil. This was triturated with ether to afford the impure pyrimidinone ester (215) which was combined with a second crop obtained by evaporating the aqueous mother liquor and triturating the oily residue with water (total 1.15g) m.p. 160°. Crystallisation from water gave the pure pyrimidinone (215) as colourless crystals (0.63g) m.p. 179°, $\nu_{max.}$ 3580, 3400, and 3100 (NH), and 1730, and 1640br (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 3.38(2H, br s,NH), 4.50(1H, pyrimidine H), 5.90(2H, q J 7Hz, CH_2), 6.66(2H, s, CH_2) and 8.80(3H, t J 7Hz, CH_3).

Found: C, 47.6; H, 5.6; N, 21.0%; M^+, 197.

$C_8H_{11}N_3O_3$ requires: C, 48.9; H, 5.8; N, 21.3%; M, 197.

Work up of the aqueous mother liquor by evaporation and trituration with water yielded an unidentified solid (0.07g) m.p. 135°.

The Reaction of the Pyrimidinone Ester (215) with Toluene-p-Sulphonyl Azide.

A solution of the pyrimidinone ester (215) (1,18g, 0.006ml) in absolute ethanol (200ml) was cooled to 0° (ice-salt bath), stirred, and treated in one portion with triethylamine (2.42g, 0.024mol). The solution was then treated dropwise with stirring with a solution of toluene-p-sulphonyl azide (2.36g, 0.012mol) in absolute ethanol (30.0 ml) and the mixture was stirred in the melting ice-bath for 2h. The mixture was then evaporated and the solid residue was triturated with ethanol-ether to give the impure diazo-ester (216) (1.12g) m.p. 90°. Crystallisation from water afforded the pure product (216) as pale yellow needles (0.86g) m.p. 207°, $\nu_{max.}$ 3400 and 3150 (NH), 2100 ($-\overset{+}{N}\equiv N$), and 1700 and 1660 (CO) cm^{-1}.

	Found:	249.056130.
$C_8H_7N_7O_3$	requires:	249.061032.

Work up of the ethanol-ether mother liquor by evaporation and trituration with water gave toluene-p-sulphonamide (0.60g) m.p. 104°, identical (i.r. spectrum) with an authentic sample.

The Attempted Reaction of the Diazo-azide (216) with Glacial Acetic Acid

The diazo-azide (216) (0.45g, 0.002mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution was then evaporated under reduced pressure and the solid residue was triturated with ethanol-ether to afford the unreacted diazo-azide (216) (0.38g) m.p. 192°, identical (i.r. spectrum)with an authentic sample.

The Attempted Cycloaddition of the Diazo-Azide (216) with Dimethyl Fumarate.

A solution of the diazo-azide (216) (0.45g, 0.002 mol) and diethyl fumarate (0.29g, 0.002 mol) in dimethylformamide (10.0ml) was left at room temperature for 24h. The solution was diluted with ether to give unreacted diazo-azide (216) (0.35g) m.p. 198°, identical (i.r. spectrum) with an authentic sample.

The dimethylformamide-ether mother liquor was evaporated and the residual oil was triturated with ethanol to give unreacted dimethyl fumarate (0.01g) m.p. 98°, which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Condensation of Urea with Diethyl Acetonedicarboxylate

A solution of urea (0.24g, 0.004 mol) and diethyl acetonedicarboxylate (0.80g, 0.004 mol) in absolute ethanol (20.0 ml) was treated with a solution of sodium (0.23g; 0.01 g atom) in absolute ethanol (10.0ml) and the mixture was heated under reflux for 1h. The mixture was evaporated and the resulting semi-solid was dissolved in water and extracted with chloroform to give a negligible amount of an unidentified oil.

The aqueous extract was acidified with aqueous dilute sulphuric acid, neutralised with solid sodium acetate and again extracted with chloroform to afford unreacted diethyl acetonedicarboxylate (0.34g), identical (i.r. spectrum) with an authentic sample.

The Attempted Condensation of Thiourea with Diethyl Acetonedicarboxylate

(a) In the Presence of Ethanolic Sodium Ethoxide

A solution of thiourea (0.3g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g, 0.004 mol) in absolute ethanol (20.0 ml) was treated with a solution of sodium (0.23g; 0.01g atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 1h. The mixture was then evaporated and the solid residue was dissolved in water and extracted with chloroform. Evaporation of the chloroform extract gave no material.

The aqueous extract was acidified with aqueous dilute sulphuric acid, and neutralised with solid sodium acetate to afford a cream solid (217) more of which was obtained from the neutral aqueous solution on standing (total 0.11g), m.p. > 290(decomp.) (from ethanol-water), $\nu_{max.}$ 3100 (NH), and 1700w, and 1680w (CO) cm^{-1}, M^+, 214.

Found: 214.039342.

$C_8H_{10}N_2O_3S$ requires: 214.041209.

Work up of the aqueous extract by extraction with chloroform gave no further product.

(b) In the Presence of Potassium Carbonate

A solution of thiourea (0.22g, 0.003 mol) in water (10.0 ml) was stirred vigorously and treated in one portion with diethyl acetonedicarboxylate (0.91g, 0.0045 mol). The mixture was then treated in portions with stirring with finely divided potassium carbonate (0.62g, 0.0045 mol). The mixture was stirred at room temperature for 2h and then neutralised with aqueous dilute sulphuric acid and extracted with chloroform to give a small amount of unidentified oil.

The aqueous extract was evaporated to give inorganic material from which no identifiable material could be obtained.

(c) In the Presence of Piperidine

A solution of thiourea (0.3g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g, 0.004 mol) in absolute ethanol (15.0 ml) containing piperidine (1.0 ml) was heated under reflux for 18h. The solution was evaporated to give an oil which was dissolved in water, acidified with aqueous dilute hydrochloric acid and extracted with chloroform. Evaporation of the chloroform extract gave an oil (0.5g) which was identified as unreacted diethyl acetonedicarboxylate by comparison (i.r. spectrum) with an authentic sample.

The aqueous extract was evaporated and the oily solid left was triturated with ethanol to give a hygroscopic solid (0.03g). No further identifiable material was obtained.

(d) In the Presence of Concentrated Hydrochloric Acid.

A solution of thiourea (1.52g, 0.02 mol) and diethyl acetonedicarboxylate (2.0g, 0.01 mol) in ethanol (60.0 ml) was stirred with concentrated hydrochloric acid (10.2 ml) at room temperature for 60h. The mixture was evaporated and the colourless solid residue was triturated with ethanol to give unreacted thiourea which was combined with a second crop obtained by evaporating the ethanol mother liquor and triturating the solid left with ethanol-ether (total 1.23g) m.p. 180°, identical (m.p. and i.r. spectrum) with an authentic sample.

The ethanol-ether mother liquor was evaporated to give unreacted diethyl acetonedicarboxylate (0.87g) which was identical (i.r. spectrum) with an authentic sample.

The Attempted Condensation of S-methyl Thiourea with Diethyl Acetonedicarboxylate

A mixture of S-methyl thiourea bisulphate (1.11g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g, 0.004 mol) in absolute ethanol (30.0 ml) was treated with a solution of sodium (0.23g; 0.01 g atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 1h. The mixture was evaporated and the solid residue was dissolved in water and extracted with chloroform. Evaporation of the chloroform extract gave no material.

The aqueous extract was acidified with aqueous dilute sulphuric acid and neutralised with solid sodium acetate. Extraction with chloroform gave no material. Further work up of the aqueous mother liquour by evaporation and trituration with water, gave no identifiable material.

The Attempted Condensation of Formamidine Acetate with Diethyl Acetonedicarboxylate

A solution of formamidine acetate (0.42g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g, 0.004 mol) in absolute ethanol (20.0 ml) was treated with a solution of sodium (0.23g; 0.01g atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 1h. Evaporation of the mixture gave a solid which was triturated with ether to give a crude solid (0.08g) m.p. 205°. This was purified by crystallisation from water to give an unidentified solid (0.04g) m.p. 220°, $\nu_{max.}$ 3480, 3400w (NH), and 1700 and 1640 (CO) cm^{-1}, M^{+} 239.

The aqueous extract was acidified with aqueous dilute sulphuric acid and neutralised with solid sodium acetate and the solid (0.13g)

m.p. 210°, was crystallised from ethanol to give another identified solid (0.06g) m.p. 217°, $\nu_{max.}$ 3050w, 2650 (NH, OH) and 1690 and 1660 (CO) cm^{-1}.

Further work up of the aqueous mother liquor by evaporation and trituration of the residue with water gave no other organic material.

The Attempted Condensation of Acetamidine Hydrochloride with the Triketone (218)

(a) In the Presence of Sodium Ethoxide

A solution of acetamidine hydrochloride (0.38g, 0.004 mol) and the triketone (218) (0.57g, 0.004 mol) in absolute ethanol (20.0 ml) was treated with a solution of sodium (0.23g; 0.1g atom) in absolute ethanol (10.0 ml) and the mixture was heated under reflux for 1h. The mixture was evaporated and the residue was dissolved in water and extracted with chloroform. Evaporation of the chloroform extract gave a negligible amount of solid material.

The aqueous extract was acidified with dilute hydrochloric acid, neutralised with solid sodium acetate and extracted with chloroform to give an oil which was triturated with ethanol-ether to give the unreacted triketone (218) (0.09g)m.p. 50°, identical (m.p. and i.r. spectrum) with an authentic sample.

Work up of the aqueous extract by evaporation and extraction of the solid residue with hot ethyl acetate gave no identifiable material.

(b) In the Presence of Potassium Carbonate

A mixture of the triketone (218) (0.63, 0.0045 mol), acetamidine hydrochloride (0.38g, 0.004 mol) and potassium carbonate (1.1g) in water (10.0 ml) was stirred at room temperature for 72h. The mixture was then extracted with chloroform to give a solid residue which was

triturated with ether to afford an unidentified yellow solid (0.06g) m.p. 177°, $\nu_{max.}$ 1640 (CO) cm^{-1}.

Found: C, 72.9; H, 6.1; N 0.0% M^+ 230.

The aqueous extract was acidified with aqueous dilute sulphuric acid and re-extracted with chloroform to give a negligible amount of an unidentified oil. Further work up of the aqueous extract gave no identifiable material.

The Attempted Condensation of Formamidine Acetate with the Triketone (218)

A mixture of formamidine acetate (0.42g, 0.004 mol) and the triketone (218) (0.57g, 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The mixture was evaporated and the oily residue was triturated with ether-ethanol to give unreacted formamidine acetate (0.22g) m.p. 158°, identical (m.p. and i.r. spectrum) with an authentic sample.

The ethanol-ether mother liquor was evaporated and the oil left was successively triturated with ethanol-ether to afford colourless crystals (total 0.16g) of an unidentified solid m.p. 129° (from light petroleum), $\nu_{max.}$ 1670 (CO) cm^{-1}.

Found: C, 67.2; H, 6.5; N, 0.0%; M^+ 124.

The Attempted Condensation of the Aminotriazole (15a) with Diethyl Acetonedicarboxylate.

A solution of the aminotriazole (15a) (0.64g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g, 0.004 mol) in ethanol (20.0 ml) containing piperidine (0.2 mol) was heated under reflux for 24h. The solution was evaporated and the oily solid remaining was triturated with ethanol-ether to afford the unreacted aminotriazole (15a) (0.09g)

m.p. 130° which was identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethanol-ether mother liquor left an oil whose t.l.c. in ether over alumina showed it to be an unresolved mixture of three components. The oil was suspended in water and extracted with chloroform to give unreacted diethyl acetonedicarboxylate (0.63g; 79%) which was identified by comparison (t.l.c. and i.r. spectrum) with an authentic sample.

2-(α-Acetoxybenzyl)-6-ethoxycarbonylmethyl pyrimidin-4 (3H)-one (225)

A mixture of the aminotriazole (15a) (0.64g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g, 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution on evaporation under reduced pressure left an oil which was cooled and triturated with ethanol-ether to afford the impure pyrimidinone (225) (0.42g) m.p. 140° which crystallised from water-ethanol as a colourless solid (0.32g) m.p. 158°, $\nu_{max.}$ 3160w (NH), 1755, and 1725 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 2.63(5H, s, Ar-H), 3.80(1H, s, pyrimidine H), 3.86(1H, s, CHOAc), 6.00(2H, q J 7Hz, CH_2), 6.50(2H, s, CH_2), 7.91(3H, s, $OCOCH_3$), and 8.90(3H, t J 7Hz, CH_3).

Found : C, 61.6; H, 5.5; N, 8.5%; M^+ 330.

$C_{17}H_{18}N_2O_5$ requires: C, 61.8; H, 5.5; N, 8.5%; M, 330.

Evaporation of the ethanol-ether mother liquor left an oil (0.32g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of three components.

6-(2-Diazoethoxycarbonylmethyl)-2-(α-hydroxybenzyl)pyrimidin-4(3H)-one(224)

A solution of the pyrimidinone (225) (0.66g, 0.002 mol) in absolute ethanol (75.0 ml) was cooled to 0° (ice-salt bath), stirred, and treated in one portion with triethylamine (0.8g, 0.008 mol) and then dropwise with stirring with a solution of toluene-p-sulphonyl azide (0.8g, 0.004 mol) in absolute ethanol (5.0 ml). The mixture was then stirred in the melting ice for 2h and evaporated to give an oil which was suspended in aqueous 2M sodium hydroxide solution and extracted with chloroform. Evaporation of the chloroform extract gave an oil (0.32g) which was identified as unreacted toluene-p-sulphonyl azide by comparison (i.r. spectrum) with an authentic sample.

The alkaline extract was acidified with aqueous dilute sulphuric acid to afford impure diazonium compound (224) (0.46g) m.p. 140° which crystallised from ethanol-light petroleum as shiny yellow crystals (0.10g) m.p. 200°, $\nu_{max.}$ 3360br, 3130w (NH), 2130($-\overset{+}{N}\equiv N$), and 1760(CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.56 - 2.83(5H, m, Ar-H), 3.45(1H, s, pyrimidine H), 3.70(1H, s, CHOH), 5.80(2H, q J 7Hz, CH_2) and 8.78(3H, t J 7Hz, CH_3).

Found: C, 56.8; H, 4.5; N, 17.5%; M^+ 314.

$C_{15}H_{14}N_4O_4$ requires: C, 57.2; H, 4.5; N, 17.8%; M, 314.

The ethanol-light petroleum mother liquor on evaporation left an oil which was triturated with ether to give toluene-p-sulphonamide (0.12g) m.p. 120° which was identical (m.p. and i.r. spectrum) with an authentic sample.

5-[2-(3-Phenyl-5-methyltriazolo[1,5-a]pyrimid-7-yl)acetonylidene]-amino-4-phenyl-1H-1,2,3-triazole (227)

A mixture of the triazole amine (15a) (0.64g, 0.004 mol) and the triketone (128) (0.56g, 0.004 mol) was heated under reflux in ethanol (20.0 ml) containing piperidine (0.2 ml) for 24h. The solution was evaporated to give an oily solid which was suspended in water and extracted with chloroform. The insoluble solid was collected and combined with further material obtained by evaporating the chloroform layer and triturating the oil with methanol-ether to give the iminotriazole derivative (227) (total 0.30g). Crystallisation from dimethylformamide-water gave the deep yellow triazolopyrimidine derivative (227) (0.20g) m.p. 244°, $\nu_{max.}$ 3140(NH) cm^{-1}, $\lambda_{max.}$ 210, 237sh, 264, 318, 344sh and 404 nm (log ε 4.49, 4.37, 4.41, 4.24, 4.03, and 4.13), τ [$CDCl_3$-$(CD_3)_2SO$] 2.08 - 2.17(5H, m, Ar-H), 2.68 - 2.76(3H, m, Ar-H), 3.02 - 3.09(2H, m, Ar-H), 2.30(1H, s, pyrimidine H), 4.52(1H, s, -CH=), 7.23(3H, s, CH_3) and 7.93(3H, s, CH_3).

Found : C, 66.9; H, 5.1; N, 27.4%; M^+ 408.

$C_{23}H_{20}N_8$ requires: C, 67.6; H, 4.9; N, 27.4%; M, 408.

1-Acetyl-5-[2-(3-phenyl-5-methyltriazolo[1,5-a]pyrimid-7-yl) acetonylidene]amino-4-phenyl-1H-1,2,3 triazole (228)

The triazolopyrimidine derivative (227) (0.2g, 0.0005 mol) was heated under reflux in acetic anhydride (8.0 ml) for 5 min. The solution was evaporated under reduced pressure to leave a gum which was cooled and triturated with ether to afford the impure acetyl derivative (228) (0.22g; 95%) m.p. 180°. Crystallisation from benzene-light petroleum gave the pure acetyl derivative (228) as a

yellow solid (0.17g) m.p. 206°, $\nu_{max.}$ 1750 (CO) cm^{-1}. $\lambda_{max.}$ 210, 262, 318, 344 and 406 nm (logε 4.54, 4.49, 4.29, 4.27 and 4.20), τ ($CDCl_3$) 2.06 - 2.20(5H, m, Ar-H), 2.76 - 2.88(2H, m, Ar-H), 3.02 - 3.09(3H, m, Ar-H), 3.57(1H, s, pyrimidine H), 4.58(1H, s, -CH=), 7.20(6H, s, CH_3) and 7.68(3H, s, CH_3).

Found: C, 67.0; H, 4.9; N, 25.2%; M^+ 450.

$C_{25}H_{22}N_8O$ requires: C, 66.6; H, 4.9; N, 24.8%; M, 450.

5-[2-(2-α-Acetoxybenzyl-6-methylpyrimid-4-yl) acetonylidene]amino-4-phenyl-1H-1,2,3-triazole (229)

The triazolopyrimidine derivative (227) (0.3g, 0.0007 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution was evaporated under reduced pressure and the oily residue was cooled and triturated with ether to afford the impure acetoxy derivative (229) (0.22g; 67%) m.p. 173° which crystallised from ethanol-water as a cream solid (0.7g) m.p. 186°, $\nu_{max.}$ 3140(NH) and 1740(CO) cm^{-1}, τ[$CDCl_3$ - $(CD_3)_2SO$] 2.16 - 2.24(2H, m, Ar-H), 2.68(3H, m, Ar-H), 2.88(5H, s, Ar-H), 3.36(1H, s, pyrimidine H), 3.62(1H, s, CHOAc), 4.82(1H, s, -CH=) 7.66(3H, s, CH_3), 8.06(3H, s, CH_3), and 8.18(3H, s, CH_3).

Found: C, 67.9; H, 5.6, N, 19.0%; M^+ 440.

$C_{25}H_{24}N_6O_2$ requires: C, 68.2; H, 5.5; N, 19.1%; M, 440.

The Acid-Catalysed Hydrolysis of the Triazolopyrimidine Derivative (227).

(a) A solution of the triazolopyrimidine (227) (0.4g, 0.001 mol) in ethanol (15.0 ml) was treated with aqueous 2M hydrochloric acid (2.5 ml) and heated under reflux for 5 min. The solution was concentrated to remove the ethanol and the aqueous residue was extracted with chloroform to give an oil which was triturated with ethanol-ether to give the impure starting material (227) (0.25g; 62%) m.p. 215°. This crystallised from dimethylformamide-water to afford the pure triazolopyrimidine derivative (227) (0.14g) m.p. 243° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) The procedure described in (a) above was repeated on the same scale but with heating under reflux for 1h. The solution was concentrated to remove the ethanol and the aqueous residue on extraction with chloroform gave an oil which was triturated with ethanol-ether to afford the starting triazolopyrimidine (227) (0.23g) m.p. 220° which was identical (i.r. spectrum) with an authentic sample.

The aqueous extract was buffered with solid sodium acetate and on evaporation left a solid. This was extracted with hot ethyl acetate to afford an oil which was triturated with light petroleum to give the aminotriazole (15a) (0.01g) m.p. 115°, identical (m.p. and i.r. spectrum) with an authentic sample.

The Acid-Catalysed Condensation of the Aminotriazole (15a) with the Triketone (218)

A mixture of the aminotriazole (15a) (0.64g, 0.004 mol) and the triketone (218) (0.56g, 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution was evaporated under reduced

pressure and the oily residue on trituration with ethanol-ether afforded the crude triazolylpyridone (237) (0.20g) m.p. 305° which crystallised from ethanol as a cream solid (0.12g) m.p. 312°, ν max. 3080w (NH), 2500br and 1930br (NH) and 1630 (CO) cm^{-1}; λ max. 213, 223sh and 267nm (log ε 4.32, 4.21 and 4.43), τ[$CDCl_3$ - $(CD_3)_2SO$] 2.60(5H, s, Ar-H), 3.80(2H, s, CH_2) and 8.14(6H, s, CH_3).

Found: C, 67.4; H, 5.1; N, 21.3%; M^+, 266.
$C_{15}H_{14}N_4O$ requires: C, 67.5; H, 5.3; N, 21.0%; M, 266.

The ethanol-ether mother liquour was evaporated and the oil obtained on standing in contact with water gave the crude isomer mixture of acetoxybenzylpyrimidines (239) and (242) or (243) (0.37g) m.p. 70° which crystallised from light petroleum as pale yellow crystals (0.28g) m.p. 90°, νmax. 1750, and 1645 (CO) cm^{-1}, τ($CDCl_3$) 2.44-2.55(2H, m, Ar-H), 2.69-2.76(3H, m, Ar-H), 3.09(1H, s, pyrimidine H), 3.30(1H, s, pyrimidine H), 3.35(1H, s, C<u>H</u>OAc), 3.58(1H, s, C<u>H</u>OAc), 4.81(1H, s, -C<u>H</u>=C), 6.22(1H, s, CH_2), 6.55(3H, s, CH_3), 6.65(3H, s, CH_3), 6.80(3H, s, CH_3),6.83(3H, s, CH_3), 6.84(3H, s, CH_3) and 6.99(3H, s, CH_3).

Found: C, 68.3; H, 6.1; N, 9.4%; M^+, 298.
$C_{17}H_{18}N_2O_3$ requires: C, 68.4; H, 6.1; N, 9.4%; M, 298.

T.l.c. of the isomer mixture in ethyl acetate over silica showed just one component.

4-Acetonyl-2-benzyl-6-methylpyrimidines (240) and (244) or (245) and Their Hydrochlorides

(a) The tautomeric mixture of acetoxy compounds (239) and (242) or (243) (0.89g, 0.003 mol) in ethanol (50.0 ml) was hydrogenated over 10% palladium-charcoal (0.3g). Evaporation of the filtered mixture gave an oil. This was triturated with water followed by aqueous sodium hydrogen carbonate solution to give the crude benzylpyrimidine mixture of (240) and (244) or (245) (0.41g) m.p. 37° which was purified by Kugelrohr distillation to afford the pure benzylpyrimidine mixture as a yellow solid m.p. 39°, $\nu_{max.}$ 1650 (CO) cm^{-1}, $\tau(CDCl_3)$ 2.63 - 2.82(5H, m, Ar-H), 3.13(1H, s, pyrimidine H), 3.63(1H, s, pyrimidine H), 4.88(1H, s, -CH=), 5.79(2H, s, CH_2), 5.89(2H, s, CH_2) 6.24(2H, s, $COCH_2$), 7.56(3H, s, CH_3) 7.64(3H, s, CH_3), 7.83(3H, s, CH_3) and 8.04(3H, s, CH_3).

Found: C, 74.9; H, 6.6; N, 11.6%; $M,^+$ 240.

$C_{15}H_{16}N_2O$ requires: C, 75.0; H, 6.7; N, 11.7%; M, 240.

(b) Hydrogenation of the acetoxybenzylpyrimidine tautomeric mixture (239), and (242) or (243)(0.60g, 0.002 mol) as in (a) above gave an oil which was treated with aqueous dilute hydrochloric acid to yield the hydrochlorides of the benzylpyrimidines as a cream solid (0.20g) m.p. 192° (from ethanol-light petroleum), $\nu_{max.}$ 2340br and 1920 ($\overset{+}{N}H$) and 1640 (CO) cm^{-1}.

Found : C, 64.5; H, 6.1; N, 10.2%; $M,^+$ 240 (cation).

$C_{15}H_{15}N_2O$ HCl requires: C, 65.1; H, 5.8; N, 10.2%; M, 275.5.

The Attempted Reaction of the Acetoxybenzylpyrimidine mixture (239) and (242) or (243) with Toluene-p-Sulphonyl Azide

A solution of the acetoxybenzylpyrimidine mixture (239) and (242) or (243) (0.6g, 0.002 mol) in absolute ethanol (20.0 ml) was cooled to 0° (ice-salt bath), stirred, and treated in one portion with triethylamine (0.4g, 0.004 mol) and then dropwise with a solution of toluene-p-sulphonyl azide (0.4g, 0.002 mol) in absolute ethanol (5.0 ml). The mixture was stirred in the melting ice for 2h and evaporated to leave an oil. The oil was suspended in aqueous dilute sodium hydroxide solution and extracted with chloroform to afford an oil (0.56g) whose t.l.c. in ethyl acetate alone or containing ethanol showed it to be a single component, $\nu_{max.}$ 2130 ($-\overset{+}{N}\equiv N$), and 1750br (CO) cm^{-1}. Trituration of this oil with various solvents failed to solidify it.

The alkaline extract on acidification with aqueous dilute sulphuric acid yielded toluene-p-sulphonamide (0.14g) m.p. 115° which was identical (i.r. spectrum) with an authentic sample.

The Attempted Reaction of the "Diazo-Compound" (241) with Glacial Acetic Acid

The diazo-compound (241) (0.56g) was heated under reflux in glacial acetic acid (10.0 ml) for 17h. The solution was evaporated under reduced pressure leaving a very dark oil whose t.l.c. in ethyl acetate over silica showed it to be a mixture of two components. Dry column chromatography of this oil in ethyl acetate over silica gave as the faster running component an oil (0.14g) whose t.l.c. in ethyl acetate over silica showed it to be a single component. Its i.r. spectrum was poorly resolved. The slower running material was also an oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of two components.

2,6-Dimethyl-1-(1-methyl-4-phenyl-1H-1,2,3-triazol-5-yl) pyridin-4 (1H)-one (238)

A solution of the triazolylpyridone (237) (0.27g, 0.001 mol) in dry acetone (50.0 ml) was treated with freshly dried potassium carbonate (0.2g) and heated under reflux with methyl iodide (0.2 ml) for 3h. The solution was hot filtered to remove inorganic material which was washed with hot acetone. Evaporation of the combined acetone filtrate and washings left a foam which was triturated with water to give the impure product (238) (0.18g) m.p. 90°. Crystallisation from benzene-light petroleum gave the triazolylpyridone (238) (0.12g) m.p. 172°, $\nu_{max.}$ 1640 (CO) cm^{-1}, $\lambda_{max.}$ 210, 223sh and 265nm ($\log\varepsilon$ 4.63, 4.48, and 4.70), τ($CDCl_3$) 2.59(5H, s, Ar-H), 3.63(2H, s, CH), 5.68(3H, s, N-CH_3) and 8.06(6H, s, CH_3).

Found: C, 67.9; H, 5.8; N, 20.1%; M^+ 280.

$C_{16}H_{16}N_4O$ requires: C, 68.6; H, 5.8; N, 20.0%; M, 280.

The Attempted Reaction of the Triazolylpyridone (237) with Toluene-p-Sulphonyl Chloride

(a) In the Presence of Triethylamine

A stirred suspension of the triazolylpyridone (237) (0.26g, 0.001 mol) in dry dioxan (30.0 ml) was treated in one portion with triethylamine (0.18 ml; 0.0012 mol), and then dropwise with a solution of toluene-p-sulphonyl chloride (0.21g, 0.0011 mol) in dry dioxan (10.0 ml). The mixture was stirred at room temperature for 0.5h. Filtration of the mixture gave unreacted starting material (237) (0.24g; 92%) m.p. 300°, identical (m.p. and i.r. spectrum) with an authentic sample.

(b) In the Presence of Sodium Hydroxide.

A solution of the triazolylpyridone (237) (0.20g, 0.001 mol) in aqueous 10% w/v sodium hydroxide solution (5.0 ml) was stirred, and treated in portions with toluene-p-sulphonyl chloride (0.21g, 0.0011 mol). The mixture was stirred at room temperature for 1h, then filtered to give unreacted toluene-p-sulphonyl chloride (0.1g; 47%) m.p. 66° which was identical (m.p. and ir. spectrum) with an authentic sample.

The alkaline filtrate was acidified with aqueous dilute hydrochloric acid to afford the unreacted triazolylpyridone (237) (0.18g; 69%) m.p. 300°, identical (m.p. and i.r. spectrum) with an authentic sample.

(c) In the Presence of Sodium Hydroxide and Dimethylformamide

A solution of the triazolylpyridone (237) (0.26g, 0.001 mol) in aqueous 10% w/v sodium hydroxide solution (5.0 ml) and dimethylformamide (5.0 ml) and toluene-p-sulphonyl chloride (0.42g, 0.0022 mol) was stirred at room temperature for 1.5h. The dark solution was diluted with water, acidified with aqueous dilute hydrochloric acid and extracted with chloroform to give an oil which was triturated with ethanol-ether to afford the unreacted triazolylpyridone (237) (0.07g) m.p. 303° which was identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ether-ethanol mother liquour left an oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of three components.

2,6-Dimethyl-1-(1,4-diphenyl-1,2,3-triazol-5-yl) pyridin-4(1H)-one (249)

A mixture of the amino-triazole (248) (0.94g, 0.004 mol) and the triketone (218) (0.56g, 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution was evaporated under reduced pressure to leave a solid which was triturated with ethanol-ether to afford the triazolylpyridone (249) as a colourless solid (0.49g) m.p. 293° (from ethanol), $\nu_{max.}$ 1650 (CO) cm^{-1}, $\lambda_{max.}$ 212, 225sh, 254, and 270 nm (log ε 4.42, 4.34, 4.44 and 4.46), $\tau(CDCl_3)$ 2.32 - 2.62(10H, m, Ar-H), 3.66(2H, s, pyridine H) and 8.12(6H, s, CH_3).

Found : C, 73.7; H, 5.3; N, 16.5%; $M,^+$ 342.

$C_{21}H_{18}N_4O$ requires: C, 73.7; H, 5.3; N, 16.4%; M, 342.

The ethanol-ether mother liquour on evaporation left an oil which solidified in contact with water and on trituration with ethanol-ether gave the unreacted triazole (248) (0.14g) m.p. 175°, identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethanol-water mother liquour left an oil (0.40g) whose t.l.c. in ethyl acetate over silica showed it to contain two components, one of which was the starting amonotriazole (248).

7-Ethoxycarbonylmethyl -1,2,3-triazolo[1,5-a]pyrimidin-5(4H)-one-3-carboxamide (252)

A mixture of the triazole amide (15b) (0.51g, 0.004 mol) and diethyl acetonedicarboxylate (0.8g; 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The dark solution on evaporation left a hard gum which was triturated with ethanol-ether to afford the impure triazolopyrimidinone (252) (0.82g) m.p. 135° which crystallised from ethanol-water as a cream solid (0.36g) m.p. 194°, $\nu_{max.}$ 3600,

3360, and 3180br (NH), 1700 and 1680br (CO) cm^{-1}, τ[$(CD_3)_2SO$] 1.94(1H, s, NH), 2.42(1H, br s, NH), 4.06(1H, s, pyrimidine H), 5.84(2H, q J 7Hz, CH_2) 6.09(2H, s, CH_2) and 8.73(3H, t J 7Hz, CH_3).

Found: C, 42.7; H, 4.5; N, 25.1%; M^+, 265.

$C_{10}H_{11}N_5O_4$ requires: C, 42.4; H, 4.6; N, 24.7%; M, 265.

The ethanol-water mother liquor was concentrated and filtered to give the impure triazolopyrimidinone (252) (0.13g) m.p. 130°.

The Attempted Reaction of the Triazolopyrimidinone (252) with Toluene-p-sulphonyl Azide

A solution of the triazolopyrimidinone (252) (0.26g, 0.001 mol) in absolute ethanol (50.0 ml) was cooled to 0° (ice-salt bath), stirred, and treated in one portion with triethylamine (0.42g, 0.004 mol) and then dropwise with a solution of toluene-p-sulphonyl azide (0.42g, 0.002 mol) in absolute ethanol (5.0 ml). The mixture was stirred in the melting ice bath for 2h and then evaporated to leave an oil which was dissolved in chloroform and washed with aqueous dilute sodium hydroxide solution. The chloroform extract left no material on evaporation.

Filtration of the chloroform-sodium hydroxide mixture gave a solid (0.08g) m.p. > 360° which crystallised from ethanol-water as a pale yellow solid (0.06g) m.p. > 360°, νmax. 3360, 3140 (NH) and 2120 ($-\overset{+}{N}\equiv N$) and 1695 and 1665 (CO) cm^{-1}, λmax. 210, 254, 272, 301inf. and 328 nm (logε 4.19, 4.30, 4.23, 4.01 and 4.19).

Found: C, 38.0; H, 2.6; N, 31.2%; M^+, No Ion Pressure.

This solid was dissolved in water and acidified with aqueous dilute sulphuric acid but gave no organic material.

The alkaline filtrate was acidified with aqueous dilute sulphuric acid to afford toluene-p-sulphonamide (0.01g) m.p. 110° which was identical (i.r. spectrum) with an authentic sample.

7-Acetonyl-5-methyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (254)

A mixture of the triazole amide (15b) (0.51g, 0.004 mol) and the triketone (218) (0.56g, 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution was evaporated under reduced pressure to leave an oil which was triturated with ethanol-ether to afford the triazolopyrimidine (254) as yellow needles (0.19g) m.p. 174° (from dimethylformamide), $\nu_{max.}$ 3420, 3320 and 3200 (NH) and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 220, 276sh, 284, 315sh, 382 and 404 nm (log ε 4.13, 4.00; 4.02, 3.85, 3.93, and 3.94).

Found: C, 51.6; H, 5.2; N, 29.7%; M^+ 233.

$C_{10}H_{11}N_5O_2$ requires: C, 51.5; H, 4.8; N, 30.0%; M, 233.

Evaporation of the ethanol-ether mother liquor left an oil (0.55g) whose t.l.c. in ethyl acetate-ethanol over silica showed it to be an unresolved mixture of two components. The oil was subjected to Kugelrohr distillation to give a negligible amount of distillate and a dark gum from which no identifiable material could be obtained.

The Attempted Reaction of the Triazolopyrimidine (254) with Toluene-p-Sulphonyl Azide

A solution of the triazolopyrimidine (254) (0.35g, 0.0015 mol) in absolute ethanol (50.0 ml) was cooled to 0° (ice-salt bath) and treated in one portion with triethylamine (0.8g, 0.008 mol) and then dropwise with stirring with a solution of toluene-p-sulphonyl azide (0.6g, 0.003 mol)

in absolute ethanol (5.0 ml). The mixture was stirred in the melting ice-bath for 2h and then filtered to give the impure starting material (254) (0.30g) m.p. 156° which crystallised from dimethylformamide to give the pure triazolopyrimidine (254) (0.19g) m.p. 190°, identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethanol filtrate left an oil which was suspended in aqueous dilute sodium hydroxide solution and extracted with chloroform to give an oil (0.40g) identified as unreacted toluene-p-sulphonyl azide by comparison (i.r. spectrum) with an authentic sample.

The alkaline mother liquor, acidified with aqueous dilute sulphuric acid and extracted with chloroform gave no further material.

The Attempted Reaction of the Triazole Amide (250) with the Triketone (218)

A mixture of the triazole amide (250) (0.81g, 0.004 mol) and the triketone (218) (0.56g, 0.004 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solution was evaporated under reduced pressure to leave an oil which was triturated with ether to afford an impure solid (1.16g) m.p. 100°. Crystallisation of this solid from ethanol-water gave the isomeric amide (251) (0.32g) m.p. 198° which was identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethanol-water mother liquour left a solid which was washed with aqueous dilute sodium hydroxide solution to give the starting triazole amide (250) (0.28g) m.p. 176°, identical (i.r. spectrum) with an authentic sample.

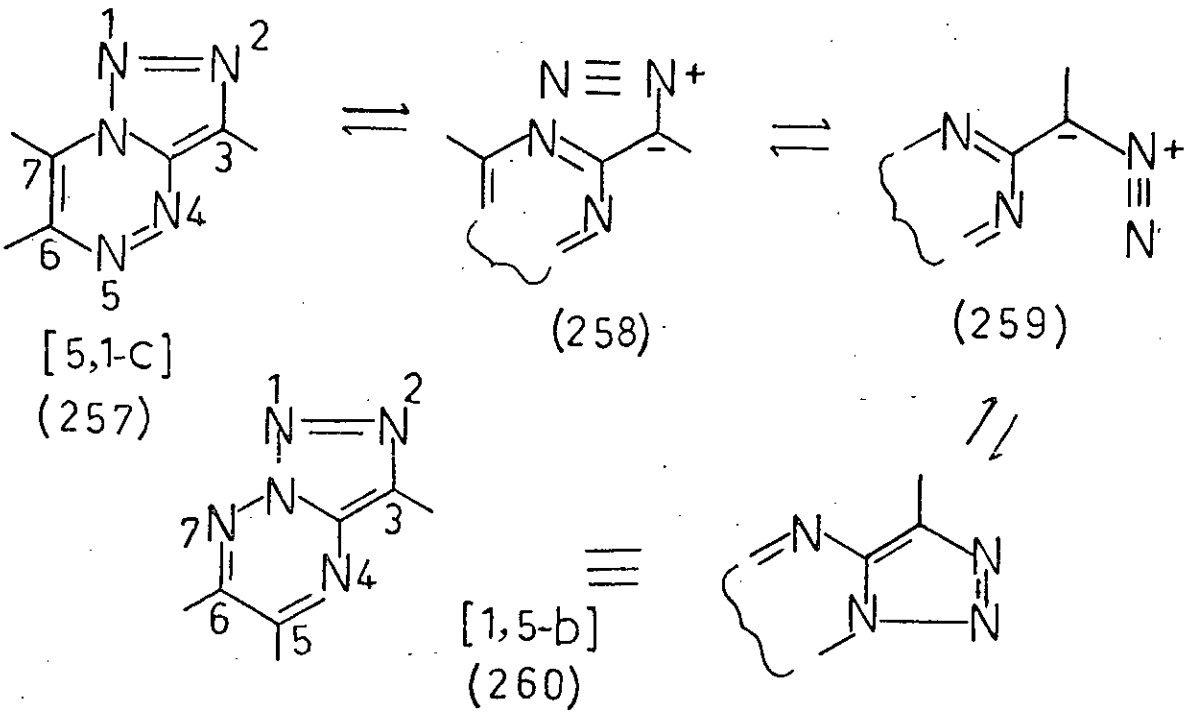
Acidification of the alkaline washings with aqueous dilute sulphuric acid gave a negligible amount of an unidentified solid.

Chapter 4

Aspects of the Synthesis and Reactivity of 1,2,3-Triazolo[5,1-c]-1,2,4-triazines and 1,2,3-Triazolo[1,5-b]-1,2,4-triazines.

4.1 Introduction

The 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system (257) is of interest in relation to the relative stabilities of the fused 1,2,3-triazine structure (257) and the diazoalkyl structure (258).

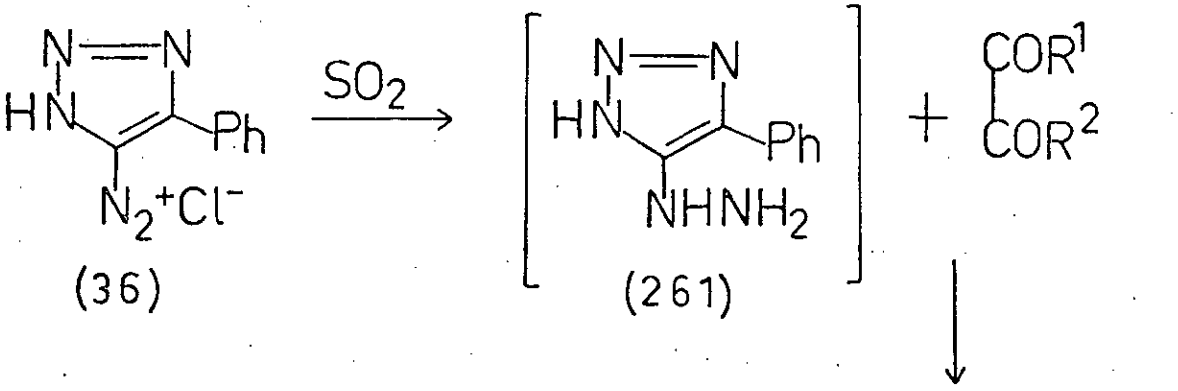


Thus, it might be expected that the strongly electron-withdrawing character of the triazine ring would stabilise (258) relative to (257). In addition to the diazoalkylideneamine-triazole tautomerism [(257) ⇌ (258)] thus expected in this system, a new type of Dimroth rearrangement [(257) ⇌ (258) ⇌ (259) ⇌ (260)] which will interconvert the 1,2,3-triazolo[5,1-c]-1,2,4-triazine system (257) with the isomeric 1,2,3-triazolo[1,5-b]-1,2,4-triazine ring system (260) is also possible. These features made it of interest in the present work to investigate

the synthesis and reactivity of derivatives of both the 1,2,3-triazolo-[5,1-c]- (257) and 1,2,3-triazolo[1,5-b]-1,2,4-triazine (260) ring systems.

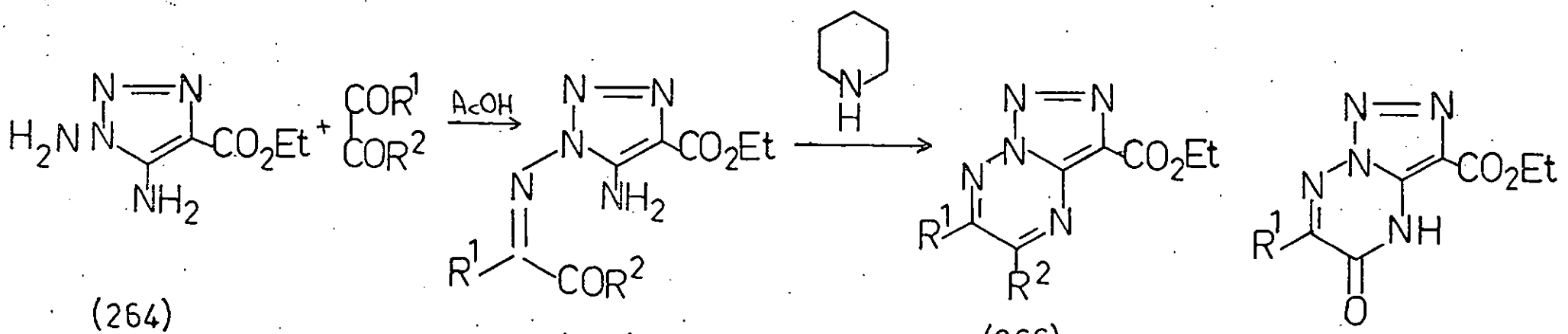
4.2 Synthetic Routes to 1,2,3-Triazolo[1,5-c]-1,2,4-Triazines

Tennant and his group[15,16] have described a general synthetic route to 1,2,3-triazolo[5,1-c]-1,2,4-triazines. Thus, it will be recalled [Chapter 1, page 6] that coupling the diazonium salts (36) and (44) with a variety of active methylene compounds affords a good route to substituted 1,2,3-triazolo[5,1-c]-1,2,4-triazines. This same group[15,16] have also shown (Scheme 60) that the diazonium salt (36) can be reduced in situ to the hydrazine (261) which can be condensed with a variety of α-dicarbonyl compounds to afford substituted 1,2,3-



	R^1	R^2
a;	Me	Me
b;	H	H
c;	Ph	Ph
d;	Ph	H

Scheme 60



(264)

(265)

(266)

(267)

	R^1	R^2
a;	Me	Me
b;	H	H
c;	Ph	Ph
d;	Me	OEt
e;	H	OH

	R^1	R^2
a;	Me	Me
b;	H	H
c;	Ph	Ph

	R^1
a;	Me
b;	H

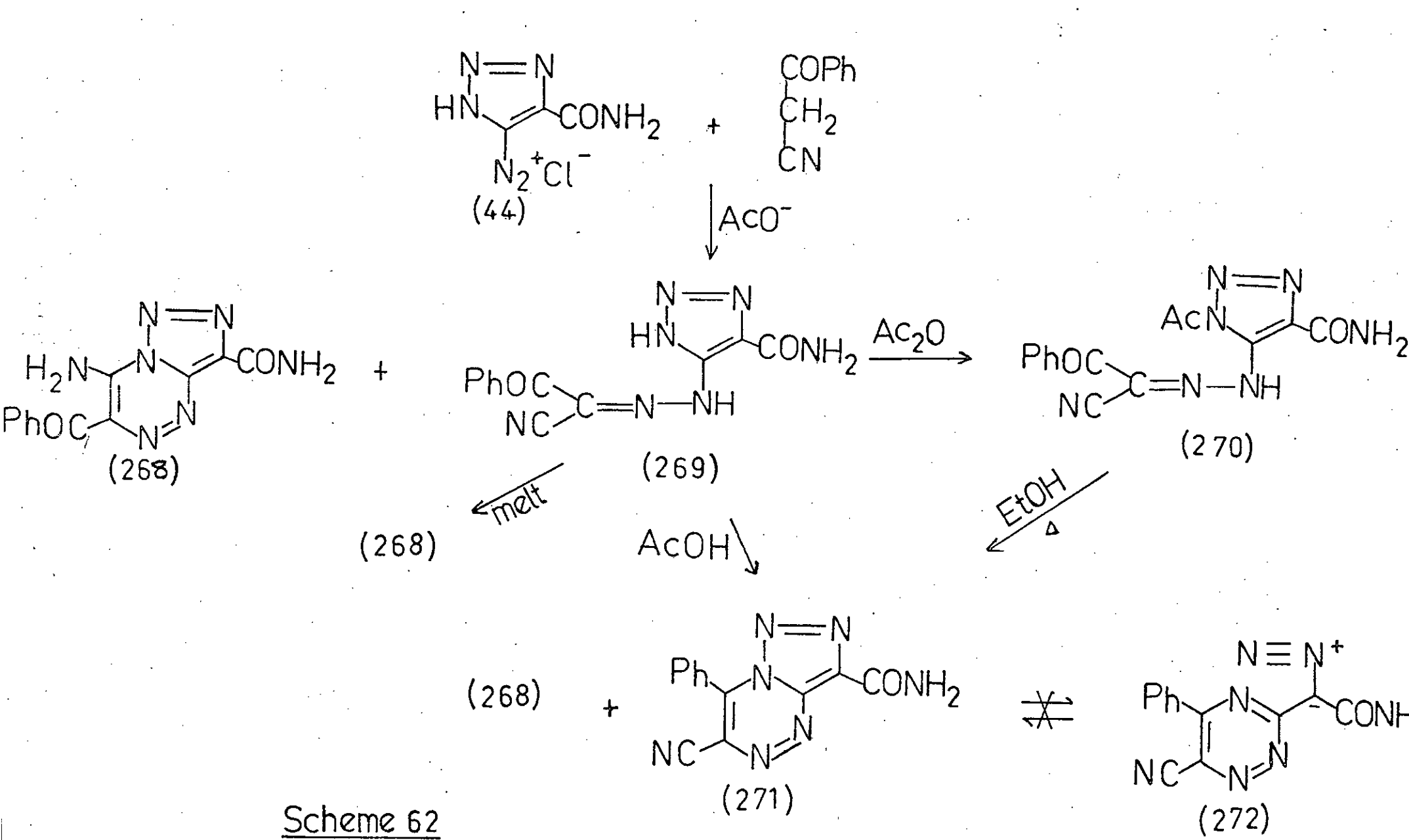
Scheme 61

triazolo[5,1-c]-1,2,4-triazines of the type (262a-d). The intermediates in these coupling reactions are the hydrazones (263a-d) which are not normally isolated.

Mackie and Tennant[38] have also described a synthesis of 1,2,3-triazolo[1,5-b]-1,2,4-triazines (Scheme 61) involving the condensation of the N-aminotriazole (264) with α-dicarbonyl compounds in the presence of glacial acetic acid. Thus, reaction of the amine (264) with glyoxal, biacetyl or benzil in acetic acid affords good yields of products whose properties are consistent with the structures (266a-c) respectively. The presummed ethylideneamino-intermediates (265a-c) in these reactions are not isolable. However, reaction of (264) with ethyl pyruvate or glyoxylic acid affords the intermediates (265d and e) which undergo piperidine-catalysed cyclisation to (267a and b).

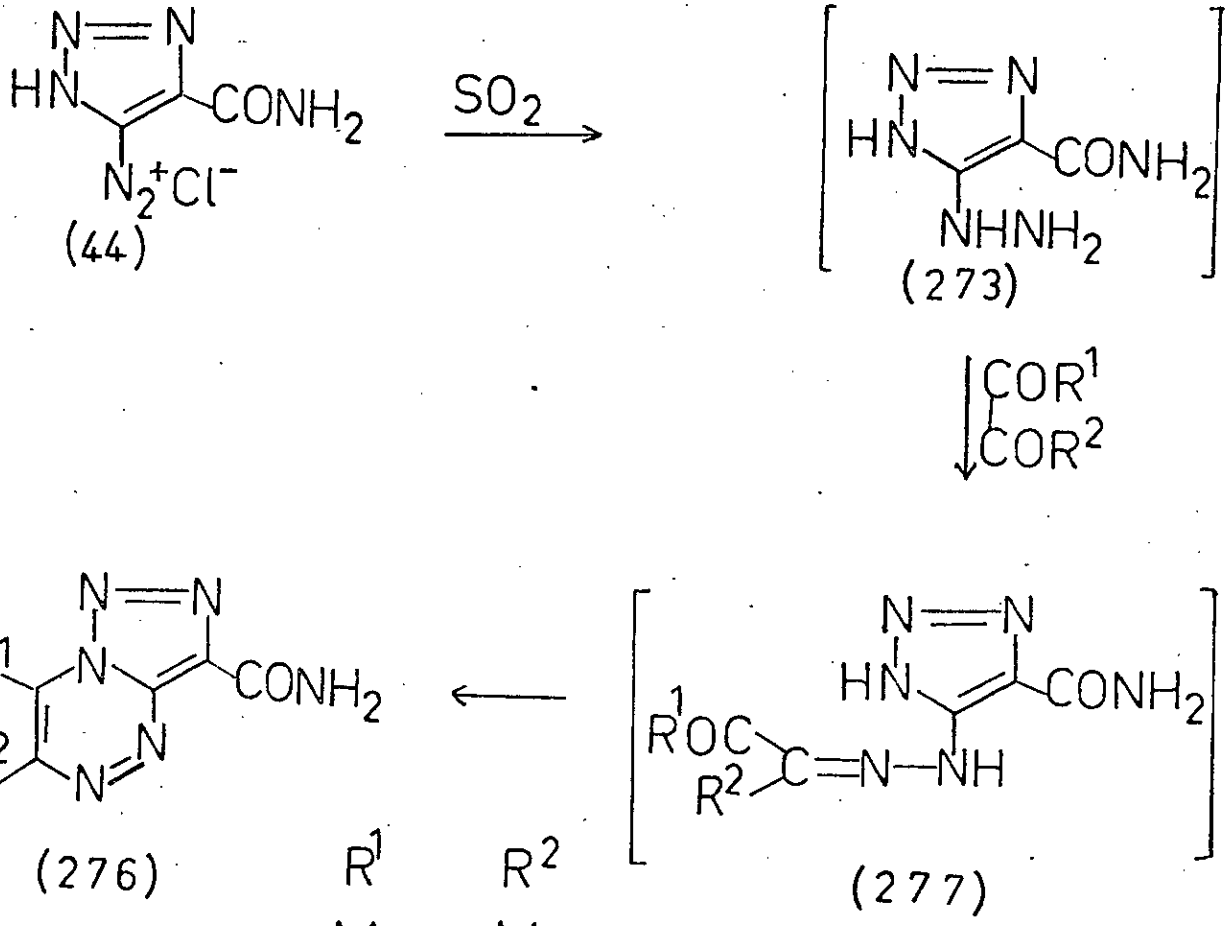
This earlier work on 1,2,3-triazolo[5,1-c]-1,2,4-triazines and 1,2,3-triazolo[1,5-b]-1,2,4-triazines failed to reveal any evidence for the corresponding diazo-tautomers [cf. (258)]. One reason for this could be that the particular derivatives studied did not contain sufficiently strongly electron-withdrawing groups either in the triazole ring or in the triazine nucleus to shift the equilibrium [(257) $\rightleftharpoons$ (258)] to the right. So in an effort to demonstrate this type of equilibrium, it was decided to extend the previous methods of synthesis to other 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives containing electron-withdrawing groups in the 1,2,3-triazole or 1,2,4-triazine rings in the hope that the diazo-tautomer (258) would become stable enough to be detected.

As an initial approach to the synthesis of a triazolo[5,1-c]-1,2,4-triazine derivative which might exist partly in the diazo-form, it was



Scheme 62

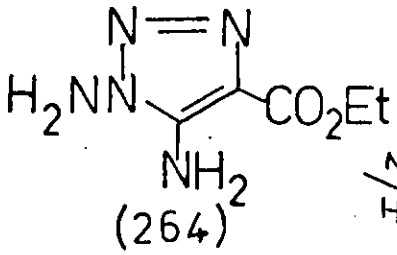
decided to attempt the synthesis of the compound (271) (Scheme 62) which contains strongly electron-withdrawing groups in both the triazole and triazine rings. Thus, it was hoped that coupling of the diazonium salt (44) with 2-cyanoacetophenone would afford a hydrazone (269) which might cyclise preferentially by way of the benzoyl group (as opposed to the cyano-group) to afford the desired product (271). In practice, when an aqueous ethanolic solution of 2-cyanoacetophenone containing sodium acetate was reacted with an aqueous ethanolic solution of the diazonium salt (44), a readily separated mixture of the triazolotriazine (268) and the hydrazone (269) [Scheme 62] was obtained. The hydrazone (269) gave an elemental analysis and mass spectrum consistent with the assigned structure. This was also confirmed by its i.r. spectrum which showed NH and carbonyl absorption and a cyano-band at 2200 cm^{-1}. The structure (269) for the hydrazone was firmly established by its acetylation to a mono-acetyl derivative (270) whose ^{1}H n.m.r. spectrum showed a three proton singlet at τ 8.10 which is typical[5a] of a ring N-acetylated 1,2,3-triazole. In accord with the assigned structure, the i.r. spectrum of the triazolotriazine (268) showed the presence of both an amino and a ketonic carbonyl group demonstrating that the cyclisation of (269) must have taken place through the cyano group and not throught the benzoyl group as desired. In support of this contention, melting the hydrazone (269) resulted in its conversion into the cyclised compound (268). However, when the hydrazone (269) was heated in glacial acetic acid for a prolonged period, a readily separated mixture of the amine (268) and a second product was obtained. The same mixture was formed when the acetyl derivative (270) was heated under reflux in ethanol. The identification of the new product as the required cyano-amide (271) is based on the following evidence. Its elemental analysis



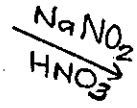
(44) (273) (277) (276)

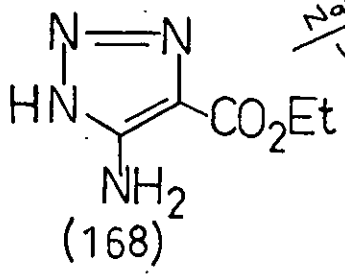
	R^1	R^2
a;	Me	Me
b;	Ph	H
c;	Ph	Ph
d;	H	H
e;	Me	H

Scheme 64

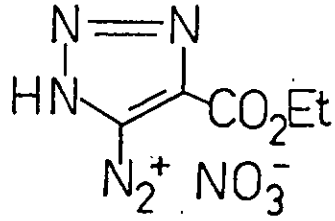


(264)

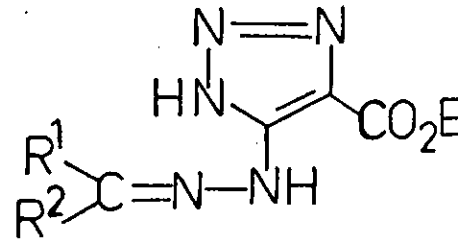




(168)

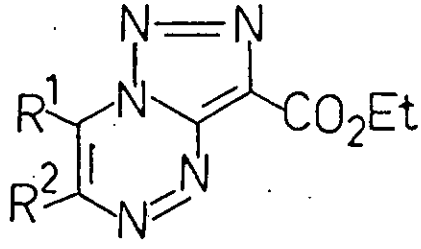


(280)

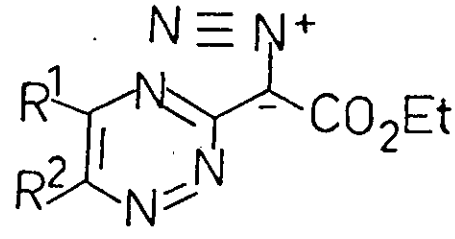


(281)

	R^1	R^2
a;	CN	CN
b;	CN	$CONH_2$
c;	CN	CO_2Et
d;	Ac	Ac
e;	Ac	CO_2Et
f;	CN	COPh
g;	Ac	COPh



(282)



(283)

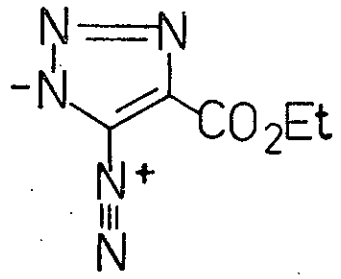
	R^1	R^2
a;	NH_2	CN
b;	NH_2	$CONH_2$
c;	NH_2	CO_2Et
d;	Me	Ac
e;	Me	CO_2Et
f;	NH_2	COPh
g;	Me	COPh

Scheme 65

by condensation with ethyl benzoylformate gave a readily separated mixture of the required triazolotriazine (274; R = Ph) and the hydrazone (275; R = Ph). The structures of these products were again fully supported by their elemental analysis and i.r. and mass spectral properties. Despite the presence of an electron-withdrawing group on the triazole ring and an electron-withdrawing triazine nucleus, the i.r. spectrum of the triazolotriazinone (274; R = Ph) showed no evidence of the diazo-tautomer (278).

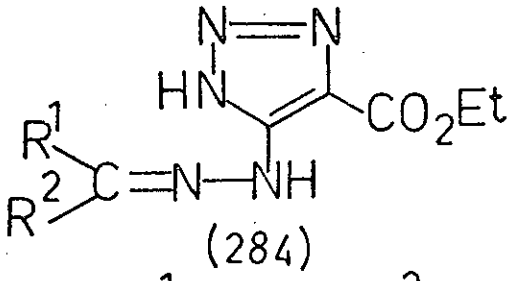
Since an ester group is significantly more electron-withdrawing than a carboxamide group, it was of interest to investigate the coupling reactions of the ester diazonium salt (280) [Scheme 65] with active methylene compounds as a source of 3-ethoxycarbonyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazines (282a-g). It was hoped that the extra electron-withdrawal in the triazole ring of these substrates coupled with the presence of suitable electron-withdrawing groups in the triazine nucleus [cf. (282a-g)] might promote their existence in the diazo-tautomeric forms (283a-g) [Scheme 65]. The diazonium salt (280) was readily prepared in situ by the diazotisation in nitric acid solution either of the amino-ester (168) or of the N-amino compound (264), the latter compound suffering deamination of the 1-amino group as well as diazotisation of the 5-amino group. The resulting solutions of the diazonium salt (280) coupled readily with a range of active methylene compounds (malononitrile, cyanoacetamide, ethyl cyanoacetate, acetylacetone, ethyl acetoacetate, 2-cyanoacetophenone and benzoylacetone) in the presence of sodium acetate to afford the corresponding triazolotriazine esters (282a-g) directly. The coupling reaction of the diazonium salt (280) with cyanoacetamide in addition to giving the triazolotriazine (282b) also afforded the betaine

(310) whose i.r. spectrum showed diazo-absorption at 2260 cm^{-1} and it



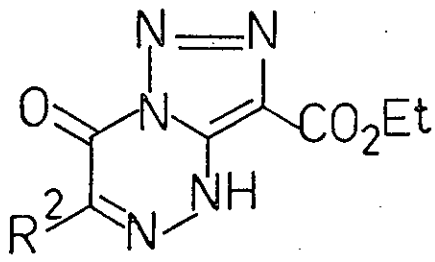
(310)

exploded when heated to 210°. These products gave the expected elemental analysis and showed i.r., u.v., ^1H n.m.r. and mass spectral properties consistent with their structures. Thus, the i.r. spectra of (282a-c) and (282f) showed primary amino absorption in addition to the ester absorption expected for all of them. The i.r. spectra of (282d, e and f) all showed two carbonyl bands due to the 3-ethoxycarbonyl group present in each of them and to the acetyl, ethoxycarbonyl and benzoyl groups respectively, also present. The ^1H n.m.r. spectra of (282b-g) all showed proton resonance due to the 3-ethoxycarbonyl group, while the spectra of (282c and e)contained additional ester absorption due to the 6-ethoxycarbonyl group. The intermediacy of the corresponding hydrazones (281a-g) in these coupling reactions [Scheme 65] was supported by the finding that the diazonium salt (280) coupled with dibenzoylmethane, diethyl malonate or ethyl benzoylacetate to give not the corresponding triazolotriazines (285a) and (286a and b) but the hydrazones (284a-c). The acidity of the hydrazones (284a-c) and their spectral properties were fully consistent with the assigned structures. The structure of the diester-hydrazone (284a) was further established by its conversion into a monoacetyl derivative (279) which showed a carbonyl band at 1760 cm^{-1} in its i.r. spectrum and a three proton singlet at τ 7.16 in its ^1H n.m.r. spectrum -



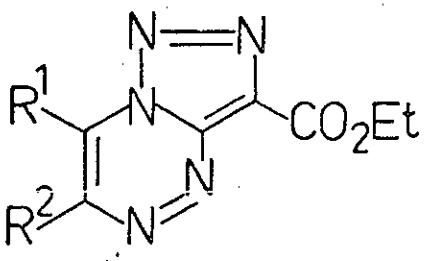
(284)

	R^1	R^2
a;	CO_2Et	CO_2Et
b;	PhCO	CO_2Et
c;	PhCO	PhCO



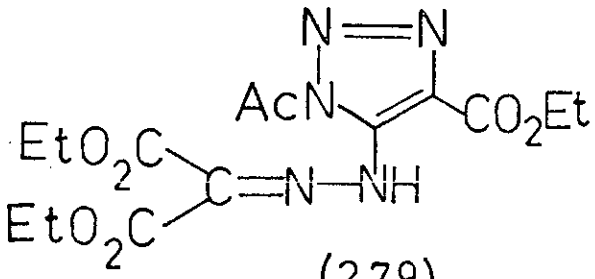
(285)

	R^2
a;	CO_2Et
b;	PhCO



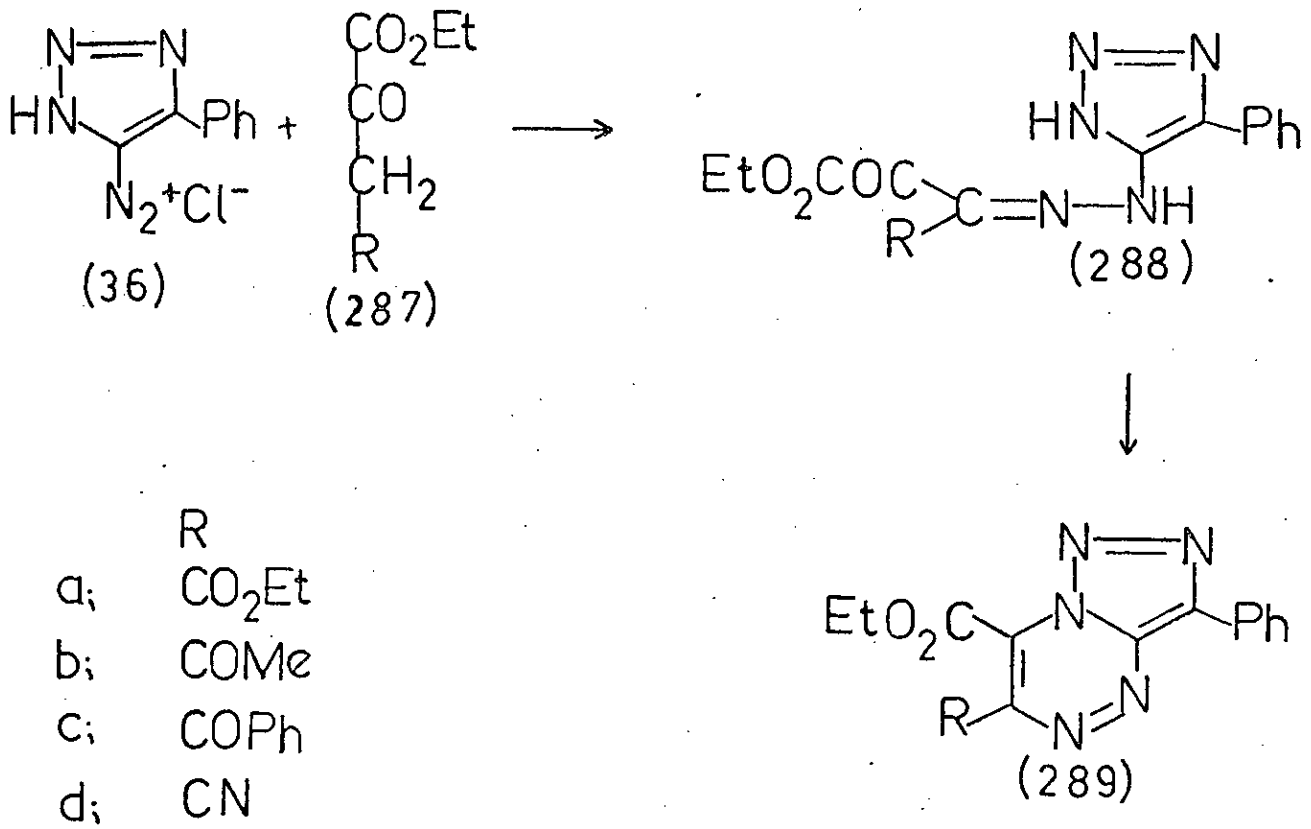
(286)

	R^1	R^2
a;	Ph	CO_2Et
b;	Ph	COPh

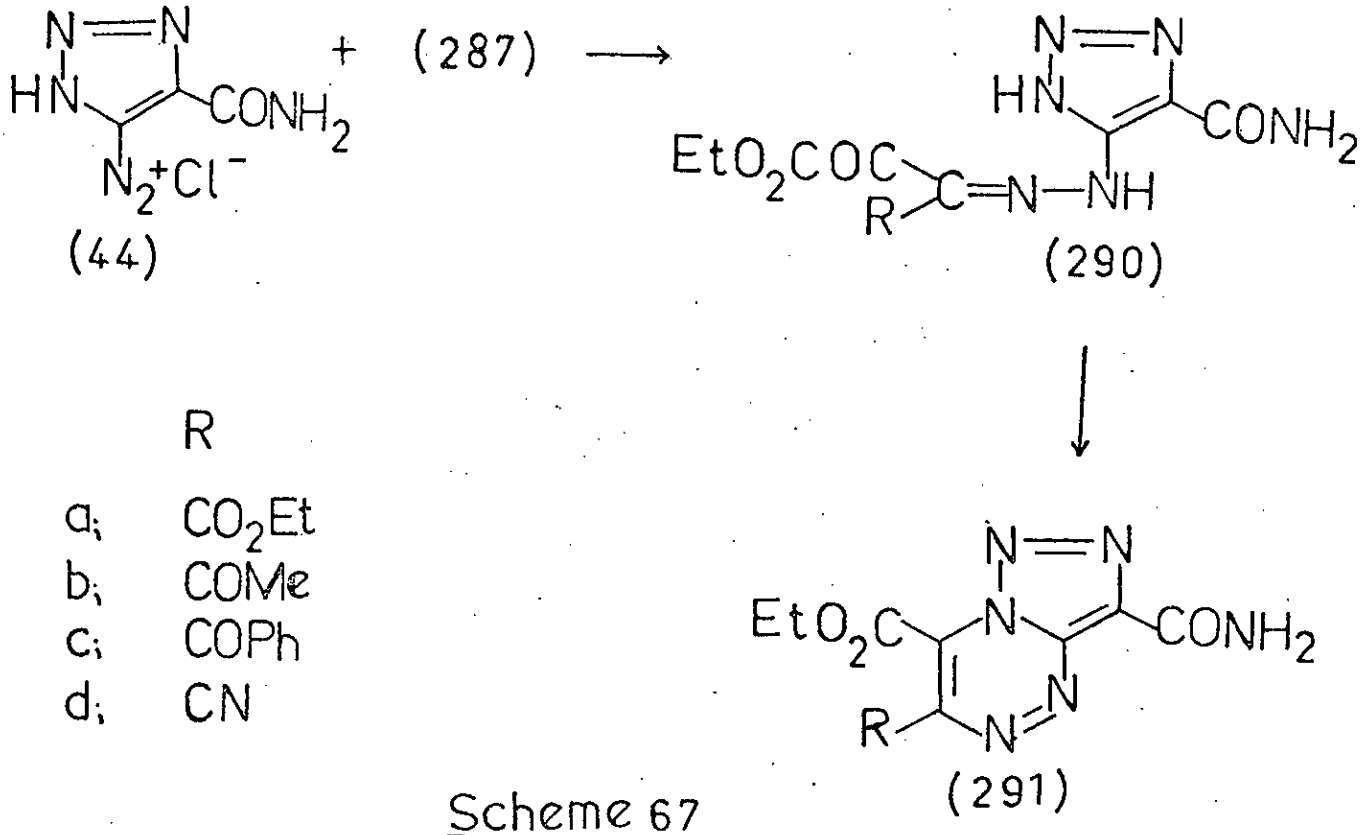


(279)

features diagnostic[5a] for a triazole ring N-acetyl group. The similar acetylation of (284 b and c) was unsuccessful. The structure of the hydrazone (284a) was further demonstrated by its conversion on heating with aqueous ethanolic sodium acetate into the expected triazolotriazinone product (285a). The structure of this compound follows from its acidic character and its i.r. and ^1H n.m.r. spectra. Cyclisation of the hydrazones (284 b and c) was readily effected in hot glacial acetic acid to give products whose spectral properties are fully in accord with the assignment of the triazolotriazine structures (286 a and b). The exclusive



Scheme 66

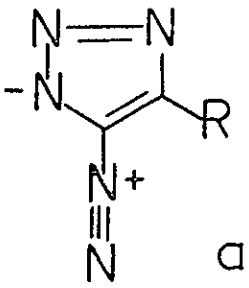


Scheme 67

formation of the compound (286a) rather than the alternative keto-triazolotriazinone (285b) demonstrates the greater reactivity of the benzoyl group compared with the ester group in the cyclisation of the hydrazone (284b).

Despite the presence of strongly electron-withdrawing substituents in both the triazole and triazine rings in all of the triazolotriazines (282a-g), (285a) and (286 a and b), none of their i.r. spectra showed the presence of diazo-absorption, demonstrating that in the solid state at room temperature they do not exist to any extent in the diazo tautomeric forms (283 a-g).

In a further attempt to synthesise 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives having several electron-withdrawing groups in the triazine and triazole rings and hence which might exist in the diazo-tautomeric form, the coupling reactions of the diazonium salts (36) and (44) with keto-diesters of the type (287) were carried out. It was anticipated that these reactions would give, possibly by way of intermediate hydrazones, fused products of the type (289) and (291), having two electron-withdrawing substituents in the triazine ring. Thus, when an aqueous ethanolic solution of the diazonium salt (36) or (44) was added to cooled solutions of diethyl oxaloacetate, ethyl acetopyruvate, or ethyl benzoylpyruvate, the hydrazones (288 a-c) and (290 a-c) were isolated in good yield and none of the corresponding triazolotriazines (289 a-c) or (291a-c) were obtained. Ethyl 2-cyanopyruvate could not be obtained in the free state and so its sodium salt was used in the coupling reactions with the diazonium salts (36) and (44) to afford the hydrazones (288d) and (290d). The betaine (292a) and the deaminated triazole (293) were obtained as by-products when the diazonium salt (36)

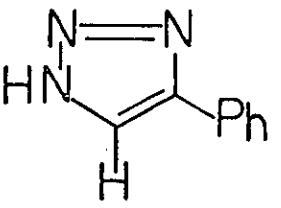


(292)

R

a; Ph

b; $CONH_2$

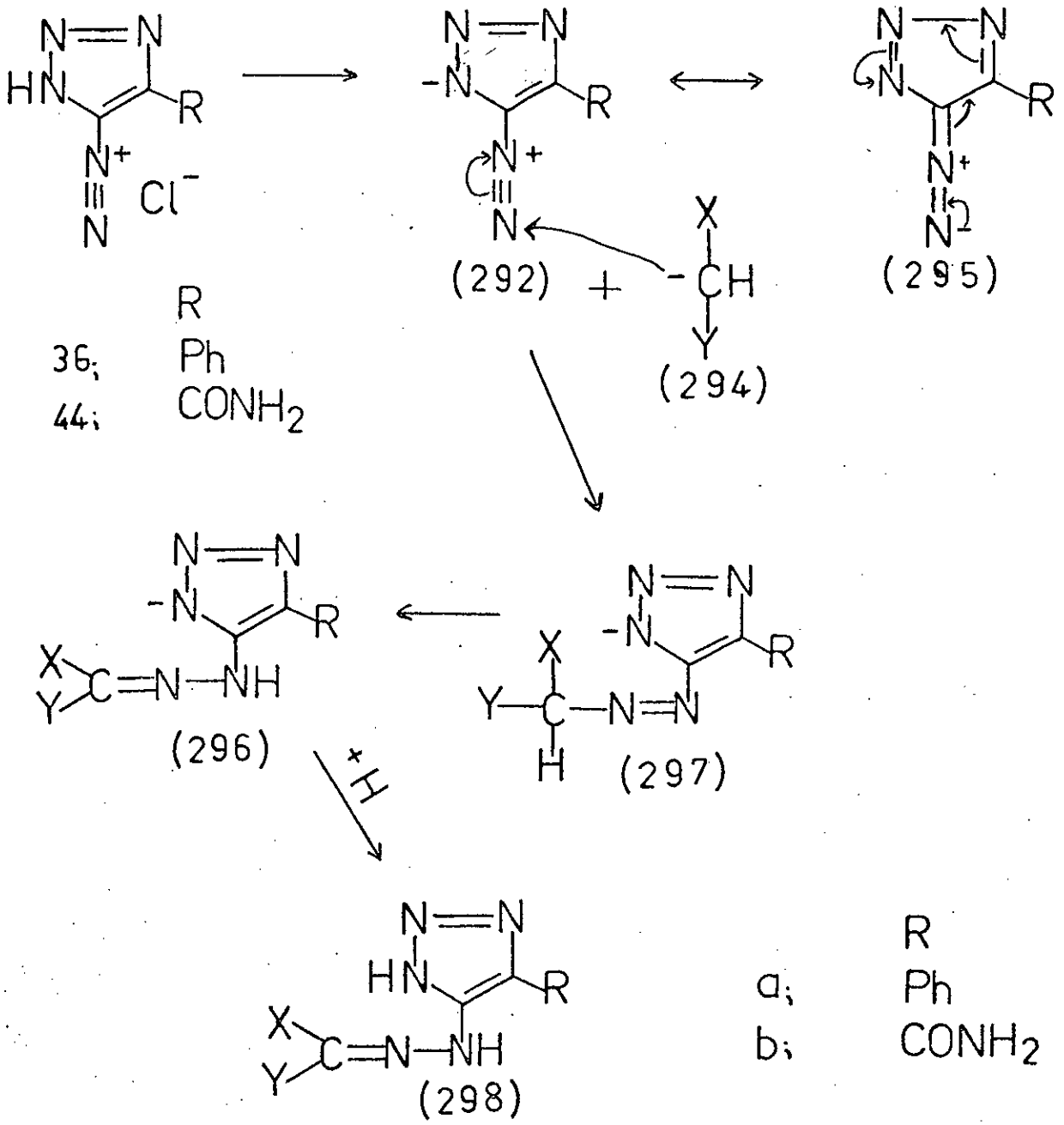


(293)

was coupled with diethyl oxalacetate in the presence of sodium acetate and sodium hydroxide respectively.

The evidence for the structures of the hydrazones (288 a, b and d) and (290 a, b and d) proved quite conclusive. In general their chemical analysis and ^1H n.m.r., i.r. and mass spectra were consistent with the assigned structures (288 a, b and c) and (290 a, b and c), although some difficulty was encountered in obtaining correct analytical data for the hydrazones (288c) and (290c). In both cases, the observed analytical data seem to lie between the values expected for the hydrazones (288c) and (290c) and those of the corresponding triazolotriazines (289c) and (291c) indicating that some cyclisation must be taking place during crystallisation of the analytical sample. The hydrazones (288c) and (290a) show fragment ions at m/e 373 and 308 corresponding to $(M^+ - H_2O)$ and indicating that cyclisation to the corresponding triazolotriazines (289c) and (291a) was taking place on electron impact. The further characterisation of (288c) and (290a) by attempted acetylation to ring N-acetyl derivatives was unsuccessful in each case, only multicomponent oils being obtained.

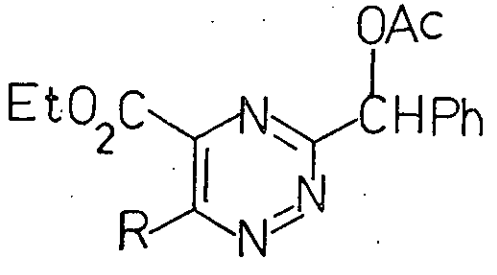
It has been mentioned (Chapter 1) that when a 1H-1,2,3-triazole diazonium salt is introduced into a basic medium, deprotonation of the cation can occur to give a 1,2,3-triazole diazonium betaine. Consequently,



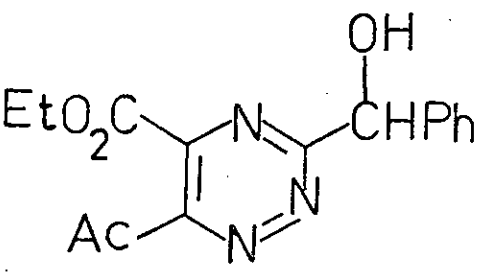
Scheme 68

the mechanism for the coupling reactions of the diazonium salts (36) and (44) with the tricarbonyl compounds (287 a-c) and the sodium salt of ethyl 2-cyanopyruvate depends on whether the triazoles (36) and (44) are deprotonated when introduced into the sodium acetate solution. It is, however, known[40] that 4-phenyltriazolediazonium chloride (36) is converted into the betaine (292a) on treatment with aqueous ethanolic sodium acetate and its isolation as a by-product in the formation of the hydrazone (288a) indicates that it and the corresponding betaine (292b) from deprotonation of the diazonium amide (44) are probable intermediates in the formation of the hydrazones (288 a-d) and (290 a-d). Thus, condensation of the betaines (292) with the deprotonated α-keto-esters (294) as shown in Scheme 68 then readily accounts for the formation of the hydrazones (288 a-d) and (290 a-d).

When the hydrazones (288a-d) and (290b-d) were heated under reflux in glacial acetic acid, the corresponding triazolotriazines (289 a-d), and (291 b-d) were formed in good yield. The hydrazone (288a) in addition to forming the triazolotriazine (289a) also afforded the acetoxy derivative (299a) whose ^{1}H n.m.r. spectrum showed a three proton



(299)

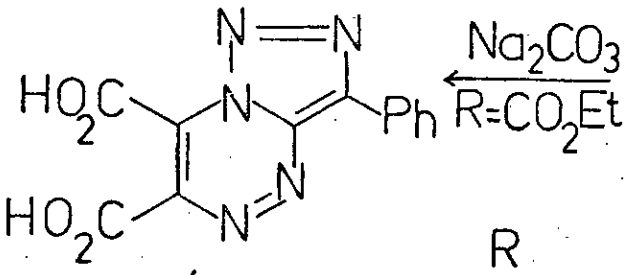


(300)

	R
a;	CO_2Et
b;	Ac

singlet at τ 7.90 similar to the acetoxy absorption observed[15] for other acetoxybenzyltriazines. In the cyclisation of the hydrazone (288b), the triazolotriazine (289b) was also accompanied by an oil whose ^{1}H n.m.r. spectrum showed it to be a mixture of the acetoxy and hydroxy derivatives (299b) and (300). This oil could not be resolved by t.l.c. in ethyl acetate over silica. The attempted cyclisation of the hydrazone (290a) in glacial acetic acid was unsuccessful (see later). The triazolotriazines (289 b and c) and (291c) were also obtained when the hydrazones (288 b and c) and (290c) were heated under reflux in aqueous ethanol. However, the attempted cyclisation of the hydrazones (290 a and b) in aqueous ethanol was unsuccessful, and in each case the unreacted hydrazones (290 a and b) were recovered. In each case, the structures of the triazolotriazines (289 a-d) and (291 b-d) were supported by elemental analysis and ^{1}H n.m.r.m i.r. and mass spectra.

When the triazolotriazine (289a) was heated under reflux with aqueous ethanolic sodium carbonate, the dicarboxylic acid [Scheme 69; (301)]



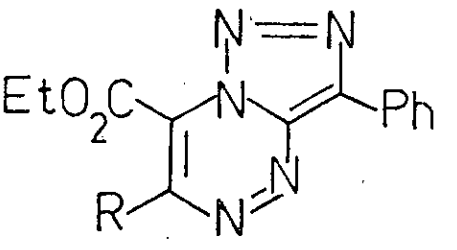
(301)

Na_2CO_3, R=CO_2Et

R

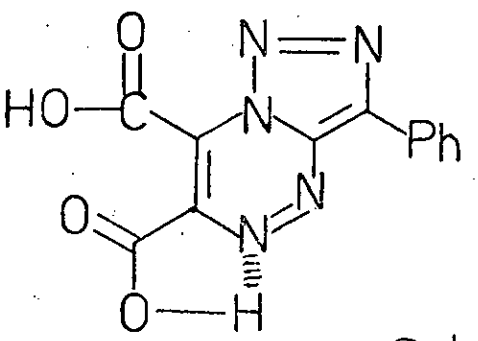
a; CO_2Et

c; COPh



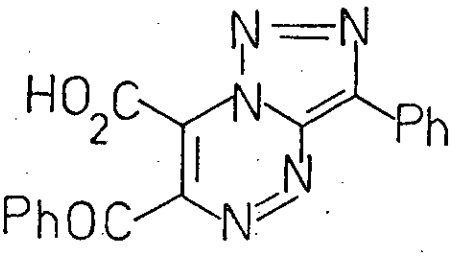
(289)

R=COPh / Na_2CO_3



(303)

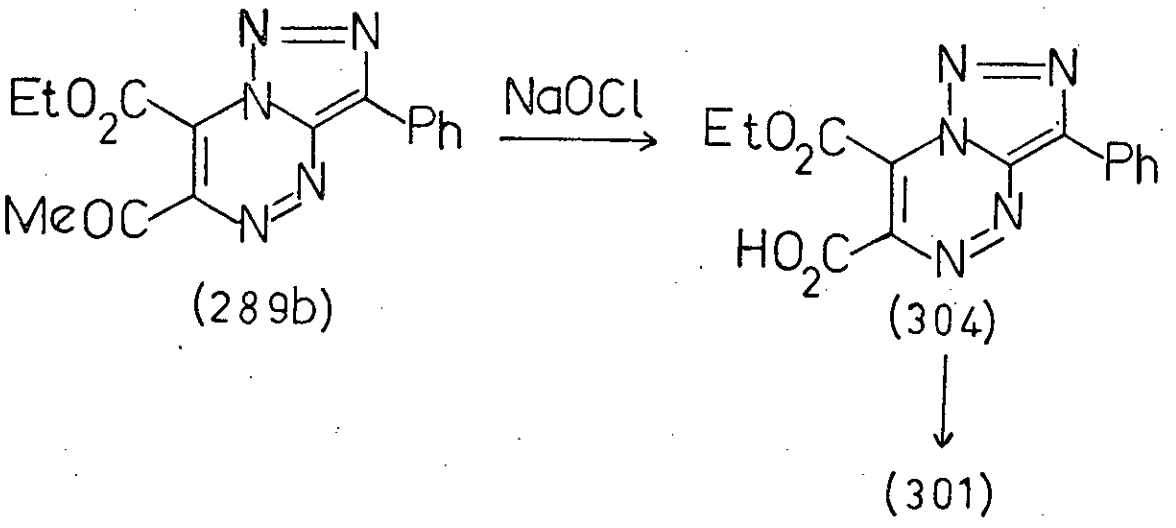
Scheme 69



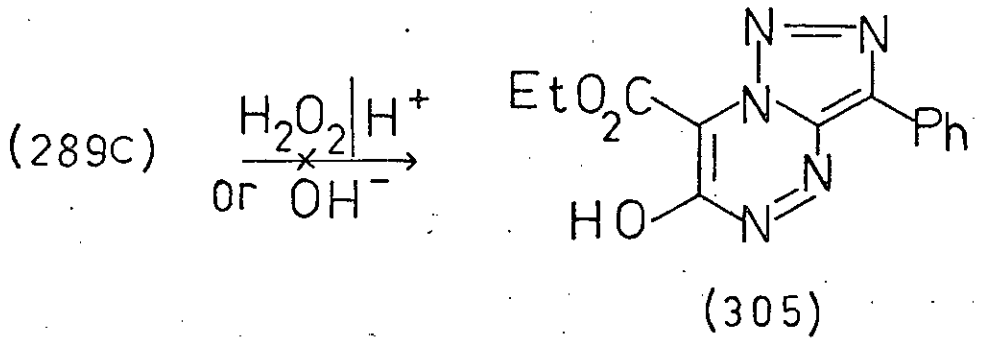
(302)

was obtained. The i.r. spectrum of (301) contained a broad hydroxyl absorption at 1900 cm^{-1} and a single carbonyl band at 1700 cm^{-1} due to the carboxyl groups but its ^1H n.m.r. spectrum lacked signals due to acidic protons. These features are surprising since the diacid (301) would be expected to show two distint carbonyl bands in the i.r. spectrum and also two acidic protons in the ^1H n.m.r. spectrum. The reason for the unexpected i.r. and ^1H n.m.r. absorption of the diacid (301) is not clear but may be associated in some way with hydrogen-bonding [cf. (303)]. A similar hydrolysis of the triazolotriazine (289c) afforded the monoacid (302) and again the ^1H n.m.r. spectrum of (302) did not show any acidic proton. However, its mass spectrum showed a peak at $(M^+ - CO_2)$ indicating that it was decarboxylating in the probe. In an effort to form the anhydride of the diacid (301), it was heated briefly with acetic anhydride but this reaction was unsuccessful, and gave back the unreacted dicarboxylic acid (301). Also the attempted thermal decarboxylation of (301) resulted in its rapid decomposition.

In an attempt to further establish the structure of the triazolotriazine (289a), it was heated under reflux in glacial acetic acid, since it is known[15] that when 3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazines are heated with glacial acetic acid, 1,2,3-triazole ring scission occurs, giving substituted 1,2,4-triazines. This reaction with (289a) gave the expected acetoxy compound (299a) earlier discussed together with some unreacted triazolotriazine (289a). Attempts were also made to degrade the triazolotriazines (289 b and c) to known compounds as a means of further confirming their structures. Thus, it was hoped that sodium hypochlorite would oxidise the triazolotriazine



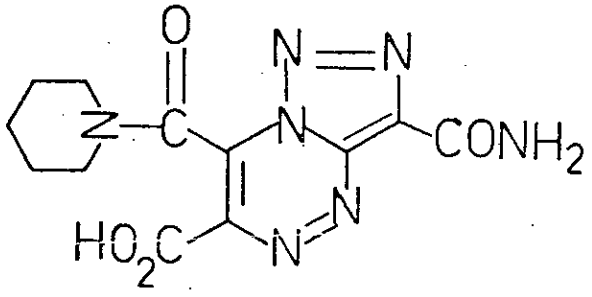
(298b) to the monocarboxylic acid (304), and thence by hydrolysis to the diacid obtained before. In practice, the oxidative degradation of the triazolotriazine (289b) using sodium hypochlorite in aqueous dioxan afforded a very low yield of the dicarboxylic acid (301) discussed earlier, together with a large quantity of unreacted triazolotriazine (289b). In the case of the triazolotriazine (289c), an attempt was made



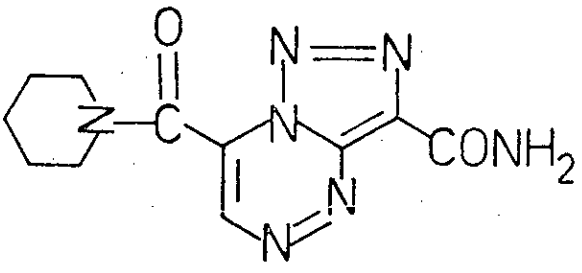
to carry out Dakin oxidation[51] to obtain the 6-hydroxytriazolotriazine (305). Unfortunately, the attempted oxidation of (389c) using hydrogen peroxide in glacial acetic acid or aqueous sodium hydroxide was unsuccessful, giving only small quantities of two unidentified solids.

The cyclisation of the hydrazone (290a) presented a problem. When

it was heated under reflux in aqueous ethanolic sodium acetate some unreacted hydrazone (290a) was recovered, together with a small quantity of an unidentified solid which had a molecular weight of 350. The attempted cyclisation of (290a) using sodium carbonate as the catalyst gave only a very high melting solid which could not be characterised. However, the use of piperidine as the catalyst in the attempted cyclisation of (290a) was more successful. In this case, two solid products with masses of 319 and 275 corresponding to the possible structures



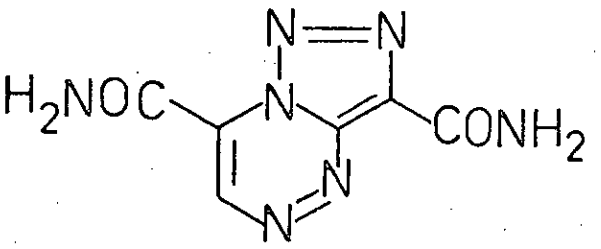
(306)



(307)

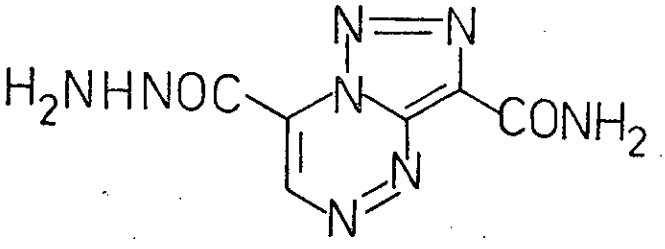
(306) and (307) respectively were obtained. The combustion analysis, i.r. and mass spectra of (306) were consistent with the structure assigned to it. Thus, the i.r. spectrum of (306) showed NH absorption and three carbonyl bands at 1730, 1700 and 1680 cm^{-1}. However, the product (306) did not effervesce with sodium hydrogen carbonate solution. The i.r. spectrum of (307) contained NH absorption and two carbonyl bands at 1740 and 1650 cm^{-1} but its combustion analysis was incorrect for the structure (307). Thus, the available evidence only permits the tentative assignment of the structure (307) to the second product of the piperidine-catalysed cyclisation of (290a). The attempted cyclisation of (290a) in ethanolic ammonia likewise afforded a very high melting solid

having a molecular weight of 207, suggesting that it might be the diamide (308). The i.r. spectrum of (308) contained NH absorption



(308)

in addition to carbonyl bands at 1790, 1740 and 1700 cm^{-1}. However, good analytical data could again not be obtained for this product. Consequently, the assigned structure (308) must remain tentative until firmer evidence is obtained. When heated with ethanolic hydrazine hydrate, the hydrazone (290a) once more yielded a very high melting solid which showed a poorly resolved i.r. spectrum and failed to give a mass spectrum due to lack of ion pressure. However, it gave an elemental analysis close to that expected for the dihydrate of the

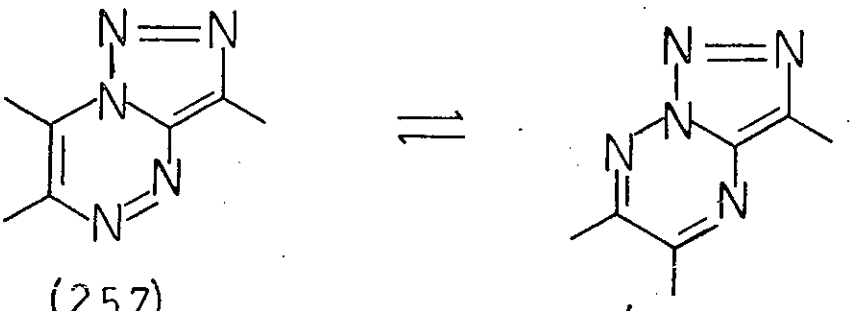


(309)

hydrazide structure (309) which it is tentatively assigned.

4.3 Some Investigations of Diazoalkylideneamine-1,2,3-Triazole Equilibria in 1,2,3-Triazolo[5,1-c]-1,2,4-triazines and 1,2,3-Triazolo[1,5-b]-1,2,4-triazines.

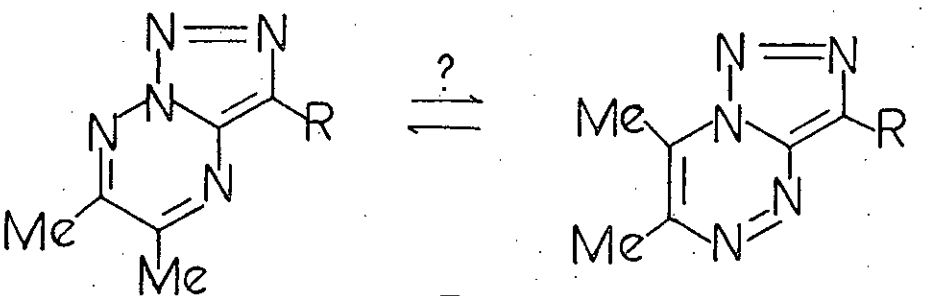
It will be recalled that as described before (Chapter 4, page 102) triazolo[5,1-c]triazines (257) and triazolo[1,5-b]triazines (260) are isomeric ring systems which are potentially interconvertible by a new type of Dimroth rearrangement [(257) ⇌ (260)]. Since this type of



(257) (260)

rearrangement had not been demonstrated before it was of interest to synthesise unambiguously two isomeric derivatives of the respective triazolo[1,5-b]- and triazolo[5,1-c]-1,2,4-triazine ring systems and to attempt their interconversion, thus demonstrating the expected rearrangement [(257) ⇌ (260)].

The compounds initially chosen for study were the isomers (318a)

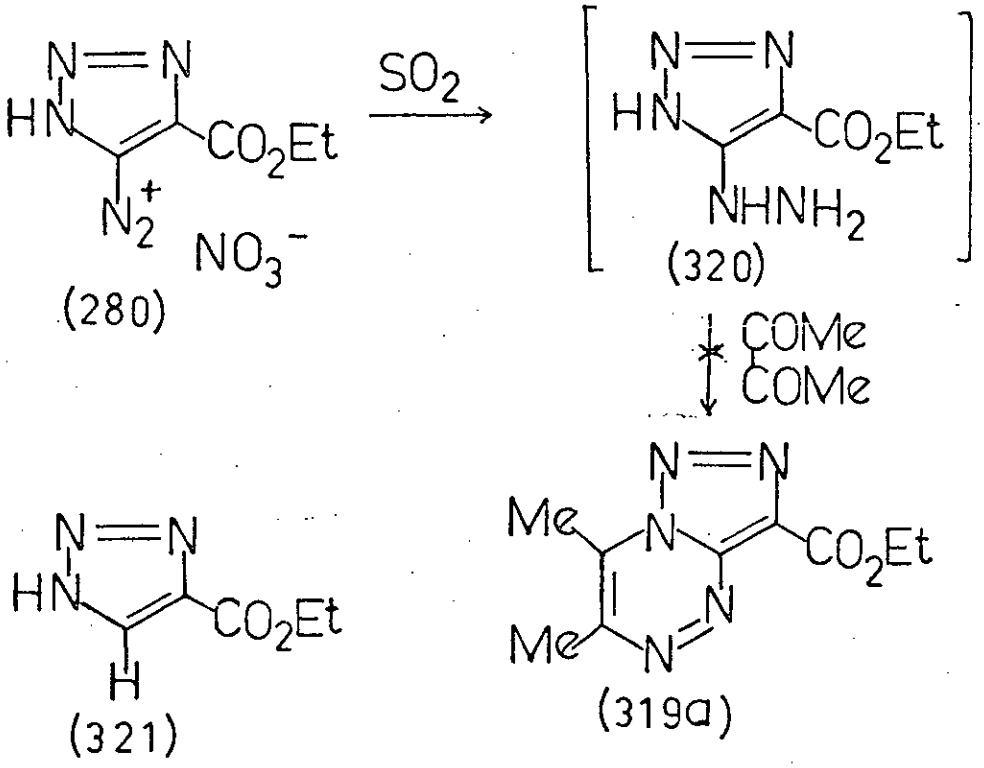


(318) (319)

a; R = CO_2Et

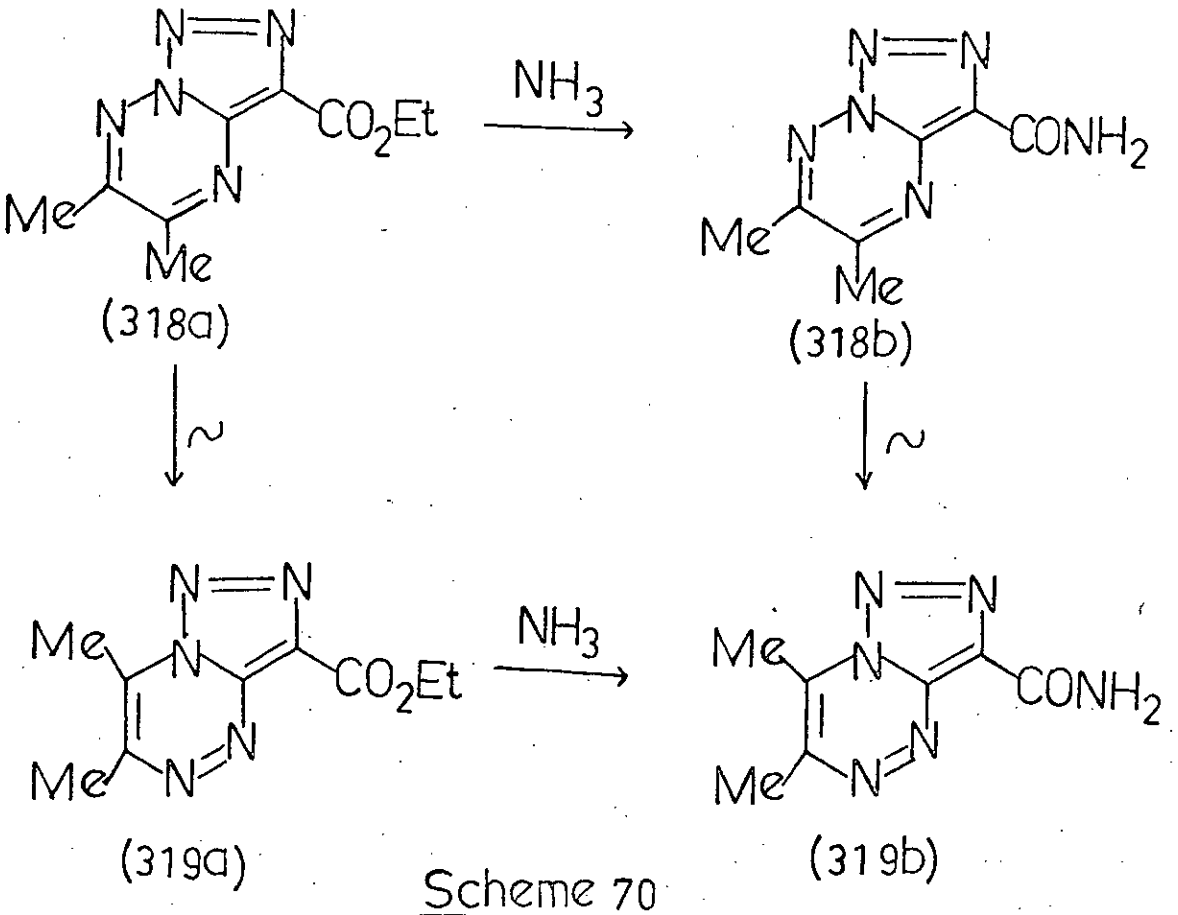
b; R = $CONH_2$

and (319a). A product whose properties and transformations were consistent with its being the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (318a) had previously[38] been synthesised by condensing the N-amino-ester (264) with biacetyl. Consequently, it only remained to devise a suitable synthesis for the isomer (319a). The method chosen involved the in situ reduction of the diazonium salt (280) to the hydrazine (320) followed by condensation of the latter with biacetyl.



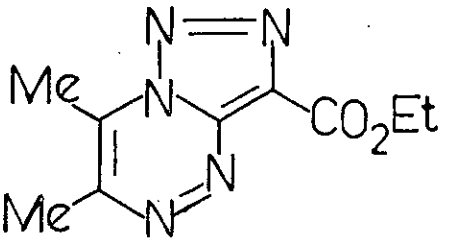
In practice, reduction of the diazonium salt (280) [prepared by diazotisation and deamination of the N-amino-ester (264) - see before] using sulphur dioxide, and attempted in situ condensation with biacetyl gave none of the required triazolotriazine (319a). The only product isolated was the deaminated triazole (321). A similar reduction of the diazonium salt (280) and attempted in situ condensation with glyoxal was also unsuccessful, giving the same deaminated triazole (321).

The failure of the attempted synthesis of the ester (319a) having prevented the study of its possible Dimroth rearrangement to the already available isomer (318a), attention was turned to the similar study of the corresponding amides (318b) and (319b). It will be recalled that a product having properties consistent with the structure (319b) had already been synthesised in the present studies (cf. page 107). It remained, therefore, to devise an unambiguous synthesis of the isomeric amide (318b). Thus, an attempt was made to convert the ester having the presumed structure [Scheme 70; (318a)] into the desired amide (318b) by reaction with ethanolic ammonia. In fact, this reaction afforded not the required amide (318b) but a product identical in all respects to the triazolo-[5,1-c]triazine derivative (319b). A logical conclusion from this result



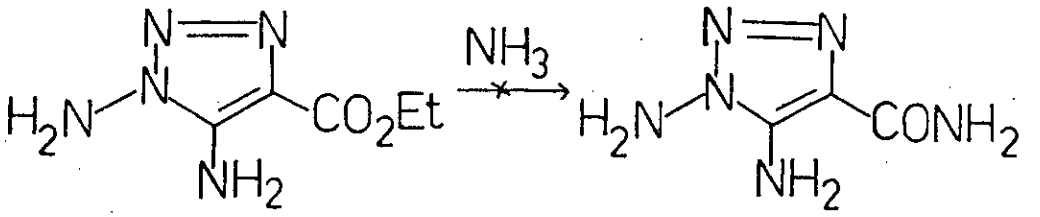
Scheme 70

is that either a rearrangement has taken place during the amination (Scheme 70) or that the original structure assigned to (318a) was incorrect and that it was in fact the isomer (319a). With a view to



(319a)

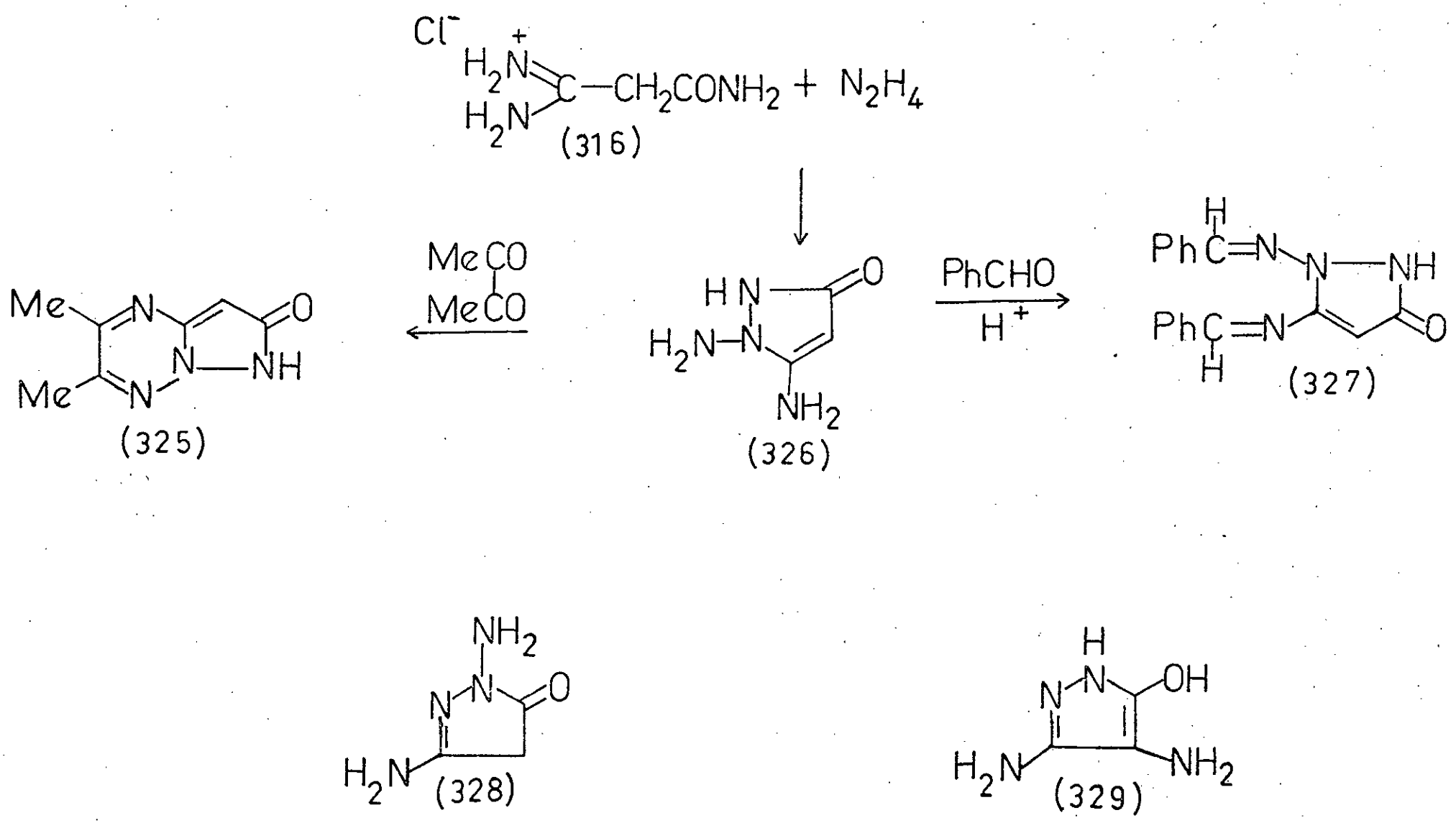
resolving this structure problem an attempt was made to convert the N-amino-ester (264) of established structure[41] into the N-amino-amide (322) and thence by unambiguous reaction with biacetyl into the



(264) (322)

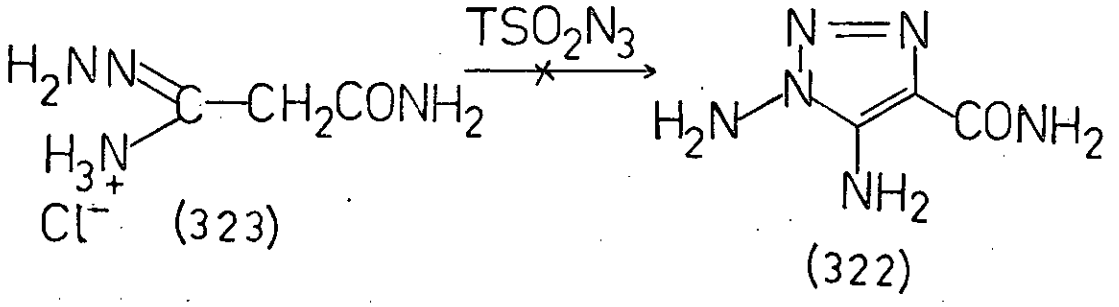
1,2,3-triazolo[1,5-b]-1,2,4-triazine amide (318b). Unfortunately, all attempts to convert the ester (264) by reaction with aminating agents (gaseous or liquid ammonia or ammonium acetate) into the N-amino-amide (322) were unsuccessful.

Other routes to the N-aminotriazole amide (322) were also investigated. Thus, by a method[41] analogous to that used successfully to synthesise the N-aminotriazole ester (264), it was hoped to prepare the amide (322) by reaction of the amidrazone amide (323) with toluene-

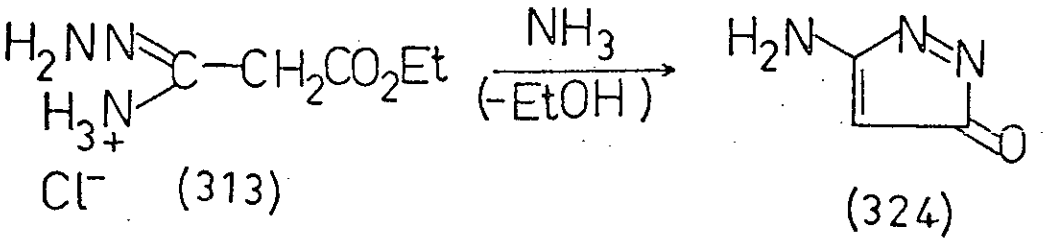

Cl⁻
H2N
H2N
C—CH2CONH2 + N2H4
(316)
MeCO
MeCO
Me
Me
N
N
NH
O
(325)
HN
H2N—N
O
NH2
(326)
PhCHO
H+
H
PhC=N
PhC=N
H
N
NH
O
(327)
NH2
N
N
O
H2N
(328)
H
N
N
OH
H2N
NH2
(329)

Scheme 71

p-sulphonyl azide. However, this approach was thwarted by the failure



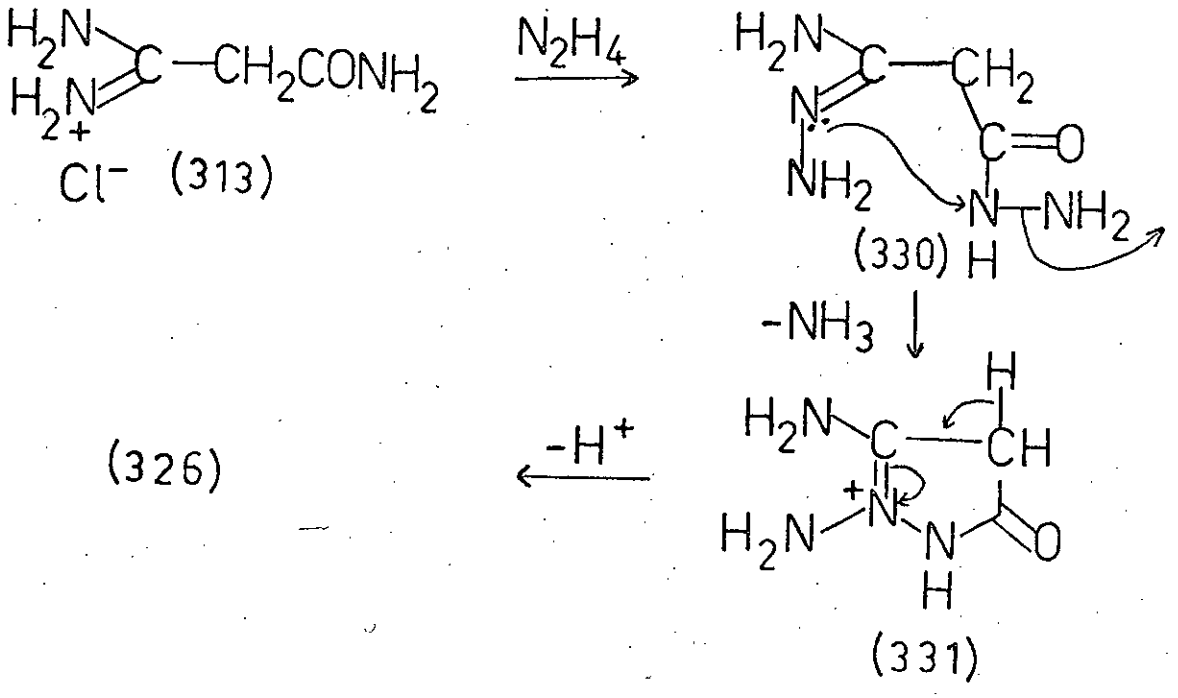
of attempts to synthesise the amidrazone amide (323). Thus, the reaction of the available[41] amidrazone ester (313) with ammonia gave not the

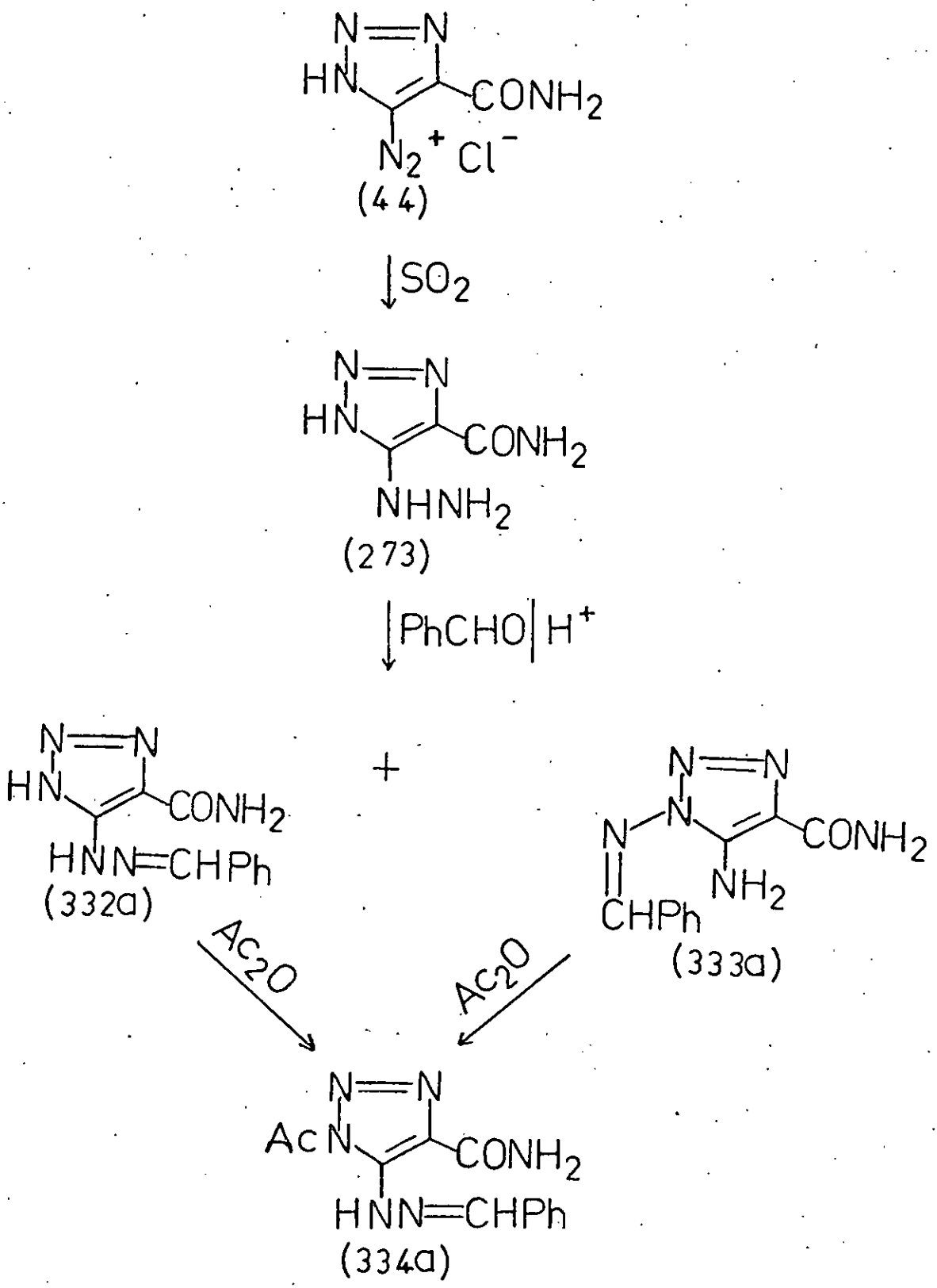


expected amidrazone amide (323) but a compound which gave an elemental analysis and showed i.r. and mass spectra consistent with its being the amino-pyrazolone (324). Thus, its i.r. spectrum showed broad primary amino absorption at 3330, 3210 and 3160 cm^{-1} and a carbonyl band at 1690 cm^{-1}. The formation of this product can be viewed as occuring by cyclisation of the amidrazone (313) with elimination of the elements of ethanol.

The attempted synthesis of the required amidrazone amide (323) by the established method[52] of reacting the known amidine amide (316) with anhydrous hydrazine was also unsuccessful. This reaction gave a product (Scheme 71) which is assigned the N-aminopyrazolone structure (326) on the basis of the following evidence. It gave analytical data consistent with the molecular formula $C_3H_6N_4O$ and its mass spectrum showed

a molecular weight of 114. Although the i.r. spectrum of (326) was not well resolved, it showed NH absorption and a carbonyl band at 1700 cm^{-1}. In accord with the diamino structure (326), it reacted with benzaldehyde to give a bis-benzylidene derivative (327). However, the formation of a bis-benzylidene could be accounted for by any of the three structures possible for the pyrazolone namely (326), (328) and (329). However, when the pyrazolone was treated with biacetyl, it afforded the pyrazolo[1,5-c]-1,2,4-triazine (325). The structure of this product (325) is fully supported by its elemental analysis and spectral properties. Thus, its i.r. spectrum showed NH absorption but no carbonyl band while its ^1H n.m.r spectrum contained a one proton singlet at τ 3.82 due to pyrazolone CH, and two three proton singlets at τ 7.36 and 7.38 due to two distinct methyl groups. The formation of this pyrazolotriazine (325) rules out the possible structure (328) while the mode of formation of the aminopyrazolone (326) eliminates (329) since it is unlikely that hydrazine would react with the amidine (316) to give such a structure. The formation of the most likely structure (326), can then be explained by the following mechanism. First, the hydrazine reacts with the amidine amide (316) to afford the intermediate (330). This loses ammonia to

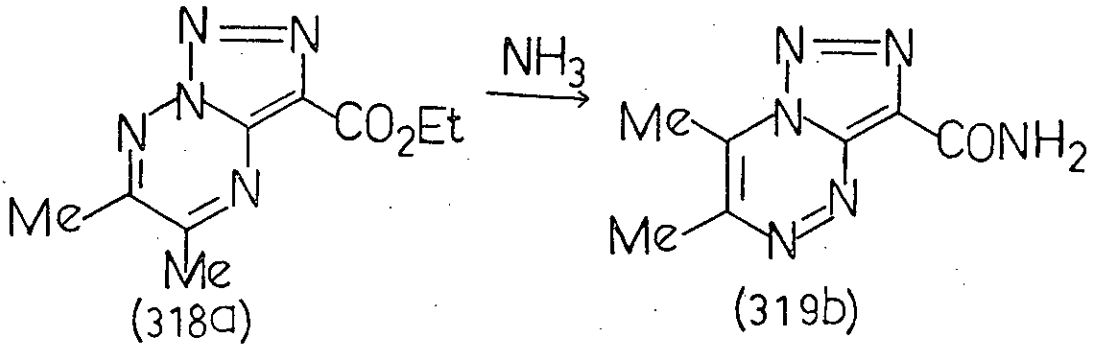




Scheme 72

give (331), which deprotonates to the aminopyrazolone (326). The attempted diazotisation of (326) gave a red oil which could not be characterised.

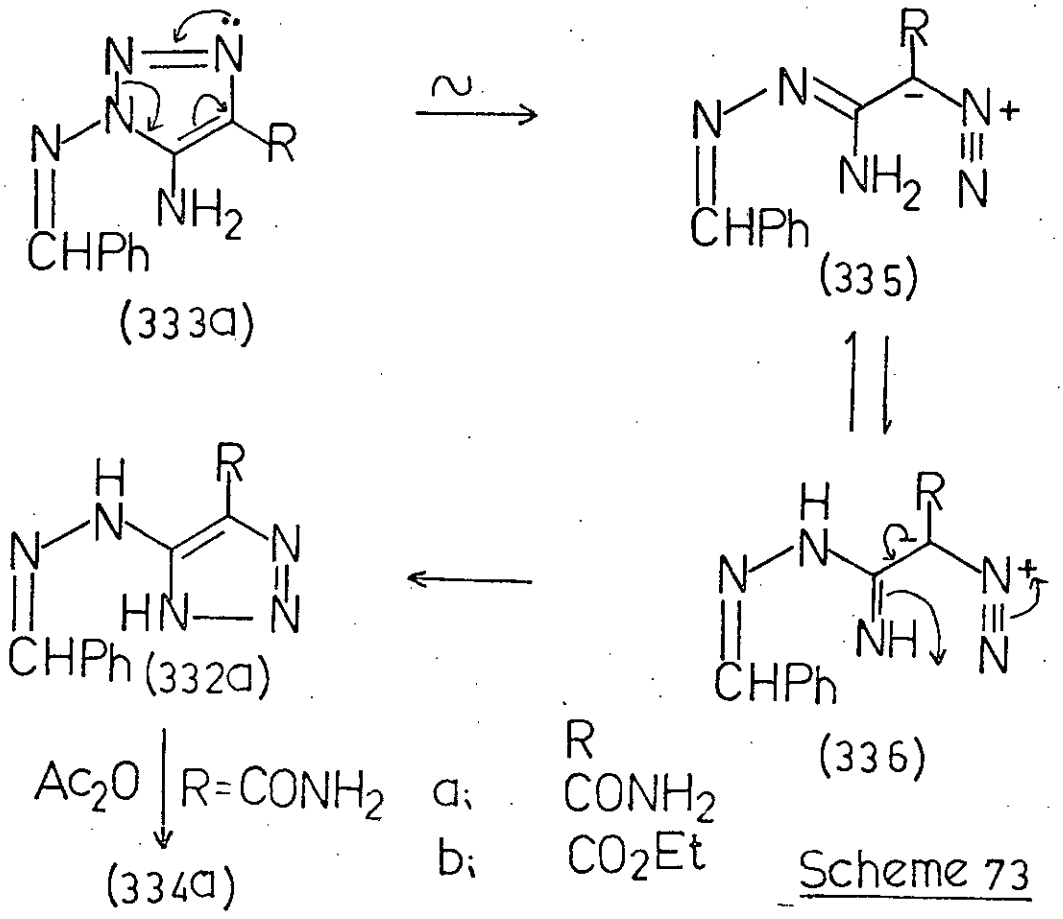
Since the attempted synthesis of the N-aminotriazole amide (322) had been unsuccessful, it was decided as an alternative approach to resolving the problem of the apparent rearrangement involved in the



(318a) (319b)

process [(318a) → (319b)] to attempt the unambiguous synthesis of the hydrazinotriazole amide [Scheme 72; (273)]. The unambiguous condensation of the hydrazine (273) with biacetyl might then produce an unambiguous synthesis of the triazolotriazine (319b), thus allowing the precise structure of the product in the transformation [(318a) → (319b)] to be determined. The projected synthesis of the hydrazine (273) involved the in situ reduction of the diazonium salt (44) using sulphur dioxide. As a model reaction, the reduction of the phenyltriazolediazonium salt (36) with sulphur dioxide was first investigated. However, this reaction merely yielded the deaminated triazole (293). On the other hand, sulphur dioxide reduction of the triazole-amide diazonium salt (44) gave two solid products whose elemental analysis indicated them to be mono-and bis-hydrogen sulphate salts of the expected hydrazine (273). All attempts to convert these salts into the free hydrazine (273) were unsuccessful. The mass spectrum of the mono-hydrogen sulphate showed a poor ion pressure while that of bis-hydrogen sulphate salt showed a molecular weight of

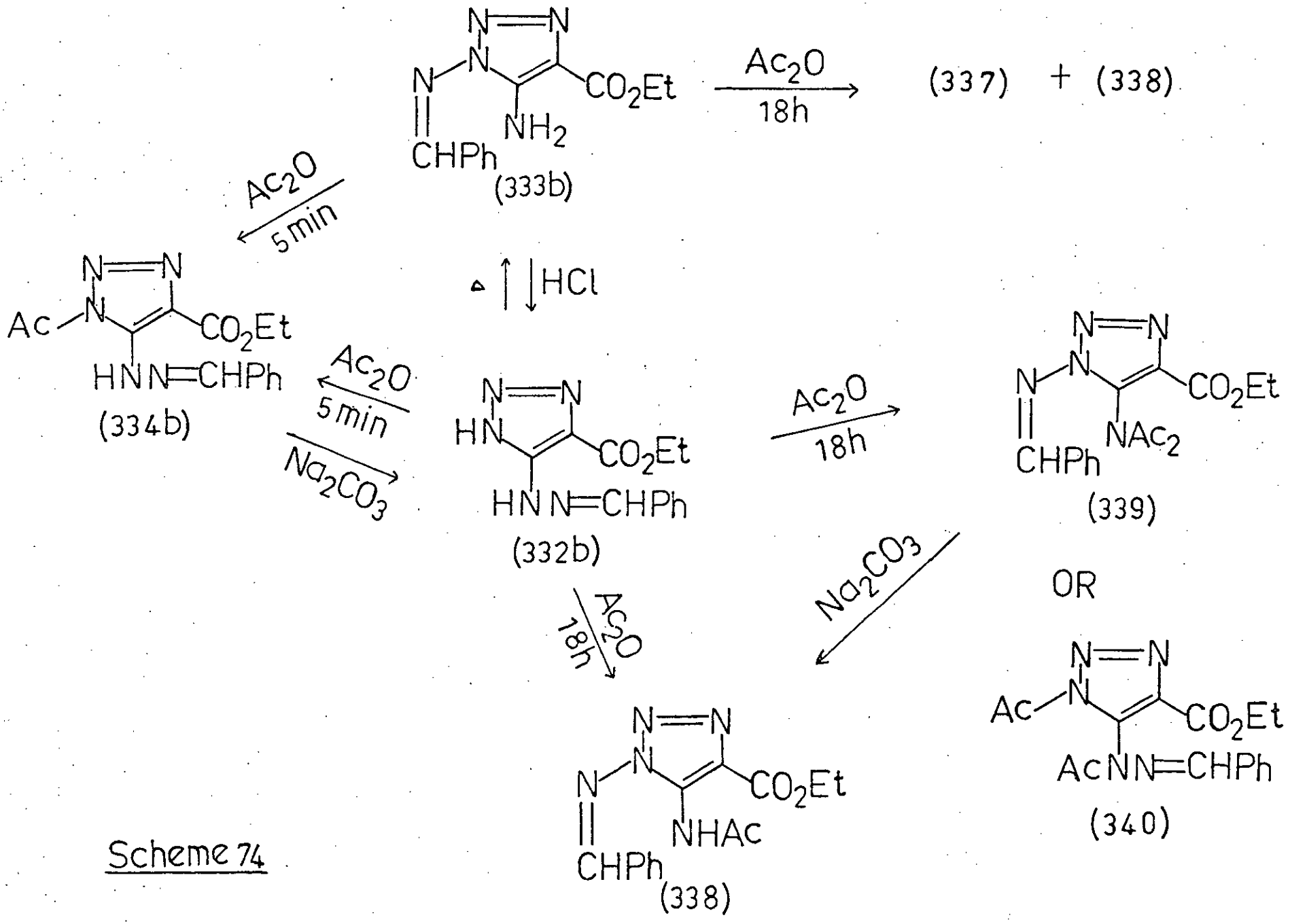
142, expected for the free hydrazine (273). In accord with the assigned constitutions of these products they both reacted with benzaldehyde to afford the same product (Scheme 72). However, closer examination of this product showed it to be a readily separated mixture of two isomeric monobenzylidene derivatives one of which was acidic and the other neutral. The i.r. spectrum of the acidic isomer showed NH absorption at 3360 and 3300 cm^{-1} and a carbonyl band at 1685 cm^{-1}. In accord with its formulation as the benzylidenehydrazine derivative (332a), the acidic product reacted under mild conditions with hot acetic anhydride to afford a monoacetyl derivative whose i.r. spectrum showed a high frequency carbonyl band at 1756 cm^{-1} and whose ^1H n.m.r. spectrum contained a three proton singlet at τ 7.30, features characteristic of a ring N-acetyl 1,2,3-triazole and hence of the N-acetyl structure (334a). The neutral product showed spectral properties consistent with its formulation as the benzylideneaminotriazole (333a). Thus, its i.r. spectrum showed NH absorption at 3470, 3400, 3370 and 3160 cm^{-1} and a carbonyl band at 1670 cm^{-1}. Owing to insufficient material, the ^1H n.m.r spectrum of (333a) could not be obtained. However, reaction of this compound with hot acetic anhydride yielded a product identical in all respects to the N-acetylated triazole (334a) obtained by acetylation of the benzylidenehydrazine isomer (332a). The formation of (334a) from (333a) is readily explained in terms of the Dimroth rearrangement shown in Scheme 73. This mechanism (Scheme 73) implies that the isomer (333a) undergoes thermal rearrangement to (332a) which then acetylates. On the assumption that the sulphur dioxide reduction products of the diazonium salt (44) are hydrogen sulphate salts of the hydrazine (273), their reaction with benzaldehyde to give the mixture of the two isomers (332a) and (333a) must involve the reverse rearrangement process of [(332a) → (333a)].



Scheme 73

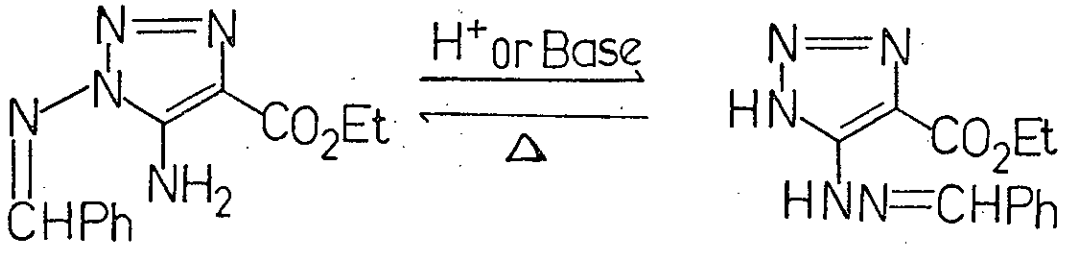
This infers that the rearrangement of [(333a) → (332a)] is reversible and in accord with this proposal, heating the benzylidenehydrazinotriazole (332a) in 2-ethoxyethanol or in pyridine resulted in its conversion into a mixture of (332a) and (333a). Owing to lack of material, the similar conversion of the benzylideneaminotriazole (333a) into an equilibrium mixture of (332a) and (333a) could not be demonstrated.

In view of the Dimroth rearrangement [(333a) ⇌ (332a)] observed with the triazole amide derivatives (332a) and (333a) it was of interest to see if the known[41] benzylideneaminotriazole ester (333b) would undergo analogous rearrangement. This turned out to be the case. Thus, heating the benzylideneaminotriazole ester (333b) with aqueous ethanolic hydrochloric acid resulted in its isomerisation to the benzylidenehydrazine


Ac2O
18h
(337) + (338)
(333b)
Ac2O
5min
HCl
Ac
CO2Et
HNN=CHPh
(334b)
Ac2O
5min
Na2CO3
HN
CO2Et
HNN=CHPh
(332b)
Ac2O
18h
NAc2
CHPh
(339)
OR
Na2CO3
Ac2O
18h
NHAc
CHPh
(338)
AcNN=CHPh
(340)

Scheme 74

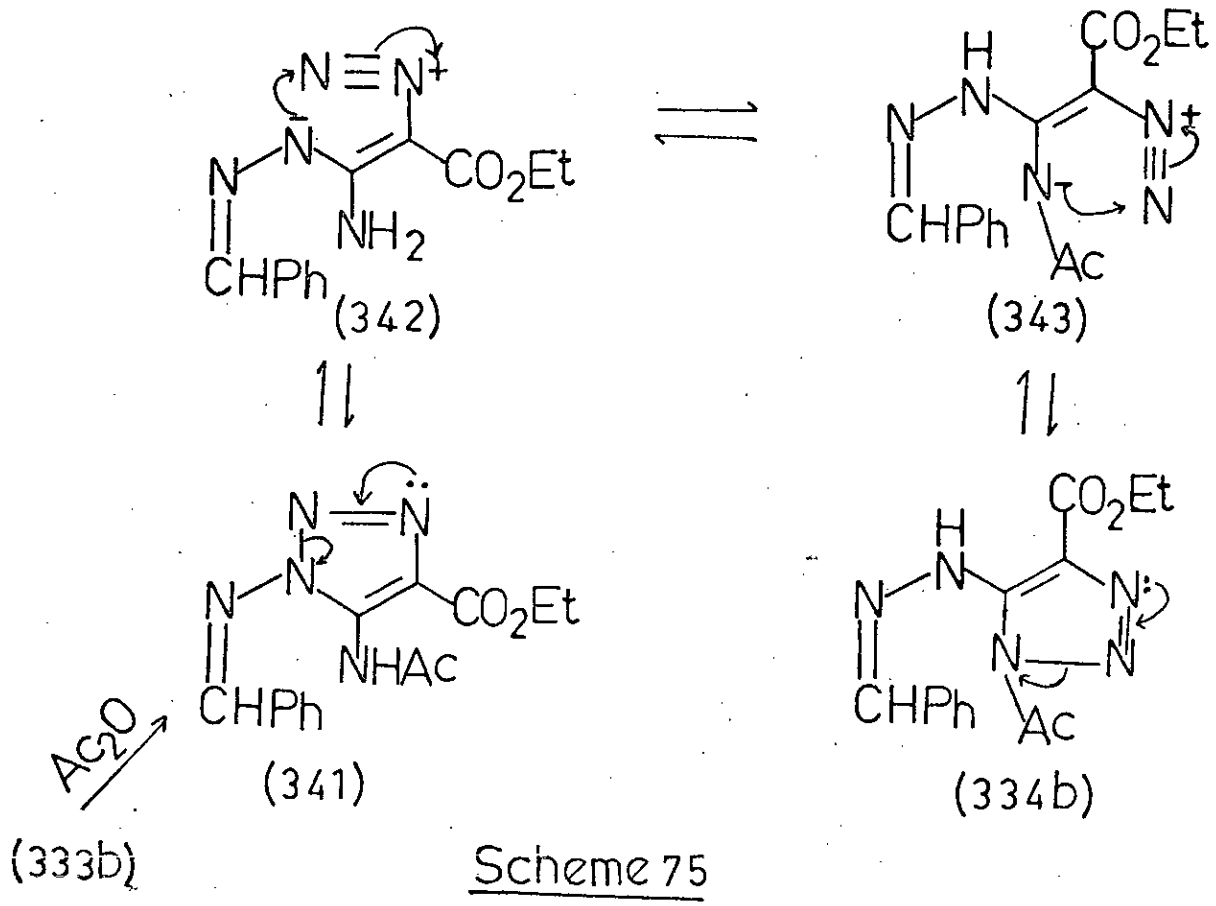
derivative [(Scheme 74; 332b)], whose structure follows from its acidity and i.r. spectrum. Thus, (332b) was easily soluble in aqueous dilute sodium hydroxide solution and was recovered on acidification with aqueous dilute hydrochloric acid. Its i.r. spectrum showed NH absorption and an ester band at 1700 cm^{-1}. Unfortunately, there was insufficient of (332b) for its ^{1}H n.m.r. spectrum to be obtained. Similarly, heating the benzylideneaminotriazole ester (333b) in pyridine caused its isomerisation to (332b). During this isomerisation a new example of Dimroth rearrangement [(333b) → (332b)] akin to that exhibited by the benzylideneaminotriazole amide [(333a) → (332a)] must have taken place. Further proof that the isomerisation [(333b) → (332b)] was acid- or base-catalysed and not a purely thermal process came from the fact that when a melt of the benzylidenemminotriazole ester (333b) was held briefly at high temperatures, the unrearranged compound (333b) was recovered unchanged. The reverse rearrangement [(332b) → (333b)] was also found to occur and could be shown to be a purely thermal process and not subject to acid- or base-catalysis as found for the reverse Dimroth rearrangement [(333b) → (332b)]. Thus, when a melt of the hydrazino derivative (332b) was held briefly at elevated temperatures, it reverted to the benzylideneaminotriazole (333b) whereas when (332b) was heated under reflux in pyridine, it was recovered unchanged. This observed



(333b) (332b)

direction of rearrangement [(333b) ⇄ (332b)] is wholly in accord with the structures assigned to the two isomers. Also in keeping with the assigned structures, (333b) should be liable to diazotisation with nitrous acid while (332b) will be unaffected by diazotisation. Thus, in an attempt to distinguish between the two isomers (333b) and (332b) – thereby further confirming their structures – they were each treated with aqueous nitrous acid solution. Unfortunately, these attempted diazotisations were unsuccessful and in each case the starting materials (333b) and (332b) were recovered unchanged in excellent yield.

In further support of its structure, the benzylidenehydrazine derivative (332b) warmed briefly with acetic anhydride afforded a monoacetyl derivative which showed an i.r. carbonyl band at 1750 cm^{-1} and a three proton ^{1}H n.m.r signal at τ 7.20 thus showing it to be the 1-N-acetyl derivative (334b).[5a] The acetyl derivative [Scheme 74; (334b)] was readily hydrolysed back to the triazole (332b) on brief warming with aqueous sodium carbonate, demonstrating that no rearrangement had occurred during the acetylation of (332b) to (334b). Unexpectedly, brief warming of the benzylideneaminotriazole (333b) in acetic anhydride also afforded the ring N-acetyl triazole (334b). This transformation requires a rearrangement at some stage and since it has already been demonstrated that (333b) does not rearrange thermally to (332b), it must be that (333b) is first acetylated to the acetylamino-derivative (341) which then undergoes a thermal Dimroth rearrangement (Scheme 75) to afford (334b). When the hydrazine derivative (332b) was heated under reflux for a long time, it afforded a monoacetyl derivative which was not identical with the 1-N-acetyl derivative (334b) and whose i.r. spectrum agreed with its formulation as (338).[38] Thus, the i.r. spectrum of (338) contained NH absorption and an acetyl band at 1720 cm^{-1}



Scheme 75

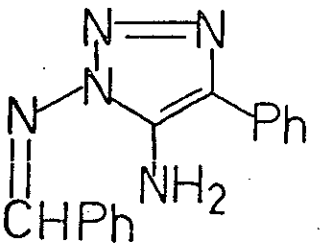
due to the acetylamino group. However, a repetition of this acetylation under the same conditions failed to give the same monoacetyl derivative (338) but instead afforded a compound whose elemental analysis was consistent with the molecular formula $C_{16}H_{17}N_5O_4$ and whose mass spectrum showed a molecular weight of 343 consistent with its formulation as either of the two diacetyl derivatives (339) or (340) (cf. Scheme 74). However, the spectral properties of this diacetyl derivative rule out structure (340) while they favour (339). Thus, the i.r. spectrum showed only two carbonyl bands at 1750 and 1720 cm^{-1}, due to two equivalent acetyl groups and an ester group respectively, while the ^1H n.m.r. spectrum contained a six proton singlet at τ 7.66 attributable to two equivalent acetyl groups. The structure assigned to (339) was further supported by the fact that when it was warmed briefly with aqueous sodium carbonate,

one of the acetyl groups was hydrolysed off to give the monoacetyl derivative (338). The formation of both (338) and (339) from the hydrazino derivative (332b) involves a rearrangement. This is expected in view of the fact that it has already been shown (see before) that (332b) is thermolabile. So when heated, it rearranges to (333b) which then acetylates to the mono- or diacetyl derivative (338) or (339). When the benzylideneaminotriazole (333b) was similarly heated under reflux in acetic anhydride for a prolonged period, it afforded two products, a very high melting compound (337) and the monoacetyl derivative (338). The high melting compound (337) analysed correctly for its being a monoacetyl derivative and its mass spectrum gave a parent peak at m/e 301, also expected for a monoacetyl derivative. Its i.r. spectrum showed NH absorption and two carbonyl bands at 1730 and 1660 cm^{-1} due to the acetyl and ester groups respectively while its ^{1}H n.m.r. spectrum in addition to showing an intact ester group contained a three proton singlet at τ7.40 attributable to an acetyl group. The assignment of a structure to this product which is different from (334b) or (338) and shows properties inconsistent with the only alternative monoacetyl structure (340; H for ring N-Ac) poses a problem and must await further work.

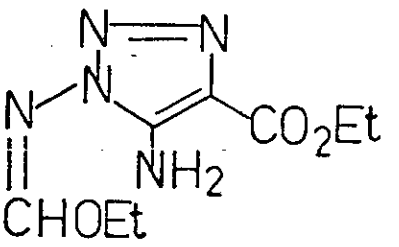
Having demonstrated the Dimroth rearrangements [Scheme 73; (333a and b) $\rightleftharpoons$ (332a and b)], an attempt was made to relate the two series by amination of the esters (333b) and (332b). However, the benzylideneaminotriazole (333b) failed to react with ethanolic ammonia. The benzylidenehydrazinotriazole (332b) also failed to undergo amination to the amide (332a) using ethanolic ammonia but was converted instead into a mixture of the starting ester (332b) and the isomer (333b). This result is surprising since it had been shown previously that the benzylidenehydrazinotriazole (332b) did not apparently rearrange under

basic conditions. However, the conversion of (332b) into what is probably an equilibrium mixture of (333b) and (332b) simply demonstrates that the position of the Dimroth equilibrium [(333b) ⇌ (332b)] is more dependent on the particular medium than indicated previously.

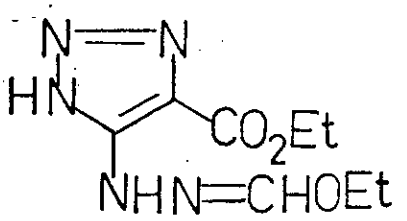
Two other benzylideneaminotriazole derivatives (314) and (315) were also examined for possible Dimroth rearrangement. However, the compound (314) was recovered unchanged after its melt was held briefly at elevated temperature and it failed to undergo rearrangement on heating under reflux in pyridine. The ethoxymethyleneaminotriazole (315) likewise failed to undergo thermal rearrangement. The resistance of the



(314)



(315)

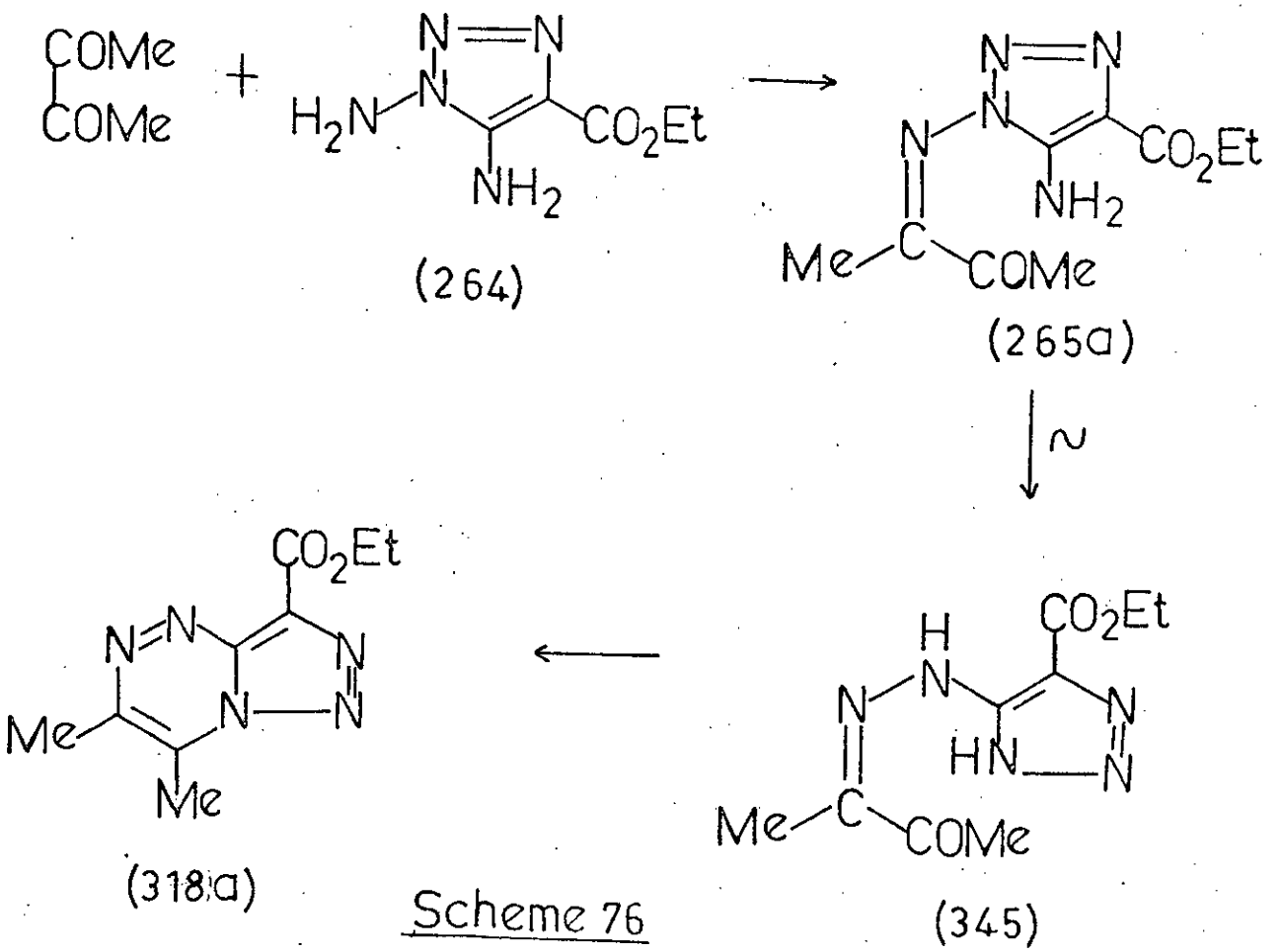


(344)

triazole derivatives (314) and (315) to rearrangement is surprising but may be due in the case of (314) to the electron-donating effect of phenyl [compared with the electron-withdrawing effect of ethoxycarbonyl (CO_2Et) or carbamoyl ($CONH_2$) in the molecules (333b) and (333a)] which will make rearrangement more difficult. Correspondingly, the resistance of (315) to rearrangement can be attributed to its greater stability [formal

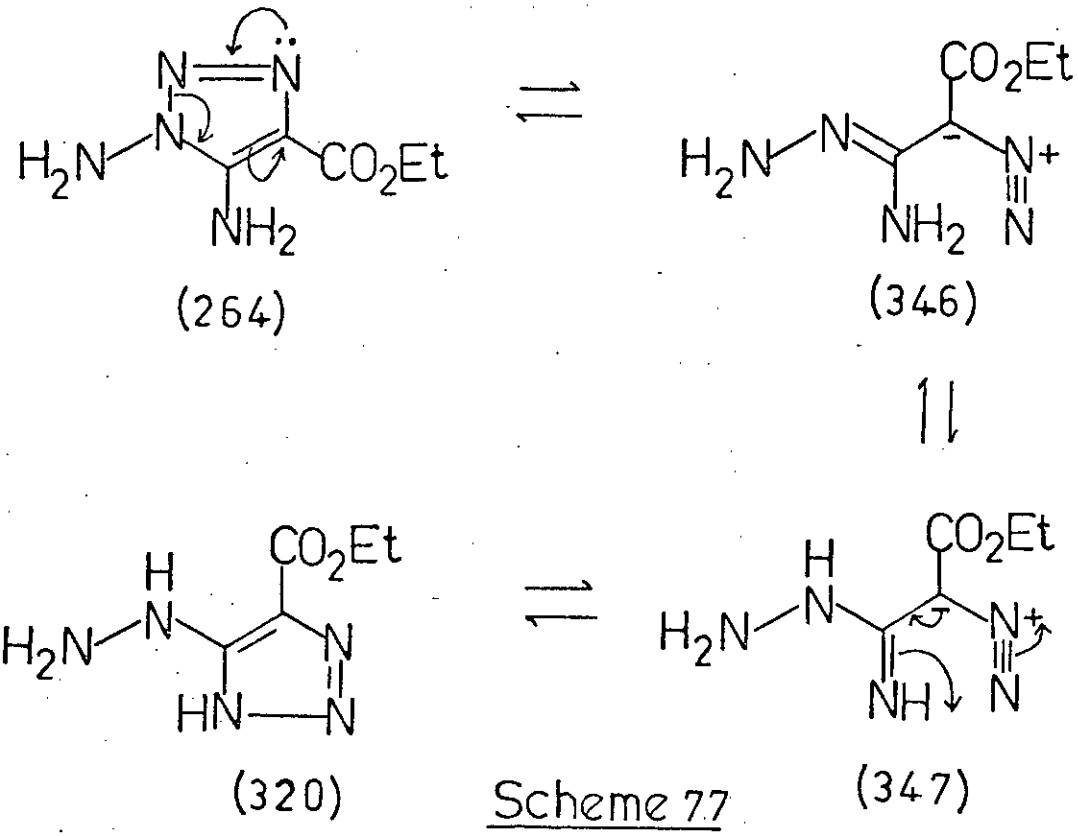
electron-donating group (N = CHOEt) attached to a ring nitrogen atom] compared to its Dimroth isomer (344) which has a formal electron-donating group (N = CHOEt) attached to an exocyclic nitrogen.[5a]

It was previously suggested (cf. page 121) that the transformation [(318a) → (319b)] probably occurred by Dimroth rearrangement of intact fused 1,2,3-triazolo[1,5-b]-1,2,4-triazine structures either before or after amination (cf. Scheme 70). However, the finding in the present studies that alkylideneamino-1,2,3-triazoles [cf. (333a and b)] are capable of undergoing Dimroth rearrangement to their alkylidenehydrazine-isomers [cf. (332 a and b)] makes it possible that rearrangement (Scheme 76) to the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system could also occur during the actual formation of the assumed[38] 1,2,3-triazolo[1,5-b]-1,2,4-triazine ester (318a) from the reaction of the N-amino-ester (264) with biacetyl -



Scheme 76

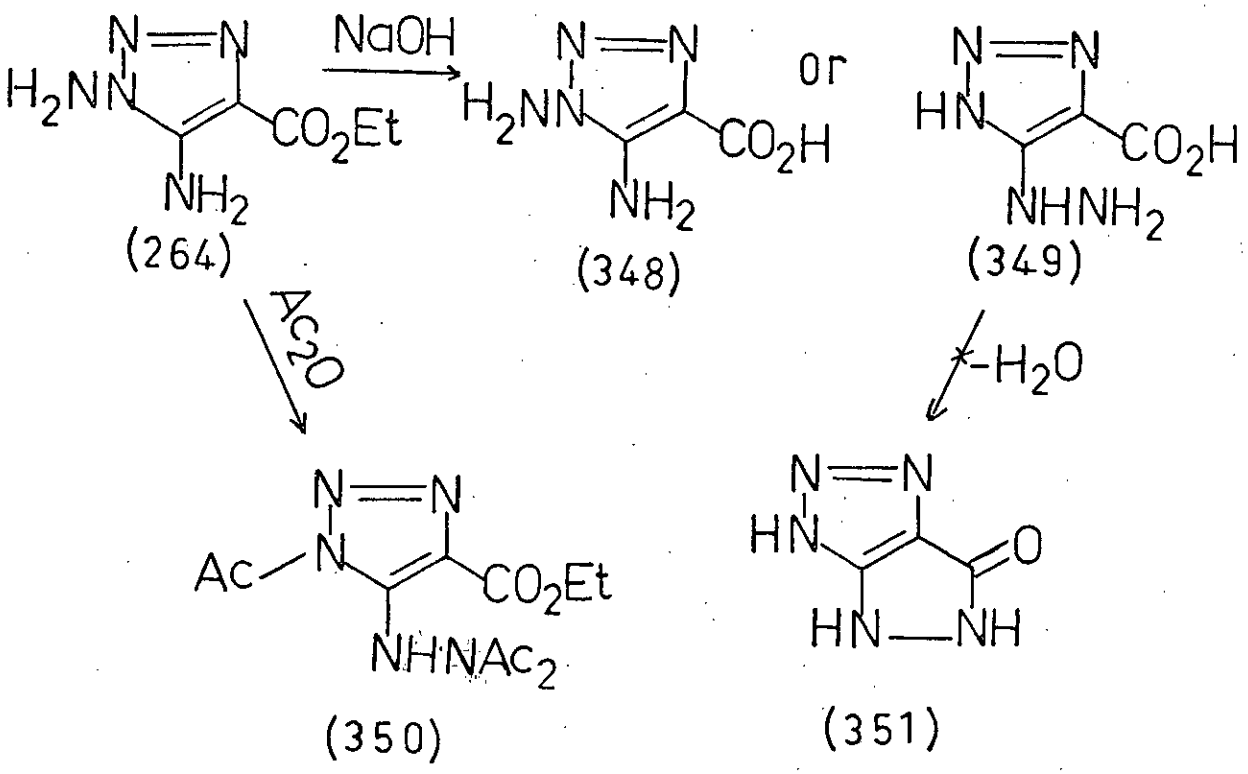
that is that the product of this reaction is not the ester (318a) as previously thought[38] but is rather the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ester (319a) derived by Dimroth rearrangement [Scheme 76; (265a) → (345)] and subsequent cyclisation of the initial condensate (265a). A further possibility is that the N-amino-ester (264) itself undergoes prior rearrangement to the hydrazine [Scheme 77; (320)] which then



(264) (346) (320) (347)

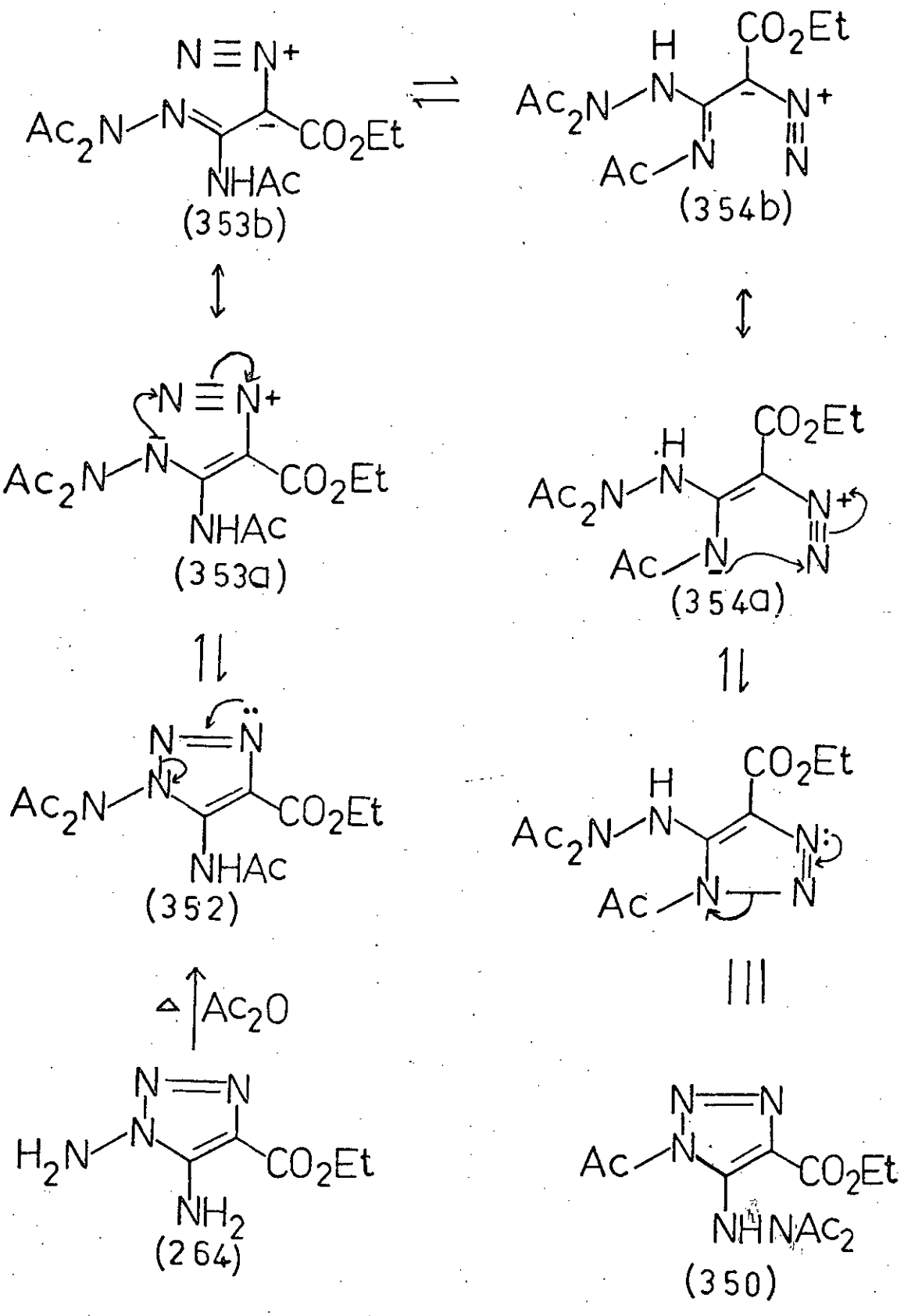
Scheme 77

condenses with biacetyl to give (319a). However, this possibility can definitely be excluded since attempts to rearrange the N-amino-ester (264) under a variety of conditions were unsuccessful. Thus, it was recovered unchanged after heating in acetic acid or pyridine and heating with aqueous sodium hydroxide merely resulted in its hydrolysis to the acid (348). The alternative structure (349) for this product can be excluded since this

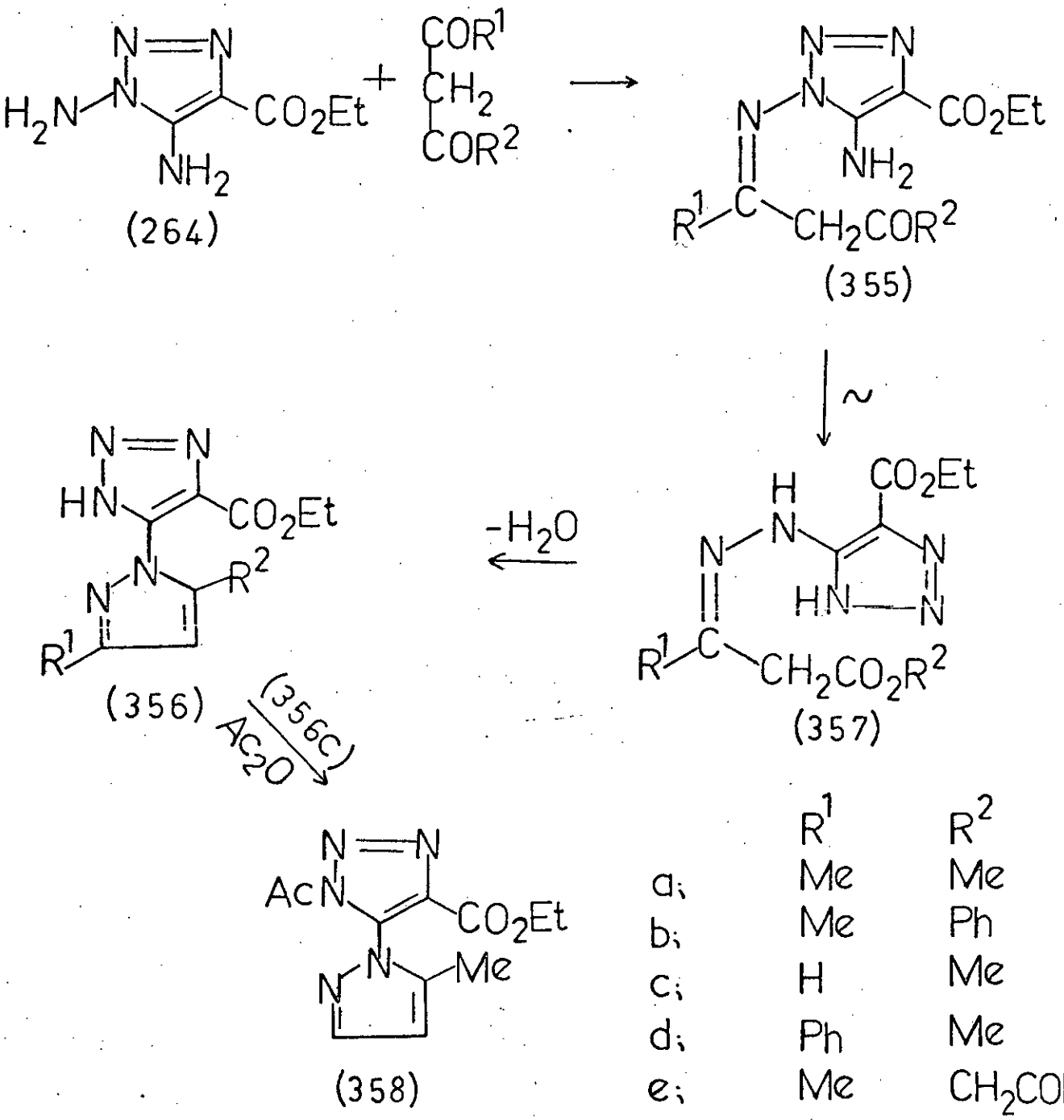


might have been expected to cyclise to the triazolopyrazolone (351) under the conditions of hydrolysis.

In contrast to its resistance to direct rearrangement, the N-amino-ester (264) was found to rearrange under the conditions of its acetylation. Thus, warming it briefly with acetic anhydride yielded a triacetyl derivative which showed a carbonyl band at 1770 cm^{-1} in its i.r. spectrum and a relatively low field three proton singlet at τ 7.26 in its ^1H n.m.r. spectrum, spectral features characteristic[5a] of a 1,2,3-triazole ring N-acetyl group. The only structure consistent with these properties is that of the triacetylated hydrazinotriazole (350) demonstrating that rearrangement occurs in the course of the acetylation of (264). The



Scheme 78



	R^1	R^2
a;	Me	Me
b;	Me	Ph
c;	H	Me
d;	Ph	Me
e;	Me	CH_2COMe
f;	CH_2COMe	Me

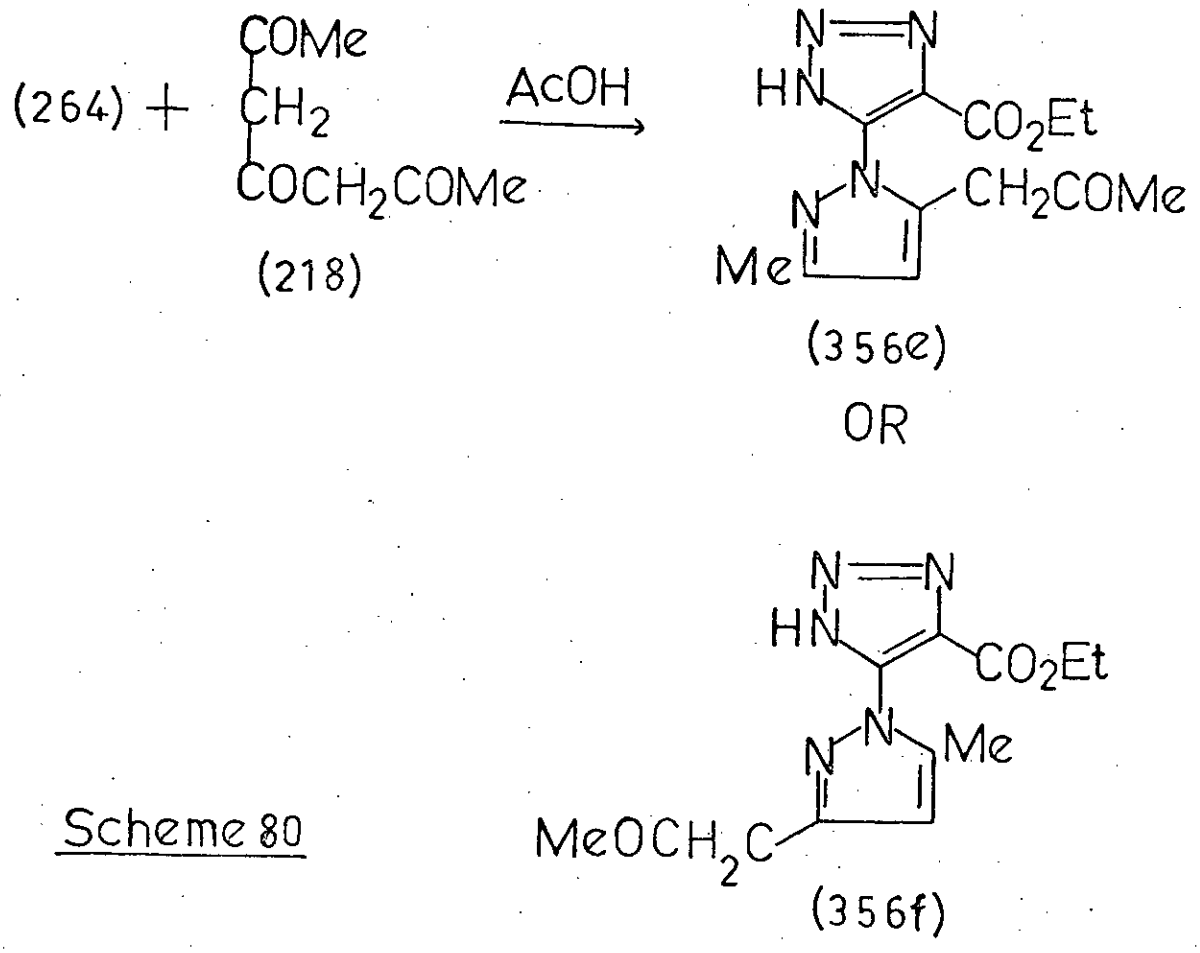
Scheme 79

mechanism (Scheme 78) suggested for this rearrangement is based on the fact that the N-aminotriazole (264) itself is stable to rearrangement which must, therefore, be preceded by acetylation to the triacetyl derivative (352). Alternatively, rearrangement may involve a mono or diacetyl derivative of (264) followed by further acetylation to (350) after rearrangement is complete.

The condensation reactions of the Namino-ester (264) with β-dicarbonyl compounds was also found to proceed with Dimroth rearrangement. Thus, heating the N-amino ester (264) with acetylacetone, benzoylacetone or acetoacetaldehyde dimethyl acetal in the presence of glacial acetic acid afforded reasonable yields of products which are formulated as the pyrazolyltriazoles (356a-d) on the basis of the following evidence. They gave analytical and mass spectral data fully consistent with the structures (356a-d). The i.r. spectrum of (356a) showed NH absorption and a carbonyl band at 1740 cm^{-1} while its ^1H n.m.r. spectrum contained two three proton singlets at τ 7.62 and 7.80 due to two distinct methyl groups. The i.r. spectrum of either of the two possible structures (356 b or d) from the condensation of the N-amino-ester (264) with benzoylacetone contained NH absorption in addition to a carbonyl band at 1725 cm^{-1} while its ^1H n.m.r. spectrum showed a three proton singlet at τ 7.60 due to the methyl group. These spectral properties could not resolve which structure (356b) or (356d) was formed but (356b) is favoured on mechanistic grounds (see later). The i.r. spectrum of (356c) showed both NH and carbonyl absorption while its ^1H n.m.r. spectrum contained two one proton doublets at τ 1.56 and 3.76 due to H(3) and H(4) respectively and a three proton singlet at τ 7.61 attributable to Me(5). In accord with its assigned structure, the pyrazolyltriazole (356c) readily afforded a monoacetyl derivative whose spectral properties are fully consistent with the ring N-acetyl structure (358).

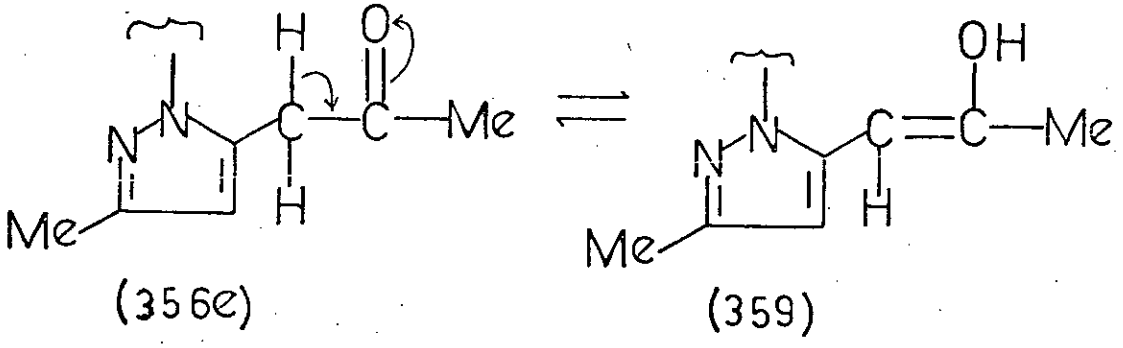
Thus, its i.r. spectrum lacked NH absorption while showing a high carbonyl band at 1780 cm^{-1} characteristic[5a] of a ring N-acetyl group. In contrast, the attempted acetylation of the pyrazolyltriazole (356a) was unsuccessful.

In contrast to the successful condensations with acetylacetone, benzoylacetone and acetoacetaldehyde diemthyl acetal, the N-amino-ester (264) failed to react with malondialdehyde dimethyl acetal, ethyl cyanoacetate, or 2-cyanoacetophenone. However, it did react readily with heptane-2,4,6-trione (218) in the presence of acetic acid to yield a product which gave analytical and mass spectral data consistent with its being either of the possible triazolylpyrazoles (356e) or (356f). The spectral properties of this product could not resolve which



Scheme 80

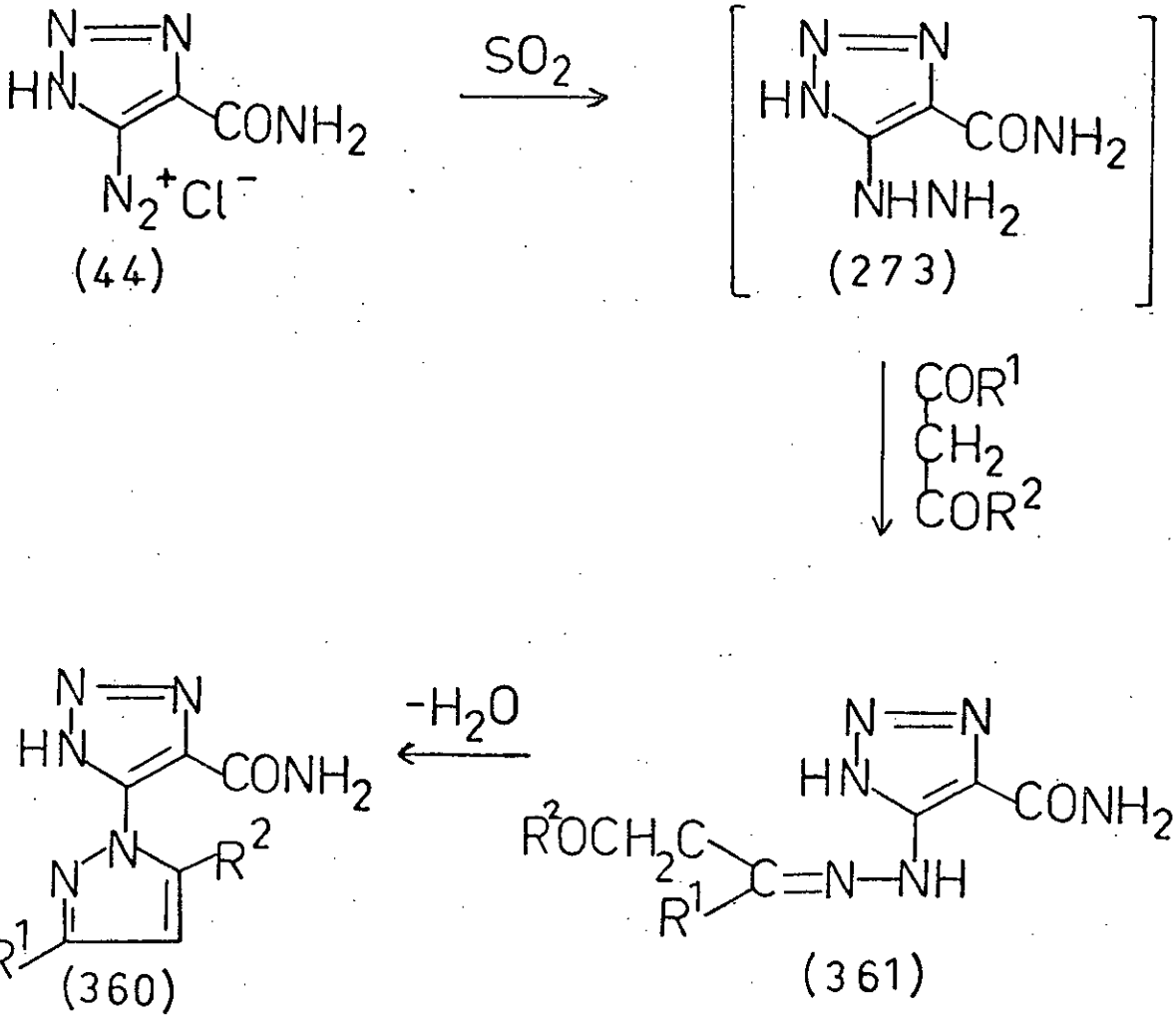
triazolylpyrazole (356e) or (356f) was formed. The ^{1}H n.m.r. spectrum showed a one proton singlet at τ 3.82, a two proton singlet at τ 6.30 and two three proton singlets at τ 7.76 and 7.95 due to the pyrazole CH, the acetonyl CH_2, the acetyl group and Me(5) respectively. The i.r. spectrum of this product contained NH absorption, and a carbonyl band at 1730 cm^{-1}. It also contained hydroxyl absorption at 2700 - 2500 cm^{-1} indicating the presence of keto-enol tautomerism [cf. (356e)⇌(359)].



(356e) (359)

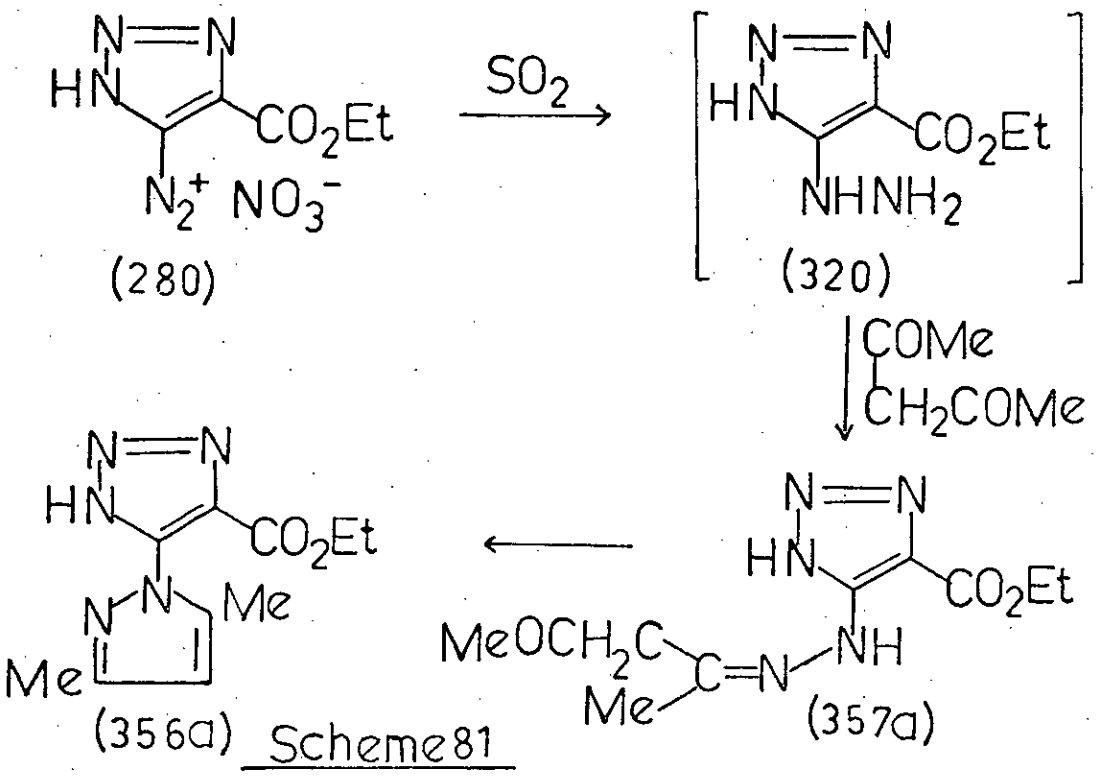
The formation of the pyrazolyltriazoles (356a-f) is readily explained in terms of a general mechanism (Scheme 79) involving initial condensation between the β-dicarbonyl compound and the more basic 1-amino-group in (264) to give an intermediate (355) which then suffers Dimroth rearrangement to yield (357) before cyclising to the corresponding pyrazolyltriazole (365). The preferential formation of (356b) as opposed to (356d) is then explained by initial condensation between the 1-amino-group of (264) with the more reactive acetyl group in benzoylacetone.

In accord with the mechanism (Scheme 81) proposed for pyrazolyltriazole formation, diazotisation and deamination of the N-amino-ester (264) to give the diazonium salt (280) followed by in situ reduction to the hydrazone (320) and condensation with acetylacetone yielded a product identical



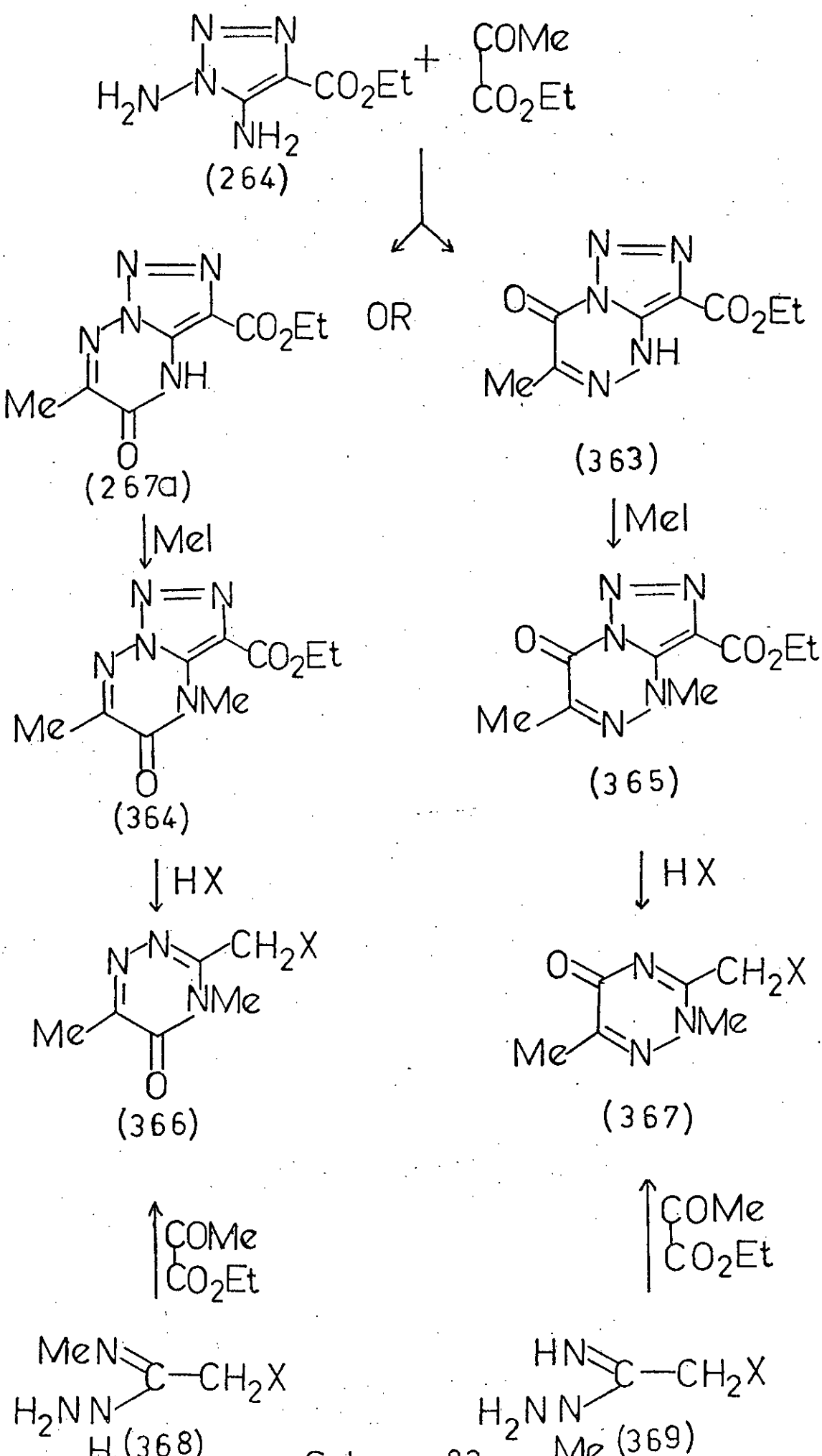
	R^1	R^2
a;	Me	Me
b;	H	H
c;	H	Me

Scheme 82



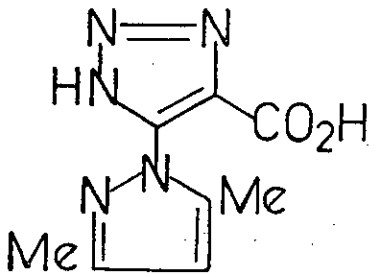
(280) (320) (356a) (357a) Scheme 81

in all respects to the pyrazolyltriazole (356a) obtained by direct condensation of (264) with acetylacetone. The analogous condensation of the hydrazine (273) produced by in situ reduction of the triazole diazonium amide (44) with acetylacetone, malondialdehyde dimethyl acetal, or acetoacetaldehyde dimethyl acetal afforded the expected pyrazolyltriazoles (360 a-c) whose structures were fully in accord with their elemental and spectral properties. Thus, the i.r. spectra of (360a-c) all showed NH absorption and amide carbonyl bands at 1680 and 1690 cm^{-1} respectively. The ^1H n.m.r. spectrum of (360a) showed a one proton singlet at τ 3.92, and two three proton singlets at τ 7.62 and 7.76 due to the pyrazole CH, and two distinct methyl groups. The ^1H n.m.r. spectrum of (360b) contained a one proton doublet at τ 1.50 due to the pyrazole CH, a two proton doublet at τ 2.20 due to CH and NH and a one proton triplet at τ 3.46 due to H(4). No ^1H n.m.r. spectrum was obtained for (360c) because of lack of material.



Scheme 83

In an effort to further substantiate the structure of the pyrazolyltriazole (356a) an attempt was made to aminate it to the amide (360a). However, this reaction was unsuccessful. On the other hand, the ester (356a) and the amide (360a) were indirectly related by their

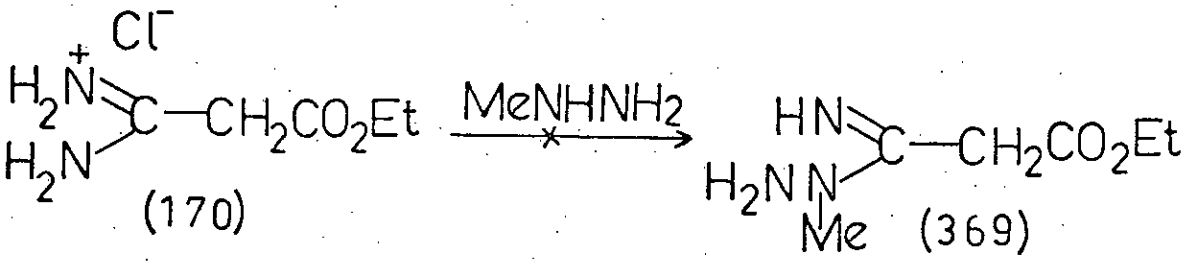


(362)

alkaline hydrolysis to the corresponding acid (362) whose elemental and mass spectral analysis are consistent with the assigned structure (362). The i.r. spectrum of (362) contained NH and hydroxyl absorption and a carbonyl band at 1700 cm^{-1}. Its ^{1}H n.m.r. spectrum showed a one proton singlet at τ 3.91 and two three proton singlets at τ 7.63 and 7.76 due to the pyrazole CH, and two distinct methyl groups but no acidic proton.

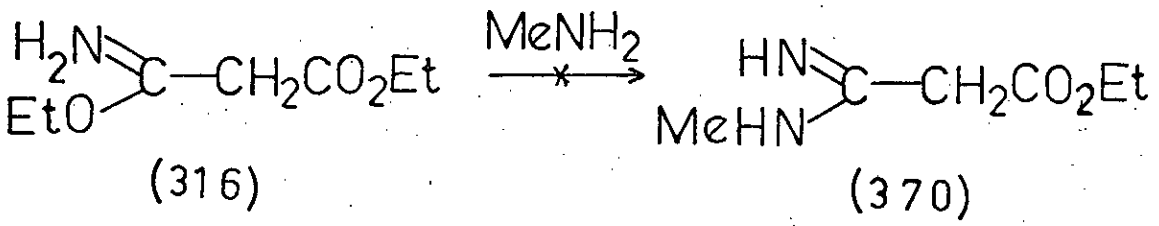
From what has been said so far (see before) the condensation of the N-aminotriazole ester (264) with α-dicarbonyl compounds could lead to either triazolo[1,5-b]triazine (267a) or to triazolo[5,1-c]triazine (363) and not solely to (267a) as was previously[38] thought. To find out which isomer (267a) or (363) was really present, it was decided to repeat the condensation[38] of the N-amino-ester (264) with ethyl pyruvate (Scheme 83), methylate the product to (364) or (365) thereby preventing it from undergoing any Dimroth rearrangement and then break down the triazole ring to afford the triazines (366) or (367). Unambiguous synthesis of both triazines (366) and (367) would then establish which isomer [(267a)or (363)] was originally present. In practice, the triazolotriazine (267a) reported by Mackie[38] was easily synthesised and its treatment with methyl iodide in the presence of anhydrous potassium

carbonate afforded an N-methylated derivative assigned the structure (364). The i.r. spectrum of (364) showed NH absorption and two carbonyl bands at 1720 and 1680 cm^{-1} while its ^1H n.m.r. spectrum contained two three proton singlets at τ 6.02 and 7.48 due to N(Me) and Me(6) respectively. An attempt was next made to carry out the unambiguous synthesis of triazines of the types (366) and (367). This involved the synthesis of the unknown N-methylamidrazone (369; X = CO_2Et) which it was hoped would react with ethyl pyruvate to give (367; X = CO_2Et). Alternatively,



(170) (369)

it was hoped to synthesise the N-methylamidine (370) and thence by reaction with hydrazine the amidrazone (368; X = CO_2Et) which should condense with ethyl pyruvate to yield (366; X = CO_2Et). Consequently, a cooled solution of the amidine hydrochloride (170) was treated with hydrazine hydrate to give an oil which could not be identified. There was no success either in the attempted synthesis of (370). Thus, when



(316) (370)

a solution of the imidate hydrochloride (316) was shaken up briefly with methylamine, it afforded two solids which could not be characterised.

4.4 Experimental (For general experimental procedures, see Appendix)

4-Phenyl-1H-1,2,3-triazole-5-diazonium Chloride (36) and 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride (44)

The diazonium salts (36) (66%) and (44) (82%) were prepared by the diazotisation of the corresponding aminotriazole (15a and b) [41] by the method described by Vevers. [16]

2-Cyanoacetophenone (311)

2-Cyanoacetophenone [49] (311) was prepared as described in the literature. [49]

Ethyl 2-(N-formylamidrazono) acetate (312)

The formylamidrazone (312) (58%) m.p. 108° (lit., [38] 109°) was prepared as described by Mackie. [38]

Ethyl 2-Amidrazonoacetate Hydrochloride (313)

The formylamidrazone (312) (122g) was stirred vigorously in 1.5M ethereal hydrogen chloride (500 ml) for 17h and the solid present was filtered off and heated under reflux in ethanol (150 ml) for 1h. The solution was concentrated to remove some of the ethanol, treated with dry ether and on standing at room temperature deposited the amidrazone hydrochloride (313) (65.17g) m.p. 117°, identical (m.p. and i.r. spectrum with an authentic sample. [41]

The ethanol-ether mother liquor on further concentration and dilution with ether, gave no material.

Ethyl 1,5-Diamino-1,2,3-triazole-4-carboxylate (264)

The diaminotriazole (264) (96%) m.p. 148° (lit.,[41] 110°) was prepared by the method of Mackie and Tennant.[41]

Ethyl 5-Amino-1H-1,2,3-triazole-4-carboxylate (168)

Ethyl 5-Amino-1H-1,2,3-triazole-4-carboxylate (168) was prepared as described in Chapter 2, page 38.

Diethyl oxaloacetate (287a), Ethyl acetopyruvate (287b), Ethyl benzoylpyruvate (287c) and the Sodium Salt of Ethyl 2-Cyanopyruvate (287d)

The substituted pyruvic esters (287 a-d) were prepared as described in the literature.[50]

Heptane-2,4,6-trione (218)

The triketone (218) was prepared as described in Chapter 3, page 75.

Ethoxymethyleneaminotriazole (314)

The ethoxymethyleneaminotriazole (314) m.p. 156° (lit., [41] 152°) was prepared by the method of Mackie and Tennant.[41]

5-Anilino-1-benzylideneamino-4-phenyl-1,2,3-triazole (315)

The benzylideneaminotriazole (135) m.p. 160° (lit., [41] 169°) was prepared by the method of Mackie and Tennant.[41]

2-Amidinoacetamide Hydrochloride (316)

The amidine hydrochloride (316) (85%) m.p. 176° (lit.,[48] 163°) was prepared as described by Challis and Clemo.[48]

Ethoxycarbonylacetamidine Hydrochloride (170)

The amidine hydrochloride (170) m.p. 100° (lit.,[46] 104°) was prepared as described in the literature.[46]

Ethyl 2-Ethoxycarbonylacetimidate Hydrochloride (317)

The imidate hydrochloride[47] (317) (88%) was prepared as described in the literature.[47]

The Coupling Reaction of 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride (44) with 2-Cyanoacetophenone, (311)

A solution of 2-cyanoacetophenone (311) (0.91g, 0.007 mol) and anhydrous sodium acetate (0.8g) in water (2.0 ml) and ethanol (5.0 ml) cooled in an ice-salt bath was treated dropwise with stirring with a solution of the diazonium salt (44) (1.2g, 0.007 mol) in water (25.0 ml) and ethanol (25.0 ml) and stirred in the melting ice bath for 2h. Filtration of the mixture afforded a mixture of the triazolylhydrazone (269) and the triazolotriazine (268) which was combined with a second crop obtained by concentrating the aqueous ethanolic filtrate (total 1.48g) m.p. 175°. The mixture was crystallised from ethanol-water with hot filtration to remove the triazolotriazine (268) as a pink solid (0.08g) m.p. 266° (from dimethylformamide), ν_{max}. 3450w, 3400, and 3160 (NH), and 1700 and 1670 (CO) cm^{-1}.

Found : C, 50.5; H, 3.1; N, 34.3%; M^+ 283.
$C_{12}H_9N_7O_2$ requires: C, 50.9; H, 3.2; N, 34.6%; M, 283.

The aqueous ethanolic filtrate on cooling deposited the triazolylhydrazone (269) as a yellow solid (0.98g) m.p. 252° (from ethanol-water; ν_{max}. 3500, 3350 and 3150 (NH), 2200 (CN), and 1680 and 1660 (CO) cm^{-1}.

Found : C, 50.2; H, 3.3; N, 33.3%; M^+ 283.
$C_{12}H_9N_7O_2$ requires: C, 50.9; H, 3.2; N, 34.6%; M, 283.

Phenylglyoxalonitrile 1-(1-Acetyl-4-carbamoyl-1H-1,2,3-triazol-5-yl) hydrazone (270)

The triazolylhydrazone (269) (0.56g, 0.002 mol) was heated under reflux in acetic anhydride (10.0 ml) for 5min. The solution was evaporated under reduced pressure to give a gummy residue which was triturated with ether to afford the acetyl derivative (270) as a yellow solid (0.54g; 77%) m.p. 187° (from benzene-ethanol), $\nu_{max.}$ 3400, 3350, 3300w and 3200 (NH), 2250 (CN), and 1750 and 1690 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 2.04(1H, br s, NH), 2.42(1H, br s NH), 2.56(5H, s, Ar-H) and 8.10(3H, s, $COCH_3$).

Found : C, 51.5; H, 3.3; N, 30.1%; M^+ 325.

$C_{14}H_{11}N_7O_3$ requires: C, 51.7; H, 3.4; N, 30.1%; M, 325.

7-Amino-6-benzoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (268) and 6-Cyano-7-phenyl-1,2,3-triazolo[5,1-c]-1,2,4,-triazine-3-carboxamide (271)

(i) A melt of the triazolylhydrazone (269) (0.28g, 0.001 mol) was held at 170° (Wood's Metal bath) for 5min. On cooling the melt formed a glass which was triturated with ether to afford the impure triazolotriazine (268) (0.24g; 92%) m.p. 255° which was purified by crystallisation from dimethylformamide-water (0.61g) m.p. 273° and was identical (m.p. and i.r. spectrum) with a sample described before.

(ii) The triazolylhydrazone (269) (0.28g, 0.001 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 24h. Filtration of the cooled solution afforded the triazolotriazine (268) (0.07g) m.p. 265° identical (m.p. and i.r. spectrum) with a sample described before.

The acetic acid filtrate was evaporated and the dark residue was triturated with methanol to give the cyanotriazolotriazine (271) as a brown solid (0.10g) m.p. 187° (from dimethylformamide-water), $\nu_{max.}$ 3450 and

3220 (NH), and 1690 (CO) cm^{-1}, $\lambda_{max.}$ 212, 227, 264sh, 318 and 352sh nm (logε 4.32, 4.34, 4.03, 4.06 and 4.00), τ[$(CD_3)_2SO$] 1.20(2H, br s,NH_2), 5.65(2H, q J 7Hz) and 8.71(3H, t J 7Hz, CH_3).

Found : C, 54.6; H, 2.7; N, 36.6%; $M,^+$ 265.
$C_{12}H_7N_7O$ requires: C, 54.3; H, 2.6; N, 37.0%; M, 265.

(iii) A solution of the N-acetyltriazole (270) (0.48g, 0.0015 mol) in ethanol (10.0 ml) was heated under reflux for 19h. Filtration of the mixture afforded the triazolotriazine (268) (0.04g) m.p. 270° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The ethanol filtrate was evaporated to give a solid (0.34g) m.p. 190° whose t.l.c. in ethanol over silica showed it to be a mixture of two components. Dry column chromatography of the solid in ethanol over silica afforded the cyanotriazolotriazine (271) (0.07g) m.p. 188° which was identical (m.p. and i.r. spectrum) with a sample described earlier.

1,2,3-Triazolo[5,1-c]-1,2,4-triazine-3-carboxamides

80% v/v Aqueous ethanol (50.0 ml) was cooled to 0° (ice-salt bath), saturated with sulphur dioxide and then treated in portions with stirring with the diazonium chloride (44) (0.88g, 0.005 mol). The mixture was resaturated with sulphur dioxide, left at room temperature overnight, and then heated under reflux with the corresponding α-dicarbonyl compound (0.005 mol) for 2h. The reaction mixtures were worked up as described for the individual reactions.

(i) 6,7-Dimethyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (276a)

The reaction mixture from biacetyl on cooling and standing afforded the triazolotriazine (276a) as a yellow solid (68%) m.p. 227° (from water), $\nu_{max.}$ 3500, 3350 and 3150 (NH), and 1670 (CO) cm^{-1}, $\lambda_{max.}$ 209sh, 230, and 329 nm (logε 3.93, 4.26 and 3.24).

Found: C, 43.4; H, 4.2; N, 44.0%; M^+ 192.

$C_7H_8N_6O$ requires: C, 43.7; H, 4.2; N, 43.7%; M, 192.

Concentration of the aqueous ethanolic mother liquour and extraction with chloroform gave a negligible amount of solid.

(ii) 7-Phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (276b)

The mixture from phenylglyoxal was cooled and filtered to afford the triazolotriazine (276b) which crystallised as yellow needles from dimethylformamide-water (50%) m.p. 259°, $\nu_{max.}$ 3400w and 3200w (NH) and 1670 (CO) cm^{-1}, $\lambda_{max.}$ 210, 229sh, 246sh, 278 and 370 nm (logε 4.24, 4.18, 4.10, 4.29 and 3.82); $\tau[(CD_3)_2SO]$ 0.41(1H, s, triazine H), 1.54 - 1.64(2H, m, Ar-H), 2.08(1H, br s, NH), 2.20(1H, br s, NH) and 2.31 - 2.38(3H, m, Ar-H).

Found : C, 55.3; H, 3.2; N, 35.1%; M^+ 240.

$C_{11}H_8N_6O$ requires: C, 55.0; H, 3.4; N, 35.0%; M, 240.

Concentration of the aqueous-ethanolic filtrate and extraction with chloroform gave a negligible amount of an unidentified solid.

(iii) 6,7-Diphenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (276c)

The reaction mixture from benzil was filtered to afford the triazolotriazine (276c) as a yellow solid (82%) m.p. 266° (from dimethylformamide-water), $\nu_{max.}$ 3450w, 3200w (NH) and 1700 (CO) cm^{-1}, $\lambda_{max.}$ 212, 229, 273 and 366 nm (logε 4.42, 4.42, 4.26 and 3.74).

Found : C, 64.2; H, 4.1; N, 26.6%; M^+, 316.

$C_{17}H_{12}N_6O$ requires: C, 64.6; H, 3.8; N, 26.6%; M, 316.

The aqueous-ethanolic filtrate was concentrated to give a solid which was washed with methanol to afford unreacted benzil (0.24g) m.p. 94°,

identical (m.p. and i.r. spectrum) with an authentic sample.

(iv) 6-Phenyl-1,2,3-triazolo[5,1-c]-1,2,3-triazin-7(4H)-one (274) and Ethyl Benzoylformate (4-Carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (275)

The reaction mixture from ethyl benzoylformate was cooled and filtered to give the triazolotriazine (274) as a yellow solid. This was combined with more material obtained by concentrating the aqueous-ethanolic filtrate, filtering and crystallising the mixture of the triazolotriazine (274) and the hydrazone (275) from aqueous dimethylformamide (total 83%) m.p. 268°, $\nu_{max.}$ 3380w and 3200w (NH) and 1750 and 1680(CO) cm^{-1}, $\lambda_{max.}$ 210, 237, 268 and 279nm (logε 4.25, 4.40, 4.18 and 4.13).

Found : C, 51.3; H, 3.2; N, 32.8%; $M,^{+}$ 256.

$C_{11}H_8N_6O$ requires: C, 51.6; H, 3.2; N, 32.8%; $M,^{+}$ 256.

Dilution of the dimethylformamide-water mother liquour with water afforded the yellow triazolylhydrazone (275) (43%) m.p. 247° (from ethanol), $\nu_{max.}$ 3500w, 3400, and 3300w (NH) and 1740, 1700 and 1680 (CO) cm^{-1}, $\tau\left[(CD_3)_2SO\right]$ 2.42 - 2.50(2H, m, Ar-H), 2.59 - 2.66(3H, m, Ar-H), 5.76(2H, q J 7Hz, CH_2) and 8.74(3H, t J 7Hz, CH_3).

Found : C, 49.4; H, 4.1; N, 29.4%; $M,^{+}$ 290.

$C_{12}H_{14}N_6O_3$ requires: C, 49.7; H, 4.8; N, 29.0%; $M,^{+}$ 290.

(v) 1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (276d)

Filtration of the cooled reaction mixture from glyoxal afforded the triazolotriazine (276d) which was combined with a second crop obtained by evaporating the aqueous-ethanolic filtrate m.p. 245° and crystallised from water to give brown needles (95%) m.p. 261°, $\nu_{max.}$ 3450, 3300 and 3200 (NH), and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 227 and 343nm (logε 4.00 and 3.06), $\tau\left[(CD_3)_2SO\right]$ 1.08(1H, d J 6Hz, triazine H), 1.08(1H, d J 6Hz, triazine H), 2.08(1H, br s, NH) and 2.18(1H, br s, NH).

Found : C, 36.5; H, 2.3; N, 51.1%; $M,^{+}$ 99.

$C_5H_4N_6O$ requires: C, 36.6; H, 2.4; N, 51.0%; M, 99.

(vi) 7-Methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (276e)

Concentration of the reaction mixture from methylglyoxal dimethylacetal and extraction with chloroform gave a negligible amount of solid.

The aqueous mother liquor on standing yielded the triazolotriazine (276e) as yellow prisms (25%) m.p. 239° (from water), ν_{max} 3350w and 3100 (NH), and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 209sh, 227 and 334nm (logε 3.93, 4.19 and 3.27), $\tau[(CD_3)_2SO]$ 1.12(1H, s, triazine H) and 6.56(3H, s, CH_3).

Found : C, 40.5; H, 3.4; N, 47.7%; $M,^{+}$ 178.

$C_6H_6N_6O$ requires: C, 40.5; H, 3.4; N, 47.2%; M, 178.

Work up of the aqueous mother liquor by constant chloroform extraction gave no further material.

Coupling Reactions of 4-Ethoxycarbonyl-1H-1,2,3-triazole-5-diazonium Nitrate (280) with Active Methylene Compounds.

A stirred solution of the aminotriazole (168) (1.17g, 0.0075 mol) in concentrated nitric acid (d 1.42; 0.75 ml) and water (1.75 ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of sodium nitrite (0.45g) in water (5.0 ml). After stirring at 0° for 5min, the pale yellow diazonium solution was added dropwise with stirring at 0-10° to a solution of the active methylene compound (0.0075 mol) and anhydrous sodium acetate (0.8g) in water (2.0 ml) and ethanol (5.0 ml). The mixture was stirred at room temperature for 2h and then worked up as described for the individual reactions.

(i) Ethyl 7-Amino-6-cyano-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-Carboxylate (282a).

Filtration of the reaction mixture from malonotrile afforded the deep yellow triazolotriazine (282a) (58%) m.p. 184°(from dimethylformamide-water), $\nu_{max.}$ 3400, 3250, and 3200 - 3100br (NH) and 1710 (CO) cm^{-1} $\lambda_{max.}$ 218, 248, 265, and 310 nm (logε 4.18, 4.28, 4.32 and 3.45).

Found: C, 41.4; H, 3.2; N, 42.0%; $M,^{+}$ 233.

$C_8H_7N_7O_2$ requires: C, 41.2; H, 3.0; N, 42.0%; M, 233.

The aqueous-ethanolic mother liquor was evaporated and the residual solid was triturated with water. Careful acidification of the aqueous solution with aqueous dilute hydrochloric acid gave no further material.

(ii) Ethyl 7-Amino-6-Carbamoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-4-carboxylate (282b)

Filtration of the reaction mixture from cyanoacetamide yielded the yellow triazolotriazine (282b) more of which was obtained by concentrating the aqueous-ethanolic filtrate and adding further water (70%) m.p. 254° (from dimethylformamide-water), $\nu_{max.}$ 3300, and 3150 (NH), and 1690 and 1640 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 1.80(1H,br s, NH), 1.93(1H, s, NH), 2.42(1H, s, NH), 5.40(2H, q J 7Hz, CH_2) and 8.52(3H, t J 7Hz, CH_3).

Found : C, 38.4; H, 3.6; N, 39.4%; $M,^{+}$ 251.

$C_8H_9N_7O_3$ requires: C, 38.3; H, 3.6; N, 39.0%; M, 251.

The aqueous-ethanolic mother liquor was evaporated and the solid obtained was triturated with ethanol to give the betaine (310) (0.93g)

which explodes at 210°, $\nu_{max.}$ 2260 ($\overset{+}{N}\equiv N$) and 1680 - 1660br (CO) cm^{-1}.

(iii) Diethyl 7-Amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3,6-dicarboxylate (282c)

The mixture from ethyl cyanoacetate was filtered to afford the crude triazolotriazine (282c) which was combined with more material obatined by concentrating the aqueous-ethanolic filtrate m.p. 221°, and crystallised to give the aminotriazolotriazine (282c) as yellow needles (89%) m.p. 237° from ethanol), $\nu_{max.}$ 3350, 3250w and 3100 (NH) and 1750 (CO) cm^{-1}, $\lambda_{max.}$ 217, 269 and 400 nm (logϵ 4.22, 4.26 and 3.15), τ [$(CD_3)_2SO$] 0.96(1H, br s,NH), 1.90(1H,br s, NH), 5.54(2H, q J 7Hz, CH_2) 5.68(2H, q J 7Hz, CH_2), 8.62(3H, t J 7Hz, CH_3) and 8.70(3H, t J 7Hz, CH_3).

Found : C, 42.6; H, 4.3; N, 30.0%; $M,^+$ 280.

$C_{10}H_{12}N_6O_4$ requires: C, 42.9; H, 4.3; N, 30.0%; M, 280.

(iv) Ethyl 6-Acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxylate (282d)

The reaction mixture from acetylacetone was filtered to give the triazolotriazine (282d) as a brown solid (35%) m.p. 120 (from dimethylformamide-water), $\nu_{max.}$ 3250 (OH), and 1690 and 1670 (CO) cm^{-1}, $\lambda_{max.}$ 210, 240 and 342 nm (logϵ 4.12, 4.45 and 3.15), τ [$(CD_3)_2SO$] 5.64(2H, q J 7Hz, CH_2), 7.58(3H, s , CH_3), 7.72(3H, s , CH_3) and 8.66(3H, t J 7Hz, CH_3).

Found : C, 48.4; H, 4.5; N, 28.4%; $M,^+$ 249.

$C_{10}H_{11}N_5O_3$ requires: C, 48.2; H, 4.4; N, 28.1%; M, 249.

The aqueous-ethanolic filtrate was concentrated and extracted with chloroform to give a negligible amount of solid.

(v) Diethyl 7-Methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3,6-dicarboxylate (282e)

The reaction mixture from ethyl acetoacetate was completely evaporated leaving an oil which solidified in contact with water and was acidified with aqueous dilute sulphuric acid to afford the impure triazolotriazine (282e) m.p. 100°. Crystallisation from ethanol gave large cream prisms (90%) m.p. 120°, $\nu_{max.}$ 1730 - 1710br (CO) cm^{-1}, $\lambda_{max.}$ 209, 236 and 340 nm (logε 4.10, 4.45 and 3.25), τ ($CDCl_3$) 5.48(2H, q J 7Hz, CH_2), 5.48(2H, q J 7Hz, CH_2), 7.02(3H, s, CH_3), 8.48(3H, t J 7Hz, CH_3) and 8.48($3H_2$, t J 7Hz, CH_3).

Found : C, 47.3; H, 4.8; N, 25.4%; $M,^+$ 279.
$C_{11}H_{13}N_5O_4$ requires: C, 47.4; H, 4.8; N, 25.1%; M, 279.

(vi) Diethyl Mesoxalate 2-(4-ethoxycarbonyl-1H-1,2,3-triazol-5-yl) hydrazone (284a)

Filtration of the reaction mixture from diethyl malonate yielded the colourless triazolylhydrazone (284a) (79%) m.p. 70° (from dimethyformamide-water), $\nu_{max.}$ 3420 - 3380br and 3180w (NH), and 1730, 1700 and 1675 (CO) cm^{-1}, τ($CDCl_3$) 5.52(2H, q J 7Hz, CH_2), 5.60(2H, q J 7Hz, CH_2), 5.66(2H, q J 7Hz, CH_2), 8.58(3H, t J 7Hz, CH_3), 8.62(3H, t J 7Hz, CH_3) and 8.66(3H, t J 7Hz, CH_3).

Found : C, 41.8; H, 5.5; N, 20.3%; $M,^+$ 327.
$C_{12}H_{17}N_5O_6$ requires: C, 41.7; H, 5.5; N, 20.3%; M, 327.

(vii) Ethyl 2-Benzoylglyoxylate 2-(4-ethoxycarbonyl-1H-1,2,3-triazol-5-yl) hydrazone (284b)

Filtration of the reaction mixture from ethyl benzoylacetate yielded the crude triazolylhydrazone (284b) m.p. 126° which crystallised from ethanol as a pale yellow solid (65%) m.p. 164°, $\nu_{max.}$ 3120 (NH) and 1700 and 1660 (CO) cm^{-1}, τ ($CDCl_3$) 2.11 - 2.20(2H, m, Ar-H), 2.52 - 2.74(3H, m, Ar-H), 5.54(2H, q J 7Hz, CH_2), 5.66(2H, q J 7Hz, CH_2), 8.56(3H, t J 7Hz, CH_3) and 8.76(3H, t J 7Hz, CH_3).

Found : C, 53.8; H, 4.9; N, 19.9%; M^+ 359.
$C_{16}H_{17}N_5O_5$ requires: C, 53.6; H, 4.7; N, 19.6%; M, 359.

Coupling Reactions of 3-Ethoxycarbonyl-1H-1,2,3-triazole-5-diazonium Nitrate (280) with Active Methylene Compounds.

A stirred solution of the 1,5-diamino-1,2,3-triazole (264) (1.28g, 0.0075 mol) in concentrated nitric acid (d 1.42; 0.75 ml) and water(1.75 ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of sodium nitrite (0.45g) in water (5.0 ml). After stirring at 0° for 5 min, the pale yellow diazonium solution was added dropwise with stirring at 0 - 10° to a solution of the active methylene compound (0.0075 mol) and anhydrous sodium acetate (0.8g) in water (2.0 ml) and ethanol (5.0 ml). The mixture was stirred at room temperature for 2h and then worked up as described for the individual reactions.

(i) Diethyl Mesoxalate 2-(4-ethoxycarbonyl-1H-1,2,3-triazol-5-yl) hydrazone (284a)

The reaction mixture from diethyl malonate was concentrated under reduced pressure and the aqueous mother liquor was extracted with chloroform to give an oil which was triturated with light petroleum to afford the

triazolylhydrazone (284a) (14%) m.p. 76, identical (m.p. and i.r. spectrum) with a sample described before. Evaporation of the light petroleum mother liquour gave no further solid material.

Working up the aqueous mother liquour gave no identifiable material.

(ii) Ethyl 6-Acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxylate (282d)

The reaction mixture from acetylacetone was concentrated to remove the ethanol and extracted with chloroform to give an oil whose t.l.c. in methanol over alumina showed it to be a single component. Trituration of the oil with ether afforded the triazolotriazine (282d) (38%) m.p. 120°, identical (m.p. and i.r. spectrum) with an authentic sample.

(iii) Ethyl 7-Amino-6-benzoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxylate (282f)

The reaction mixture from 2-cyanoacetophenone was filtered to afford the impure triazolotriazine (282f) which was combined with a second crop obtained by concentrating the filtrate, extracting with chloroform and triturating the resulting oil with light petroleum, m.p. 120°. Crystallisation from ethanol-water gave yellow needles (45%) m.p. 226°, ν max. 3300, and 3150 (NH), and 1740 and 1655(CO) cm^{-1}, λmax. 210, 237sh, 257sh and 270 nm (logε 4.25, 4.30, 4.37 and 4.37), τ [$(CD_3)_2SO$] 1.80 - 1.98(2H, m, Ar-H), 2.18 - 2.40(3H, m, Ar-H), 5.62(2H, q J 7Hz, CH_2) and 8.66(3H, t J 7Hz, CH_3).

Found : C, 54.3; H, 3.9; N, 27.2%; M^+ 312.

$C_{14}H_{12}N_6O_3$ requires: C, 53.9; H, 3.9; N, 26.9%; M, 312.

The light petroleum mother liquor on evaporation gave a semi-solid

which was washed with methanol to give a solid (0.26g) m.p. 183°. This was washed with aqueous dilute sodium hydroxide to leave the insoluble triazolotriazine (282f) m.p. 200°, identical (i.r. and mass spectra) with an authentic sample.

The alkaline extract was acidified with aqueous dilute hydrochloric acid to give unreacted 2-cyanoacetophenone (0.09g) m.p. 80° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(iv) Ethyl 6-Benzoyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxylate (282g)

The reaction mixture from benzoylacetone was concentrated and extracted with chloroform to give an oil which was triturated with ethanol to yield the triazolotriazine (282g) (32%) m.p. 155°. Crystallisation from ethanol gave yellow plates (0.46g) m.p. 164°, νmax. 1720, and 1680 (CO) cm^{-1}, λmax. 215sh, 228, 247 and 271 nm (logε 4.36, 4.40, 4.38, and 4.15), τ ($CDCl_3$) 1.96 - 2.06(2H, m, Ar-H), 2.28 - 2.55(3H, m, Ar-H), 5.47(2H, q J 7Hz, CH_2), 7.18(3H, s, CH_3) and 8.54(3H, t J 7Hz, CH_3).

Found : C, 57.8; H, 4.2; N, 22.6%; M^+ 311.
$C_{15}H_{13}N_5O_3$ requires: C, 57.9; H, 4.2; N, 22.5%; M, 311.

1,3-Diphenylpropane-1,2,3-trione 2-(4-ethoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (284c)

Filtration of the reaction mixture from dibenzoyl-methane gave a solid m.p. 115° which was crystallised from benzene to afford the triazolylhydrazone (284c) as yellow prisms (31%) m.p. 116°, νmax. 3245 (NH) and 1670 and 1650 (CO) cm^{-1}.

Found : C, 59.9; H, 4.5; N, 17.9%; P^+ 373 ($M^+ - H_2O$)
$C_{20}H_{15}N_5O_3$ requires: C, 61.2; H, 4.4; N, 17.9%; M, 391.

The benzene mother liquor on evaporation left a residue which was triturated with ether to yield unreacted dibenzoylmethane which was combined with a second crop obtained by evaporating the ether mother liquor (68%) m.p. 80°, identical (m.p. and i.r. spectrum) with an authentic sample.

The Reactions of the Triazolylhydrazones (284a-c) with Acetic Anhydride

The triazolylhydrazones (284a-c) (0.002 mol) were heated under reflux in acetic anhydride (10.0 ml) for 5min. The solutions were evaporated under reduced pressure and the resulting oils were triturated as described for the various reactions.

(i) Diethyl Mesoxalate 2-(1-Acetyl-4-ethoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (279)

Triturating the oil from (284a) with ether afforded the impure acetyl derivative (279) (70%) which crystallised from ethanol-light petroleum as a colourless solid m.p. 100°, $\nu_{max.}$ 1760, 1715, 1695 and 1670w (CO) cm^{-1}, τ ($CDCl_3$) 5.46(2H, q J 7Hz, CH_2), 5.64(4H, q J 7Hz, CH_2), 7.16(3H, s, $COCH_3$), 8.54(3H, t J 7Hz, CH_3) and 8.62(6H, t J 7Hz, CH_3).

Found: C, 45.3; H, 5.1; N, 18.9%; M^+ 369.

$C_{14}H_{19}N_5O_7$ requires: C, 45.5; H, 5.2; N, 19.0%; M, 369.

The ether mother liquor on evaporation left an oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of two components, one of which was the acetyl derivative (279).

(ii) The oil from (284b) was triturated with ethanol-ether to afford the unreacted triazolylhydrazone (284b) (27%) m.p. 170°, identical (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the

ethanol-ether mother liquor left an oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of two components, one of which was the starting material.

(iii) The oil from (284c) was triturated with ethanol-water to give a solid m.p. 215° which had a poorly resolved i.r. spectrum. This was crystallised from ethanol-ethyl acetate to afford the unreacted hydrazone (284c) which was combined with a second crop obtained by evaporating the ethanol-water mother liquour and triturating the resulting oil with water (yield 55%) m.p. 120° identical (m.p. and i.r. spectrum) with an authentic sample.

Cyclisations of the Triazolylhydrazones (284a-c) to the 1,2,3-triazolo-[5,1-c]-1,2,4-triazines (286a and b) and (285a)

(a) Using Ethanolic Sodium Acetate

A solution of the hydrazone (284a) (0.65g, 0.002 mol) in ethanol (20.0 ml) and water (10.0 ml) was heated under reflux with anhydrous sodium acetate (0.32g) for 1h. The solution on evaporation afforded an oil which was treated with water to give the unreacted triazolylhydrazone (284a) (0.17g) m.p. 76°, identical (m.p. and i.r. spectrum) with an authentic sample.

Acidification of the aqueous mother liquor and extraction with chloroform yielded a solid which was triturated with water to afford the triazolotriazinone (285a) as a colourless solid (0.23g) m.p. 144° (from ethanol), $\nu_{max.}$ 3100w (NH, OH) and 1730, 1710 and 1690 (CO) cm^{-1}, $\lambda_{max.}$ 210, 229, 283 and 370 nm (log ε 4.24, 4.32, 4.12 and 3.72), τ [$CDCl_3$ - $(CD_3)_2SO$] 5.42 - 5.70(4H, 2 overlapping quartets J 7Hz, CH_2) and 8.52 - 8.68(6H, 2 overlapping triplets J 7Hz, CH_3).

Found: C, 42.8; H, 4.0; N, 24.9%; M^+ 281.

$C_{10}H_{11}N_5O_5$ requires: C, 42.7; H, 3.9; N, 24.9%; M, 281.

(b) Using Glacial Acetic Acid

The triazolylhydrazones (284a and b) (0.001 mol) were heated under reflux in glacial acetic acid (10.0 ml) for 1h. The solutions were evaporated under reduced pressure and the oils obtained were triturated with ether and water respectively to afford the triazolotriazines (286a and b) (92-97%).

Diethyl 7-Phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3,6-dicarboxylate (286a) was obtained as a yellow solid m.p. 120° (from ethanol) νmax. 1730 and 1710 (CO) cm^{-1}, λmax. 208, 242, 270sh and 347 nm (logε 4.11, 4.44, 4.05 and 3.67), τ ($CDCl_3$) 2.14-2.24(2H, m, Ar-H), 2.38-2.48(3H, m, Ar-H), 5.40(2H, q J 8Hz, CH_2), 5.58(2H q J 8Hz, CH_2), 8.52(3H, t J 8Hz, CH_3) and 8.72(3H, t J 8Hz, CH_3).

Found: C, 56.2; H, 4.5; N, 20.4%; M^+ 341.

$C_{16}H_{15}N_5O_4$ requires: C, 56.3; H, 4.4; N, 20.5%; M, 341.

Ethyl 6-Benzoyl-7-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxylate (286b) was obtained as a pale yellow solid m.p. 135° (from ethanol), ν max. 1728 and 1660 (CO) cm^{-1}, λ max. 211, 233, 255sh and 277sh and 370 nm (logε 4.40, 4.40, 4.33, 4.28 and 3.72), τ [$(CD_3)_2SO$] 1.83-2.00(2H, m, Ar-H), 2.38-2.60(8H, m, Ar-H), 5.63(2H, q J 7Hz, CH_2) and 8.70(3H, t J 7Hz, CH_3).

Found: C, 64.0; H, 4.0; N, 18.8%; M^+ 373.

$C_{20}H_{15}N_5O_3$ requires: C, 64.3; H, 4.1; N, 18.8%; M^+ 373.

Coupling Reactions of 4-phenyl-1H-1,2,3-triazole-5-diazonium Chloride (36) and 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride (44) with Substituted Pyruvic Esters (287)

A solution of diethyl oxaloacetate (287a), ethyl acetopyruvate (287b), ethyl benzoylpyruvate (287c) or the sodium salt of ethyl 2-cyanopyruvate (287d) and anhydrous sodium acetate (0.54g) in water (10.0 ml) and ethanol (10.0 ml) was treated dropwise with stirring at 0° (ice-salt bath) with a solution of the diazonium salts (36) or (44) in water (10.0 ml) and ethanol (10.0 ml). The mixture was stirred in the melting ice-bath for 2h and then worked up as described for the individual reactions.

(i) Ethyl 2-Ethoxycarbonyl-2-(4-phenyl-1H-1,2,3-triazol-5-ylhydrazono)-pyruvate (288a)

Filtration of the reaction mixture from diethyl oxaloacetate (287a) and (36) gave the impure triazolylhydrazone (288a) m.p. 160°, which crystallised from a mixture of benzene-ethanol-light petroleum as colourless prisms (88%) m.p. 184°, $\nu_{max.}$ 3360br and 3220 - 3180br (NH), and 1740 and 1710 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 2.12 - 2.24(2H, m, Ar-H), 2.58 - 2.72(3H, m, Ar-H), 5.66(2H, q J 7Hz, CH_2), 5.78(2H, q J 7Hz, CH_2), 8.68(3H, t J 7Hz, CH_3) and 8.80(3H, t J 7Hz, CH_3).

Found: C, 53.2; H, 4.6; N, 19.4%; M^+ 359.

$C_{16}H_{17}N_5O_5$ requires: C, 53.4; H, 4.7; N, 19.5%; M, 359.

The aqueous ethanolic filtrate was concentrated and extracted with chloroform to give a gum which was triturated with ethanol-ether to afford the betaine[39] (292a) m.p. 132° (from ethanol-light petroleum) (lit.,[39] 124°) which was identical (m.p. and i.r. spectrum) with an authentic sample.[39]

(ii) Ethyl 2-Acetyl-2-(4-phenyl-1H-1,2,3-triazol-5-ylhydrazono)pyruvate (288b)

The reaction mixture from (36) and ethyl acetopyruvate (287b) was concentrated to remove the ethanol and extracted with chloroform. Evaporation of the chloroform gave a foam which was triturated with ether to give the impure triazolylhydrazone (288b) m.p. 155°. Crystallisation from ethanol-water gave the pure hydrazone (69%) m.p. 167°, $\nu_{max.}$ 3260br (NH) and 1760 and 1660 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 2.12 - 2.26(2H, m, Ar-H), 8.52 - 8.68(3H, m, Ar-H), 5.75(4H, q J 7Hz, CH_2), 8.73(3H, t J 7Hz, CH_3) and 8.85(3H, t J 7Hz, CH_3).

Found: C, 55.3; H, 4.5; N, 21.5%; M^+ 329.

$C_{15}H_{15}N_5O_4$ requires: C, 54.7; H, 4.6; N, 21.3%; M, 329.

(iii) Ethyl 2-Benzoyl-2-(4-phenyl-1H-1,2,3-triazol-5-ylhydrazono)pyruvate (288c)

The reaction mixture from the phenyltriazole (36) and ethyl benzoylpyruvate (287c) was concentrated to remove the ethanol and extracted with chloroform to give a foam which was triturated with hot water to afford the triazolylhydrazone (288c) as a pale yellow solid (97%) m.p. 101° (from benzene), $\nu_{max.}$ 3540 (NH) and 1735 and 1640 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 1.48(1H, s, NH), 2.07 - 2.16(4H, m, Ar-H), 2.41 - 2.60(6H, m, Ar-H), 5.78(2H, q J 7Hz, CH_2) and 8.88(3H, t J 7Hz, CH_3).

Found: C, 59.8; H, 4.4; N, 17.2%; P^+, 373 ($M^+ - H_2O$).

$C_{20}H_{17}N_5O_4$ requires: C, 61.5, H, 4.4; N, 18.8%; M, 391.

(iv) Ethyl 2-Cyano-2-(4-phenyl-1H-1,2,3-triazol-5-ylhydrazono)pyruvate (288d)

The reaction mixture from the phenyltriazole (36) and the sodium salt of ethyl 2-cyanopyruvate (287d) was concentrated and extracted with chloroform. The two phase system was filtered to afford the impure

triazolylhydrazone (288d) which was combined with a second crop obtained by evaporating the chloroform extract and triturating the oil obtained with ether. Crystallisation from ethanol-water gave the pure hydrazone as a pale pink solid (55%) m.p. 152°, $\nu_{max.}$ 3330wbr, 3210w, and 3160br (NH), 2240(C≡N), and 1760 (CO) cm^{-1}, τ[$CDCl_3$ - $(CD_3)_2SO$] 2.12 - 2.22(2H, m, Ar-H), 2.42 - 2.65(3H, m, Ar-H), 5.-6(2H, q J 7Hz, CH_2) and 8.74(3H, t J 7Hz, CH_3).

Found: C, 54.2; H, 3.9; N, 26.8%; M^+ 312.

$C_{14}H_{12}N_6O_3$ requires: C, 53.8; H, 3.9; N, 26.9%; M, 312.

(v) Ethyl 2-Ethoxycarbonyl-2-(4-carbamoyl-1H-1,2,3-triazol-5-ylhydrazono)-pyruvate (290a)

The reaction mixture from the triazole amide (44) and diethyl oxaloacetate (287a) was concentrated to remove the ethanol and filtered to yield the impure triazolylhydrazone (290a) m.p. 145° which was purified by crystallisation from aqueous-ethanol (45%) m.p. 166°, $\nu_{max.}$ 3450, 3320 and 3200 br (NH) and 1770, 1720 and 1680 (CO) cm^{-1}, τ[$CDCl_3$ - $(CD_3)_2SO$] 1.74(1H, s, NH), 2.56(1H, s, NH), 3.01(1H, s, NH), 5.70(2H, q J 7Hz, CH_2), 5.80(2H, q J 7Hz, CH_2), 8.70(3H, t J 7Hz, CH_3) and 8.98(3H, t J 7Hz, CH_3).

Found: C, 39.8; H, 4.4; N, 25.4%; P^+, 308 (M^+-H_2O).

$C_{11}H_{14}N_6O_6$ requires: C, 40.5; H, 4.3; N, 25.8%; M, 326.

Extraction of the aqueous mother liquor with chloroform gave no material.

(vi) Ethyl 2-Acetyl-2-(4-carbamoyl-1H-1,2,3-triazol-5-ylhydrazono)-pyruvate (290b)

Filtration of the reaction mixture from the triazole amide (44) and ethyl acetopyruvate (287b) afforded the triazolylhydrazone (290b) which

was combined with a second crop obtained by concentrating the ethanol-water mother liquor m.p. 175° and crystallised from ethanol-light petroleum (72%) m.p. 187°, νmax. 3560, 3420, 3360 and 3260 (NH) and 1750, 1740 and 1670 (CO) cm^{-1}.

Found: C, 40.6; H, 4.1; N, 28.4%; M^+, 296.

$C_{10}H_{12}N_6O_5$ requires: C, 40.5; H, 4.1; N, 28.4%; M, 296.

(vii) Ethyl 2-Benzoyl-2-(4-carbamoyl-1H-1,2,3-triazol-5-ylhydrazono)-pyruvate (290c)

The reaction mixture from the triazole amide (44) and ethyl benzoylpyruvate (287c) was concentrated and extracted with chloroform to give an oil which was triturated with ethanol-ether to afford the triazolylhydrazone (290c) (95%) m.p. 178° which crystallised from ethanol-light petroleum as a cream solid m.p. 177°, νmax. 3450, 3330 and 3180br (NH) and 1765 and 1675 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 1.40(1H, s, NH), 2.00 - 2.17(2H, m, Ar-H), 2.36 - 2.50(3H, m, Ar-H), 5.76(2H, q J 7Hz, CH_2) and 8.88(3H, t J 7Hz, CH_3).

Found: 358.101644 .

$C_{15}H_{14}N_6O_5$ requires: 358.102559.

(vii) Ethyl 2-Cyano-2-(4-carbamoyl-1H-1,2,3-triazol-5-ylhydrazono)-pyruvate (290d)

The reaction mixture from the triazole amide (44) and the sodium salt of ethyl 2-cyanopyruvate (287d) was concentrated to remove the ethanol and filtered to afford the impure triazolylhydrazone (290d) m.p. 146° which formed pale yellow prisms (76%) m.p. 152° (from water), νmax. 3540br, 3430, 3280 and 3140br (NH), 2240 (C≡N), and 1750 and 1660 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 1.90(1H, s, NH), 2.33(1H, s, NH), 5.68(2H, q J 7Hz,

CH_2) and 8.80(3H, t J 7Hz, CH_3).

Found: C, 38.5; H, 3.2; N, 35.2%; M^+ 279.

$C_9H_9N_7O_4$ requires: C, 38.7; H, 3.2; N, 35.1%; M, 279.

The Attempted Coupling of the Diazonium Salt (36) with Diethyl Oxaloacetate (287a) in the Presence of Sodium Hydroxide

A solution of the keto-diester (287a) (0.37g, 0.002 mol) in ethanol (5.0 ml) and aqueous 2M sodium hydroxide (5.0 ml) was treated dropwise with stirring at 0° (ice-salt bath) with a solution of the diazonium salt (44) (0.42g, 0.002 mol) in ethanol (10.0 ml) and water (10.0 ml), and the mixture was stirred in the melting ice-bath for 2h. The solution was concentrated and extracted with chloroform to afford a negligible amount of solid.

The aqueous extract was acidified with aqueous dilute hydrochloric acid and extracted with chloroform to yield a small amount of solid which was triturated with ether to afford the deaminated triazole (293) (0.01g) m.p. 140°, identical (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Acetylation of the Triazolylhydrazones (288a) and (290a)

The hydrazones (288a) and (290a) (0.002 mol) were heated under reflux in acetic anhydride (10.0 ml) for 5min. The solutions were evaporated under reduced pressure and the resulting red oil or foam was treated as described for each reaction below.

(i) The oil from (288a) was suspended in water and extracted with chloroform to afford a gum which in contact with water afforded a solid (0.25g) m.p. 90°. The solid had a poorly resolved i.r spectrum and decomposed rapidly at room temperature.

Evaporation of the aqueous mother liquor left a small amount of oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of three components.

(ii) The foam (0.63g) from (290b) showed a poorly resolved i.r. spectrum and its t.l.c. in ethyl acetate alone or containing ethanol over silica showed it to be an unresolved mixture of three components, one of which was the starting triazolylhydrazone (290b). Trituration of the foam with various solvents gave no identifiable material.

The Cyclisations of the Triazolylhydrazones (288a-d) and (290b-d) to the 1,2,3-triazolo[5,1-c]-1,2,4-triazines (289a-d) and (291b-d)

(a) In Glacial Acetic Acid

The triazolylhydrazones (288a-d) and (290b-d) (0.001 mol) were heated under reflux in glacial acetic acid (10.0 ml) for 3h. The solutions were evaporated under reduced pressure and the oils left were triturated with ether to afford the corresponding triazolotriazines (289a-d) and (291b-d) (36 - 90%) or the unreacted triazolylhydrazone (290a) (78%).

(i) Diethyl 3-Phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6,7-dicarboxylate (289a) was obtained as bright orange plates m.p. 132° (from ethanol), $\nu_{max.}$ 1740 and 1720w (CO) cm^{-1}, $\lambda_{max.}$ 210, 222inf., 260, 320 inf. and 430 nm (logε 4.26, 4.10, 4.37, 3.48 and 3.45), τ($CDCl_3$) 1.59 - 1,68(2H, m, Ar-H), 2.48 - 2.56(3H, m, Ar-H), 5.44(2H, q J 7Hz, CH_2), 5.46(2H, q J 7Hz, CH_2), 8.52(3H, t J 7Hz, CH_3) and 8.52(3H, t J 7Hz, CH_3).

Found: C, 56.1; H, 4.4; N, 20.7%; M^+ 341.

$C_{16}H_{15}N_5O_4$ requires: C, 56.3; H, 4.4; N, 20.5%; M, 341.

The ether mother liquor on standing deposited the yellow acetoxy derivative (299a) (22%) m.p. 71° (from ethanol) $\nu_{max.}$ 1750, 1740w and 1725 (CO) cm^{-1}, τ($CDCl_3$) 2.50 - 2.59(2H, m, Ar-H), 2.66 - 2.82(3H,

m, Ar-H), 3.16(1H, s, CHOAc), 5.58(2H, q J 7Hz, CH_2), 5.74(2H, q J 7Hz, CH_2), 7.90(3H, s, CH_3), 8.70(3H, t J 7Hz, CH_3) and 8.72(3H, t J 7Hz, CH_3).

Found: C, 57.5; H, 4.9; N, 13.6%; $M,^+$ 373.
$C_{18}H_{19}N_3O_6$ requires: C, 57.9; H, 5.1; N, 11.3%; M, 373.

(ii) Ethyl 6-Acetyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylate (289b) crystallised as yellow needles from ethanol m.p. 158°, ν max. 1735 and 1700 (CO) cm^{-1}, λ max. 211, 226inf., 260, 315 and 430 nm (logε 4.34, 4.16, 4.33, 3.63 and 3.27), $\tau(CDCl_3)$ 1.65 - 1.74(2H, m, Ar-H), 2.52 - 2.60(3H, m, Ar-H), 5.50(3H, q J 7Hz, CH_2), 7.20(3H, s, CH_3) and 8.58(3H, t J 7Hz, CH_3).

Found: C, 57.8; H, 4.2; N, 22.5%; $M,^+$ 311.
$C_{15}H_{13}N_5O_3$ requires: C, 57.8; H, 4.2; N, 22.5%- M, 311.

The ether mother liquor on evaporation left an oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of three components. The ^1H n.m.r. spectrum of the oil $\tau(CDCl_3)$ 2.50(23 units, m, Ar-H), 2.94(4 units, s, CH), 3.02(2units, s, CH), 5550(10 units, m, CH_2), 7.10(10 units, s, CH_3), 7.62(10 units, s, CH_3), 7.84(3 units, s, CH_3) and 8.16(10 units, m, CH_3) showed it to contain the acetoxy and hydroxyl derivatives (299b) and (300).

(iii) Ethyl 6-Benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylate (289c) crystallised as bright orange prisms (72%) from benzene-light petroleum, m.p. 127° νmax. 1750 and 1700 (CO) cm^{-1}, λmax. 211, 257 and 430 nm (logε 4.47, 4.50 and 3.54), $\tau(CDCl_3)$ 1.50 - 1,59(2H, m, Ar-H), 1.86 - 1.96(3H, m, Ar-H), 2.24 - 2.36(2H, m, Ar-H),

2.42 - 2.49(3H, m, Ar-H), 5.54(2H, q J 7Hz, CH_2) and 8.66(3H, q J 7Hz, CH_3).

Found: C, 64.4; H, 4.1; N, 19.0%; M^+ 373.

$C_{20}H_{15}N_5O_3$ requires: C, 64.3; H, 4.1; N, 18.8%; M, 373.

(iv) Ethyl 6-Cyano-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylate (289d) had m.p. 205° (from dimethyformamide-water), νmax. 1710 (CO) cm^{-1}, λmax. 211, 252, 270 and 333 nm (logε 4.37, 4.27, 4.31 and 3.58).

Found: C, 57.1; H, 3.4; N, 28.0%; M^+ 294.

$C_{14}H_{10}N_6O_2$ requires: C, 57.1; H, 3.4; N, 28.5%; M, 294.

Evaporation of the ether mother liquor gave an oil whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable mixture of three components containing both the triazolotriazine (289d) and the unreacted triazolylhydrazone (288d).

(v) Ethyl 6-Acetyl-3-carbamoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylate (291b) had m.p. 136°, νmax. 3420, 3270 and 3140br (NH) and 1725, 1690 and 1675 (CO) cm^{-1}.

Found: C, 40.6; H, 4.1; N, 28.8%; M^+, 278.

$C_{10}H_{10}N_6O_4H_2O$ requires: C, 40.5; H, 4.1; N, 28.4%; M(monohydrate), 296.

(vi) Ethyl 6-Benzoyl-3-carbamoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylate (291c) crystallised as yellow prisms from ethanol m.p. 217° νmax. 3460 and 3350 (NH) and 1730, 1685 and 1670 (CO) cm^{-1}, λmax. 210sh, 231sh, 249 and 341 nm (logε 3.90, 4.10, 4.16 and 3.42), τ[$(CD_3)_2SO$] 1.74 - 1,93(2H, m, Ar-H), 2.08 - 2.46(3H, m, Ar-H), 5.65(2H, q J 7Hz, CH_2) and 8.81(3H, t J 7Hz, CH_3).

Found: C, 52.5; H, 3.5; N, 24.8%; M_+ 340.

$C_{15}H_{12}N_6O_4$ requires : C, 52.9; H, 3.6; N, 24.7%; M, 340.

(vii) Ethyl 3-Carbamoyl-6-cyano-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylate (291d) crystallised as a pale yellow solid from water, m.p. 149°, νmax. 3360, 3270w and 3150 (NH), and 1720 and 1675 (CO) cm^{-1}, λmax. 211, 250, 322 and 376 nm (logϵ 4.08, 3.93, 4.17 and 3.90), τ[$CDCl_3$ - $(CD_3)_2SO$] 2.00 - 2.50(2H, m, NH), 5.42(2H, q J 7Hz, CH_2) and 8.51(3H, t J 7Hz, CH_3).

Found: C, 41.5; H, 2.8; N, 37.6%; M_+ 261.

$C_9H_7N_7O_3$ requires : C, 41.4; H, 2.7; N, 37.5%; M, 261.

(viii) Ethyl 2-Ethoxycarbonyl-2-(4-carbamoyl-1H-1,2,3-triazol-5-yl-hydrazono)pyruvate (290a) had m.p. 162° (from ethanol-water) and was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) In Ethanol

The triazolylhydrazones (288 b and c) and (290 a-c) (0.001 mol) were heated under reflux in ethanol (10.0 ml) for 3h. The solutions were evaporated to give oils or a foam which were worked up as described for the individual reactions.

(i) The oil from (288b) was triturated with ether to give the triazolotriazine (289b) (22%) m.p. 145° which was identical (i.r. spectrum) with the sample prepared above.

The ether mother liquor" on evaporation left an oil whose t.l.c. in ethyl acetate over silica showed it to contain two components one of which had the same Rf value as the triazolotriazine (289b). No attempt was made to resolve the oil into its components.

(ii) The oil from (288c) was triturated with ether to yield the triazolotriazine (289c) (65%) m.p. 125° identical (m.p. and i.r. spectrum) with the sample prepared before.

Evaporation of the ether mother liquor left a small amount of oil whose t.l.c. in ethyl acetate over silica showed it to be a mixture of two components, one of which was the triazotriazine (289c).

(iii) Trituration of the oil from (290b) with ethanol-ether afforded the unreacted triazolylhydrazone (290b) (55%) m.p. 165° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The ethanol-ether mother liquor on evaporation left an oil (0.12g) whose t.l.c. in ethyl acetate or ethyl acetate-ethanol over silica showed it to be a single component which was not further investigated.

(iv) Trituration of the oily solid from (290c) with ether gave the triazolotriazine (290c) (95%) m.p. 217° which was identical (m.p. and i.r. spectrum) with the sample prepared before.

(v) The foam from (290a) was triturated with light petroleum to afford a solid m.p. 75° which crystallised from ethanol-water to give the unreacted triazolylhydrazone (290a) (65%) m.p. 162° which was identical (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.

The Attempted Cyclisation of the Triazolylhydrazone (290a)

(a) In the Presence of Sodium Acetate

A solution of the triazolylhydrazone (290a) (0.65g, 0.002 mol) in water (5.0 ml) and ethanol (10.0 ml) was treated with anhydrous sodium acetate (0.16g) and heated under reflux for 1h. The mixture was evaporated and the residue was triturated with water and filtered to yield the unreacted triazolylhydrazone (290a) (0.22g) m.p. 140°, identical (i.r. spectrum) with an authentic sample.

The aqueous mother liquor was acidified with aqueous dilute sulphuric acid to give an unidentified solid (0.08g) m.p. 170° which was crystallised from ethanol-water (0.01g) m.p. 240°, νmax. 3450, 3320 and 3200 (NH) and 1740, 1710, and 1660 (CO) cm^{-1}, M^+, 350.

The acidic aqueous mother liquor on standing deposited more unreacted triazolylhydrazone (290a) (0.04g) m.p. 165° which was identified by comparison (i.r. spectrum) with an authentic sample. The aqueous acidic mother liquor was evaporated and the residue was extracted with hot absolute ethanol to give an oil whose trituration with various solvents yielded no more material.

(b) In the Presence of Piperidine

A solution of the triazolylhydrazone (290a) (0.65g, 0.002 mol) in ethanol (15.0 ml) containing piperidine (0.2 ml) was heated under reflux for 24h. The solution was evaporated and the reddish brown solid obtained was dissolved in water, acidified with aqueous dilute sulphuric acid and extracted with chloroform. The insoluble solid present in the chloroform-water mixture was filtered off (0.10g) m.p. 200° and crystallised from ethanol to afford the acid (306) (0.04g) m.p. 227°, νmax. 3400, 3250w and 3200 (NH) and 1730, 1700 and 1680 (CO) cm^{-1}.

Found: C, 44.7; H, 4.2; N, 30.1%; M^+, 319.

$C_{12}H_{13}N_7O_4$ requires: C, 45.0; H, 4.2; N, 30.0%; M, 319.

Evaporation of the chloroform extract gave a gum from which no identifiable material could be obtained.

The aqueous extract was neutralised with solid sodium acetate and on standing yielded the piperidide (307) (0.05g) m.p. 168°, which was crystallised from ethanol-light petroleum (0.03g) m.p. 186°, νmax. 3450w and 3350w (NH), and 1740 and 1650 (CO) cm^{-1}.

Found: 275.111516.

$C_{11}H_{13}N_7O_2$ requires: 275.113066.

(c) In the Presence of Sodium Carbonate

A solution of the triazolylhydrazone (290a) (0.65g, 0.002 mol) in ethanol (20.0 ml) and aqueous 1M sodium carbonate solution (10.0 ml) was heated under reflux for 1h. The mixture was filtered hot and the solid obtained was dissolved in water and acidified with aqueous dilute hydrochloric acid to afford a solid. This was combined with more material obtained by concentrating the alkaline filtrate, acidifying with aqueous dilute hydrochloric acid, evaporating the acidic aqueous mother liquor, and triturating the residue with water (total 0.23g) m.p. $>320^\circ$; $\nu_{max.}$ 3370wbr, 3320w and 3200br (NH) and 1735, 1700 and 1650 (CO) cm^{-1}. This solid was left standing in sodium hydrogen carbonate for 0.5h when it left a solid which tarnished on filtration.

The Reaction of the Triazolylhydrazone (290a) with Ammonia.

A solution of the hydrazone (290a) (0.32g, 0.001 mol) in absolute ethanol (25.0 ml) was cooled to 0° (ice-salt bath), saturated with ammonia gas and left at room temperature for 16h. Filtration of the mixture yielded a solid (0.32g) m.p. $>320^\circ$ which showed a poorly resolved i.r. spectrum. This solid was suspended in water and acidified with aqueous dilute hydrochloric acid to give a solid (0.22g) m.p. $>320^\circ$ which was crystallised from dimethylformamide-water to afford an unidentified product (0.08g) m.p. $>320^\circ$, $\nu_{max.}$ 3460, 3390 and 3320 - 3200br (NH) and 2740wbr (NH, OH) and 1790, 1740 and 1700br (CO) cm^{-1}.

Found: 207.050202.

$C_6H_5N_7O_2$ requires: 207.050468.

The Reaction of the Triazolylhydrazone (290a) with Hydrazine Hydrate

A solution of the hydrazone (290a) (0.65g, 0.002 mol) in absolute ethanol (30.0 ml) was treated with 100% hydrazine hydrate (0.5 ml) and heated under reflux for 1.5h. The mixture (which contained solid) was concentrated and diluted with water to afford a solid (0.47g) m.p. >300°, which showed a poorly resolved i.r. spectrum. This solid was stirred in aqueous dilute acetic acid and then crystallised from water to give the hydrazide (309) (0.32g) m.p. >320° which showed a poorly resolved i.r. spectrum and gave no ion pressure on attempted mass spectral analysis.

Found: C, 29.3; H, 3.5; N, 43.0%.

$C_6H_6N_8O_2H_2O$ requires: C, 28.0; H, 3.8; N, 43.4%.

The Hydrolysis of the Triazolotriazines (289a) and (289c) with Aqueous Sodium Carbonate Solution.

Solutions of the triazolotriazines (289a) and (289c) (0.001 mol) in ethanol (15.0 ml) were heated under reflux with aqueous 2M sodium carbonate solution (2.0 ml) for 2h and 3h respectively. The reaction mixtures were then worked up as described for the individual reactions.

(i) 3-Phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6,7-dicarboxylic Acid (301)

The reaction mixture from (289a) was filtered to afford a solid which was dissolved in water, acidified with aqueous dilute hydrochloric acid and the resulting solution was concentrated to give the dicarboxylic acid (301). This was combined with a second crop obtained by concentrating the aqueous-ethanolic filtrate, dissolving the solid obtained in water and acidifying the solution with aqueous dilute hydrochloric acid, to give the crude diacid (301) m.p. 192°. Crystallisation from water afforded the pure yellow diacid (301) (91%) m.p. 204° (decomp.),

ν max. 1900br (OH) and 1730 (CO) cm^{-1}, λmax. 212, 256 and 408 (logε 4.18, 4.32 and 3.84), τ[$CDCl_3$ - $(CD_3)_2SO$] 1.62 - 1.72(2H, m, Ar-H) and 2.46 - 2.53(3H, m, Ar-H).

Found: C, 47.5; H, 3.0; N, 22.7%; M^+ 285.

$C_{12}H_7N_5O_4H_2O$ requires: C, 47.5; H, 3.0; N, 23.0%; M(monohydrate), 303.

(ii) 6-Benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7-carboxylic Acid (302)

The mixture from (289c) was hot filtered to remove inorganic material and the filtrate was concentrated, diluted with water and acidified with aqueous dilute hydrochloric acid to afford the monoacid (302) (97%) m.p. 206° which crystallised from ethanol as a yellow solid m.p. 212°, ν max. 1730 and 1670 (CO) cm^{-1}, λmax. 212, 255 and 418 nm (logε 4.45, 4.51 and 3.44), τ[$CDCl_3$ - $(CD_3)_2SO$] 1.57 - 1.67(2H, m, Ar-H), 1.88 - 1,98(3H, m, Ar-H) and 2.37 - 2.54(5H, m, Ar-H).

Found: C, 62.6; H, 3.2; N, 20.2%; P,$^+$ 301 (M^+ CO_2).

$C_{18}H_{11}N_5O_3$ requires: C, 62.6; H, 3.2; N, 20.2%; M, 345.

The Attempted Reaction of the Dicarboxylic Acid (301) with Acetic Anhydride

The dicarboxylic acid (301) (0.14g, 0.0005 mol) was treated with acetic anhydride (0.36 ml) and heated at 100° for 10 min. Dilution of the cooled solution with ether gave no solid and so the mixture was evaporated under reduced pressure to give a dark residue which was triturated with ether to yield a solid (0.04g) m.p. 190° (decomp.). Crystallisation of the impure solid from ethanol-ether gave the unreacted diacid (301) (0.01g) m.p. 180° which was identical (i.r. spectrum) with an authentic sample.

Evaporation of the ether mother liquor left an intractable red oil.

The Attempted Thermal Decarboxylation of the Acid (301)

The carboxylic acid (301) (0.34g, 0.001 mol) was heated to 180° (oil bath) in a cold finger sublimation apparatus. The solid melted and then rapidly decomposed.

Diethyl 2-(2-Acetoxybenzyl)-1,2,4-triazine-5,6-dicarboxylate (299a)

The triazolotriazine (289a) (0.34g, 0.001 mol) was heated under reflux in glacial acetic acid (10.0 ml) for 16h. The solution was evaporated under reduced pressure and the residue was triturated with ether to afford the unreacted triazolotriazine (289a) (0.18g) m.p. 125°, identical (m.p. and i.r. spectrum) with an authentic sample.

The ether mother liquour on evaporation yielded the acetoxy-derivative (299a) (0.11g) m.p. 70° which was identical (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Oxidative Degradation of the Triazolotriazine (289c)

(a) Using Hydrogen Peroxide in Glacial Acetic Acid

(i) The triazolotriazine (289c) (0.74g, 0.002 mol) suspended in glacial acetic acid (15.0 ml) was treated with 30% hydrogen peroxide (5.0 ml) and heated at 50° (oil bath) for 17h. Filtration of the cooled mixture yielded the unreacted triazolotriazine (289c) (0.42g, 55%) m.p. 131° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The acidic filtrate was diluted with water and the resulting cloudy solution was extracted with chloroform. Evaporation of the chloroform extract gave a negligible amount of oil.

(ii) When the procedure described in (i) above was repeated at 80° for 17h, filtration of the mixture gave the unreacted triazolotriazine (289c) (0.50g; 68%) m.p. 120° which was identical (i.r. spectrum) with a sample of the triazolotriazine (289c) prepared before.

(b) Using Hydrogen Peroxide in Aqueous Sodium Hydroxide

The triazolotriazine (289c) (0.37g, 0.001 mol) was treated with aqueous 2.5M sodium hydroxide (8.0 ml) and 30% hydrogen peroxide (10.0 ml) and the mixture was stirred at room temperature until effervescence ceased. The mixture was then heated under reflux for 2h. The solution was cooled, acidified with aqueous dilute hydrochloric acid and extracted with chloroform. A solid which was insoluble in the chloroform and aqueous phases was collected (0.02g) m.p. 282°, $\nu_{max.}$ 3480 and 1870br (OH) and 1680 (CO) cm^{-1}, M^+, 402.

The chloroform extract on evaporation left a residue which was triturated with ether to afford an unidentified solid (0.02g) m.p. 140° which showed a poorly resolved i.r. spectrum.

The ether mother liquor on evaporation left an unidentified solid (0.05g) m.p. 80° whose i.r spectrum could not be run because it was hygroscopic.

The Attempted Oxidative Degradation of the Triazolotriazine (289b) Using Sodium Hypochlorite

A solution of the triazolotriazine (289b) (0.62g, 0.002 mol) in dioxan (20.0 ml) and water (2.0 ml) was treated with aqueous 3.85N sodium hypochlorite solution (1.56 ml) and the mixture was stirred at 70° (oil bath) for 1.5h. The mixture was treated with a saturated solution of sodium bisulphite (2.0 ml), diluted with water (20.0 ml) and extracted with chloroform to give an oil which was triturated with ether to afford the unreacted triazolotriazine (289b) (0.20g) m.p. 140°, identical (i.r. spectrum) with an authentic sample.

The aqueous extract was acidified with aqueous dilute hydrochloric

acid and concentrated to give a solid which was combined with more solid obtained from the aqueous concentrate on standing (total 0.04g) m.p. 190°. This was crystallised from water to give a solid (0.01g) m.p. 193° which was identical (m.p., mixed m.p. and i.r. spectrum) with the diacid (301) described earlier.

The Attempted Reaction of Ethyl 1H-1,2,3-triazole-4-carboxylate-5-diazonium Nitrate (280) with Biacetyl and Glyoxal in the Presence of Sulphur Dioxide

A solution of the N-aminotriazole (264) (0.68g, 0.004 mol) in concentrated nitric acid (d 1.42; 0.8 ml) and water (2.4 ml) was cooled to 0° (ice-salt bath) and treated dropwise with stirring with a solution of sodium nitrite (0.6g) in water (2.4 ml). 80% v/v. Aqueous ethanol (40.0 ml) was added and the mixture was saturated at 0° with sulphur dioxide, left at room temperature for 3h, and then heated under reflux with glyoxal or biacetyl (0.004 mol) for 2h. The reaction mixtures were concentrated to remove the ethanol and the aqueous mother liquors were extracted with chloroform to give oils which were triturated with benzene to afford,, in each case, ethyl 1H-1,2,3-triazole-4-carboxylate (321) (<1%) m.p. 110° (from benzene), $\nu_{max.}$ 3200br (NH) and 1720 (CO) cm^{-1}, τ($CDCl_3$) 1.68(1H, s, CH), 5.56(2H, q J 7Hz, CH_2) and 8.62(3H, t J 7Hz, CH_3).

Found: C, 42.5; H, 5.0; N, 29.3%; M^+, 141.

$C_5H_7N_3O_2$ requires: C, 42.6; H, 5.0; N, 29.8%; M, 141.

Work up of the aqueous mother liquors by neutralisation with solid sodium acetate and extraction with chloroform gave no further material.

Ethyl 5,6-Dimethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (318a)

The triazolotriazine (318a) (60%) m.p. 85° (lit.,[38] 89°) was prepared as described in the literature.[38]

6,7-Dimethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxamide (319b)

A solution of the triazolotriazine (318a) (0.88g, 0.004 mol) in absolute ethanol (40.0 ml) was cooled to 0° (ice-salt bath), saturated with ammonia and left at room temperature for 24h. Evaporation of the solution gave a pink solid which was triturated with ethanol-ether to afford the triazolotriazine amide (319b) (0.25g; 33%) m.p. 228° (from dimethylformamide-water) which was identical (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Conversion of the N-Aminotriazole-Ester (264) into the N-Amino Amide (322)

(i) Using Ethanolic Ammonia

A solution of the triazole ester (264) (0.68g, 0.004 mol) in absolute ethanol (40.0 ml) was cooled to 0° (ice-salt bath), saturated with ammonia gas and left at room temperature for 16h. The clear solution was evaporated and the solid left was triturated with ethanol-ether to afford the unreacted triazole ester (264) (0.53g; 78%) m.p. 148°, identical (m.p. and i.r. spectrum) with an authentic sample.

(ii) Using Ammonia in Dimethylformamide

A solution of the triazole ester (264) (0.68g, 0.004 mol) in dimethylformamide (15.0 ml) was cooled to 0° (ice-salt bath) and saturated with ammonia gas. The mixture was left at room temperature for 16h and then evaporated under reduced pressure to give a solid which was triturated with ethanol-ether to afford the unreacted triazole ester (264) (0.60g; 88%) m.p. 152° which was identical (m.p. and i.r. spectrum)

with an authentic sample.

(iii) Using Liquid Ammonia

The N-aminotriazole (264) (0.68g, 0.004 mol) was treated with liquid ammonia (25.0 ml), cooled to -20° (drikold - acetone bath) and the solution was stirred at -20° for 6h. The ammonia was allowed to evaporate and the solid obtained was triturated with ethanol-ether to afford the unreacted N-aminotriazole (264) (0.54g; 79%) m.p. 148° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(iv) Using Ethanolic Ammonium Acetate

A solution of the triazole ester (264) (0.68g, 0.004 mol) in ethanol (20.0 ml) was treated with solid ammonium acetate (0.62g, 0.008 mol) and heated under reflux for 1h. Evaporation of the clear yellow solution gave a solid which was successively treated with water to afford the starting material (264) (total 0.42g; 62%) m.p. 146°, which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

5-Aminopyrazol-3-one (324)

The amidrazone (313) (9.4g, 0.05 mol) was added with stirring at 0° (ice-salt bath) to absolute ethanol (70.0 ml) saturated with ammonia gas and the mixture was stirred in the melting ice bath for 3h. Filtration of the wine-coloured mixture yielded the pyrazolone (324) (3.8g; 77%) m.p. 200° which formed colourless prisms (3.42g) m.p. 215° (from ethanol), ν max. 3330br, 3210wbr and 3160br (NH), 1680 (CO), and 1650 (NH) cm^{-1}.

Found: C, 36.0; H, 5.2; N, 41.9%; M^+ 99.

$C_3H_5N_3O$ requires: C, 36.4; H, 5.1; N, 42.4%; M, 99.

1,5-Diamino-Δ^4-pyrazolin-3-one (326)

A solution of the amidine hydrochloride (316) [for the method of preparing (316) see Chapter 4, page 143] (1.4g, 0.01 mol) in absolute ethanol (60.0 ml) was cooled to 0° (ice-salt bath), stirred, and treated

dropwise with anhydrous hydrazine (0.32g, 0.01 mol). The mixture was stirred for 2 min and then evaporated to give a solid which was triturated with methanol to yield the pyrazolinone (326) (0.79g; 69%) m.p. 165° which formed pink prisms (0.44g) m.p. 185° (from methanol-water), $\nu_{max.}$ 3330 and 3200 - 3100br (NH), and 1700br (CO) cm^{-1}.

Found: C, 31.5; H, 5.4; N, 49.0%; M^+ 114.
$C_3H_6N_4O$ requires: C, 31.6; H, 5.3; N, 49.0%; M, 114.

Evaporation of the methanol mother liquor left a negligible amount of solid.

The Attempted Diazotisation of the Diaminopyrazolinone (326)

A stirred mixture of the pyrazolinone (326) (0.45g, 0.004 mol), concentrated nitric acid (0.25 ml) and water (0.68 ml) was cooled to 0° (ice-salt bath) and treated dropwise with stirring over 10 min with a solution of sodium nitrite (0.20g) in water (1.0 ml). The mixture was then heated on a steam bath for 0.5h and the resulting dark solution was extracted with chloroform. Evaporation of the chloroform extract gave a negligible amount of oil.

The aqueous acid mother liquor was treated with aqueous dilute sodium hydroxide solution but re-extraction with chloroform gave no material. The aqueous phase was neutralised with dilute acetic acid and evaporated to afford a solid. This was extracted with hot n-propanol to afford a red oil (1.39g) from which no identifiable material could be obtained.

The Bisbenzylidene Derivative (327) of the Pyrazolinone (326).

A solution of the pyrazolinone (326) (0.23g, 0.002 mol) in methanol (5.0 ml) was treated with concentrated sulphuric acid (1.0 ml) and water (2.5 ml) followed by a solution of freshly distilled benzaldehyde

(0.21g, 0.002 mol) in methanol (5.0 ml) and the mixture was left at room temperature for 16h. The mixture was concentrated to remove the methanol, extracted with chloroform, and filtered to give the insoluble bisbenzylidene derivative (327) (0.48g) which was purified by crystallisation from ethanol-water as a cream solid (0.10g) m.p. 218°, $\nu_{max.}$ 3160w (NH) cm^{-1}.

Found: N, 19.8%; $M,^{+}$ 290.
$C_{17}H_{14}N_4O$ requires: N, 19.3%; M, 290.

Evaporation of the chloroform extract gave no material. The aqueous extract was buffered with solid sodium acetate and evaporated to leave a solid, extraction of which with hot ethyl acetate gave only a negligible amount of oil.

5,6-Dimethylpyrazolo[1,5-b]-1,2,4-triazin-2(1H)-one (325)

A solution of the pyrazolinone (326) (0.46g, 0.004 mol) in ethanol (20.0 ml) containing glacial acetic acid (2.0 ml) was heated under reflux with biacetyl (0.34g, 0.004 mol) for 17h. Evaporation of the solution left a dark solid which was triturated with ethanol-ether to afford the crude product (325) which crystallised from ethanol as a pale yellow solid (0.20g) m.p. 250° (decomp.), $\nu_{max.}$ 3140 (NH) cm^{-1}, $\lambda_{max.}$ 210, 242 and 263 nm ($\log\varepsilon$ 4.10, 4.78 and 3.98), $\tau\left[(CD_3)_2SO\right]$ 3.82(1H, s, CH), 7.36(3H, s, CH_3), and 7.38(3H, s, CH_3).

Found: C, 50.8; H, 4.8; N, 33.8%; $M,^{+}$ 164.
$C_7H_8N_4O$ requires: C, 51.2; H, 4.9; N, 34.1%; M, 164.

The ethanol mother liquor on evaporation left only a negligible amount of solid.

4-Phenyl-1H-1,2,3-triazole (293)[40]

80% v/v Aqueous ethanol (50.0 ml) was cooled to 0° (ice-salt bath), stirred and saturated with sulphur dioxide. The solution was then treated in portions with the diazonium salt (36) (0.83g, 0.004 mol) and the mixture was resaturated with sulphur dioxide and left at room temperature for 16h. The solution was then concentrated to remove the ethanol and extracted with chloroform to give the impure triazole[40] (293) (0.17g) m.p. 120° which was crystallised from water (0.07g) m.p. 140° and was identical (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Synthesis of the Triazolylhydrazine (273)

80% v/v Aqueous ethanol (120 ml) was cooled to 0° (ice-salt bath), saturated with sulphur dioxide and treated in portions with stirring with the diazonium salt (44) (6.0g, 0.06 mol). The mixture was again cooled to 0°, re-saturated with sulphur dioxide and left at room temperature for 16h. Filtration of the mixture gave a solid which was combined with a second crop obtained by concentrating the aqueous ethanolic filtrate (total 1.68g) m.p. 178°. This was dissolved in water with heating and treated with a small amount of solid sodium acetate to give, on cooling, a colourless bis-hydrogen sulphate salt (1.01g) m.p. 200° (decomp.) (from water), $\nu_{max.}$ 3560, 3440, 3280 and 3120 (NH), and 1670 (CO) cm^{-1}.

Found: C, 11.9; H, 3.5; N, 28.5%; $M,^{+}$ 142.

The original aqueous mother liquor was heated up with a little quantity of sodium acetate and on cooling, gave pale yellow crystals (2.13g) m.p. 120° which were crystallised from water to give the pure mono-hydrogen sulphate salt (1.5g) m.p. 151°, $\nu_{max.}$ 3360 and 3200 (NH) and 1680 (CO) cm^{-1}.

Found: C, 19.3; H, 3.4; N, 40.6%; M^{+} (no ion pressure).

The Formation of the Isomeric Benzylidene Derivatives (332a) and (333a)

A solution of the mono- or bis- hydrogen sulphate salt of the hydrazine (273) (0.004 mol) in methanol (10.0 ml) was treated with concentrated sulphuric acid (2.0 ml) and water (5.0 ml) followed by a solution of freshly distilled benzaldehyde (0.42g, 0.004 mol) in methanol (10.0 ml). The mixtures were left at room temperature for 16h and then worked up as described for the individual reactions.

(a) 5-Amino-1-benzylideneamino-1H-1,2,3-triazole-4-carboxamide (333a) and 5-N-Benzylidenehydrazino-1H-1,2,3-triazole-4-carboxamide (332a)

Filtration of the reaction mixture from the bis-hydrogen sulphate salt afforded a solid (50%) m.p. 220°, νmax. 3360, 3330 and 3200 (NH), and 1670 (CO) and 1635 (NH) cm^{-1} which was suspended in aqueous dilute sodium hydroxide and the insoluble benzylideneamino-triazole (333a) (30%) was collected and crystallised to afford colourless prisms m.p. 257° (from dimethylformamide-water), νmax. 3470, 3400, 3370 and 3160br (NH), and 1670 (CO) cm^{-1}.

Found: C, 52.0; H, 4.4; N, 36.7%; M^+ 230.

$C_{10}H_{10}N_6O$ requires: C, 52.0; H, 4.4; N, 36.5%; M, 230.

The alkaline mother liquor was neutralised with aqueous dilute hydrochloric acid to afford the benzylidenehydrazinotriazole (332a) (70%) as a cream solid which was washed several times with water m.p. 256°, ν max. 3360 and 3200 (NH) and 1685 (CO) cm^{-1}.

Found: C, 51.8;H, 4.3; N, 36.5%; M^+ 230.

$C_{10}H_{10}N_6O$ requires: C, 52.2; H, 4.4; N, 36.6%; M, 230.

(b) Filtration of the reaction mixture from the mono-hydrogen sulphate salt again afforded the isomer mixture of (332a) and (333a) (30%) m.p. 210°,

ν max. 3360, 3320 and 3200 (NH), 1670 (CO) and 1640 (NH) cm^{-1}, which in this case was completely soluble in aqueous dilute sodium hydroxide. Acidification of the alkaline solution yielded the hydrazinobenzylidene derivative (332a) m.p. 250° which was identical (m.p. and i.r. spectrum) with the sample described in (a) above.

The acidic methanol mother liquor was concentrated, diluted with water and extracted with chloroform but gave no further material.

The Reaction of the Benzylidene Derivatives (332a) and (333a) with Acetic Anhydride

The benzylidene derivatives (332a) and (333a) (0.11g, 0.0005 mol) were heated under reflux in acetic anhydride (8.0 ml) for 5min. The solutions on evaporation left oils which were triturated with ether to afford the same colourless 1-acetyl-5-N-benzylidenehydrazino-1,2,3-triazole-4-carboxamide (334a)(73%) and (46%) respectively, m.p. 197° (from ethyl acetate), νmax. 3400, 3340 and 3200wbr (NH), and 1756 and 1680 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.70(1H, s, CH), 1.81(1H, br s, NH), 2.14(1H, s, NH), 2.36(2H, m, Ar-H), 2.60-2.72(3H, m, Ar-H) and 7.30(3H, s, CH_3CO).

Found: C, 52.7; H, 4.5; N, 30.6%; M^+ 272.

$C_{12}H_{12}N_6O_2$ requires: C, 52.9; H, 4.4; N, 30.9%; M, 272.

The Conversion of the Benzylidene Derivative (332a) into a Mixture of (333a) and (332a).

(a) In 2-Ethoxyethanol

The benzylidenehydrazinotriazole (332a) (0.46g; 0.002 mol) was heated under reflux in 2-ethoxyethanol (20.0 ml) for 1h. The cooled solution was diluted with water to afford a mixture of the two isomers (332a) and (333a) (0.23g; 50%). This was suspended in aqueous dilute sodium hydroxide and the insoluble benzylideneamino-triazole (333a) was

filtered off (0.11g) m.p. 252°, identical (m.p. and i.r. spectrum) with an authentic sample.

Acidification of the alkaline mother liquour afforded the benzylidenehydrazinotriazole (332a) (0.10g) m.p. 250° which was identical (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the 2-ethoxyethanol mother liquor with chloroform gave no further material.

(b) In Pyridine

The benzylidenehydrazinotriazole (332a) (0.23g, 0.001 mol) was heated under reflux in pyridine (10.0 ml) for 3h. Evaporation of the solution left the isomer mixture (332a) and (333a) (0.21g; 91%) m.p. 252°, identical (m.p. and i.r. spectrum) with the sample prepared before.

The Conversion of the Benzylideneaminotriazole (333b) into the 5-Benzylidenehydrazinotriazole (332b) using Ethanolic Hydrochloric Acid.

The benzylideneaminotriazole ester (333b) (1.02g, 0.002 mol) in ethanol (35.0 ml) was treated with aqueous 2M hydrochloric acid solution (5.0 ml) and heated under reflux for 0.5h. The solution was evaporated and the residue was treated with water to give the isomeric ethyl 5-N-benzylidenehydrazino-1H-1,2,3-triazole-4-carboxylate (332b) as colourless plates (0.74g; 74%) m.p. 194° (from ethanol), $\nu_{max.}$ 3450, 3200 and 3180w (NH) and 1700 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 0.75(1H, s, CH), 1.86-1.95(2H, m, Ar-H). 2.44-2.50(3H, m, Ar-H), 3.10(2H, s. NH), 5.70(2H, q J 7Hz, CH_2) and 8.70(3H, t J 7Hz, CH_3).

Found: C, 55.3; H, 4.9; N, 27.0%; M^+ 259.

$C_{12}H_{13}N_5O_2$ requires: C, 55.6; H, 5.0; N, 27.0%; M, 259,

which was easily soluble in aqueous dilute sodium hydroxide solution and was recovered on acidification with aqueous dilute hydrochloric acid.

The Attempted Reaction of the Benzylidene Isomers (332b) and (333b) with Nitrous Acid.

The benzylidene derivatives (332b) and (333b) (0.78g, 0.003 mol) were added in portions with stirring to solutions of concentrated hydrochloric acid (0.6 ml) in water (3.0 ml) at 0° (ice-salt bath). Solutions of sodium nitrite (0.25g) in water (1.0 ml) were added dropwise with stirring and the mixtures were stirred in the melting ice for 0.5h. Filtration of the reaction mixtures yielded the unreacted benzylidene derivatives (332b) and (333b) (87 - 95%) m.p. 193° and 180° respectively which were identical (i.r. spectrum, and m.p. and i.r. spectrum) with authentic samples.

The Reactions of the Benzylidene Derivatives (333b) and (332b) with Pyridine.

(i) The benzylideneaminotriazole (333b) (0.86g, 0.0035 mol) was heated under reflux in pyridine (15.0 ml) for 3h. The solution was evaporated to give the benzylidenehydrazinotriazole (332b) (0.66g; 77%) m.p. 194° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(ii) When the procedure described in (i) above was repeated with the benzylidenehydrazinotriazole (332b) (0.51g, 0.002 mol), the benzylidene-hydrazinotriazole (332b) was recovered unchanged (0.47g; 92%) m.p. 190°, identical (m.p. and i.r. spectrum) with an authentic sample.

The Thermal Rearrangement of the Benzylidenehydrazinotriazole (332b) to the Benzylideneaminotriazole (333b).

(i) A melt of the benzylidenehydrazinotriazole (332b) (0.26g, 0.001 mol) was kept at 200-220° (Wood's Metal Bath) for 5min. The melt on cooling formed a dark solid which was triturated with methanol to afford the rearranged isomer (333b) (0.15g; 58%) m.p. 190°, identical (m.p. and

i.r. spectrum) with an authentic sample.

(ii) When the procedure described in (i) above was repeated on the same scale with the benzylideneaminotriazole (333b) the unrearranged benzylideneaminotriazole (333b) was obtained (0.17g; 65%) m.p. 195° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The Reaction of the Benzylidene Derivatives (332b) and (333b) with Acetic Anhydride

The benzylidene derivatives (332b) and (333b) (1.04g, 0.004 mol) were heated under reflux in acetic anhydride (8.0 ml) for 5 min. The solutions were evaporated under reduced pressure to give a gum and an oil respectively which were triturated with ether to give, in each case, ethyl 1-acetyl-5-N-benzylidenehydrazino-1,2,3-triazole-4-carboxylate (334b) (62% and 76%) m.p. 110°. This crystallised from both ethyl acetate and ethanol as colourless prisms m.p. 118°, $\nu_{max.}$ 3300 (NH), and 1750 and 1700 (CO) cm^{-1}, $\tau(CDCl_3)$ 0.88(1H, s, CH), 1.98(1H, s, NH), 2.24-2.34(2H, m, Ar-H), 2.62-2.68(3H, m, Ar-H), 5.55(2H, q J 7Hz, CH_2), 7.20(3H, s, CH_3CO), and 8.58(3H, t J 7Hz, CH_3).

Found: C, 58.8; H, 5.1; N, 23.0%; M^+ 301.

$C_{14}H_{15}N_5O_3$ requires: C, 58.8; H, 5.1; N, 23.3%; M, 301.

The Hydrolysis of the N-Acetyltriazole (334b) to the Benzylidenehydrazino-triazole (332b)

A solution of the N-acetyltriazole (334b) (0.15g, 0.0005 mol) in ethanol (5.0 ml) was treated with aqueous 2M sodium carbonate solution (2.5 ml) and the mixture was heated at 50° (oil bath) for 0.5h. The mixture was filtered hot to remove inorganic material and acidified with aqueous dilute hydrochloric acid to afford the benzylidenehydrazinotriazole (332b) (0.10g) m.p. 187° which was purified by crystallisation from ethyl

acetate (0.03g) m.p. 194°, identical (m.p. and i.r. spectrum) with an authentic sample.

The Reaction of the Benzylidene Derivatives (333b) and (332b) with Acetic Anhydride under Various Conditions:

(i) Prolonged Heating

The benzylideneaminotriazole (333b) (0.26g, 0.001 mol) was heated under reflux in acetic anhydride (10.0 ml) for 18h. Evaporation of the mixture left an oil which was suspended in water to give a gum which was triturated with methanol to afford the monoacetyl derivative (337) (0.12g) m.p. 215°. Crystallisation from ethanol gave the pure compound as colourless needles (0.08g) m.p. 240°, $\nu_{max.}$ 3060 (NH), and 1730 and 1660 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 2.12-2.30(2H, m, Ar-H), 2.50-2.60(3H, m, Ar-H), 2.53(1H, s, CHPh), 5.70(2H, q J 7Hz, CH_2), 7.40(3H, s, CH_3CO) and 8.71(3H, t J 7Hz, CH_3).

Found: C, 56.1; H, 5.1; N, 23.0%; $M,^+$ 301.

$C_{14}H_{15}N_5O_3$ requires: C, 56.1; H, 5.0; N, 23.3%; M, 301.

The methanol mother liquor was evaporated and the oil left solidified and was triturated with methanol to give a small amount(0.01g) of the monoacetyl derivative (338) m.p. 185° identical (m.p. and i.r. spectrum) with an authentic sample.

Ethyl 1(N-Benzylideneamino)-5-diacetamido-1H-1,2,3-triazole-4-carboxylate (339)

The benzylidenehydrazinotriazole (332b) (0.52g, 0.002 mol) was heated under reflux in acetic anhydride (10.0 ml) for 18h. The solution was evaporated under reduced pressure and the oil obtained was cooled and triturated with ether to afford the diacetyl derivative (339) more of which was obtained from the ether mother liquor on evaporation (total 0.39g, 57%), m.p. 95°. This crystallised from ethanol as colourless prisms

(0.24g) m.p. 99°, $\nu_{max.}$ 1750w and 1720 (CO) cm^{-1}, τ ($CDCl_3$) 0.58(1H, s, CH), 2.09-2.19(2H, m, Ar-H), 2.46-2.51(3H, m, Ar-H), 5.57(2H, q J 7Hz, CH_2), 7.66(6H, s, $COCH_3$) and 8.60(3H, t J 7Hz, CH_3).

Found: C, 55.8; H, 4.9; N, 20.3%; M^+ 343.

$C_{16}H_{17}N_5O_4$ requires: C, 56.0; H, 5.0; N, 20.4%; M, 343.

Ethyl-1(N-Benzylideneamino)-5-acetamido-1H-1,2,3-triazole-4-carboxylate (338)

(a) The benzylidenehydrazinotriazole (332b) (0.26g, 0.001 mol) was heated under reflux in acetic anhydride (8.0 ml) for 18h. The solution was evaporated under reduced pressure leaving a gummy solid which was triturated with ethanol-ether to give the acetyl derivative (338) (0.15g) m.p. 183° which was purified by crystallisation form ethanol (0.13g) m.p. 185°, identical (m.p. and ir. spectrum) with an authentic sample.[38]

(b) Hydrolysis of the Diacetyl Derivative (339)

The diacetyl derivative (339) (0.17g, 0.0005 mol) in ethanol (5.0 ml) was heated at 50° (oil bath) with aqueous 2M sodium carbonate solution (2.5 ml) for 0.5h. The mixture was hot filtered to remove inorganic material, concentrated to remove the ethanol, and filtered to afford the acetyl derivative[38] (338) which was combined with a second crop obtained by neutralising the alkaline mother liquor with aqueous dilute sulphuric acid (total 0.08g) m.p. 188°, identical (i.r. spectrum) with a sample of (338) prepared before.

The Attempted Amination of the Triazole Esters (333b) and (332b).

(i) A solution of the benzylideneaminotriazole (333b) (0.52g, 0.002 mol) in ethanol (20.0 ml) was cooled to 0° (ice-salt bath), saturated with ammonia gas and shaken up at room temperature for 16h. Filtration of the mixture afforded the unreacted starting material (333b) (0.47g; 88%) m.p. 194° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(ii) The procedure described in (i) above was repeated with the benzylidenehydrazinotriazole (332b). Filtration of the mixture afforded the benzylideneaminotriazole (333b) (0.14g) m.p. 200° which was identical (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the ethanolic mother liquor left a residue which was triturated with ether to give the starting benzylidenehydrazinotriazole (332b) (0.30g; 85%) m.p. 190, identical (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Thermal and Base-catalysed Rearrangement of the Benzylideneaminotriazole (314)

(a) A melt of the benzylideneaminotriazole (314) (0.17g, 0.0005 mol) was held at 160° (Wood's Metal Bath) for 5 min. The solid obtained on cooling was triturated with methanol to afford the unreacted benzylideneaminotriazole (314) (0.10g; 59%) m.p. 165° which was identical (m.p. and i.r. spectrum) with an authentic sample. The methanol mother liquor on evaporation left a dark oil from which no identifiable material could be obtained.

(b) The benzylideneaminotriazole (314) (0.34g, 0.001 mol) was heated under reflux in pyridine (10.0 ml) for 3h. The solution was evaporated to give the unreacted benzylideneaminotriazole (314) (0.32g; 94%) m.p. 160° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Thermal Rearrangement of the Ethoxymethyleneaminotriazole (315)

A melt of the triazole derivative (315) (0.10g, 0.0005 mol) was held at 160 - 170° (Wood's Metal Bath) for 5 min. The glass which formed on cooling was triturated with methanol to give the unreacted ethoxymethylenetriazole (315) (0.04g) m.p. 145° which was identical (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Isomerisation of the N-Aminotriazole (264)

(a) Using Glacial Acetic Acid In Ethanol

A solution of the N-aminotriazole ester (264) (0.68g, 0.004 mol) in ethanol (15.0 ml) containing glacial acetic acid (2.0 ml) was heated under reflux for 17h. The solution was evaporated to leave a residue which was repeatedly triturated with methanol to afford the unreacted N-aminotriazole (264) (0.47g; 69%) m.p. 156°, which was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) Using Pyridine

The N-aminotriazole (264) (0.68g, 0.004 mol) was heated under reflux in pyridine (15.0 ml) for 3h. The solution was evaporated to afford the starting material (264) (0.52g; 76%) m.p. 148° which was identical (i.r. spectrum) with an authentic sample.

1,5-Diamino-1H-1,2,3-triazole-4-carboxylic Acid (348)

A solution of the N-aminotriazole ester (264) (0.68g, 0.004 mol) in ethanol (10.0 ml) was treated with aqueous 2M sodium hydroxide solution (2.0 ml) and heated under reflux for 3h. Hot filtration afforded a solid (0.51g) m.p. 264° which was dissolved in water and acidified with dilute hydrochloric acid to afford the acid (348) (0.11g) m.p. 164°, which crystallised from ethanol-water as a pale yellow solid (0.07g) m.p. 174°, $\nu_{max.}$ 3450, 3300 and 3250br (NH), 2640br and 2500br (NH, OH) and 1710 (CO) cm^{-1}, $\tau[(CD_3)_2SO]$ 3.60(2H, s, NH) and 4.02(2H, s, NH).

Found: C, 25.1; H, 3.7; N, 49.1%; $M,^+$ 143.

$C_3H_5N_5O_2$ requires: C, 25.2; H, 3.5; N, 49.0%; M, 143.

The Triacetyl Derivative (350) of the Triazole Ester (264)

The triazole ester (264) (0.68g, 0.004 mol) was heated under reflux in acetic anhydride (5.0 ml) for 5 min. The solution on evaporation under reduced pressure left an oil which was treated with water to yield the triacetyl derivative (350) (0.40g) m.p. 135° which crystallised from ethanol as colourless prisms (0.25g) m.p. 144°, $\nu_{max.}$ 3340 (NH), and 1770 and 1720br (CO) cm^{-1}, τ ($CDCl_3$) 2.08(1H, s, NH), 5.48(2H, q J 7Hz, CH_2), 7.26(3H, s, CH_3CO-N-), 7.50(6H, s, CH_3CO) and 8.55(3H, t J 7Hz, CH_3).

C, 44.7; H, 5.1; N, 24.0%; P,$^+$ 255 ($M^+ - CH_3CO$).

$C_{11}H_{15}N_5O_5$ requires: C, 44.5; H, 5.1; N, 23.6%; M, 297.

The Condensation Reactions of Ethyl 1,5-Diamino-1H-1,2,3-triazole (264) with Active Methylene Compounds

A solution of the N-amino ester (264) (0.68g, 0.004 mol) and the corresponding active methylene compound (0.004 mol) in ethanol (15.0 ml) containing glacial acetic acid (1.0 ml) was heated under reflux for 16-18h. The solutions were evaporated under reduced pressure and the resulting oil or gum was worked up as described for the individual reactions.

(i) Ethyl 5-(3,5-Dimethylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (356a)

The oil from acetylacetone was triturated with water to give the pyrazolyltriazole (356a) as a colourless solid (73%) m.p. 137° (from benzene), $\nu_{max.}$ 3080, 2700-2600br (NH) and 1740 (CO) cm^{-1}, τ ($CDCl_3$) 3.96(1H, s, CH), 5.50(2H, q J 7Hz, CH_2), 7.62(3H, s, CH_3), 7.80(3H, s, CH_3) and 8.74(3H, t J 7Hz, CH_3).

Found: C, 51.1; H, 5.6; N, 30.1%; M,$^+$ 235.

$C_{10}H_{13}N_5O_2$ requires: C, 51.0; H, 5.5; N, 29.8%; M, 235.

(ii) Ethyl 5-(5-Methyl-3-phenylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (356b)

Trituration of the oil from benzoylacetone with ether afforded a solid (40%) m.p. 136° identified (i.r. spectrum) as unreacted N-amino ester (264).

Evaporation of the ethereal mother liquour left an oily solid which in contact with ether yielded the pyrazolyltriazole (356b) as pale pink prisms (48%) m.p. 166° (from ethanol-water), $\nu_{max.}$ 3100 (NH), and 1725 (CO) cm^{-1}, $\tau(CDCl_3)$ 2.80(5H, s, Ar-H), 3.64(1H, s, CH), 5.94(2H, q J 7Hz, CH_2), 7.60(3H, s, CH_3) and 8.92(3H, t J 7Hz, CH_3).

Found: C, 60.7; H, 5.1; N, 23.8%; $M,^+$ 297.

$C_{15}H_{15}N_5O_2$ requires: C, 60.6; H, 5.1; N, 23.6%; M, 297.

(iii) Ethyl 5-(5-Methylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (356b)

The oil from acetoacetaldehyde dimethyl acetal was repeatedly triturated with benzene to afford the pyrazolyltriazole (356c) as colourless needles (59%) m.p. 79° (from benzene-light petroleum), $\nu_{max.}$ 3150 (NH) and 1720 (CO) cm^{-1}, $\tau(CDCl_3)$ 1.56(1H, d J 2Hz, CH), 3.76(1H, d J 2Hz, CH), 5.60(2H, q J 7Hz, CH_2), 7.61(3H, s, CH_3) and 8.64(3H, t J 7Hz, CH_3),

Found: C, 50.8; H, 5.1; N, 30.0%; $M,^+$ 221.

$C_9H_{11}N_5O_2$ requires: C, 48.8; H, 5.0; N, 31.7%; M, 221.

(iv) Ethyl 5-(5-Acetonyl-3-methylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (356e or f)

The oil from the triketone (218) was repeatedly triturated with ethanol-ether and on standing gave the pyrazolyltriazole (356e or f) as a colourless solid (34%) m.p. 128° (from water), $\nu_{max.}$ 3100 (NH) and 2700 - 2500br (OH), and 1730 (CO) cm^{-1}, $\tau[CDCl_3 - (CD_3)_2SO]$ 3.82(1H, s, CH), 5.76(2H, q J 7Hz, CH_2), 6.30(2H, s, CH_2), 7.76(3H, s, COMe),

7.95(3H, s, CH_3) and 8.80(3H, t J 7Hz, CH_3).

Found: C, 51.9; H, 5.5; N, 25.2%; M^+ 227.

$C_{12}H_{15}N_5O_3$ requires: C, 52.0; H, 5.4; N, 25.3%; M, 227.

Evaporation of the ethanol-ether mother liquor left an oil whose t.l.c. in ethanol-ethyl acetate over silica showed it to be an unresolved multicomponent mixture.

(v) The gummy solid from malondialdehyde bis(dimethyl acetal) was triturated with ether to give the unreacted N-amino ester (264) (88%) m.p. 138°, identical (i.r. spectrum) with an authentic sample.

(vi) The solid residue from ethyl cyanoacetate on trituration with water gave the unreacted N-amino ester (264) (72%) m.p. 145° which was identical (i.r. spectrum) with an authentic sample.

(vii) The residual oil from 2-cyanoacetophenone was triturated with ether to give an impure solid m.p. 95°. Crystallisation of this solid from ethanol gave the unreacted N-amino ester (264) (37%) m.p. 146° which was identified by comparison (m.p. and i.r spectrum) with an authentic sample.

The ethanol mother liquor on evaporation gave unreacted 2-cyano-acetophenone (35%) m.p. 95° which was identical (i.r spectrum) with an authentic sample.

The Reactions of the Pyrazolyltriazoles (256a and c) with Acetic Anhydride

The pyrazolyltriazoles (356a and c) (0.0015 mol) were heated under reflux in acetic anhydride (8.0 ml) for 5 min and 0.5h respectively and then worked up as described for each reaction.

(i) Ethyl 1-Acetyl-5-(5-methylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (358)

The reaction mixture from (356c) was evaporated under reduced pressure to give the acetyl derivative (358) as colourless shiny plates (77%) m.p. 95° (from ethanol-light petroleum), $\nu_{max.}$ 1780, and 1740 (CO) cm^{-1}, $[(CD_3)_2SO]$

1.83(1H, d J 2Hz, CH), 3.68(1H, d J 2Hz, CH), 5.72(2H, q J 7Hz, CH_2), 7.75(3H, s, CH_3) and 8.78(3H, t J 7Hz, CH_3).

Found; C, 50.0; H, 5.1; N, 26.9%; $M,^+$ 263.

$C_{11}H_{13}N_5O_3$ requires: C, 50.0; H, 5.0; N, 26.6%; M, 263.

(ii) Evaporation of the solution from (356a) left an oil which was triturated with water and on standing gave the unreacted pyrazolyltriazole (356a) (83%) m.p. 130°, which was identical (m.p. and i.r. spectrum) with an authentic sample.

The Diazotative Reaction of the N-Amino Ester (264) with Acetylacetone.

The N-amino ester (264) (1.28g, 0.0075 mol) was stirred with a solution of concentrated nitric acid (0.75 ml) in water (1.75 ml), cooled to 0° (ice-salt bath), and treated dropwise with a solution of sodium nitrite (0.45g) in water (5.0 ml). The resulting pale yellow solution was treated with 80% v/v aqueous ethanol (50.0 ml), cooled to 0°, saturated with sulphur dioxide and left at room temperature for 16h. Acetylacetone (0.75g, 0.0075 mol) was added to the yellow solution which was then heated under reflux for 2h. The solution was concentrated to remove the ethanol, neutralised with solid sodium acetate and extracted with chloroform to give an oil which was triturated with ether to afford ethyl 5-(3,5-dimethylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (356a) (0.15g) m.p. 112°, identical (i.r. spectrum) with an authentic sample prepared earlier.

The Reactions of 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride (44) with Active Methylene Compounds in the Presence of Sulphur Dioxide

80% v/v Aqueous ethanol (50.0 ml) was cooled to 0° (ice-salt bath), saturated with sulphur dioxide and treated in portions with stirring with the diazonium salt (44) (0.88g, 0.005 mol). The mixture was

resaturated with sulphur dioxide, left at room temperature overnight, heated under reflux with the active methylene compounds (0.005 mol) for 2h and then worked up as described for the individual reactions.

(i) 5-(3,5-Dimethylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxamide (360a)

The clear reaction mixture from acetylacetone was evaporated and the oil left was dissolved in water and neutralised with solid sodium acetate to afford the impure pyrazolyltriazole (360a) more of which was obtained from the aqueous mother liquor on standing m.p. 180°. Crystallisation from water gave the pure product as yellow crystals (55%) m.p. 208°, ν max. 3400 (NH), 1680 (CO), and 1660 (NH) cm^{-1}, τ[$CDCl_3$ - $(CD_3)_2SO$] 1.26(1H, br s, NH), 2.32(1H, br s, NH), 3.92(1H, s, CH), 7.62(3H, s, CH_3) and 7.76(3H, s, CH_3).

Found : C, 46.7; H, 5.0; N, 41.3%; M^+ 206.

$C_8H_{10}N_6O$ requires: C, 46.6; H, 4.9; N, 40.7%; M, 206.

(ii) 5-(Pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxamide (360b)

Filtration of the reaction mixture from malondialdehyde bis(dimethyl acetal) gave the pale yellow pyrazolyltriazole (360b) more of which was obtained when the filtrate was evaporated and the oily solid obtained was triturated with ethanol (75%) m.p. 286° (from dimethylformamide-water), νmax. 3350, and 3080w (NH), and 1690 (CO) cm^{-1}, τ[$CDCl_3$ - $(CD_3)_2SO$] 1.50(1H, d J 3Hz, CH), 2.20(2H, d, CH, NH), 3.46(1H, t J 2Hz, CH).

Found: C, 40.6; H, 3.5; N, 46.6%; M^+ 178.

$C_6H_6N_6O$ requires: C, 40.5; H, 3.4; N, 47.3%; M, 178.

(iii) 5-(5-Methylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxamide (360c)

The reaction mixture from acetoacetaldehyde dimethyl acetal was concentrated to remove the ethanol and the aqueous mother liquour was neutralised with solid sodium acetate and extracted with chloroform. The insoluble solid was collected by filtration to give the crude

pyrazolyltriazole (360c) m.p. 225°. Crystallisation from dimethylformamide-water afforded the pure product as colourless prisms (33%) m.p. 240°, $\nu_{max.}$ 3350, and 3100 (NH), and 1690 (CO) cm^{-1}.

Found: C, 43.8; H, 4.3; N, 43.1%; $M,^{+}$ 192.

$C_7H_8N_6O$ requires: C, 43.7; H, 4.2; N, 43.7%; M, 192.

Evaporation of the chloroform extract gave an oil which was triturated with methanol-ether to give a negligible amount of an unidentified solid.

(iv) The reaction mixture from ethyl cyanoacetate was evaporated and the oil left was triturated with ethanol-ether to afford an unidentified solid (0.08g) m.p. > 360° which showed a poorly resolved i.r. spectrum. This solid was dissolved in water but acidification of the solution with aqueous dilute hydrochloric acid gave no identifiable product.

Evaporation of the ethanol-ether mother liquour left an oil which was treated with water to afford a solid (0.18g) m.p. 170° which had a poorly resolved i.r. spectrum. A solution of this solid in water was neutralised with solid sodium acetate but gave no identifiable product.

The Attempted Conversion of the Pyrazolyl-1,2,3-triazole Ester (356a) into the Amide (360a)

A solution of the pyrazolyltriazole (356a) (0.94g, 0.004 mol) in absolute ethanol (30.0 ml) was cooled to 0° (ice-salt bath) and saturated with ammonia gas. The flask was stoppered and left at room temperature for 24h. The yellow solution was then evaporated to afford an ammonium salt (0.91g) m.p. 174°, which was dissolved in water and the solution neutralised with aqueous dilute sulphuric acid to afford the unreacted ester (356a) (0.73g; 78%) m.p. 134°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Hydrolysis of the Pyrazoyltriazole Ester (356a) and Pyrazolyltriazole Amide (360a) to the Pyrazolyltriazole Carboxylic Acid (362).

(a) Solutions of thepyrazolytriazoles (356a) and (360a) (0.002 mol) in ethanol (10.0 ml) were heated under reflux with aqueous 20% w/v potassium hydroxide solution (2.0 ml) and (5.0 ml) respectively for 3h. The solutions were evaporated and the residual solids were dissolved in water and acidified with aqueous dilute sulphuric acid to give the same acid, 5-(3,5-Dimethylpyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylic Acid (362) (97%) and (49%) respectively, m.p. 219° (from dimethylformamide-water), $\nu_{max.}$ 3500,3400, 3150, 2700-2600br and 1930-1900br (NH, OH) and 1700 (CO) cm^{-1} $\tau[(CD_3)_2SO]$ 3.91(1H, s, CH), 7.63 (3H, s, CH_3) and 7.76(3H, s, CH_3).

Found: C, 46.3; H, 4.4; N, 34.2%; $M,^+$ 207.

$C_8H_9N_5O_2$ requires: C, 46.4; H, 4.4; N, 33.8%; M, 207.

(b) When the procedure described in (a) above was repeated using the ester (356a) and aqueous 2M sodium carbonate solution, the ester (356a) was recovered unchanged (80%) m.p. 127°, identical (m p. and i.r spectrum) with an authentic sample.

(c) When the procedure described in (a) above was repeated using the amide (360a) and 20% w/v aqueous potassium hydroxide solution but heating under reflux for only 1h, the amide (360a) was recovered unchanged (70%) m.p. 196°, and was identical (m.p. and i.r. spectrum) with an authentic sample.

Ethyl 5-Amino-1-(1-ethoxycarbonylethylideneamino)-1H-1,2,3-triazole-4-carboxylate (372).

This compound (372) (75%) m.p. 75° (lit., m.p. 38°) was prepared as described by Mackie.[38]

Ethyl 6-Methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one-3-carboxylate(276a)

This triazolotriazine (276a) m.p. 226° (lit.,[38] m.p. 226°) was prepared as described by Mackie.[38]

Ethyl 4,6-Dimethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one-3-carboxylate (364)

A solution of the triazolotriazinone (276a) (0.46g, 0.002 mol) in anhydrous acetone (50.0 ml) was treated with freshly dried anhydrous potassium carbonate (0.4g) followed by methyl iodide (0.4 ml) and the mixture was heated under reflux for 3h. The mixture was hot filtered to remove inorganic material and the acetone filtrate was evaporated to give a solid which was triturated with ethanol-ether to afford the impure triazolotriazinone (364) (0.42g). Crystallisation from water gave the pure product as a colourless solid (0.16g) m.p. 112°, νmax. 1720 and 1680 (CO) cm^{-1}, τ($CDCl_3$) 5.56(2H, q J 7Hz, CH_2), 6.02(3H, s, CH_3), 7.48(3H, s, CH_3) and 8.55(3H, t J 7Hz, CH_3), λmax. 210, and 237 nm (logε 3.99 and 4.32).

Found: C, 46.1; H, 4.6; N, 30.0%; M^+ 237.

$C_9H_{11}N_5O_3$ requires: C, 45.6; H, 4.6; N, 29.8%; M, 237.

The Attempted Synthesis of the N-Methylamidrazone (369)

A solution of the amidine hydrochloride(170) (3.34g, 0.02 mol) in absolute ethanol (25.0 ml) was cooled to 0° (ice-salt bath), stirred and treated dropwise with methyl hydrazine (0.92g, 0.02 mol). The mixture

was stirred in the melting ice for 2min and the solution was then evaporated below 35° to give an oil whose i.r. spectrum was poorly resolved. T.l.c. of the oil in methanol over silica showed it to be a single component.

A quantity of the oil was dissolved in ethanol, treated with ether, cooled to 0° and saturated with hydrogen chloride. The mixture was left in the refrigerator overnight to give a solid which liquified on attempted isolation.

The Attempted Reaction of the Imidate Hydrochloride (316) with Methylamine

A solution of the imidate hydrochloride (316) (3.9g, 0.02 mol) in ethanol (60.0 ml) was treated with methylamine (2.4g, 0.02 mol) and shaken at room temperature for 2h. The clear solution was left in the refrigerator overnight and then diluted with ether to give a hydroscopic solid whose trituration with ethanol afforded a solid (0.32g) m.p. 180° which showed a poorly resolved i.r. spectrum and could not be characterised.

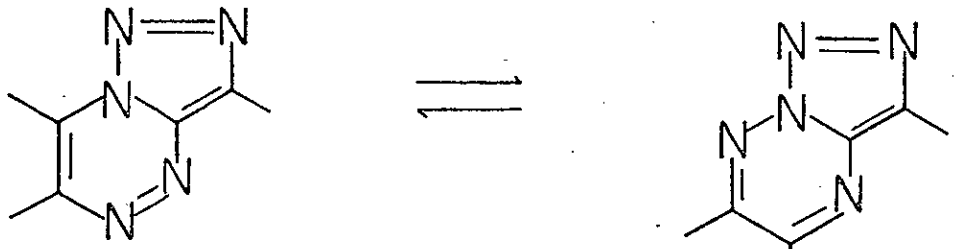
The ethanol-ether mother liquor on evaporation left an oil which was triturated with ethanol-ether to give a second solid (0.15g) m.p. 120° which again showed a poorly resolved i.r. spectrum and could not be characterised.

Chapter 5

The Synthesis and Reactivity of 1,2,3-Triazolo[1,5-d]-1,2,4-triazines

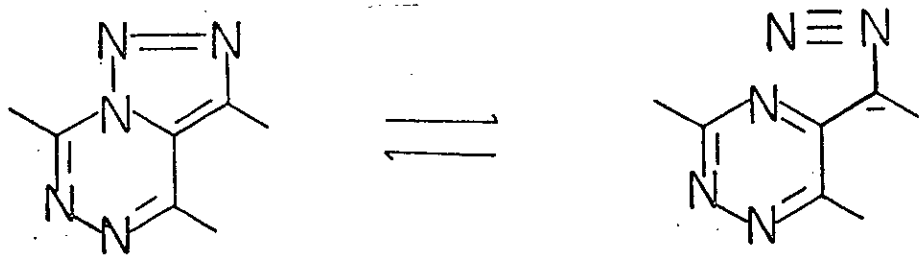
5.1 Introduction

As discussed before, there are only four bridgehead-fused 1,2,3-triazolo-1,2,4-triazines having a single nitrogen atom common to both rings - namely, the [5,1-c] (257) and [1,5,b] (260) ring systems discussed in Chapter 4 and the [1,5-d] (373) and [5,1-f] (375) ring



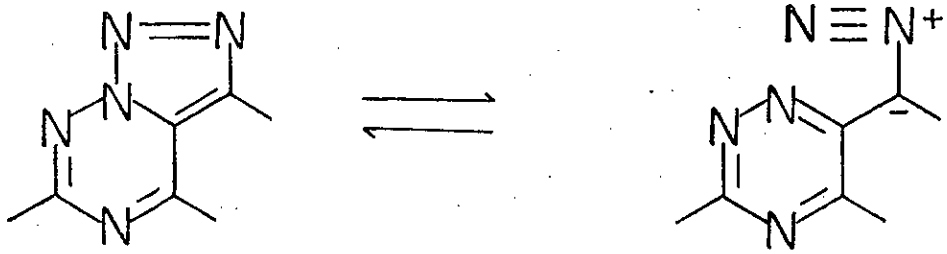
[5,1-C]
(257)

[1,5-b]
(260)



[1,5-d]
(373)

(374)

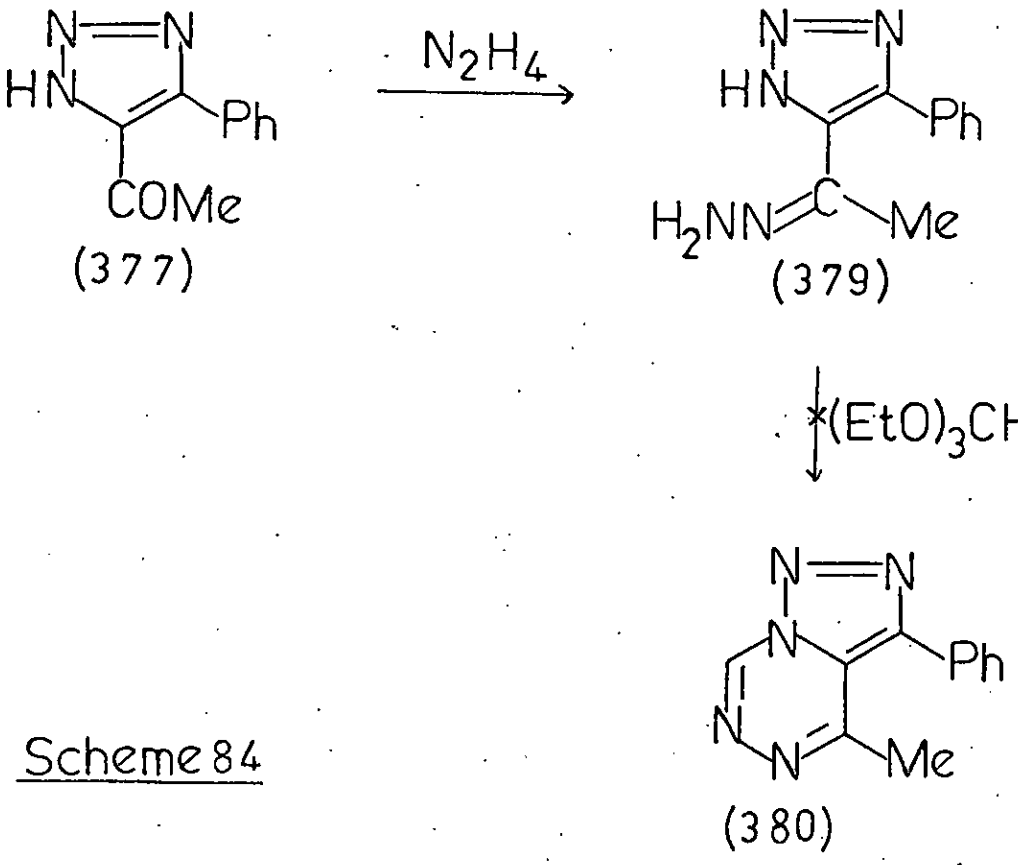


[5,1-f]
(375)

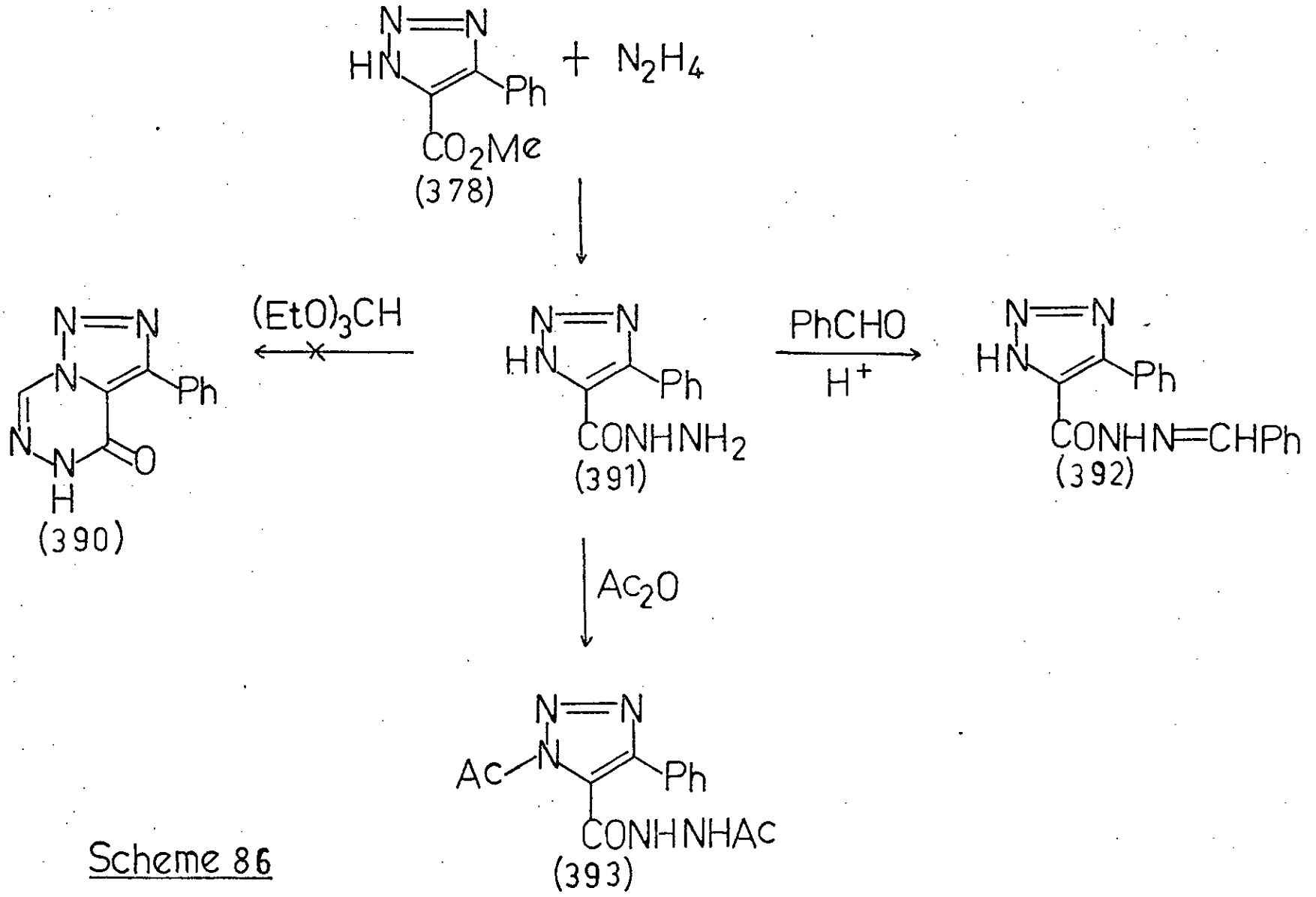
(376)

systems, examples of which are yet unknown. Since the 1,2,3-triazolo-[1,5-d]-1,2,4-triazine and 1,2,3-triazolo[5,1-f]-1,2,4-triazine ring systems are capable of diazoalkylideneamine-1,2,3-triazole tautomerism [(373) ⇌ (374)] and [(375) ⇌ (376)] but not Dimroth rearrangement of the type [(257) ⇌ (260)] (cf. Chapter 4) it was of interest to synthesise derivatives of these ring systems in the hope that they might ring-open to or coexist in equilibrium with, diazo-tautomers of the type (374) and (376). In the present chapter, studies of the synthesis and reactivity of 1,2,3-triazolo[1,5-d]-1,2,4-triazine derivatives are described, while in Chapter 6 approaches to the synthesis of 1,2,3-triazolo[5,1-f]-1,2,4-triazines are discussed.

Two approaches for the synthesis of 1,2,3-triazolo[1,5-d]-1,2,4-triazine derivatives were investigated. The first approach involved the attempted cyclisative condensation of hydrazones derived from 5-acyl-1H-1,2,3-triazoles (cf. Scheme 84) with triethyl orthoformate.



Scheme 84


+ N_2H_4
CO_2Me
(378)
$(EtO)_3CH$
PhCHO
H^+
Ac_2O
Ph
$CONHNH_2$
(391)
(390)
$CONHN{=}CHPh$
(392)
Ac
$CONHNHAc$
(393)

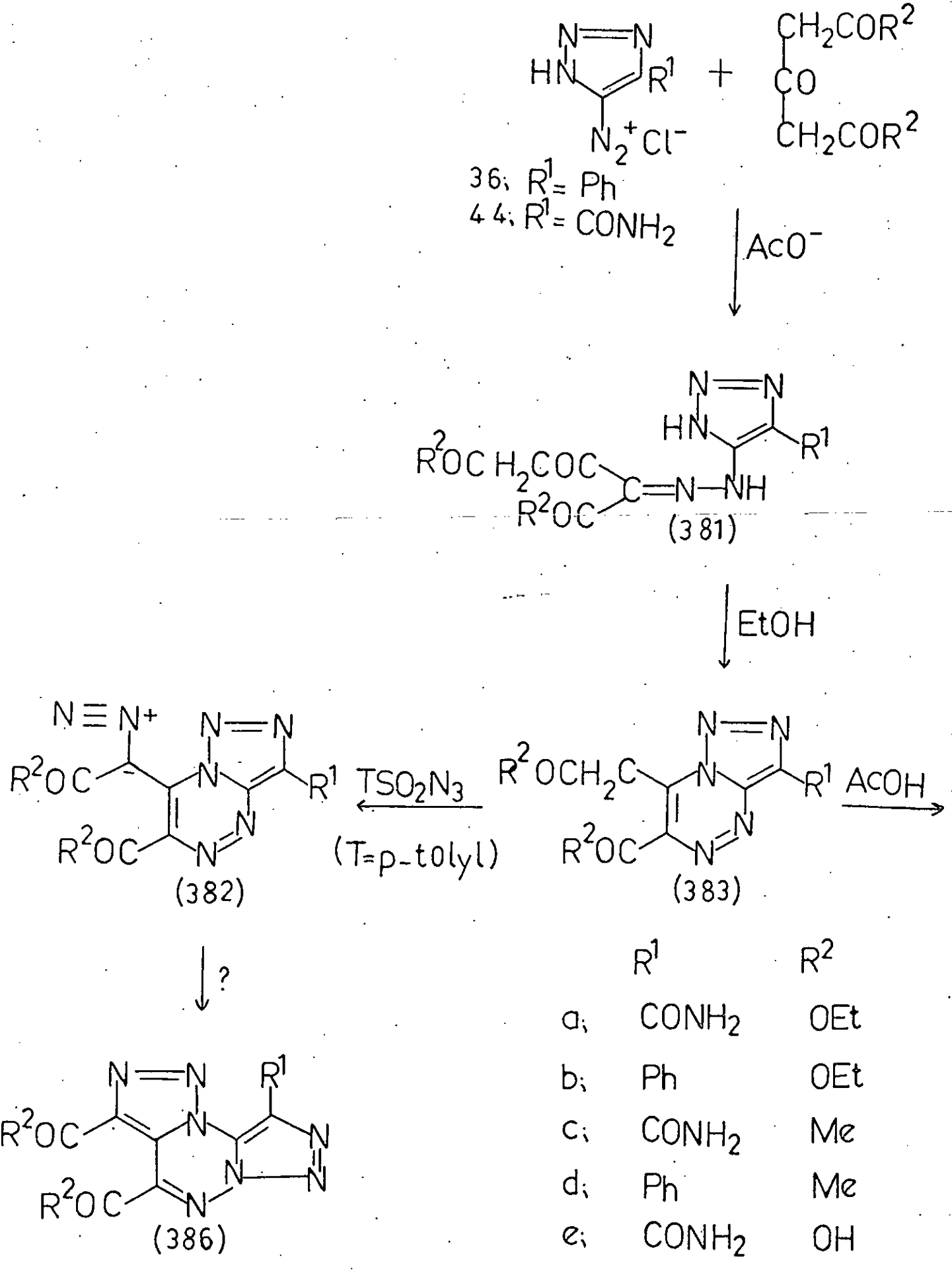
Scheme 86

In the second approach it was hoped to react 1,2,3-triazolo[5,1-c]-1,2,4-triazines (383) having a C(7) active methylene side-chain, before or after triazole scission, with toluene-p-sulphonyl azide to afford simple (387) or fused (386) 1,2,3-triazolo[1,5-d]-1,2,4-triazine derivatives (cf. Scheme 85).

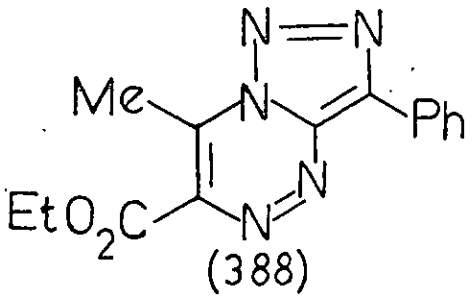
5.2 The Attempted Synthesis of 1,2,3-Triazolo[1,5-d]-1,2,4-triazines from 5-Acyl-1H-1,2,3-Triazoles

When the acetyltriazole (377) was heated under reflux with hydrazine hydrate in methanol, the hydrazone (379) was obtained in very good yield. However, when this hydrazone (379) was heated under reflux with triethyl orthoformate in an attempt to obtain the hoped-for triazolotriazine (380) only an unidentified oil was obtained whose ^1H n.m.r. spectrum showed the presence of unreacted triethyl orthoformate.

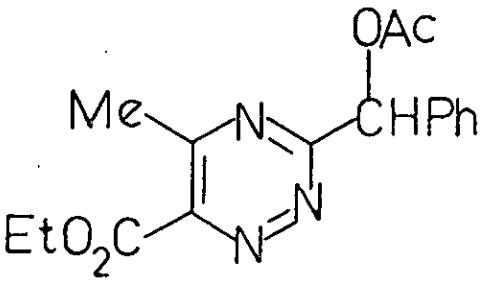
The ester (378) also readily reacted with hydrazine hydrate in methanol to afford the carbohydrazide [Scheme 86; (391)]. The structure of this product was established by its reaction with benzaldehyde to afford a monobenzylidene derivative (392) and by its reaction with acetic anhydride under mild conditions to give a diacetyl derivative (393) whose i.r. spectrum showed carbonyl absorption at 1740 cm^{-1}, characteristic of 1,2,3-triazole N-acetyl derivatives.[5a] However, the attempted reaction of the carbohydrazide (391) with triethyl orthoformate failed to afford the hoped-for 1,2,3-triazolo[1,5-d]-1,2,4-triazine (390). Instead this reaction gave only a small quantity of an unidentified solid.


36; R1 = Ph
44; R1 = CONH2
AcO−
(381)
EtOH
TSO2N3
(T=p-tolyl)
AcOH
(382)
(383)
?
(386)
R1 R2
a; CONH2 OEt
b; Ph OEt
c; CONH2 Me
d; Ph Me
e; CONH2 OH

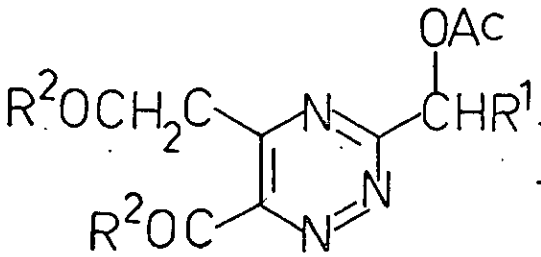
R^2 = OEt or Me



(388)

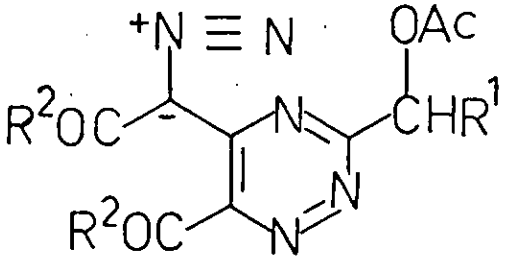


(389)



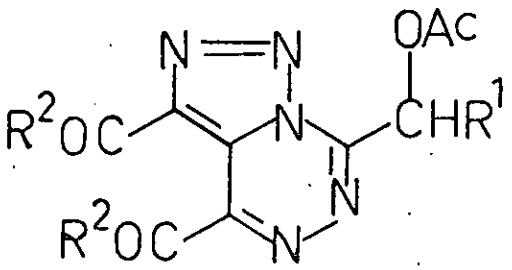
(384)

TSO_2N_3



(385)

?

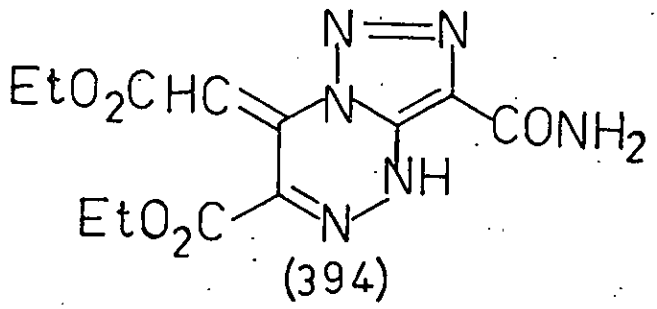


(387)

Scheme 85

5.3 The Synthesis and Reactivity of 1,2,3-Triazolo[1,5-d]-1,2,4-triazines Derived from 1,2,3-Triazolediazonium Salts

The diazonium salt (44) reacted readily at low temperature with diethyl acetonedicarboxylate in the presence of sodium acetate to yield the hydrazone [Scheme 85; (381a)]. The spectral properties of this hydrazone (381a) were in accord with the assigned structure. Thus, its i.r. spectrum showed NH absorption and carbonyl bands at 1720 and 1660 cm^{-1} while its ^1H n.m.r. spectrum in addition to showing two intact ester groups also contained a two proton doublet at τ 5.93 due to the methylene protons. When heated under reflux in ethanol for a long period, the hydrazone (381a) cyclised to the triazolotriazine (383a) while the same cyclisation could be effected by heating the hydrazone (381a) with aqueous ethanolic sodium acetate for a short time. The i.r. spectrum of (383a) showed NH absorption and ester bands at 1740, 1700 and 1670 cm^{-1} while its ^1H n.m.r. spectrum showed it was a mixture of two tautomers, (383a) and (394). Thus, it contained a one proton singlet at τ 4.18 due to the methine proton in (394) and a two proton singlet at τ 5.58 due to the methylene



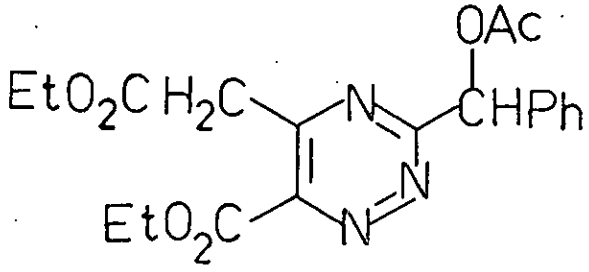
(394)

protons in (383a). Also, its ^1H n.m.r. spectrum contained multiplets in the ester region indicating again the presence of two tautomers (383a) and (394). The compound (383a) also gave analytical, mass spectral and u.v.

data in accord with the assigned structure. The attempted further characterisation of the diester (383a) by hydrolysis to the diacid (383e) was unsuccessful. Thus, the triazolotriazine (383a) was unaffected by heating with aqueous ethanolic sodium carbonate. The attempted hydrolysis of (383a) using alkali on the other hand led to its decomposition while its attempted acidic hydrolysis using dilute acid was unsuccessful, giving instead the unreacted triazolotriazine (383a).

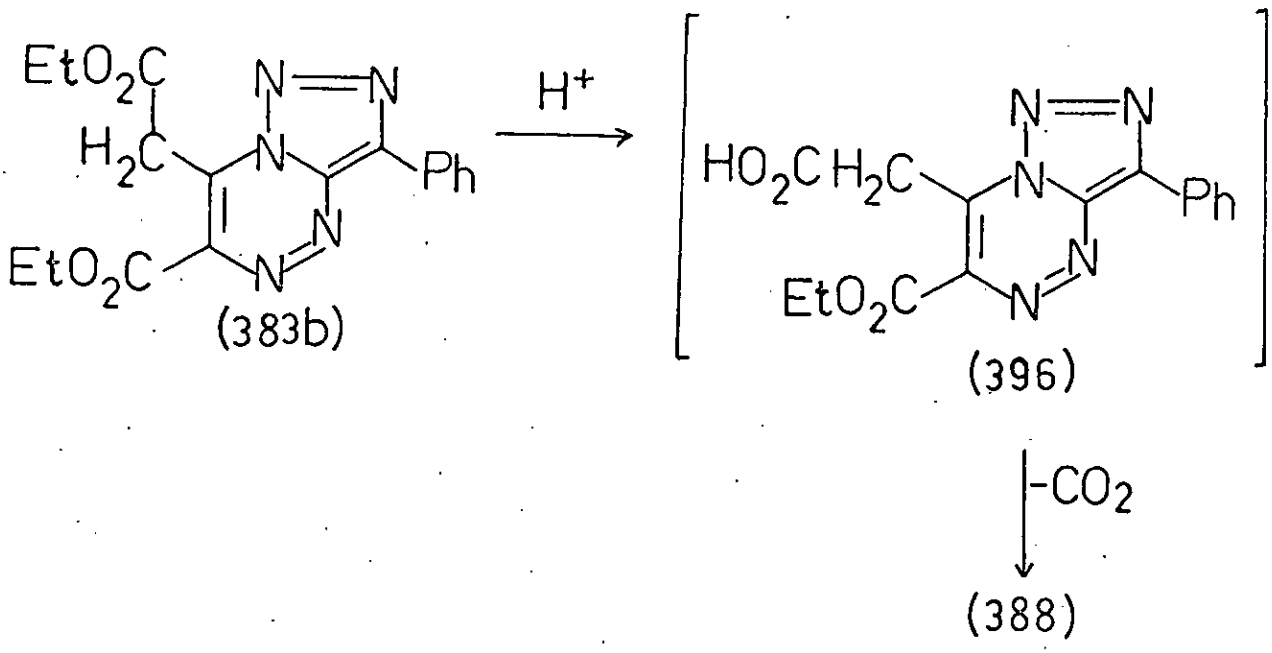
The coupling reaction of 4-phenyl-1H-1,2,3-triazole-5-diazonium chloride (36) with diethyl acetonedicarboxylate resulted not in the formation of the expected hydrazone (381b) but rather in a mixture of the triazolotriazine (383b) and the known[41] triazolotriazine (388). The latter product was identical in all respects with an authentic sample.[41] The triazolotriazine (388) was further characterised by heating it under reflux in glacial acetic acid to give an oily acetate (389) whose structure is fully supported by its i.r. spectrum which contained broad carbonyl absorption at 1740-7120 cm^{-1} and its ^1H n.m.r. spectrum which showed a three proton singlet at τ 7.26 due to the methyl protons of the acetoxy group. When the coupling reaction of the diazonium salt (36) with diethyl acetonedicarboxylate was repeated but with heating under reflux, only the triazolotriazine (383b) was obtained. The triazolotriazine (383b) gave analytical data and showed spectral properties consistent with its assigned structure, but its i.r. spectrum showed only one carbonyl band, indicating that the two ester groups are superimposed, due probably to the fact that the 6-ethoxycarbonyl group attached to the electron-withdrawing triazine ring absorbs at higher frequency than would have been expected. The ^1H n.m.r. spectrum of (383b) in addition to showing two intact ester absorptions also contained a two proton singlet at τ 5.61 due to the methylene group. In accord with the assigned structure, heating the diester (383b) in glacial acetic acid

resulted in acid-catalysed triazole scission to give an oil which was shown to contain two components, one of which was the acetoxy derivative (395) as confirmed by the ^{1}H n.m.r. spectrum of the oil. This showed



(395)

a signal at τ 3.08 attributable to a benzylic proton and a three proton singlet at τ 7.80 due to the protons of the acetoxy group. In an effort to further establish the structure of (383b), it was decided to degrade it to known compounds. Thus, when heated under reflux with aqueous ethanolic sulphuric acid solution, the triazolotriazine (383b) underwent decarbethoxylation to afford the known[41] compound (388). The transformation [(383b) → (388)] probably involves initial hydrolysis to the carbxoylic acid (396) which

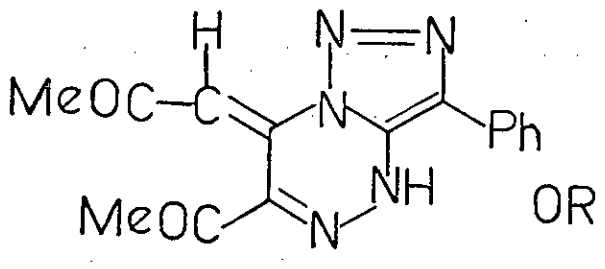


(383b) (396) (388)

on further heating undergoes decarboxylation to (388).

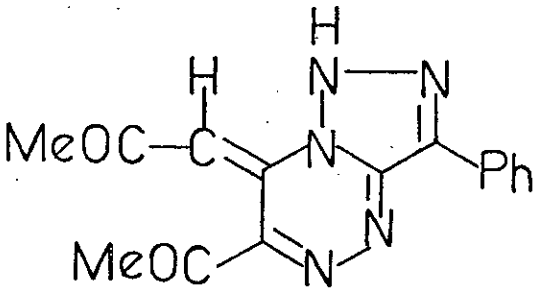
The amide (44) also coupled readily with the triketone (218) in the presence of sodium acetate to afford the 7-acetonyltriazolotriazine (383c). In this case, the hydrazone stage (381c) was not isolated. The triazolotriazine (383c) gave analytical and i.r. and mass spectral data consistent with the assigned structure. Thus, its i.r. spectrum showed NH absorption and again only one carbonyl band at 1680 cm^{-1} like (383b). Unfortunately, there was insufficient material for (383c) to have its ^{1}H n.m.r. spectrum run.

When the triazolediazonium chloride (36) was coupled with the triketone (218), the triazolotriazine (383d) was obtained. However, when this coupling reaction was repeated on a ten-fold scale, a readily separated mixture of the triazolotriazine (383d) and an isomeric product was obtained. The elemental analysis of (383d) was consistent with the molecular formula $C_{15}H_{13}N_5O_2$ and the mass spectrum showed a molecular weight of 295. Its i.r. spectrum contained only one carbonyl absorption at 1705^{-1} indicating once again that the two carbonyl groups are superimposed. However, the ^{1}H n.m.r. spectrum of (383d) showed that it existed in the form (397a) or (397b) rather than as (383d). Thus, its ^{1}H n.m.r. spectrum contained



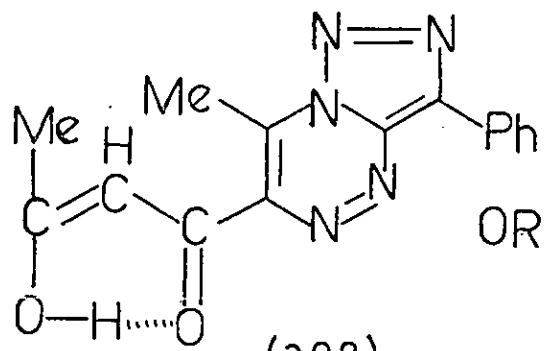
(397a)

OR

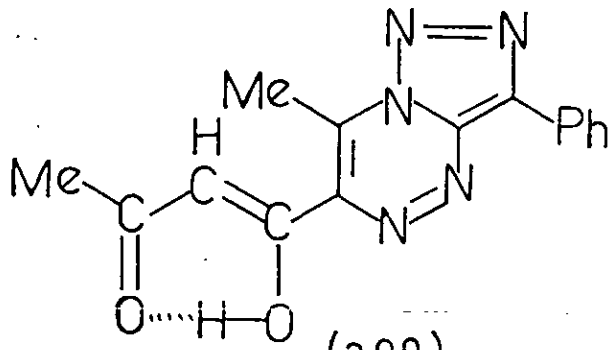


(397b)

a one proton singlet at τ 3.32 and two three proton singlets at τ 7.60 and 7.91 due to the methine proton and the two methyl groups in (397a) or (397a) respectively. The isomer also showed the expected analytical and mass spectral data and its i.r. spectrum contained hydroxyl and carbonyl signals at 3120 and 1710 cm^{-1} respectively. This compound is formulated as (398) or (399) on the basis of its ^1H n.m.r. spectrum which shows a one proton singlet at τ 3.52 due to the methine hydrogen and

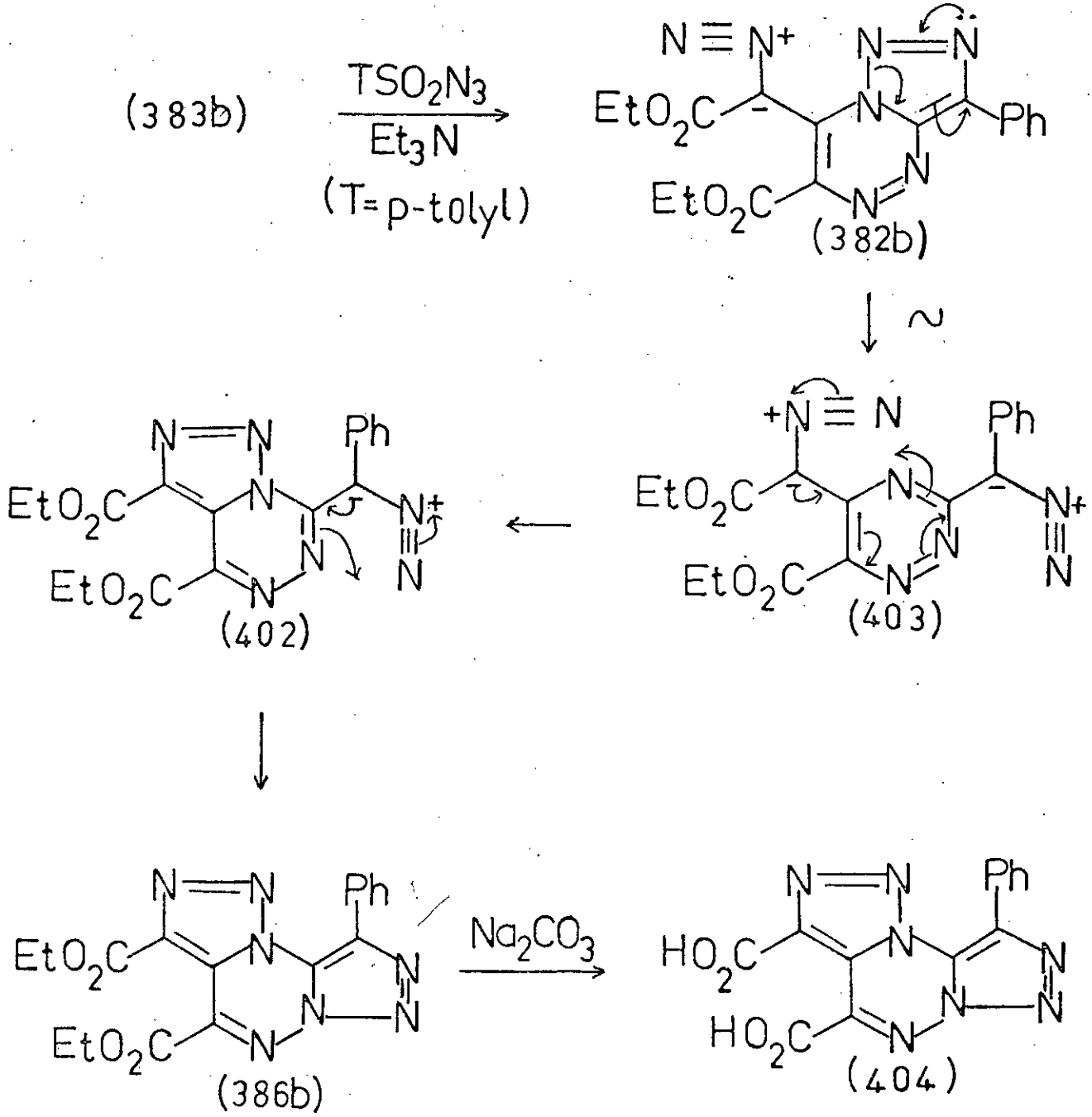


(398)

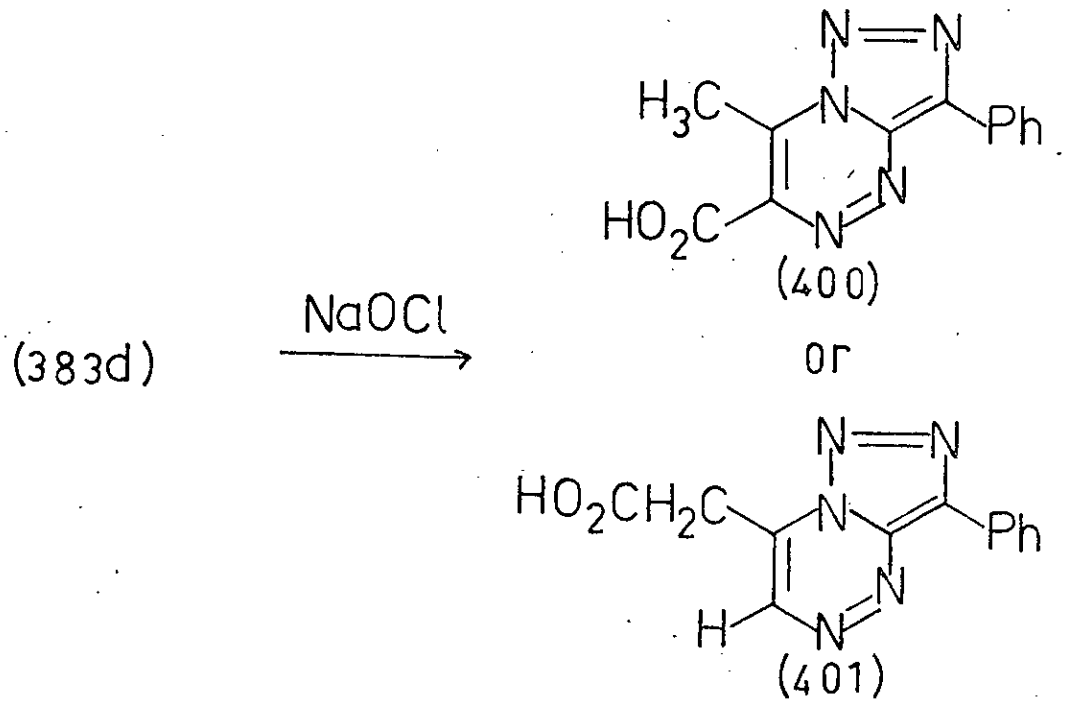


(399)

two three proton singlets at τ 7.16 and 7.74 attributable to the two methyl groups in (398) or (399). However, the structures assigned to these two isomers (397a) or (397b) and (398) or (399) are tentative and must await further confirmation. In an attempt to further establish the structure of the triazolotriazine (383d) it was subjected to alkaline hydrolysis. However, warming (383d) with either aqueous sodium hydroxide or potassium hydroxide resulted in its decomposition. The attempted degradation of (383d) using aqueous sodium hypochlorite was also unsuccessful, giving mainly unreacted starting material plus a small amount of an acidic product whose i.r. spectrum indicated it to be a carboxylic acid. Thus, it showed hydroxyl absorption at 3100 cm^{-1} and a carbonyl band at 1725 cm^{-1}. However,



Scheme 87



its mass spectrum showed a parent ion at m/e 253, two units below the expected value for either of the two possible acid structures (400) and (401) and it gave analytical data also inconsistent with these structures. Further work will be needed to identify this compound. The attempted triazole scission of the triazolotriazine (383d) using glacial acetic acid or aqueous ethanolic sulphuric acid solution was unsuccessful giving, in each case, the unreacted triazolotriazine (383d).

When the triazolotriazine (383a) was treated with toluene-p-sulphonyl azide in the presence of triethylamine at a low temperature, there was no reaction and the starting material (383a) was recovered in modest yield. However, repetition of this 'diazo-transfer'reaction[17] using the triazolotriazine (383b) afforded toluene-p-sulphonamide and a product formulated as the tricyclic diester (386b) (cf. Scheme 87) on the basis of the following evidence. It gave analytical and mass spectral data consistent with the molecular formula $C_{17}H_{15}N_7O_4$. Its i.r. spectrum showed a single carbonyl band at 1740 cm^{-1} indicating the close similarity of the two ester groups. The similar environment of the two ester groups

in (386b) was further borne out by its ^{1}H n.m.r. spectrum which showed superposition of the four methylene hydrogens and six methyl hydrogens of the two ester substituents. The diester (386b) was further characterised by its hydrolysis to the diacid (404) which gave analytical and mass spectral data and showed an i.r. spectrum consistent with the assigned structure (404). Thus, its i.r. spectrum contained a broad hydroxyl absorption and two carbonyl bands at 1740 and 1725 cm^{-1}. The fused structure (386b) failed to undergo acid-catalysed scission on heating in glacial acetic acid for a short time and on prolonged heating, it decomposed to a tar. The formation of this tricyclic diester (386b) can be explained in terms of the following mechanism (Scheme 87). First, 'diazo-transfer' reaction occurs to afford the diazo-intermediate (382b), which ring opens and suffers Dimroth rearrangement to the bis-diazo intermediate (403) and this ring closes to the diester (386b).

The acetonyltriazolotriazine (383d) failed to react when it was treated in the cold with toluene-p-sulphonyl azide in the presence of triethylamine and a similar reaction using sodium hydride as the base, at room temperature was also unsuccessful.

5.4 Experimental (For general experimental procedures, see Appendix)

4-Phenyl-1H-1,2,3-triazole-5-diazonium Chloride (36) and 1H-1,2,3-triazole-3-carboxamide-5-Diazonium Chloride (44)

The diazonium salts (36) and (44) were prepared as described in Chapter 4, page 142.

Heptane-2,4,6-trione (218)

Heptane-2,4,6-trione (218) was prepared as described in Chapter 3, page 75.

5-Acetyl-4-phenyl-1H-1,2,3-triazole (377)

5-Acetyl-4-phenyl-1H-1,2,3-triazole[53] (377) m.p. 106° (lit.,[53] 112°) was prepared as described in the literature.[53]

Methyl 4-Phenyl-1H-1,2,3-triazole-5-carboxylate (378)

Methyl 4-phenyl-1H-1,2,3-triazole-5-carboxylate[53] (378) (71%) m.p. 105° (lit., [53] 113°) was prepared as described in the literature.[53]

4-Phenyl-1H-1,2,3-triazole-5-carbohydrazide (391)

Methyl 4-phenyl-1H-1,2,3-triazole-5-carboxylate (378) (0.82g, 0.004 mol) was heated under reflux with 85% hydrazine hydrate (1.0 ml) in methanol (15.0 ml) for 1.5h. Evaporation of the mixture and trituration of the residue with ethanol-ether gave the hydrazide (391) as a cream solid (1.2g) m.p. 115° (from ethanol), $\nu_{max.}$ 1660 (CO) cm^{-1},

Found: 203.079216.

$C_9H_9N_5O$ requires: 203.080705.

The Benzylidene Derivative (392) of 3-phenyl-1H-1,2,3-triazole-5-carbohydrazide (391)

A solution of the hydrazide (391) (0.41g, 0.002 mol) and concentrated sulphuric acid (1.0 ml) in water (2.5 ml) and methanol (5.0 ml) was treated with a solution of freshly distilled benzaldehyde (0.21g, 0.002 ml) in methanol (5.0 ml). The mixture was stirred at room temperature for 17h and then extracted with chloroform to give an oil which was triturated with ethanol-ether to yield the benzylidene derivative (392) as large plates (0.34g) m.p. 253° (from dimethylformamide-water), $\nu_{max.}$ 3300, and 3100 (NH) and 1660 (CO) cm^{-1}.

Found: C, 65.6; H, 4.5; N, 24.1%; $M,^{+}$ 291.

$C_{16}H_{13}N_5O$ requires: C, 66.0; H, 4.5; N, 24.0%; M, 291.

The Preparation of the Diacetyl Derivative (393) of the Hydrazide (391)

The hydrazide (391) (0.20g, 0.001 mol) was heated under reflux with acetic anhydride (15.0 ml) for 15 min. Evaporation of the solution followed by trituration with water gave on standing the diacetyl derivative (393) as a cream solid (0.19g). Crystallisation from dimethylformamide-water gave the pure product, m.p. 161°, $\nu_{max.}$ 3400, and 3200 (NH), 1740 and 1680 (CO) cm^{-1}.

Found: C, 54.1; H, 4.5; N, 24.4%; $M,^{+}$ 287.

$C_{13}H_{13}N_5O_3$ requires: C, 54.3; H, 4.5; N, 24.4%; M, 287.

The Attempted Reaction of the Hydrazide (391) with Triethyl orthoformate

The hydrazide (391) (0.41g, 0.002 mol) was heated under reflux with triethyl orthoformate (10.0 ml) for 18h. The mixture was cooled to give an unidentified solid (0.03g) m.p. 297°, $\nu_{max.}$ 3400 and 3210 (NH), and 1700 (CO) cm^{-1}; M^{+} 255.

Evaporation of the triethyl orthoformate under reduced pressure

gave an oil which was triturated with ethanol-ether to give a hygroscopic solid. The ethanol-ether mother liquor on evaporation left an oil whose i.r. was poorly resolved.

6-Ethoxycarbonyl-7-ethoxycarbonylmethyl-7-hydroxy-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (383a)

(a) Solutions of the diazonium salt (44) (0.53g, 0.003 mol) in water (10.0 ml) and ethanol (10.0 ml) and diethyl acetonedicarboxylate (0.61g, 0.003 mol) and sodium acetate (0.4g) in water (2.0 ml) and ethanol (5.0 ml) were mixed and stirred at 0° (ice-salt bath) for 2h. Filtration of the mixture gave the impure cream hydrazone (381a) which was combined with a second crop obtained by evaporating the ethanol from the filtrate (total 0.82g). Crystallisation from ethanol-light petroleum gave the pure product, m.p. 158°, νmax. 3400, 3300, and 3200br, (NH), and 1720 and 1660 (CO) cm^{-1}, τ [$CDCl_3$ - $(CD_3)_2SO$] 2.61(1H, br s, NH), 3.04(1H, br s, NH), 5.70(2H, q J 7Hz, CH_2), 5.93(2H, d J 2Hz, CH_2), 6.00(2H, q J 7Hz, CH_2), 8.66(3H, t J 7Hz, CH_3) and 8.88(3H, t J 7Hz, CH_3).

Found: C, 42.3; H, 4.6; N, 25.1%; M^+ 322.

$C_{12}H_{16}N_6O_6$ requires: C, 42.3; H, 4.7; N, 24.6%; M, 340.

(b) The hydrazone (381a) (0.34g, 0.001 mol) was heated under reflux in ethanol (10.0 ml) for 17h. Evaporation of the solution left a solid which was successively triturated with ethanol-ether to give 6-ethoxycarbonyl-7-ethoxycarbonylmethyl-7-hydroxy-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (383a) as yellow needles (total (0.24g; 75%) m.p. 180° (from ethanol), νmax. 3500, 3300, and 3150 (NH), and 1740, 1700 and 1670 (CO) cm^{-1}, λmax. 212sh, 228, 281 and 341 nm (logε 4.24, 4.30, 4.12 and 3.57). τ [$CDCl_3$ - $(CD_3)_2SO$] 2.19(br s, NH), 2.48(br s, NH), 4.18(1H, s, CH), 5.40-5.88(m, CH_2), 5.58(2H, s, CH_2), and 8.46-8.90(m, CH_3).

Found: C, 44.6; H, 4.4; N, 26.2%; M^+ 322.

$C_{12}H_{14}N_6O_5$ requires: C, 44.7; H, 4.4; N, 26.1%; M, 322.

(c) A solution of the hydrazone (381a) (0.68g, 0.002 mol) in water (5.0 ml) and ethanol (10.0 ml) was heated under reflux with anhydrous sodium acetate (0.16g) for 1h. The mixture was evaporated and the oil left was triturated with water to afford the triazolotriazine (383a) more of which was obtained by acidifying the aqueous mother liquor with aqueous dilute acetic acid, extraction with chloroform and trituration of the resulting oil with ethanol (total 0.16g) m.p. 174° (from ethanol), identical (m.p. and i.r. spectrum) with a sample prepared in (b). The oil obtained by evaporating the ethanol mother liquor was shown by t.l.c. in ethyl acetate over silica to be an unresolved mixture of three components.

The Attempted Hydrolysis of 6-Ethoxycarbonyl-7-ethoxycarbonylmethylene-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (383a)

(a) Using Ethanolic Sodium Carbonate Solution

A solution of the triazolotriazine (383a) (0.64g, 0.002 mol) in ethanol (25.0 ml) was heated under reflux with aqueous 2M sodium carbonate solution (2.0 ml) for 3h. The mixture was filtered to give a solid which was suspended in water and acidified with aqueous dilute sulphuric acid to afford the unreacted starting material (383a) (0.54g; 84%) m.p. 178° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) Using Aqueous Sodium Hydroxide Solution

The triazolotriazine derivative (383a) (0.54g, 0.0016 mol) was heated under reflux with aqueous 2M sodium hydroxide (10.0 ml) for 1h. The solution was neutralised with aqueous dilute sulphuric acid, evaporated and the residue treated with water to give a filterable solid (0.18g)

m.p. $> 360^{\circ}$ whose i.r. spectrum showed it to be inorganic.

No further identifiable material could be isolated.

6-Ethoxycarbonyl-7-ethoxycarbonylmethylene-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (383b)

(a) Solutions of 4-phenyl-1H-1,2,3-triazole-5-diazonium chloride (36) (4.9g, 0.012 mol) in water (60.0 ml) and ethanol (60.0 ml) and diethyl acetonedicarboxylate (4.9g, 0.012 mol) and sodium acetate (3.2g) in water (16.0 ml) and ethanol (40.0 ml) were mixed, cooled in an ice-salt bath and stirred. Stirring was continued in the melting ice-bath for 2h. The ethanol was removed from the mixture under reduced pressure and the aqueous mohter liquor was extracted with chloroform to give an oil, which was triturated with ethanol to yield 6-ethoxycarbonyl-7-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (388) (0.55g) m.p. 174° (from ethanol), identical (m.p. and i.r. spectrum) with an authentic sample.[41]

The ethanol mother liquor was heated under reflux for a few minutes and concentrated to give 6-ethoxycarbonyl-7-ethoxycarbonylmethylene-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (383b) as orange needles (2.86g) m.p. 104° (from benzene-light petroleum), ν max. 1730 (CO) cm^{-1}, λmax. 210, 228, 281 and 341 nm (logε 4.44, 4.30, 4.12 and 3.57) τ ($CDCl_3$) 1.62-1.71(2H, m, Ar-H), 2.50-2.58(3H, m, Ar-H), 5.50(2H, q J 7Hz, CH_2), 5.61(2H, s, CH_2), 5.83(2H, q J 7Hz, CH_2), 8.52(3H, t J 7Hz, CH_3) and 8.72(3H, t J 7Hz, CH_3).

Found: C, 57.6; H, 4.8; N, 20.0%; $M,^{+}$ 355.

$C_{17}H_{17}N_5O_4$ requires: C, 57.5; H, 4.8; N, 19.7%; M, 355.

(b) Solutions of the diazonium chloride (36) (0.62g, 0.003 mol) in water (10.0 ml) and ethanol (10.0 ml) and diethyl acetonedicarboxylate (0.61g, 0.002 mol) and sodium acetate (0.4g) in water (5.0 ml) and

ethanol (2.0 ml) were mixed, cooled in an ice-salt bath and stirred for 2h. The mixture was then heated under reflux for 1h. The ethanol was removed under reduced pressure and the aqueous mother liquour was extracted with chloroform to give an oil which on trituration with ethanol-ether gave the triazolotriazine (383b) more of which was obtained by evaporating the ethanol-ether mother liquour and retriturating the resulting oil with ether (total 0.3g; 32%) m.p. 94°, identical (i.r. spectrum) with a sample prepared in (a).

3-(α-Acetoxybenzyl)-6-ethoxycarbonyl-5-methyl-1,2,4-triazine (388).

The triazolotriazine (388) (0.37g, 0.001 mol) was heated under reflux in glacial acetic acid (15.0 ml) for 3h. Evaporation of the solution gave a residue which was triturated with ethanol-ether to give unreacted triazolotriazine (388) (0.08g) m.p. 169°, identical (i.r. spectrum) with an authentic sample.

The ethanol-ether mother liquor on evaporation left an oil (0.23g) which was shown to be 3-(α-acetoxybenzyl)-6-ethoxycarbonyl-5-methyl-1,2,3-triazine (389) νmax. 3400, 2990 and 1740-1720 br (CO) cm^{-1}, τ ($CDCl_3$) 2.38-2.47(2H, m, Ar-H), 2.65-2.72(3H, m, Ar-H), 3.12(1H, s, CH), 5.52(2H, q J 6Hz, CH_2), 7.26(3H, s, CH_3), 7.78(3H, s, CH_3) and 8.58(3H, t J 6Hz, CH_3).

7-Acetonyl-6-acetyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (383c)

Solutions of the diazonium chloride (44) (0.53g, 0.003 mol) in water (10.0 ml) and ethanol (10.0 ml) and the triketone (218) (0.43g, 0.003 mol) and sodium acetate (0.4g) in water (2.0 ml) and ethanol (5.0 ml) were mixed and stirred at 0° (ice-salt bath) for 2h. The mixture was concentrated to remove the ethanol and filtered to give the triazolotriazine (383c) (0.40g; 51%) m.p. 150°. Crystallisation from diemthylformamide-water

gave the pure product, m.p. 186°, $\nu_{max.}$ 3440, and 3140 (NH) and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 225 and 290 nm (log ε 4.32 and 4.34).

Found: C, 45.8; H, 3.9; N, 32.5%; $M,^{+}$ 262.

$C_{10}H_{10}N_6O_3$ requires: C, 45.8; H, 3.8; N, 32.1%; M, 262.

Work up of the aqueous filtrate by acidification and extraction with chloroform gave no further product.

7-Acetonyl-6-acetyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (383d) and its Isomer (398) or (399)

(a) Solutions of the diazonium chloride (36) (0.62g, 0.003 mol) in ethanol (10.0 ml) and water (10.0 ml), and the triketone (218) (0.43g, 0.003 mol) and sodium acetate (0.4g) in ethanol (5.0 ml) and water (2.0 ml) were mixed and stirred at 0° (ice-salt bath) for 2h. The mixture was concentrated to remove the ethanol and extracted with chloroform to give an oil which was successively triturated with ethanol to afford the triazolotriazine (383d) as a yellow solid (total 0.47g), m.p. 167° (from ethanol), $\nu_{max.}$ 1705 (CO) cm^{-1}, $\lambda_{max.}$ 211, 261 and 306sh nm (log ε 4.34, 4.37 and 4.09), τ [$CDCl_3$ - $(CD_3)_2SO$] 2.58(5H, s, Ar-H), 3.32(1H, s, CH), 7.60(3H, s, CH_3) and 7.91(3H, s, CH_3).

Found: C, 61.1; H, 4.5; N, 24.0%; $M,^{+}$ 295.

$C_{15}H_{13}N_5O_2$ requires: C, 61.0; H, 4.4; N, 23.7%; M, 295.

Evaporation of the ethanol mother liquor left an oil whose t.l.c. in ether over alumina showed it to be an unresolved mixture of three components.

(b) The experiment described in (a) above was repeated exactly on a ten-fold scale. Successive trituration of the oil, obtained after the chloroform extraction, with ethanol gave the isomer mixture (383d) and

(398) or (399). Crystallisation of this mixture from ethanol-water gave the two isomers, (383d) (0.21g) m.p. 168°, described in (a) and the second isomer (398) or (399) was a yellowish-brown solid (4.65g; 55%) m.p. 210° (from ethanol), νmax 3120 (OH) and 1710 (CO) cm^{-1}, λmax. 211, 261, 305 nm (log ε 4.34, 4.37 and 4.08), τ[$CDCl_3$ - $(CD_3)_2SO$] 1.65-1.74(2H, m, Ar-H), 2.40-2.62(3H, m, Ar-H), 3.52(1H, s, CH), 7.16(3H, s, CH_3) and 7.74(3H, s, CH_3).

Found: C, 60.7; H, 4.7; N, 23.5%; M_+ 295.

$C_{15}H_{13}N_5O_2$ requires: C, 61.0; H, 4.4; N, 23.7%; M, 295.

The ethanol mother liquor on evaporation left an oil whose t.l.c. in ether over alumina showed it to be a resolvable mixture of four components. Consequently, it was subjected to dry column chromatography in ethanol-ether over alumina to give as the faster running component an unidentified solid, (0.07g) m.p. 107° and as the slower running component a little quantity of the triazolotriazine (398) or (399) (0.03g) m.p. 190°, identical (m.p. and i.r. spectrum) with the sample described earlier.

The Attempted Hydrolysis of the Triazolotriazine (383d)

(a) Using Aqueous Sodium Hydroxide Solution

The triazolotriazine (383d) (0.30g, 0.001 mol) was heated under reflux with aqueous 2M sodium hydroxide solution (10.0 ml) for 1h. The dark solution was acidified with aqueous dilute sulphuric acid and filtered to give a very dark solid which rapidly decomposed at room temperature.

The acidic mother liquour was extracted with chloroform to give a negligible amount of an unidentified oil.

(b) Using Aqueous Potassium Hydroxide Solution

The triazolotriazine (383d) (0.59g, 0.002 mol) was heated under reflux with aqueous 20% w/v potassium hydroxide solution (5.0 ml) for 1h. The

dark solution was acidified with aqueous dilute sulphuric acid and extracted with chloroform. Filtration of the chloroform-acid mixture gave a solid (0.64g) which decomposed rapidly at room temperature. Evaporation of the chloroform extract gave a negligible amount of an unidentified solid.

The Reaction of the Triazolotriazine (383d) with Aqueous Sodium Hypochlorite

A solution of the triazolotriazine (383d) (0.59g, 0.002 mol) in water (2.0 ml) and dioxan (30.0 ml) was treated with aqueous 3.85N sodium hypochlorite solution (1.56 ml) and stirred at 70° (oil-bath) for 1.5h. The mixture was treated with a saturated solution of sodium bisulphite (2.0 ml), diluted with water (20.0 ml) and extracted with chloroform to give a negligible amount of oil. The aqueous layer was acidified with aqueous dilute hydrochloric acid and extracted with chloroform to give a foam which on trituration with ethanol-ether gave an acidic product (400) or (401) as a pale yellow solid (0.10g) m.p. 247° (from ethanol-water), $\nu_{max.}$ 3100 (OH) and 1725 (CO) cm^{-1},

Found: C, 56.2; H, 3.7%; M^+ 253.

$C_{12}H_9N_5O_2$ requires: C, 56.5; H, 3.6%; M, 255.

Concentration of the aqueous layer left a solid (0.26g) m.p. 190° which was identified (i.r. spectrum) as unreacted triazolotriazine (383d) by comparison with an authentic sample.

The Attempted Reaction of the Triazolotriazine (383a) with Toluene-p-Sulphonyl Azide.

A solution of the triazolotriazine (383a) (0.32g, 0.001 mol) in absolute ethanol (30.0 ml) was stirred and treated at 0°(ice-salt bath) with triethylamine (0.20g, 0.002 mol) and then dropwise with a solution of toluene-p-sulphonyl azide (0.40g, 0.002 mol) in absolute ethanol (15.0 ml).

The mixture was stirred in the melting ice-salt bath for 2h, and then filtered to give unreacted starting material (0.14g) m.p. 177°, identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethanol mother liquor left a gum which was suspended in water and extracted with chloroform to give an oil (0.32g) identified as toluene-p-sulphonyl azide by comparison (i.r. spectrum) with an authentic sample.

The Reaction of the Triazolotriazine (383b) with Toluene-p-sulphonyl Azide in the Presence of Triethylamine

A solution of the methylene compound (383b) (1.4g, 0.004 mol) in absolute ethanol (200 ml) was stirred at 0°(ice-salt bath) and treated in one portion with triethylamine (0.81g, 0.008 mol) and then dropwise with a solution of toluene-p-sulphonyl azide (0.80g, 0.004 mol) in absolute ethanol (20.0 ml). The mixture was stirred in the melting ice-bath for 2h and then filtered to give unreacted diester (383b) (0.50g) m.p. 90°, which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The ethanol filtrate was evaporated and the resulting oil was triturated with ethanol-ether to give the tricyclic compound(386b) as yellow needles (0.41g) m.p. 171° (from diemthylformamide-ethanol), $\nu_{max.}$ 1740 (CO) cm^{-1}, $\lambda_{max.}$ 211, 221sh, and 281 nm (logε 4.44, 4.40 and 4.34) $\tau(CDCl_3)$ 1.58-1,68(2H, m, Ar-H), 2.48-2.56(3H, m, Ar-H), 5.48(4H, q J 7Hz, CH_2, and 8.56(6H, t J 7Hz, CH_3).

Found: C, 53.3; H, 4.0; N, 26.2%; $M,^+$ 381.
$C_{17}H_{15}N_7O_4$ requires: C, 53.5; H, 3.9; N, 25.8%; M, 381.

The ethanol-ether mother liquor on evaporation left an oil which was treated with chloroform, and dilute aqueous sodium hydroxide solution.

Evaporation of the chloroform extract gave an oil which solidified in contact with water to give more of the product (386b) (0.37g) m.p. 156°, identical (i.r. spectrum) with the sample obtained before. Acidification of the aqueous alkaline extract with dilute aqueous sulphuric acid gave toluene-p-sulphonamide (0.11g) m.p. 122° (from ethanol), identical (m.p. and i.r. spectrum) with an authentic sample.

The Hydrolysis of the Tricyclic Diester (386b) to the Tricyclic Diacid (404)

A solution of the tricyclic diester (386b) (0.38g, 0.001 mol) in ethanol (25.0 ml) was heated under reflux with aqueous 2M sodium carbonate solution (2.0 ml) for 3h. The mixture on evaporation left a residue which was dissolved in water, acidified with dilute aqueous hydrochloric acid and extracted with chloroform. Evaporation of the chloroform extract gave an oily solid which in contact with methanol-light petroleum gave the diacid (404) as a pale pink solid (0.70g) m.p. 121° (from benzene), $\nu_{max.}$ 3520, 3340br and 1940br (OH) and 1740w, and 1725 (CO) cm^{-1}, $\lambda_{max.}$ 213, 221sh, 275sh, and 284 nm (logε 4.43, 4.40, 4.44 and 4.41).

Found: C, 49.1; H, 3.5; N, 25.5%; $M,^{+}$ 325.

$C_{13}H_7N_7O_4$ requires: C, 48.0; H, 2.2; N, 30.1%; M, 325.

The Attempted Reaction of the Tricyclic Compound (386b) with Acetic Acid

(a) The tricyclic diester (386b) (0.28g) was heated under reflux with glacial acetic acid (10.0 ml) for 3h. Evaporation of the solution left an oil which was triturated with ether to yield the unreacted starting material (386b) (0.18g) m.p. 165°, identical (i.r. spectrum) with an authentic sample.

(b) When the procedure described in (a) was repeated for 24h, a dark gum

was left after evaporating the solution. Trituration of this gum with various solvents gave no solid and its t.l.c. in ethyl acetate and ethanol over both silica and alumina showed it to be one component which tailed on the plate.

The Attempted Reaction of 7-Acetonyl-6-acetyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (383d) with Toluene-p-sulphonyl Azide.

(a) In the Presence of Triethylamine

A solution of the acetonyltriazolotriazine (383d) (0.59g, 0.002 mol) in absolute ethanol (60.0 ml) was stirred, cooled to 0° (ice-salt bath) and treated in one portion with triethylamine (0.40g, 0.004 mol) and then dropwise with a solution of toluene-p-sulphonyl azide (0.40g, 0.002 mol) in absolute ethanol (5.0 ml). The mixture was stirred in the melting ice-bath for 2h and then evaporated and the oil obtained was dissolved in chloroform and washed with aqueous dilute sodium hydroxide solution. The chloroform extract gave an oil (0.36g) which was identified (i.r. spectrum) as an authentic sample of toluene-p-sulphonyl azide.

The alkaline extract was acidified with aqueous dilute sulphuric acid and extracted with chloroform to give an oil which was triturated with ethanol to yield the starting triazolotriazine (383d) (0.16g) m.p. 187° (from ethanol-water), identical (i.r. spectrum) with an authentic sample.

Evaporation of the ethanol mother liquor gave an unidentified oil which tailed on attempted t.l.c.

(b) In the Presence of Sodium Hydride

A solution of acetonyltriazolotriazine (383d) (0.59g, 0.002 mol) in dry dimethylformamide (5.0 ml) and a suspension of sodium hydride (0.2g, 0.004 mol) in dry dimethylformamide (5.0 ml) were mixed and stirred vigorously at room temperature for 15min. The resulting mixture was

treated dropwise with a solution of toluene-p-sulphonyl azide (0.40g, 0.002 mol) in dry dimethylformamide (1.0 ml) and stirred at room temperature for 3h. The mixture was diluted with water and extracted with chloroform to give an oil which was identified as unreacted toluene-p-sulphonyl azide by comparison (i.r. spectrum) with an authentic sample.

The aqueous extract was acidified with aqueous dilute sulphuric acid and extracted with chloroform to give an oil which was triturated with ethanol to afford the unreacted triazolotriazine (383d) (0.16g) m.p. 208°, identical (m.p. and i.r spectrum) with an authentic sample.

The aqueous extract was buffered with solid sodium acetate and on evaporation left a solid which was extracted with hot ethyl acetate to give a negligible amount of an unidentified oil.

2-(α-Acetoxybenzyl)-6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,4-triazine (395)

The diester (383b) (0.71g, 0.002 mol) was heated under reflux with glacial acetic acid (15.0 ml) for 3h. Evaporation of the solution left an oil which on trituration with ether gave unreacted diester (383b) (0.39g) m.p. 99°, identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ether mother liquour yielded an oil (0.21g) $\nu_{max.}$ 1750-1730br (CO) cm^{-1}, whose t.l.c. in ethyl acetate over silica showed it to contain two components one of which was the acetoxy derivative (395) $\tau(CDCl_3)$ 2.42-2.53(2H, m,Ar-H), 2.60-2.73(3H, m, Ar-H), 3.08(1H, s, CHOAc), 5.80(2H, s, CH_2), 5.86(2H, q J 7Hz, CH_2), 6.54(2H, q J 7Hz, CH_2), 7.80(3H, s, CH_3), 8.59(3H, t J 7Hz, CH_3) and 8.82(3H, t J 7Hz, CH_3).

Ethyl 7-Methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (388)

The triazolotriazine ester (383b) (0.71g, 0.002 mol) was heated under

reflux with aqueous 4N sulphuric acid (4.0 ml) in ethanol (15.0 ml) for 24h. On cooling the solution gave the triazolotriazine ester (388) more of which was obtained by evaporating the aqueous ethanolic filtrate treatment with water, extraction with chloroform and trituration of the oil obtained with ether (total 0.32g) m.p. 163° (from ethanol), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.[41]

Evaporation of the ether mother liquor gave an oil which was shown by t.l.c. in ethyl acetate over silica to be a multicomponent mixture.

The Attempted Reaction of the Triazolotriazine (383d) with Hot Glacial Acetic Acid.

The methylene compound (383d) (0.59g, 0.002 mol) was heated under reflux in glacial acetic acid for 17h. Evaporation of the dark solution left a residue which was triturated with ethanol-ether to give an impure solid (0.44g) m.p. 140°. This crystallised from water to give the unreacted triazolotriazine (383d) (0.36g) m.p. 190°, identical (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.

The Attempted Hydrolysis of the Triazolotriazine (383d) with Hot Aqueous Sulphuric Acid.

The methylene compound (383d) (0.59g, 0.002 mol) was heated under reflux with aqueous 4N sulphuric acid (4.0 ml) in ethanol (15.0 ml) for 3h. The solution was concentrated to remove the ethanol and the aqueous mother liquour was extracted with chloroform to give a foam which was triturated with ethanol to afford the unreacted triazotriazine (383d) (0.47g; 80%) m.p. 198°, identical (m.p. and i.r. spectrum) with an

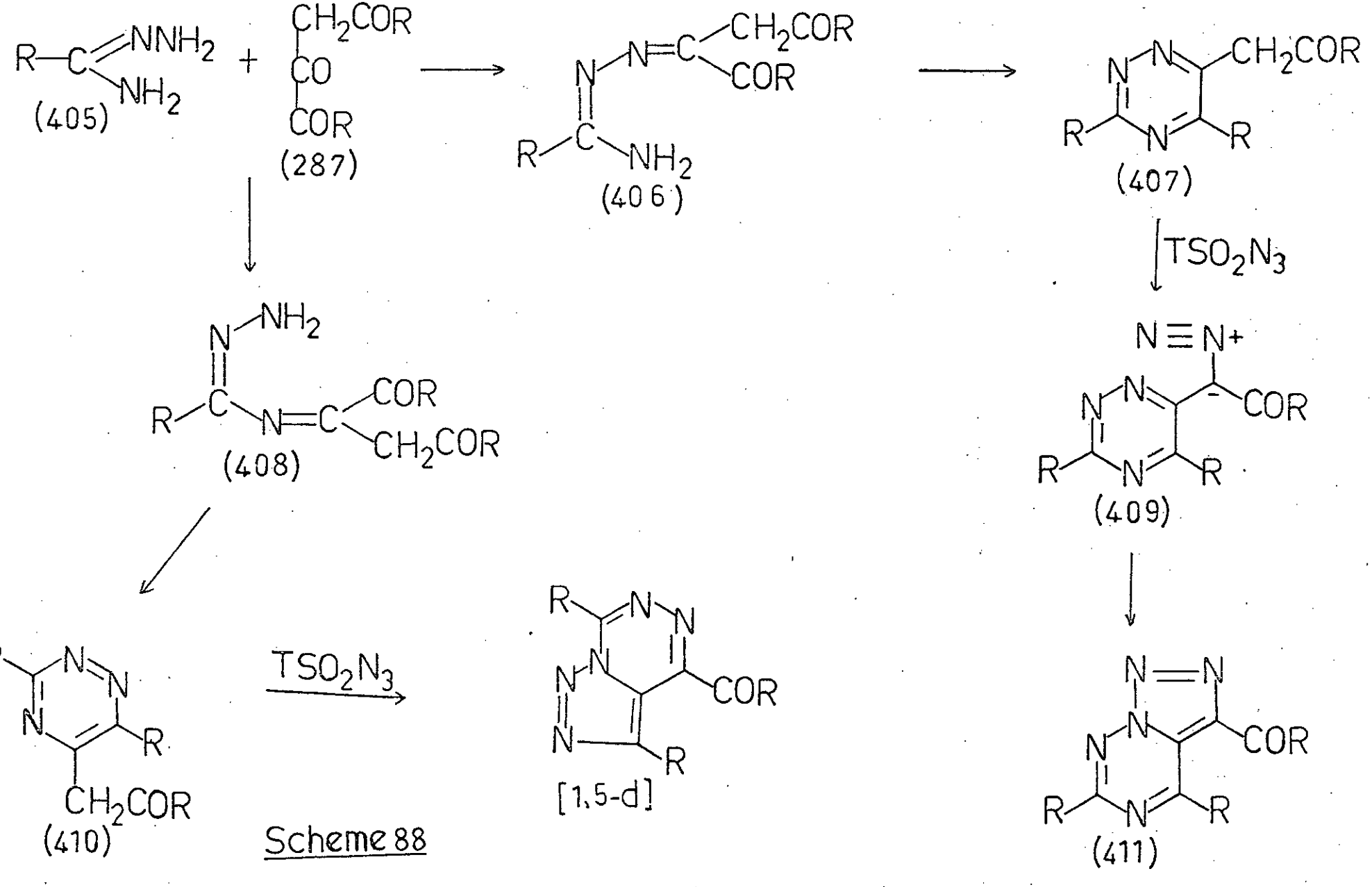
authentic sample.

The Attempted Reaction of the Triazolotriazine (383a) with Hot Aqueous Sulphuric Acid.

A solution of the triazolotriazine (383a) (0.32g, 0.001 mol) in ethanol (10.0 ml) was heated under reflux with aqueous 20% w/v sulphuric acid solution (2.5 ml) for 1h. The mixture was concentrated to remove the ethanol, diluted with water, and extracted with chloroform to give a gummy solid which in contact with ether gave an impure solid (0.20g). This was extracted with cold benzene-ethanol to afford the starting triazolotriazine (383a) (0.08g) m.p. 160°, identical (i.r. spectrum) with an authentic sample.

Chapter 6

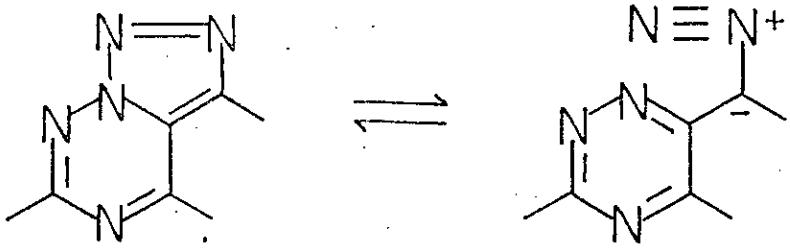
Approaches to the Synthesis of 1,2,3-Triazolo[5,1-f]-1,2,4-triazine Derivatives



Scheme 88

6.1 Introduction

It will be recalled (Chapter 5, Introduction) that there are four possible bridgehead-fused ring systems derived by the fusion of a 1,2,3-triazole ring with a 1,2,4-triazine ring such that a single nitrogen atom is common to both rings. Also that these ring systems are of interest in relation to their possible diazoalkylideneamine-1,2,3-triazole ring-chain tautomerism. The study of the synthesis and reactivity of three of these ring systems namely the [5,1-c], the [1,5-b] and the [1,5-d] fused systems was described in Chapters 4 and 5 and the present chapter describes the attempted synthesis of derivatives of the remaining and so far unknown 1,2,3-triazolo[5,1-f]-1,2,4-triazine ring system. As in the other bridgehead-fused 1,2,3-triazolo-1,2,4-triazine ring systems, diazoalkylideneamine-triazole ring-chain tautomerism [(375) ⇌ (376)] is also possible in the triazolo[5,1-f]triazine ring system but for



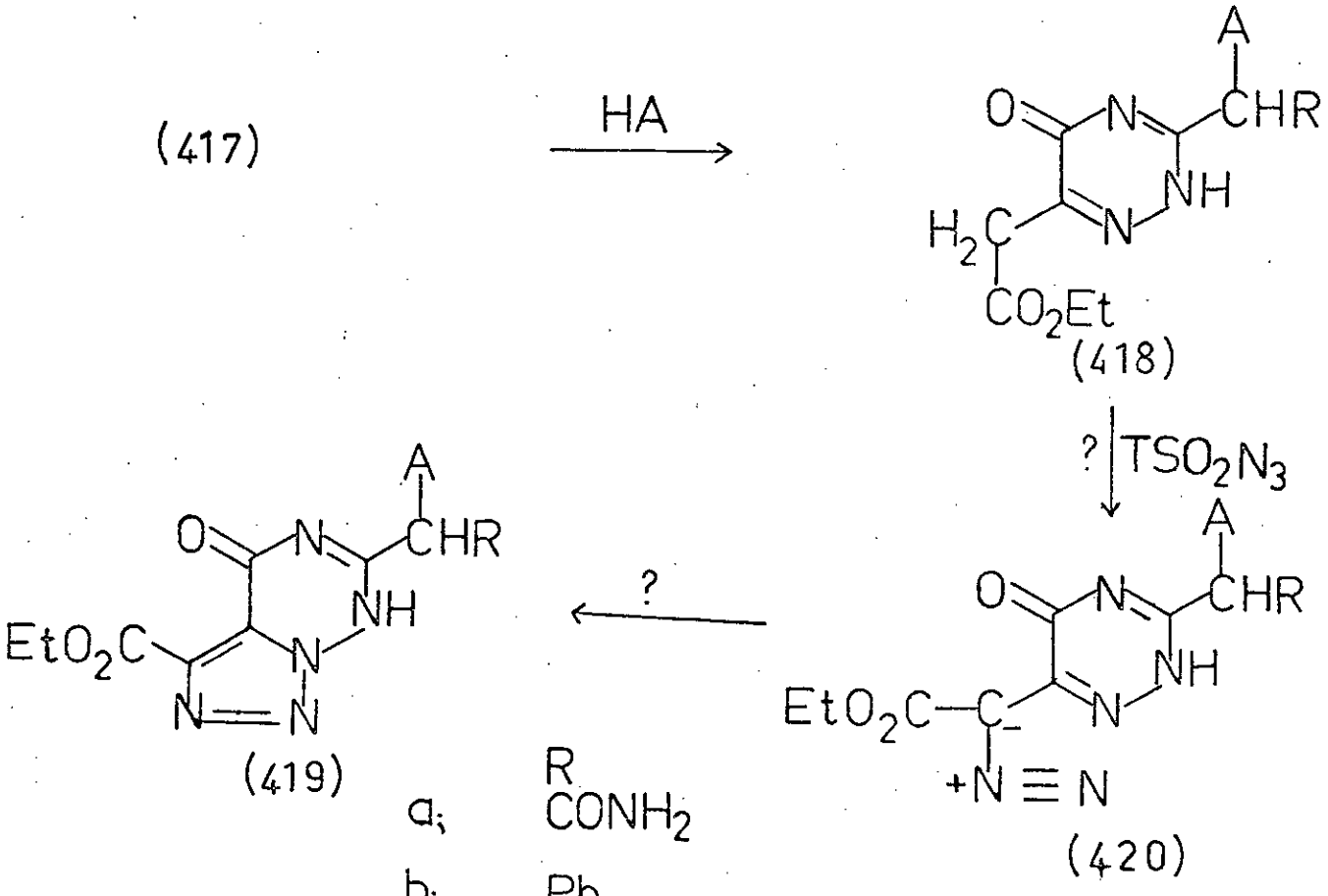
[5,1-f]
(375)

(376)

structural reasons subsequent Dimroth rearrangement is not possible.

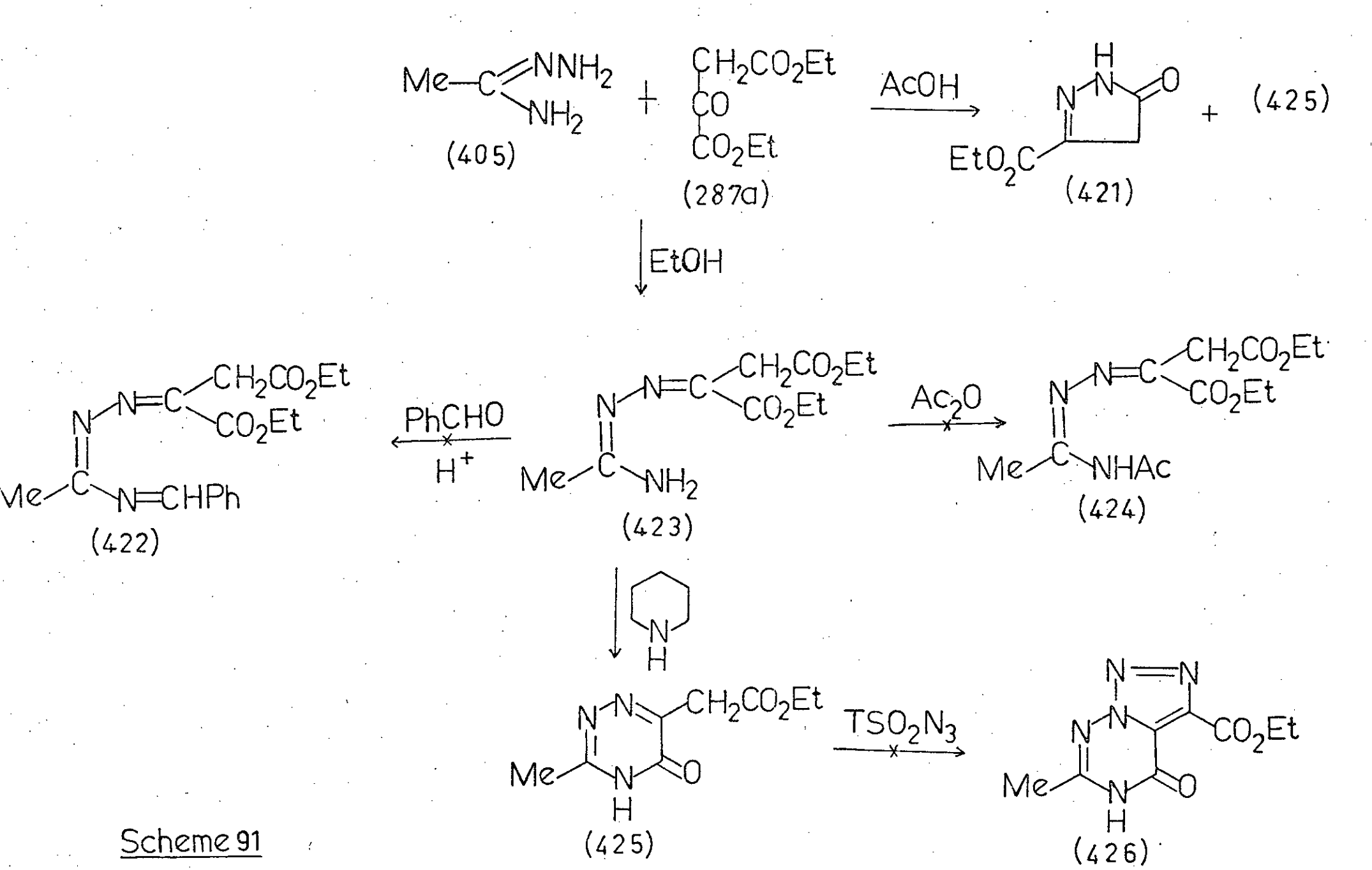
In the attempted synthesis of derivatives of the 1,2,3-triazolo-[5,1-f]-1,2,4-triazine ring system, two synthetic approaches were again followed. The first approach involved the construction of a 1,2,4-triazine derivative (407) (Scheme 88) having an active methylene group at C(6) with the aim of reacting this with toluene-p-sulphonyl azide

Scheme 89


(417)
HA
A
CHR
O
N
NH
N
H2C
CO2Et
(418)
?
TSO2N3
A
CHR
O
N
NH
N
EtO2C
C
+N≡N
(420)
?
A
CHR
O
N
NH
N
EtO2C
N=N
(419)
R
a; CONH2
b; Ph
c; CO2Et

Scheme 90

('diazo-transfer reaction') to afford the diazo-intermediate (409), ring closure of which would yield the required 1,2,3-triazolo[5,1-f]-1,2,4-triazine derivative (411) (Scheme 88). It was hoped to obtain the methylene-1,2,4-triazines (407) required for study by the condensation of an amidrazone (405) with a suitable tricarbonyl compound (287) (Scheme 88). If the amidrazone (405) condensed with the tricarbonyl compound (287) through the primary amino-group and not through the hydrazino-group, a 1,2,4-triazine (410) (Scheme 88) bearing an active methylene group at C(5) would be obtained and treatment of this with toluene-p-sulphonyl azide would lead to a 1,2,3-triazolo[1,5-d]-1,2,4-triazine derivative (see Scheme 88) as opposed to a [5,1-f] structure [cf. (411)]. However this alternative pathway was considered unlikely due to the expected greater nucleophilicity of the hydrazino-group compared with the primary amino-group, thus ensuring the condensation of the amidrazone (405) with the tricarbonyl compound (287) to give (406) and not (408). In the second approach (Scheme 89) it was proposed to reduce the diazonium salts (412) in situ to the hydrazinotriazoles (413) condensation of which with diethyl oxaloacetate (287a) should yield the corresponding triazolylhydrazones (414). Cyclisation of (414) would then lead to 1,2,3-triazolo[5,1-c]-triazinones (417) bearing an active methylene group at C(6). Treatment of these with toluene-p-sulphonyl azide might then furnish the diazo-compounds (416) and then the fused 1,2,3-triazolo[5,1-f]-1,2,4-triazines (415). Alternatively, the triazolotriazines (417) could first be subjected to acid-catalysed triazole scission to give triazinones (418) (Scheme 90) bearing an active methylene group at C(6). These on treatment with toluene-p-sulphonyl azide would hopefully lead to the diazo-compounds (420) and thence the triazolo[5,1-f]-1,2,4-triazines (419).

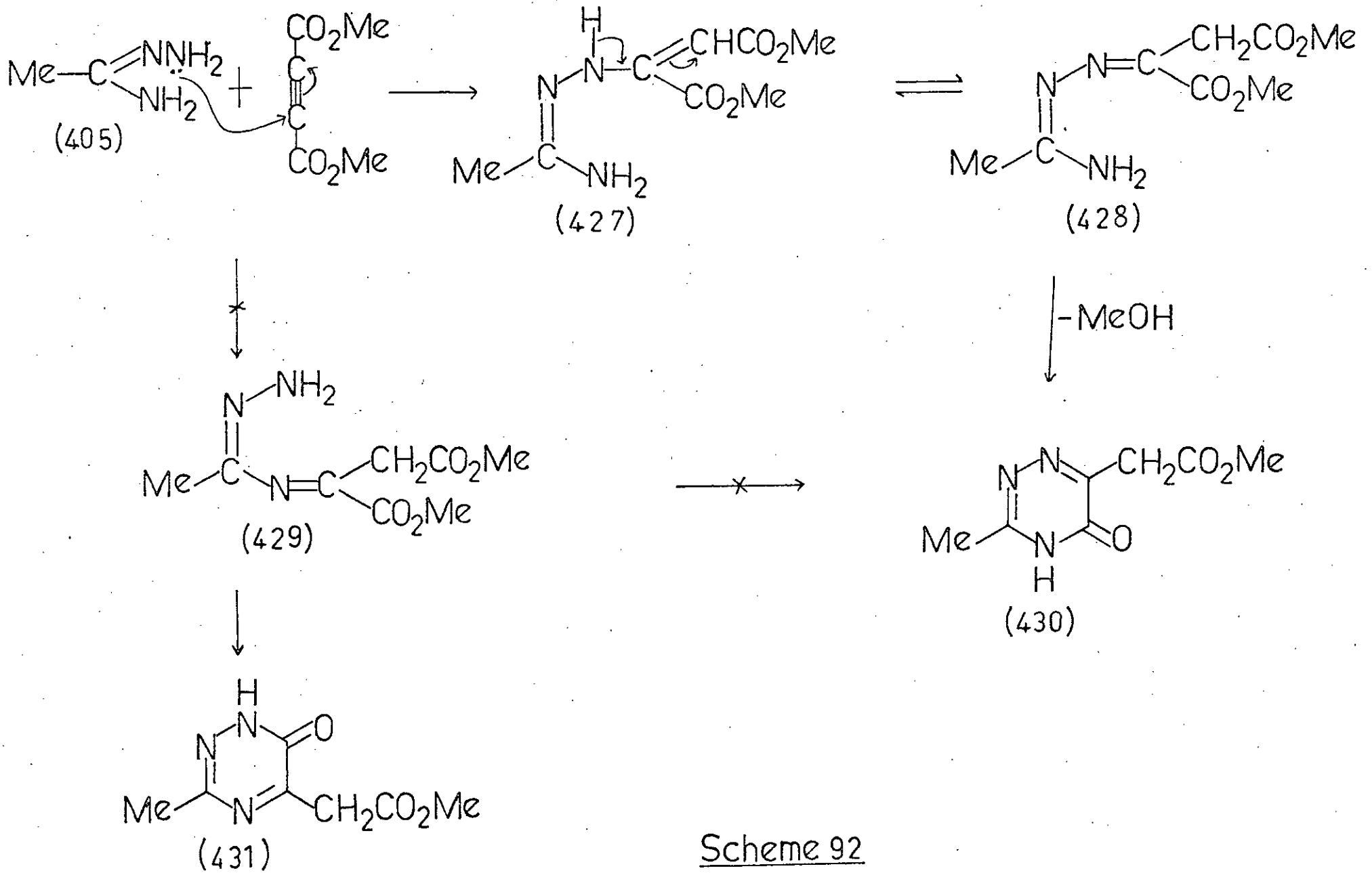

Me—C(=NNH2)—NH2
(405)
CH2CO2Et
CO
CO2Et
(287a)
AcOH
(421)
(425)
EtOH
(422)
PhCHO
H+
(423)
Ac2O
(424)
(425)
TSO2N3
(426)

Scheme 91

6.2 The Attempted Synthesis of 1,2,3-Triazolo[5,1-f]- 1,2,4-triazines from 6-Methylene-1,2,4-triazines

Heating the keto-diester (287a) with acetamidrazone (405) in the presence of glacial acetic acid yielded a mixture of two products one of which gave mass spectral data consistent with its being the triazinone (425) (Scheme 91). However, it failed to give a correct elemental analysis for this structure and its i.r. spectrum was different from that of an authentic sample of (425) prepared later. Possibly, this product is a salt of the triazinone (425) although attempts to convert it into the latter were unsuccessful. The second product is assigned the pyrazolone structure (421) on the basis of the following evidence. Its analytical and mass spectral data were in agreement with the molecular formula $C_6H_8N_2O_3$ while its i.r. spectrum contained NH absorption and a carbonyl band at 1700 cm^{-1}. No ^1H n.m.r. spectrum was obtained for (421) because of lack of material.

Because of the complicating formation of the pyrazolone (421) and the difficulty encountered in obtaining correct analytical data for the presumed triazinone (425) obtained when the amidrazone (405) was condensed with diethyl oxaloacetate (287a) under acidic conditions, it was decided to reinvestigate this condensation in an essentially neutral medium. Thus, when an ethanolic solution of acetamidrazone (405) and the keto-diester (287a) was stirred at room temperature, the sole product was the condensate (423). ^1H N.m.r., i.r., and mass spectral data were consistent for the structure assigned to the condensate (423) but there was difficulty in obtaining correct analytical data for it. Thus, its i.r. spectrum contained primary amino absorption and two carbonyl bands at 1735 and 1720 cm^{-1} while its mass spectrum gave it the expected molecular weight of 243. The ^1H n.m.r. spectrum of (423) in addition to showing two intact


Me
NNH2
NH2
(405)
CO2Me
CO2Me
H
N
CHCO2Me
CO2Me
Me
NH2
(427)
CH2CO2Me
CO2Me
(428)
-MeOH
NH2
CH2CO2Me
CO2Me
(429)
(430)
O
(431)

Scheme 92

ester groups also contained a two proton singlet at τ 5.80 and a three proton singlet at τ 7.50 due to the methylene and methyl hydrogens respectively. In an effort to establish the structure of (423) with certainty, it was warmed briefly with acetic anhydride but this attempt failed to give the expected acetyl derivative (424). The attempted conversion of the condensate (423) into a benzylidene derivative (422) was also unsuccessful. However, in accord with its assigned structure, stirring the condensate (423) with ethanolic piperidine at room temperature gave a low yield of a compound assigned the triazinone structure [Scheme 91; (425)] on the basis of the following evidence. Its i.r. spectrum showed NH absorption and a carbonyl band at 1715 cm^{-1}. The ^1H n.m.r. spectrum of (425) in addition to showing an intact ester group also contained a two proton singlet at τ 6.30 and a three proton singlet at τ 7.44 due to the methylene and methyl groups respectively. Lack of time and material prevented the study of the conversion of the triazinone (425), by reaction with toluene-p-sulphonyl azide, into the 1,2,3-triazolo[5,1-f]-1,2,4-triazinone (426).

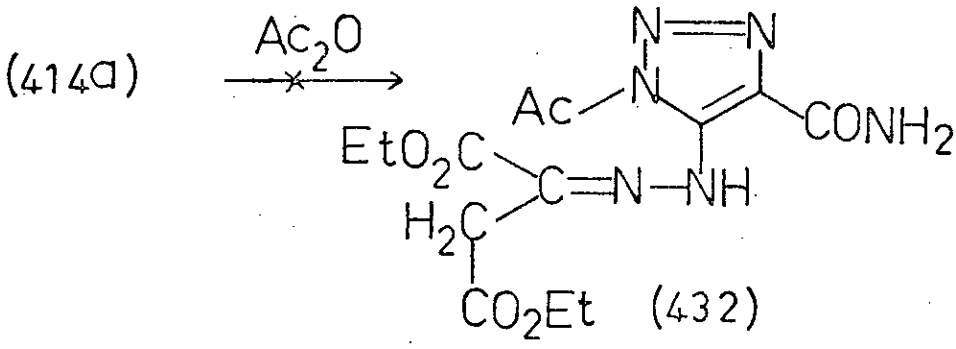
The low yields obtained in the condensation of acetamidrazone (405) with diethyl oxaloacetate (287a) to obtain initially the condensate (423) and further by cyclisation of the latter, the required triazinone (425), made it of interest to seek an alternative route to compounds of type (423) and (425). The route proposed (Scheme 92) involved the nucleophilic addition of acetamidrazone (405) to dimethyl acetylenedicarboxylate hopefully to give the adduct (427). This would then undergo a 1,3 hydrogen shift to form the hydrazone (428) subsequent cyclisation of which (with loss of methanol) would afford the triazinone (430). If the nucleophilic addition of acetamidrazone (405) to diethyl acetylenedicarboxylate occurred via the primary amino-group instead of at the hydrazino-group,

the adduct (429) would be obtained and this would cyclise to (431) rather than (430). However, as has been said before, the greater nucleophilicity of the hydrazino-group compared with the primary amino-group would ensure the formation of (428) rather than (429). In practice, the attempted condensation of acetamidrazone (405) with dimethyl acetylenedicarboxylate either in toluene or in the melt was unsuccessful and in both cases, the unreacted acetamidrazone (405) was recovered unchanged. However, when an ethanolic solution of acetamidrazone (405) and dimethyl acetylenedicarboxylate was heated under reflux, the triazinone (430) was obtained in modest yield. The spectral properties of this triazinone (430) were in accord with the assigned structure. Thus, its i.r. spectrum showed NH absorption and a carbonyl band at 1740 cm^{-1} while its ^1H n.m.r. spectrum contained two three proton singlets at τ 6.34 and 7.64 and a two proton singlet at τ 6.40 due to two distinct methyl groups and a methylene group respectively. The attempted reaction of the triazinone (430) with toluene-p-sulphonyl azide in the presence of triethylamine was unsuccessful, the unreacted triazinone (430) being recovered unchanged.

6.3 The Attempted Synthesis of 1,2,3-Triazolo[5,1-f]-1,2,4-triazines using 1,2,3-Triazolylhydrazines

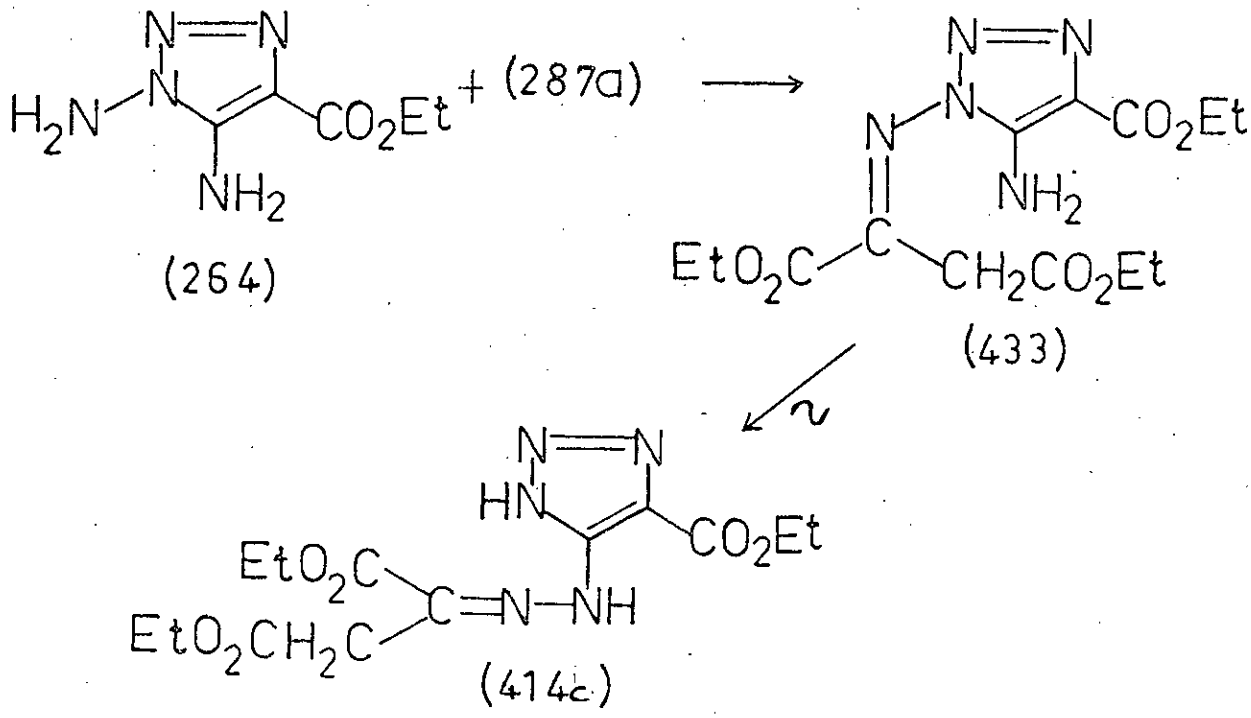
The first stage in this synthetic route to 1,2,3-triazolo[5,1-f]-1,2,4-triazines (cf. Scheme 89) involved the in situ generation of triazolylhydrazines (413) and their in situ condensation with diethyl oxaloacetate (287a). Thus, the diazonium salt (412a) was reduced in situ using sulphur dioxide to give the hydrazine (413a) which was then heated under reflux with diethyl oxaloacetate (287a) to afford a product whose properties are fully consistent with its being the hydrazone (414a). Thus, it was easily soluble in aqueous dilute sodium hydroxide and its i.r. spectrum contained NH absorption and two ester bands at 1735 and

1700 cm^{-1}. In addition, its mass spectrum and combustion analysis were in accord with its formulation as the hydrazone (414a). As a further comfirmation of the structure of (414a), it was decided to convert it into the N-acetylated derivative (432). Unfortunately, warming



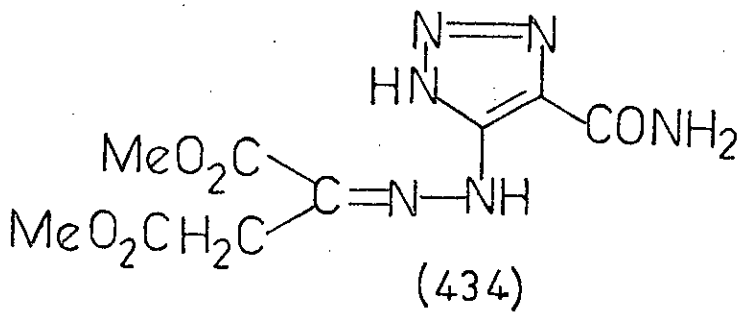
(414a) briefly in acetic anhydride failed to afford the expected acetyl derivative (432), giving instead a foam which was shown by t.l.c. to be a single component but could not be characterised. In contrast to the successful reaction observed with the diazonium salt (412a), the attempted reductive condensation of the phenyltriazolediazonium salt (412b) with diethyl oxaloacetate (287a) was unsuccessful, the only product obtained being the deaminated triazole (293).

Since it was known (cf. Chapter 4) that the triazole ester diazonium salt (280) readily underwent reductive loss of nitrogen in the presence of sulphur dioxide, no attempt was made to study its in situ reduction to the hydrazine (320) required in the present studies. As an alternative route to this compound the condensation of the N-aminotriazole (264) with diethyl oxaloacetate (287a) under acidic conditions was studied in the expectation that the initial condensate (433) of this reaction would undergo Dimroth rearrangement (cf. Chapter 4, page 133) to the required hydrazone (414c). Thus, when a solution of the N-aminotriazole ester (264)



and the keto-diester (287a) in ethanol containing glacial acetic acid was heated under reflux, the expected hydrazone (414c) was obtained. The hydrazone (414c) was soluble on brief treatment with dilute aqueous sodium hydroxide solution - a behaviour which is consistent with the acidity of the proton at N(1) on the triazole ring. The analytical, ^{1}H n.m.r., i.r. and mass spectral data obtained for (414c) were in accord with the hydrazone structure. Thus, its i.r. spectrum contained NH absorption and carbonyl bands at 1715 and 1690 cm^{-1} while its ^{1}H n.m.r. spectrum in addition to showing two intact ester groups also contained a two proton singlet at τ 6.33 due to the methylene group.

As an alternative route to hydrazones of the type (414), the reductive condensation of the diazonium salt (412a) with dimethyl acetylenedicarboxylate was also investigated. Thus, in situ reduction of the salt (412a) to the hydrazine (413a) followed by heating with dimethyl acetylenedicarboxylate gave a product whose properties were fully consistent with the hydrazine structure (434). Thus, the mass

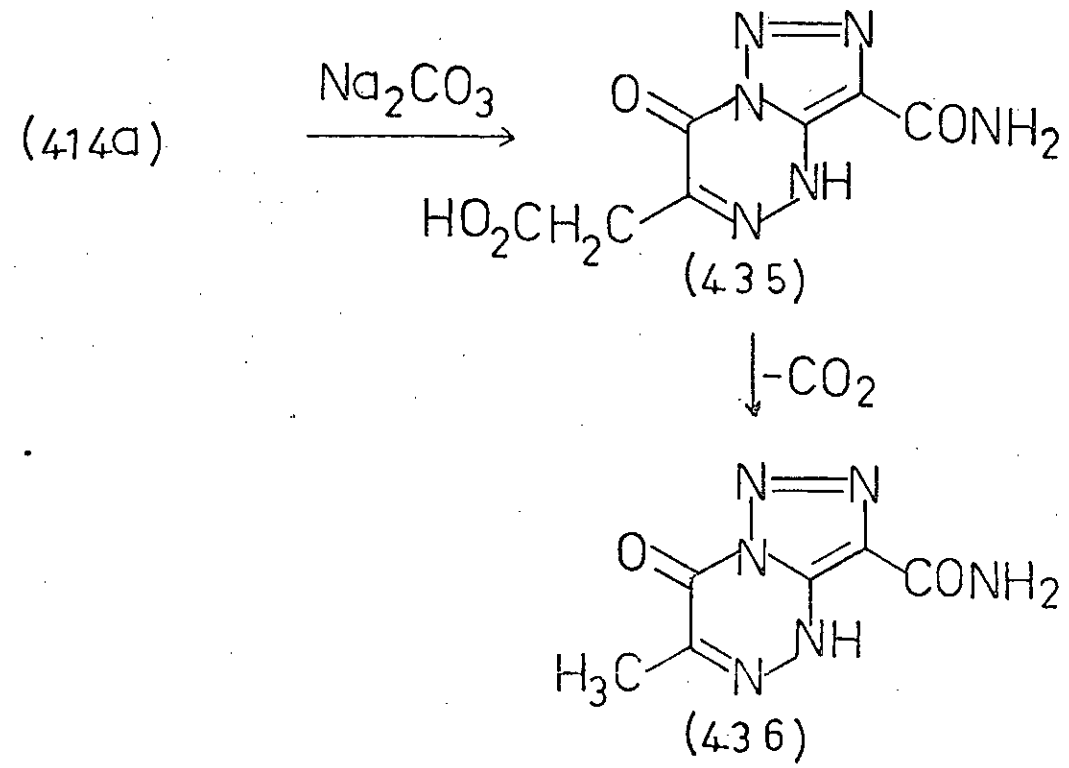


(434)

spectrum and elemental analysis of (434) were in accord with the assigned structure. Its i.r. spectrum showed NH absorption at 3400, 3320, 3220 and 1650 cm^{-1} and two carbonyl bands at 1740 and 1700 cm^{-1} while its ^{1}H n.m.r. spectrum contained two three proton singlets at τ5.18 and 6.08 and a two proton singlet at τ 6.20 due to two distinct methyl groups and two methylene protons respectively. The analogous reductive condensation of the diazonium salt (412b) (Scheme89) with dimethyl acetylenedicarboxylate was unsuccessful, giving an unidentified solid. The acid-catalysed condensation of the N-amino ester (264) with dimethyl acetylenendicarboxylate was likewise unsuccessful, and the unreacted starting triazole ester (264) was recovered together with an unidentified solid.

A lot of effort was put into trying to cyclise the triazolylhydrazone (414a). Thus, when it was heated under reflux in aqueous ethanolic sodium acetate, only the unreacted hydrazone (414a) was recovered. The attempted cyclisation of (414a) using sodium ethoxide as the catalyst also afforded unreacted starting material. However, there was more success when sodium carbonate was used as the catalyst in the attempted cyclisation of (414a). Thus, in this case, the triazolotriazinone (436) was obtained.

The i.r. spectrum of (436) contained NH absorption and hydroxyl



and carbonyl bands at 1920 and 1725 cm^{-1} respectively. The elemental analysis of (436) was slightly out for the monohydrate of the triazolotriazinone (436). The formation of the compound tentatively assigned the triazolotriazinone structure (436) can be explained by the following mechanism. First, (414a) cyclises with subsequent hydrolysis to give the acid (435) which suffers decarboxylation to afford the triazolotriazinone (436).

The attempted cyclisation of (414a) under acidic conditions was also unsuccessful. Thus, heating (414a) with ethanolic acetic acid gave only a good recovery of the starting material. The analogous attempted cyclisation of (414a) by brief heating with ethanolic sulphuric acid also gave only the starting material whereas prolonged heating in this medium gave a low yield of the triazolotriazinone (436) obtained before.

6.4 Experimental (For general experimental procedures, see Appendix)

4-Phenyl-1H-1,2,3-triazole-5-diazonium Chloride (36) and 1H-1,2,3-triazole-5-diazonium Chloride-3-Carboxamide (44)

The diazonium salts (36) and (44) were prepared as described in Chapter 4, page 142.

Diethyl Oxaloacetate (287a)

The keto-diester (287a) was prepared as described in Chapter 4, page 143.

Ethyl 1,5-Diamio-1,2,3-triazole-4-carboxylate (264)

For the method of preparing the diaminotriazole (264) see Chapter 4, page 143.

Acetamidrazone (405)[54]

Acetamidrazone[54] (405) m.p. 128° (lit.,[54] 132°) was prepared as described in the literature.[54]

The Condensation of Acetamidrazone (405) with Diethyl Oxaloacetate (287a)

(a) In the Presence of Glacial Acetic Acid

A solution of the keto-diester (287a) (11.28g, 0.06 mol) and acetamidrazone (405) (4.4g, 0.006 mol) in ethanol (100 ml) containing glacial acetic acid (5.0 ml) was heated under reflux for 18h. The solution was evaporated and the residue was triturated with methanol-ether to yield a cream solid (3.86g) which was purified by dissolving it in methanol and reprecipitation with ethyl acetate, m.p. 236°, νmax. 3100 (NH), 2600 (OH), and 1740 (CO) cm^{-1}.

Found: C, 29.5; H, 5.6; N, 25.9%; M^+ 197.

Evaporation of the methanol-ether mother liquor left an oil which solidified on cooling and trituration with benzene to give the impure

pyrazolone (421) (1.30g) m.p. 170° which crystallised from water as colourless needles (0.81g) m.p. 182°, $\nu_{max.}$ 3350 (NH) and 1700 (CO) cm^{-1}.

Found: C, 45.6; H, 5.0; N, 18.0%; M^+ 156.

$C_6H_8N_2O_3$ requires: C, 46.20; H, 5.1; N, 18.0%; M, 156.

(b) In Ethanol Solution

A solution of acetamidrazone (405) (0.15g, 0.002 mol) in ethanol (10.0 ml) was stirred at room temperature with the keto-diester (287a) (0.38g, 0.002 mol) for 17h. The solution was evaporated and the residue was repeatedly triturated with ethanol-ether to give the amidrazone (423) as a colourless solid (0.31g; 61%) m.p. 148° (from ethanol-light petroleum), $\nu_{max.}$ 3390, and 2760br (NH), and 1735, 1720 and 1680 (CO) cm^{-1} τ [$(CD_3)_2SO$] 5.74(2H, q J 7Hz, CH_2), 5.80(2H, s, CH_2), 5.88(2H, q J 7Hz, CH_2), 7.50(3H, s, CH_3), 8.72(3H, t J 7Hz, CH_3) and 8.82(3H, t J 7Hz, CH_3).

Found: 243.121373.

$C_{10}H_{17}N_3O_4$ requires: 243.121897.

The Attempted Preparation of the Acetyl Derivative (424) of the Amidrazone (423)

The amidrazone (423) (0.49g, 0.002 mol) was heated under reflux in acetic anhydride (8.0 ml) for 5 min. Evaporation of the solution under reduced pressure left an oil (0.20g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of two components.

The Attempted Preparation of the Benzylidene Derivative (422) of the Amidrazone (423)

Solutions of the amidrazone (423) (0.49g, 0.002 mol) in ethanol (10.0 ml) and concentrated sulphuric acid (1.0 ml) in water (3.0 ml) were mixed and treated with a solution of freshly distilled benzaldehyde (0.21g, 0.002 mol) in methanol (5.0 ml). The mixture was stirred at room temperature

for 17h and then diluted with water and extracted with chloroform to give an oil (0.30g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolved mixture of three components, one of which was benzaldehyde.

6-Ethoxycarbonylmethyl-3-methyl-1,2,4-triazin-(4H)-one (425)

A solution of the amidrazone (423) (0.49g, 0.002 mol) in methanol (10.0 ml) was stirred at room temperature with piperidine (0.17g) for 17h. The solution was evaporated and the residue was dissolved in water and acidified with dilute aqueous hydrochloric acid. Extraction with chloroform gave a solid which was washed with ethanol-ether to give the triazinone (425) (0.12g) as a colourless solid, m.p. 144° (from ethanol-light petroleum), $\nu_{max.}$ 3120br (OH) and 1715 (CO) and 1650 (NH) cm^{-1}, τ ($CDCl_3$) 5.82(2H, q J 7Hz, CH_2), 6.30(2H, s, CH_2), 7.44(3H, s, CH_3) and 8.76(3H, t J 7Hz, CH_3).

Found: C, 48.5; H, 5.6; N, 21.2%; M^+ 197.

$C_8H_{11}N_3O_3$ requires: C, 48.7; H, 5.6; N, 21.3%; M, 197.

The aqueous extract on evaporation left a solid which was triturated with ethanol to give an unidentified solid (0.17g) m.p. 210° which had a poorly resolved i.r. spectrum.

The Attempted Reaction of Acetamidrazone (405) with Dimethyl Acetylenedicarboxylate

(a) In the Presence of Toluene

A solution of acetamidrazone (405) (0.29g, 0.002 mol) and dimethyl acetylenedicarboxylate (0.57g, 0.004 mol) in dry toluene (20.0 ml) was heated under reflux for 2h. Hot filtration of the mixture gave a semi-solid which was triturated with ethanol-ether to afford unreacted acetamidrazone (405)

(0.27g; 93%) m.p. 130° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) In the Melt

A melt of acetamidrazone (405) (0.29g, 0.002 mol) and dimethyl acetylenedicarboxylate (0.57g, 0.004 mol) was held at 120 - 130° (oil bath) for 1h. The mixture on cooling formed a glass which was triturated with ethanol-ether to give unreacted acetamidrazone (405) (0.20g; 69%) m.p. 135°, identical (m.p. and i.r. spectrum) with an athentic sample.

(c) 3-Methyl-6-methoxycarbonylmethyl-1,2,4-triazin-5(4H)-one (430)

A mixture of acetamidrazone (405) (1.16g, 0.016 mol) and dimethyl acetylenedicarboxylate (2.75g, 0.016 mol) was heated under reflux in ethanol (20.0 ml) for 17h. The clear reddish-brown solution on evaporation left an oily solid which was triturated with ethanol-ether to give the impure triazinone (430) (0.81g) m.p. 130°. Crystallisation of the impure product from ethanol gave the pure triazinone (430) as a colourless solid (0.43g) m.p. 176°, $\nu_{max.}$ 3260w, and 3200w (NH) and 1740 (CO) cm^{-1}, τ[$CDCl_3$-$(CD_3)_2SO$] 6,34(3H, s, CH_3), 6.40(2H, s, CH_2) and 7.64(3H, s, CH_3).

Found: C, 46.1; H, 4.9; N, 23.0%; M^+ 183.

$C_7H_9N_3O_3$ requires: C, 45.9; H, 4.9; N, 22.9%; M, 183.

The ethanol mother liquour on evaporation left a solid which was triturated with ethanol-ether to give unreacted acetamidrazone (405) (0.21g) m.p. 120° which was identical (i.r. spectrum) with an authentic sample.

The original ethanol-ether filtrate on evaporation left an oil whose t.l.c. in both ethyl acetate and ethyl acetate - ethanol over silica showed it to contain two components. Dry column chromatography of the oil in ethyl acetate over silica gave an oil which had a poorly resolved i.r. spectrum.

Trituration of this oil with ethanol-ether gave an unidentified solid (0.03g) m.p. 256°, M^+ 183.

The Attempted Reaction of the Triazinone (430) with Toluene-p-Sulphonyl Azide

A solution of the triazinone (430) (0.18g, 0.001 mol) in absolute ethanol (15.0 ml) was cooled to 0° (ice-salt bath) and treated in one portion with triethylamine (0.3g, 0.003 mol) and then dropwise with stirring with a solution of toluene-p-sulphonyl azide (0.2g; 0.001 mol) in absolute ethanol (2.0 ml). The mixture was stirred in the melting ice bath for 2h, and then evaporated to give a semi-solid which was triturated with ethanol-ether to afford the unreacted triazinone (430) (0.08g) m.p. 170°, identical (m.p. and i.r. spectrum) with an authentic sample.

The ethanol-ether mother liquour on evaporation left an oil (0.16g) identical (i.r. spectrum) with an authentic sample of toluene-p-sulphonyl azide.

Diethyl Oxaloacetate (4-Carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (414a)

80% v/v Aqueous ethanol (200 ml) was cooled to 0° (ice-salt bath), saturated with sulphur dioxide and treated in portions with stirring with the diazonium chloride (412a) (5.25g, 0.03 mol). The mixture was re-saturated with sulphur dioxide and left at room temperature overnight. The keto-diester (287a) (5.64g, 0.03 mol) was then added and the mixture was heated under reflux for 2h. Concentration of the solution to remove the ethanol followed by filtration gave the triazolylhydrazone (414a) as a yellow solid (4.6g; 47%) m.p. 204° (from ethanol-water), νmax. 3400br, 3300br and 3200br (NH), 1735 and 1700 (CO), and 1650 (NH) cm^{-1}.

Found: C, 42.1; H, 5.1; N, 27.3%; $M,^+$ 312.

$C_{11}H_{16}N_6O_5$ requires: C, 42.3; H, 5.1; N, 26.9%; M, 312,

which was soluble in aqueous dilute sodium hydroxide.

The Attempted Acetylation of the Triazolylhydrazone (414a)

The triazolylhydrazone (414a) (0.62g, 0.002 mol) was heated under reflux in acetic anhydride (10.0 ml) for 5min. Evaporation of the solution left an oil whose t.l.c. in ethyl acetate and ethyl acetate-ethanol over silica showed a single component. The oil was suspended in water and extracted with chloroform to give a foam (0.30g) whose t.l.c. in ethyl acetate alone or containing ethanol over silica showed a single spot which tailed on the t.l.c. plate. Attempts to isolate solid material from the foam were unsuccessful.

The Attempted Reductive Coupling of the Diazonium Salt (412b) with the Keto-diester (287a)

80% v/v Aqueous ethanol (50.0 ml) was cooled to 0° (ice-salt bath) and saturated with sulphur dioxide. The diazonium chloride (412b) (0.62g, 0.003 mol) was then added in portions with stirring and the mixture was re-saturated with sulphur dioxide and left at room temperature overnight. This mixture was then treated with the keto-diester (287a) (.56g, 0.003 mol) and heated under reflux for 2h. The solution was evaporated and the resulting oil was suspended in water, neutralised with solid sodium acetate and extracted with chloroform. Evaporation of the chloroform extract left an oil which was triturated with ethanol to give 4-phenyl-1H-1,2,3-triazole (293) (0.17g) m.p. 143° (from ethanol-water), identical (m.p. and i.r. spectrum) with an authentic sample.

The neutral aqueous extract was evaporated to give a residue from which no identifiable solid could be isolated.

Diethyl Oxaloacetate (4-ethoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (414c)

A solution of the N-amino ester (264) (0.68g, 0.004 mol) and the keto-diester (287a) (0.75g, 0.004 mol) in ethanol (15.0 ml) containing

glacial acetic acid (1.0 ml) was heated under reflux for 18h. The solution was evaporated under reduced pressure to give an oil which was suspended in water and neutralised with solid sodium acetate to afford the impure triazolylhydrazone (414c) (0.53g) m.p. 95°. Crystallisation from benzene-light petroleum gave the pure triazolylhydrazone (414c) as a colourless solid (0.20g) m.p. 108°, $\nu_{max.}$ 3150 and 3080 (NH), and 1715 and 1690 (CO) cm^{-1}, $\tau(CDCl_3)$ 5.60(2H, q J 7Hz, CH_2), 5.83(2H, q J 7Hz, CH_2), 6.33(2H, s, CH_2), 8.58(3H, t J 7Hz, CH_3) and 8.76(3H, t J 7Hz, CH_3).

Found: C, 45.9; H, 5.6; N, 20.5%; M^+ 341.

$C_{13}H_{19}N_5O_6$ requires: C, 45.8; H, 5.6; N, 20.5%; M, 341,

which was soluble in aqueous dilute sodium hydroxide but was not reprecipitated on acidification with aqueous dilute sulphuric acid.

The original neutral aqueous mother liquor on extraction with chloroform gave a negligible amount of an unidentified oil.

The Reductive Coupling of the Diazonium Salt (412a) with Dimethyl Acetylenedicarboxylate to give the Triazolylhydrazone (434)

80% v/v Aqueous ethanol (50.0 ml) was cooled to 0° (ice-salt bath), and saturated with sulphur dioxide. The solution was stirred and treated in portions with the diazonium chloride (412a) (0.70g, 0.004 mol) and the mixture was re-saturated with sulphur dioxide and left at room temperature overnight. The resulting mixture was then heated under reflux with dimethyl acetylenedicarboxylate for 2h. The solution was concentrated to remove the ethanol and the solid was collected and washed with ethanol to give the triazolylhydrazone (434) as a colourless solid (0.17g) m.p. 218° (from ethanol-water), $\nu_{max.}$ 3400, 3320 and 3220 (NH), and 1740 and 1700 (CO) and, 1650 (NH def.) cm^{-1} $\tau(CF_3CO_2D)$ 5.18(3H, s, CH_3),

6.08(3H, s, CH_3) and 6.20(2H, s, CH_2).

Found: C, 38.3; H, 4.4; N, 29.3%; $M,^+$ 284.

$C_9H_{12}N_6O_5$ requires: C, 38.1; H, 4.2; N, 29.6%; M, 284.

Work up of the aqueous mother liquour by neutralisation with solid sodium acetate and extraction with chloroform gave no further identifiable material.

The Attempted Reductive Coupling of the Diazonium Salt (412b) with Dimethyl Acetylenedicarboxylate

The reaction described above was repeated on the same scale with 4-phenyl-1H-1,2,3-triazole-5-diazonium chloride (412b) (0.83g, 0.004 mol). The mixture was concentrated to remove the ethanol and the aqueous mother liquour was extracted with chloroform to give a mobile oil which was successively triturated with ether to afford an unidentified colourless solid (total 0.08g) m.p. 189° (from ethanol), νmax. 3120 and 3100 (NH), and 1760 and 1750 (CO) cm^{-1}.

Found: C, 61.0; H, 4.9; N, 19.4%; $M,^+$ 432.

The Attempted Condensation of the N-Amino Ester (264) with Dimethyl Acetylenedicarboxylate

A mixture of the N-amino ester (264) (0.68g, 0.004 mol) and dimethyl acetylenedicarboxylate (0.57g, 0.004 mol) was heated under reflux in absolute ethanol (5.0 ml) for 2h. The mixture on evaporation left an oily solid which was repeatedly triturated with ethanol-ether to give the unreacted N-amino ester (264) (total 0.16g) m.p. 154° (from ethanol), identical (m.p. and i.r. spectrum) with an authentic sample.

T.l.c. of the oil from the ethanol-ether mother liquour in ethyl acetate over alumina showed it to contain two components. The oil was subjected to Kugelrohr distillation giving a negligible amount of oily

distillate and a dark gum which when triturated with ether gave an unidentified solid (0.50g) m.p. 90°, $\nu_{max.}$ 3300 - 3160br (OH) and 1720 (CO) cm^{-1}, M^+, 455.

The Attempted Cyclisation of the Triazolylhydrazone (414a)

(a) Using Aqueous Ethanolic Sulphuric Acid

(i) A solution of the triazolylhydrazone (414a) (0.62g, 0.002 mol) in ethanol (20.0 ml) was heated under reflux in 20% w/v aqueous sulphuric acid (5.0 ml) for 0.5h. The ethanol was evaporated and the aqueous residue was diluted with water to give the crude unreacted starting material (414a) (0.40g) m.p. 145°. Crystallisation from ethanol-water gave pure (0.28g) m.p. 200°, identical (m.p. and i.r. spectrum) with an authentic sample.

(ii) When the procedure described in (i) above was repeated for 3h, a crude solid (0.26g) m.p. 170° was obtained. Crystallisation of this solid from dimethylformamide-water gave the triazinone (436) (0.09g) m.p. 244°, identical (m.p. and i.r. spectrum) with a sample obtained earlier.

(b) Using Ethanolic Sodium Ethoxide

A solution of the triazolylhydrazone (414a) (0.62g, 0.002 mol) in ethanol (10.0 ml) was heated under reflux with a solution of sodium (0.046g; 0.002 g atom) in ethanol (10.0 ml) for 1h. The mixture was evaporated and the solid residue was dissolved in water and acidified with aqueous dilute hydrochloric acid to give the unreacted triazolylhydrazone (414a) which was combined with further material obtained by evaporating the aqueous acidic mother liquor and triturating the residue with water (total 0.40g; 64%) m.p. 171°, identified by comparison (i.r. spectrum) with an authentic sample.

(c) Using Aqueous Ethanolic Sodium Acetate

A solution of the triazolylhydrazone (414a) (0.31g, 0.001 mol) in ethanol (10.0 ml) and water (5.0 ml) was heated under reflux with anhydrous sodium acetate (0.08g) for 1h. The mixture was evaporated and the residue was triturated with water to afford the unreacted triazolylhydrazone (414a) more of which was obtained by acidifying the aqueous mother liquor with aqueous dilute sulphuric acid (total 0.12g) m.p. 205° (from ethanol-water), identical (m.p. and i.r. spectrum) with an authentic sample.

(d) Using Glacial Acetic Acid in Ethanol

A solution of the hydrazone (414a) (0.62g, 0.002 mol) in ethanol (20.0 ml) containing glacial acetic acid (5.0 ml) was heated under reflux for 1h. Evaporation of the solution left a solid which was triturated with methanol-ether to give the unreacted triazolylhydrazone (414a) more of which was obtained by evaporating the methanol-ether mother liquor and crystallisating the resulting impure solid from ethanol-water (total 0.41g; 66%) m.p. 204°, identical (m.p. and i.r. spectrum) with an authentic sample.

6-Methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one-3-carboxamide (436)

A solution of the triazolylhydrazone (414a) (0.62g, 0.002 mol) in ethanol (20.0 ml) was heated under reflux with aqueous 1M sodium carbonate solution (10.0 ml) for 17h. The solution was concentrated to remove the ethanol and the aqueous residue was acidified with aqueous dilute hydrochloric acid solution to give 6-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazin-7-(4H)-one-3-carboxamide (436) (0.35g) m.p. 240° (decomp.) (from water) $\nu_{max.}$ 3430, 3350 (NH), 1920br (OH), 1725 (CO) and 1660br (NH) cm^{-1}.

Found: C, 33.2; H, 4.1; N, 38.2%; $M,^{+}$ 194.

$C_6H_6N_6O_2$ requires: C, 33.8; H, 3.8; N, 39.6%; M, (Monohydrate) 212.

APPENDIX

General Experimental Details

Solvents were of Technical grade and light petroleum had b.p. 40 - 60°C.

Organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure.

Infrared spectra were measured for nujol suspensions or thin films using a Pye-Unicam S.P. 200 Spectrophotometer or a Perkin-Elmer 157G Infrared Spectrophotometer. I.r. bands were either strong or very strong, unless otherwise specified as weak (w) or broad (br).

Ultraviolet spectra were measured for ethanol solutions using a Pye-Unicam S.P. 800 Spectrophotometer.

Nuclear magnetic resonance (^1H n.m.r.) spectra were measured at 100MHz using a Varian HA100 instrument with tetramethylsilane as the internal standard.

Mass spectra were measured at 800Kv on an A.E.I. MS902 instrument.

Microanalyses were carried out by Mr. John Grunbaum, Department of Chemistry, Edinburgh University. Melting points (uncorrected) of all analytical samples were determined on a Kofler block.

Thin layer chromatography (t.l.c.) was carried out over Kieselgel or Alumina GF_{254} nach Stahl (Type 60).

Dry column chromatography was carried out over Activity III alumina or Activity III silica containing added fluorescor.

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