STUDIES IN THE CHEMISTRY OF SOME POLYAZAHETEROCYCLIC COMPOUNDS

by

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SUMMARY

The subject matter of this thesis concerns the synthesis, structure and properties of some polyazaheterocyclic compounds.

The diazotization of some simple aminotriazoles is described. It is shown that 1,4-disubstituted 5-amino-1,2,3-triazoles undergo replacement of the 5-amino group by a halogen atom when they are diazotized in aqueous hydrochloric or hydrobromic acid. 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium chloride and 2H-1,2,4-triazole-3-diazonium nitrate have been prepared and their bifunctional reactivity is demonstrated by their condensation with a series of active methylene compounds providing synthetic routes to the 1,2,3-triazolo[5,1-c]-1,2,4-triazine and 1,2,4-triazolo[5,1-c]-1,2,4-triazine ring systems. The structures of the fused triazolotriazine products have been established by physical methods and chemical transformations.

Synthetic routes to the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system have been investigated. The most satisfactory method involves the reaction of 5-amino-4-phenyl-1H-1,2,3-triazole with isocyanates and the subsequent reaction of the adducts obtained with orthoesters. The reactivity of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine derivatives provides a new route to 2-substituted 1,3,5-triazines.

Further studies have been carried out on the synthesis and reactivity of the 1,2,3-triazolo[1,5-a]pyrimidine ring system. In particular, variable temperature ^{1}H n.m.r. studies with various 1,2,3-triazolo[1,5-a]pyrimidine derivatives have provided conclusive evidence for the existence of diazoalkylideneamine-triazole tautomerism in fused 1,2,3-triazoles.

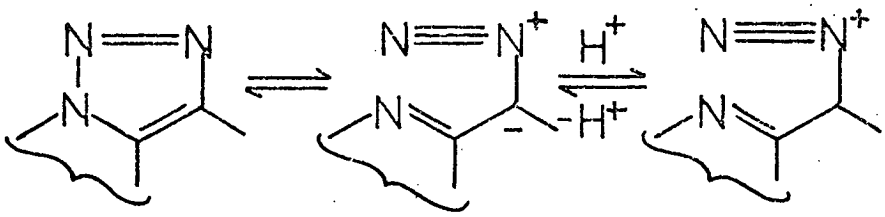
CONTENTS

CHAPTER 1

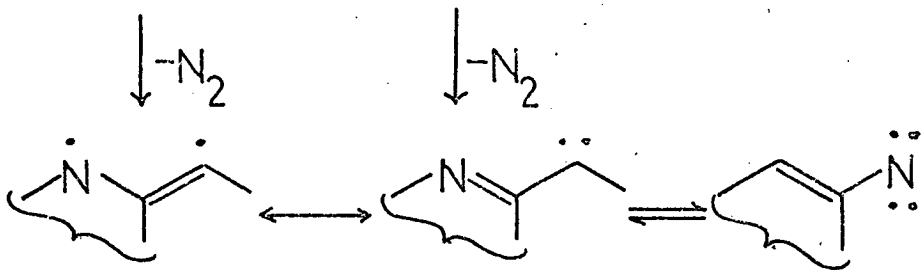
A Review of Some Aspects of Polyazaheterocyclic Chemistry

1.1. Introduction

Molecules containing a fused 1,2,3-triazole nucleus (1) are potential sources of a variety of reactive species. Nuclei of the type (1) undergo reactions which can be explained in terms of diradical (4)[1], carbene (5)[1,2], nitrene (6)[1,2], or diazonium cation (3)[3-6] intermediates.

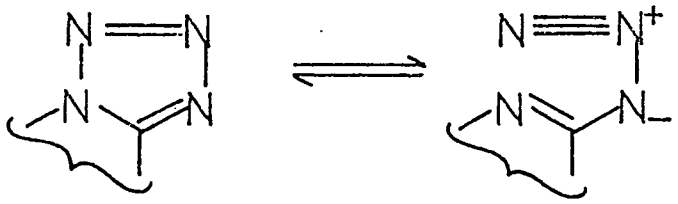


(1) (2) (3)



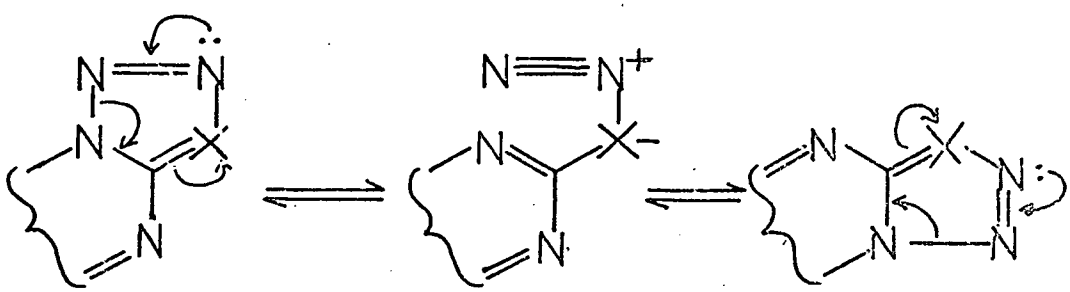
(4) (5) (6)

The reactive species [(3) - (6)] are derived by homolytic[1,2,7] or heterolytic[3-6,8-13] ring scission involving the loss of molecular nitrogen[14-19] indicating a marked diazo character for the 1,2,3-triazole nucleus (1). Another implication of this 'diazo-character' is the possible existence[10,11b,12,13] of diazoalkylidene-amine-triazole tautomerism [(1) $\rightleftharpoons$ (2)] in fused 1,2,3-triazolo-heterocycles analogous to the ring-chain, azidoazomethine-tetrazole equilibrium [(7) $\rightleftharpoons$ (8)] exhibited by fused tetrazoloheterocycles.[20]



(7) (8)

As a consequence of this equilibrium [(7) ⇌ (8)], Dimroth-type rearrangements of fused tetrazoles [(9) ⇌ (10) ⇌ (11); X = N] are possible and well documented.[21,22] In contrast, little is known[13] of the corresponding rearrangement [(9) ⇌ (10) ⇌ (11); X = CR]

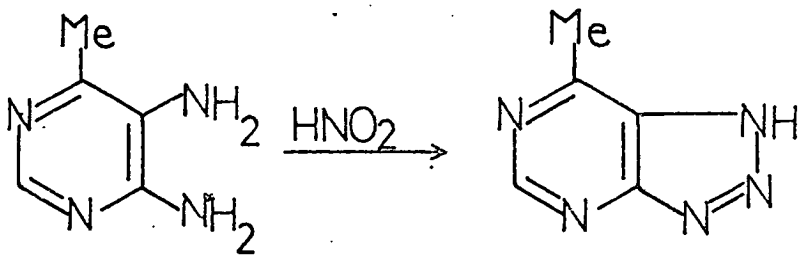


(9) (10) (11)

of fused 1,2,3-triazoles and unlike the tetrazole case[21,22], the intermediate [(10); X = CR] has not as yet been detected.[13]

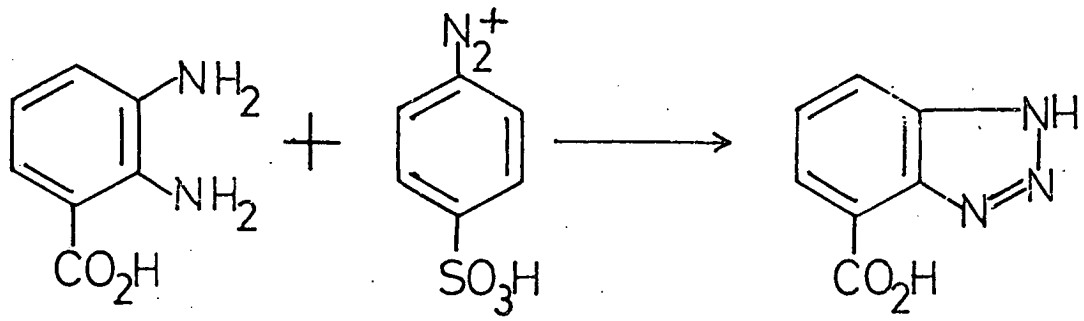
1.2. The Synthesis of Fused 1,2,3-Triazoloheterocycles

The synthesis of fused 1,2,3-triazolo[4,5]heterocycles has most commonly been carried out by the treatment of an ortho-diamine with nitrous acid[23], as exemplified by the synthesis of 7-methyl-1,2,3-triazolo[4,5-d]pyrimidine(13)[24] from 4,5-diamino-6-methylpyrimidine(12). Sometimes a monoacylated ortho-diamine



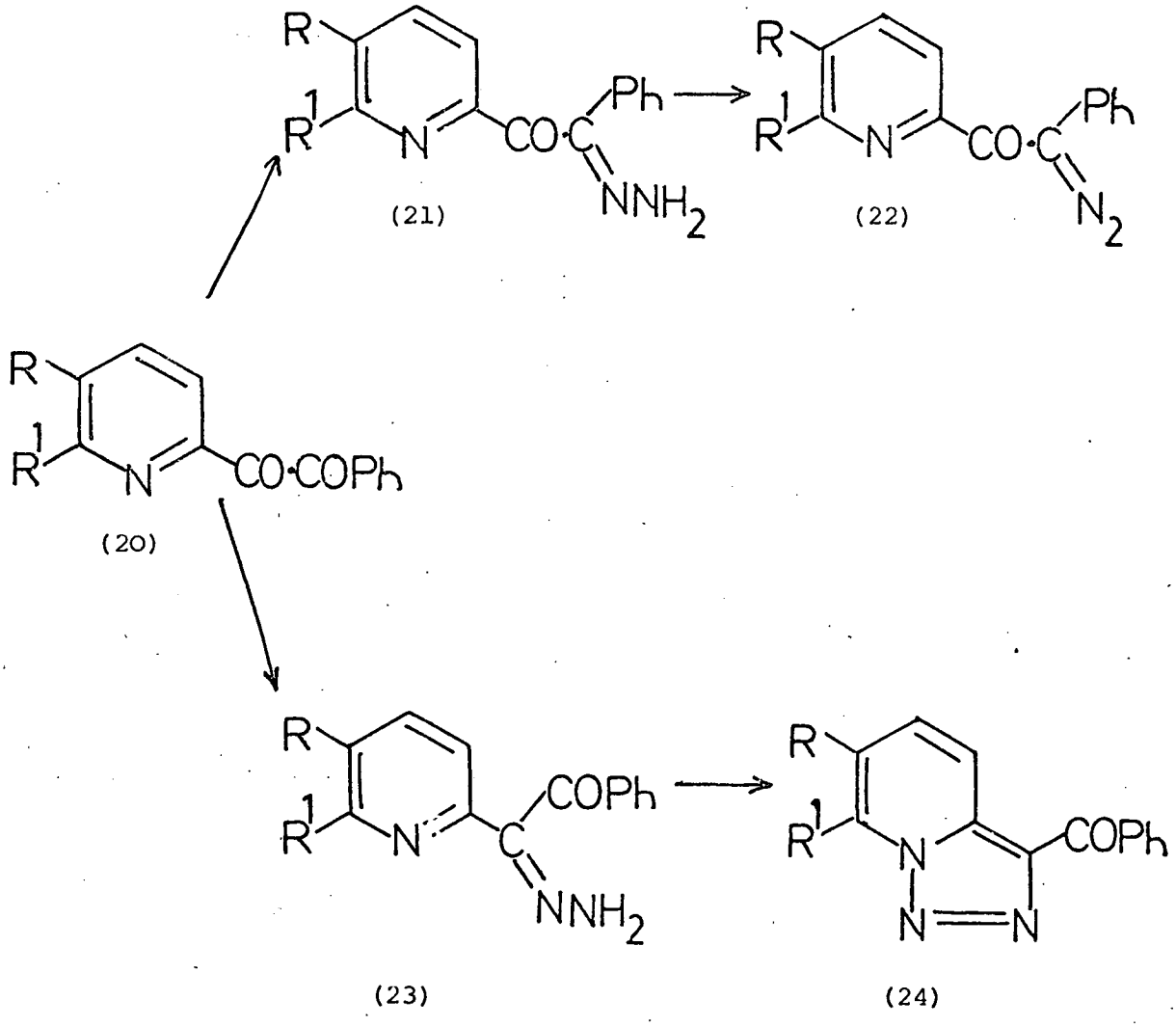
(12) (13)

is employed[23,25], the acyl group being lost during diazotization. As an alternative to diazotizing the ortho-diamine, the middle nitrogen of the 1,2,3-triazole ring may be introduced by employing a diazonium salt[23] as in the reaction[26] of 2,3-diaminobenzoic acid (14) with diazotized sulphanilic acid (15) to give benzotriazole-4-carboxylic acid (16).



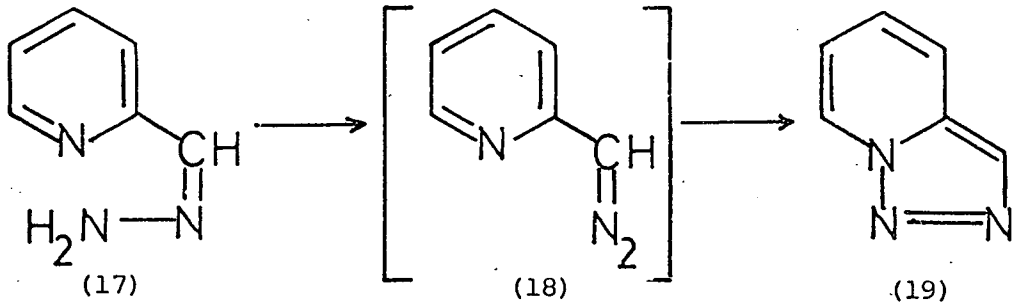
(14) (15) (16)

Fused 1,2,3-triazoloheterocycles containing a bridgehead nitrogen atom may be obtained in general by either starting with a suitable heterocycle and building the triazole nucleus onto it, or conversely by constructing the system starting with a suitable 1,2,3-triazole derivative.



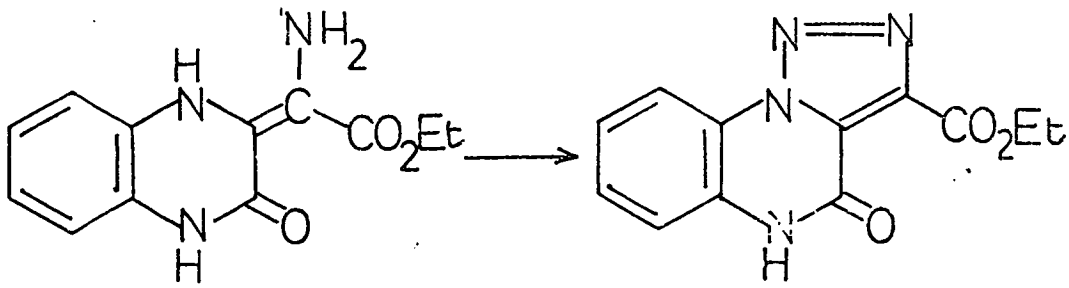
Scheme 1

The former approach has generally been carried out[27] by preparing a compound which contains a suitably situated diazo group which then cyclizes *in situ* to the desired fused 1,2,3-triazole. The demonstration[27] that diazo group transfer onto β-iminoketones generally leads to 1,2,3-triazoles and not the expected diazo tautomers is consistent with the observation by Boyer *et.al.*[28] and Bower *et.al.*,[29] that dehydrogenation of α-pyridinealdehyde-hydrazone (17) yields, not α-pyridyldiazomethane (18), but the cyclic isomer 1,2,3-triazolo[1,5-a]pyridine (19). A good example



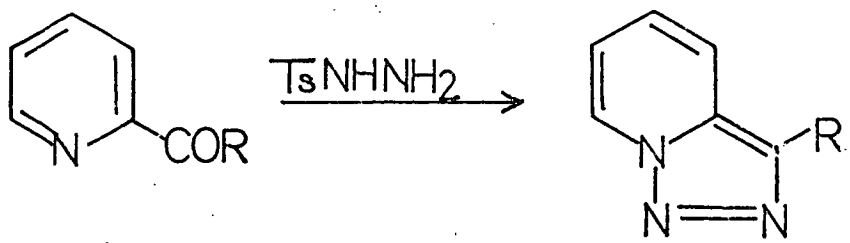
(17) (18) (19)

demonstrating the intermediacy of a diazo tautomer in such reactions has been reported by Eistert and Endres[30] in their work (Scheme 1) on the reactions of phenyl-2-pyridylglyoxals (20) with hydrazine. Oxidation of the resultant isomeric monohydrazones (21) and (23) gave the diazoketones (22) and the 1,2,3-triazolo[1,5-a]-pyridines (24) respectively. As in the case of fused 1,2,3-triazolo-[4,5]heterocycles[23], diazotization of a suitably situated amino group may also lead to ring closure as demonstrated by a recent synthesis[31] of 4,5-dihydro-4-oxo-1,2,3-triazolo[1,5-a]quinoxaline-3-carboxylate (26) from the aminoquinoxalone (25).



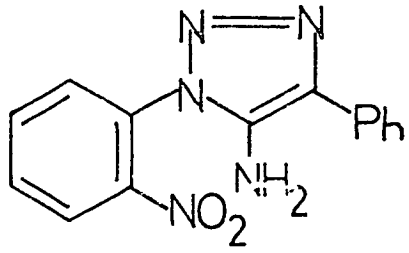
(25) (26)

Reimlinger[32] has modified the 'diazo' method of synthesis by treating an α-pyridylketone (27) with para-toluenesulphonylhydrazide to give the corresponding 1,2,3-triazolo[1,5-a]pyridine (28) directly. This one step synthesis involves the formation *in situ* of the diazo intermediate which then cyclizes to the 1,2,3-triazolo-heterocycle (28).



(27) (28)

Lieber and his co-workers observed[33] that whereas azido-benzene derivatives react as expected with phenylacetonitrile under basic conditions to afford 5-amino-1-aryl-4-phenyl-1,2,3-triazoles, ortho-nitrophenylazide behaves anomalously giving 3-phenyl-1,2,3-triazolo[1,5-a]benzo-1,2,4-triazine 5-oxide (30). This compound is presumably formed by an aldol-type condensation [(29) → (30)] between the nitro- and amino-groups in the initially formed 1,2,3-triazole (29). This work has been extended[10a] using



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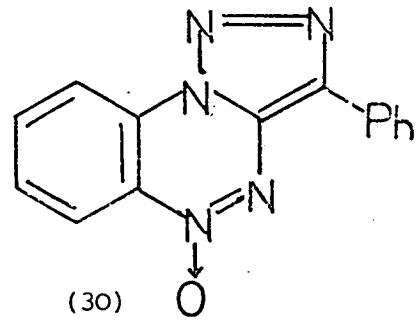
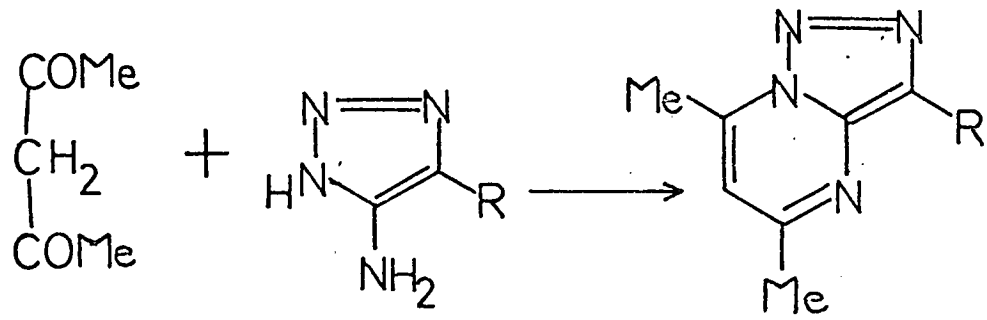


(30)

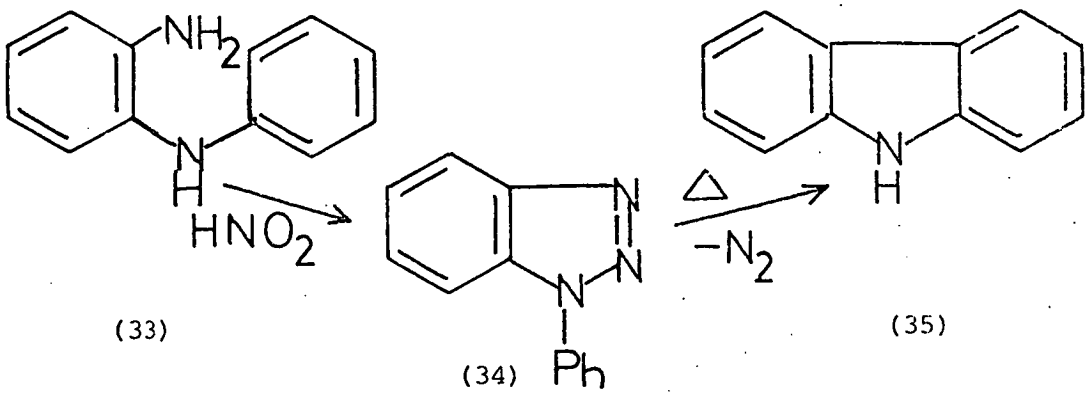
ortho-azidobenzoic acid instead of ortho-nitrophenylazide to afford the first reported examples of the 1,2,3-triazole[1,5-a]quinazoline ring system. This type of reaction may be regarded as the synthesis of a fused 1,2,3-triazoloheterocycle using a preformed triazole intermediate. The construction of fused 1,2,3-triazoloheterocycles from a preformed triazole derivative has provided routes to other ring systems[10-13], a typical example being the extension of work originally, briefly described by Birr[34] to the synthesis of the 1,2,3-triazolo[3,4-a]pyrimidine ring system.[11b] Here, amino-1,2,3-triazoles (31) condense smoothly under basic or acidic conditions with β-dicarbonyl compounds to give for example, 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (32, R = Ph).



(31) (32)

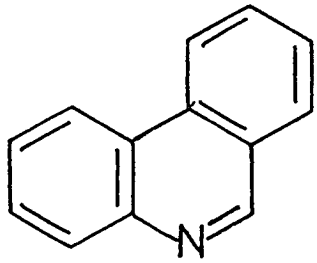
1.3. The Loss of Molecular Nitrogen from Fused 1,2,3-Triazolo-heterocycles (1,2,3-Triazole Scission)

In 1896, Graebe and Ullmann observed[14] that by heating 1-phenylbenzo-1,2,3-triazole (34), [prepared by diazotizing ortho-aminodiphenylamine (33)] elimination of nitrogen occurred to give carbazole (35). More recent extensions of this type[15,17,18]



(33) (34) (35)

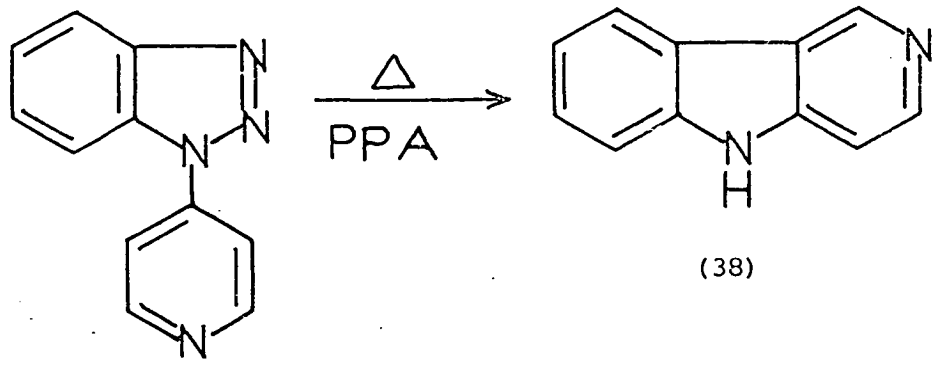
of reaction have been carried out, notably by Gibson[18] in his synthesis of phenanthrene (36).



(36)

Such reactions probably occur by a radical type of mechanism involving the so-called homolytic scission[1,2,13] of the triazole ring (see later).

Robinson and Thornley[16] found that the Graebe-Ullmann reaction of 1-γ-pyridylbenzotriazole (37) to give the carboline (38) was facilitated by the presence of polyphosphoric acid. A similar observation has been made by Kermack and Storey[19] and such apparently

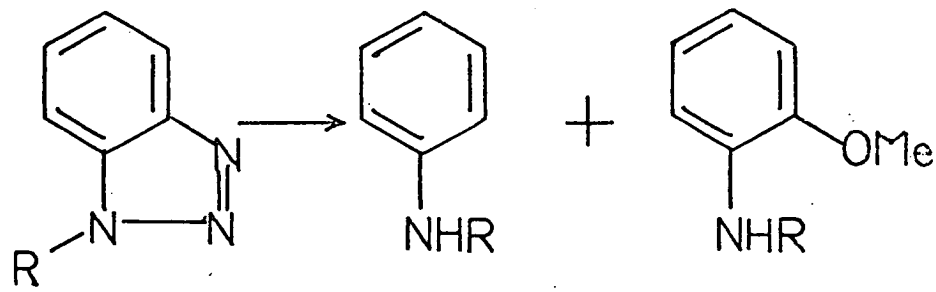


(37) (38)

acid-catalysed processes may occur by heterolytic scission[3-6,8-13], of the triazole ring (see later).

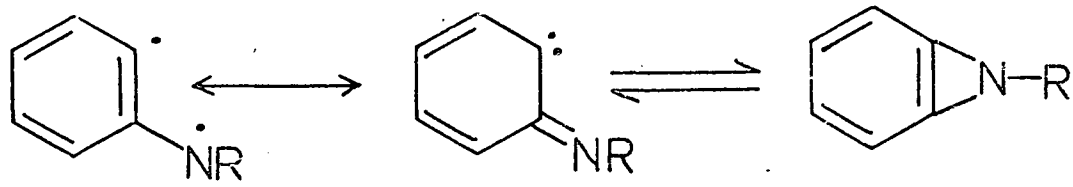
(a) Homolytic Scission

Boyer and Selvarajan synthesized carbazole (35) by photolysing[7] a methanolic solution of 1-phenylbenzo-1,2,3-triazole (34). However, when benzo-1,2,3-triazole (39; R = H) or its 1-methyl derivative (39; R = Me) was subjected[7] to the same treatment, mixtures of the corresponding aniline (40) and ortho-anisidine (41) were obtained. Boyer suggested[7] a mechanism for these reactions



(39) (40) (41)

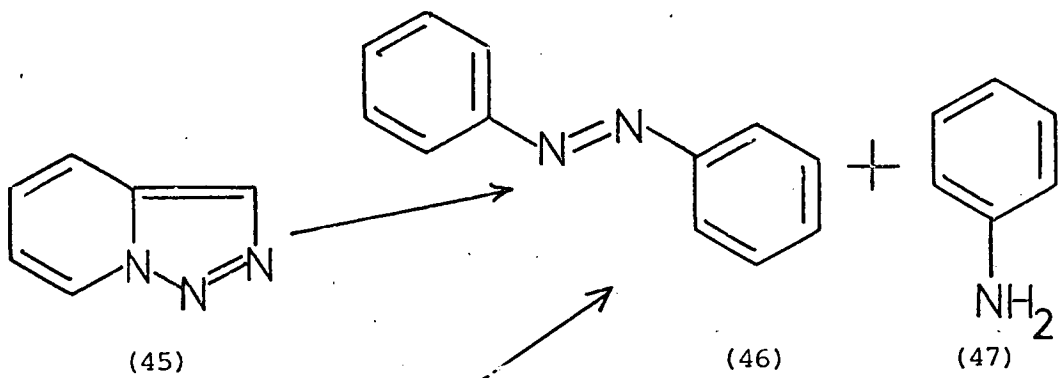
involving the loss of nitrogen to give an intermediate which could have the diradical (42), carbene (43) or aziridine (44) structures.



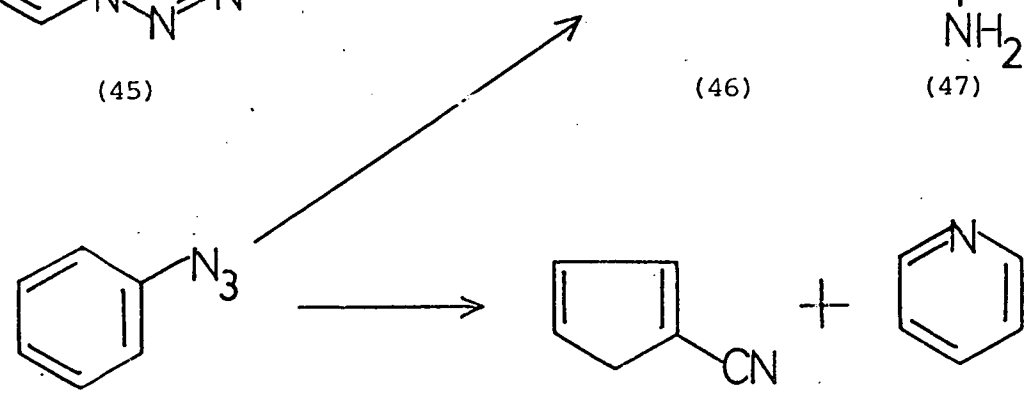
(42) (43) (44)

Subsequent intramolecular rearrangement to carbazole (35) or reaction with methanol then yields the anilines (40) and anisidines (41) observed as products.

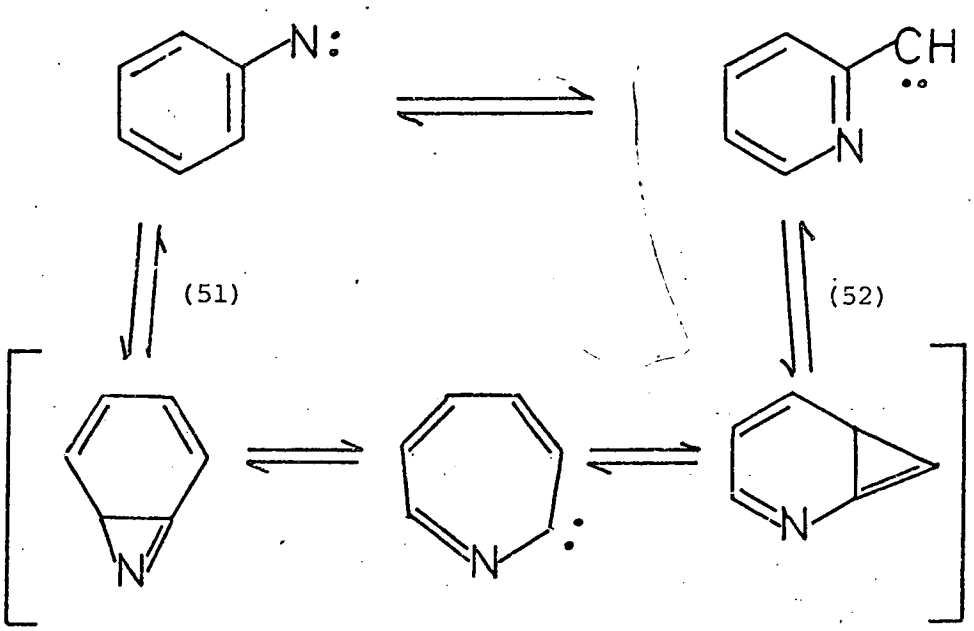
Crow and Wentrup have shown[1] that the gas-phase pyrolysis of 1,2,3-triazolo[1,5-a]pyridine (45) affords a mixture of azobenzene (46) and aniline (47), and the same products result[35] from the



(45) (46) (47)



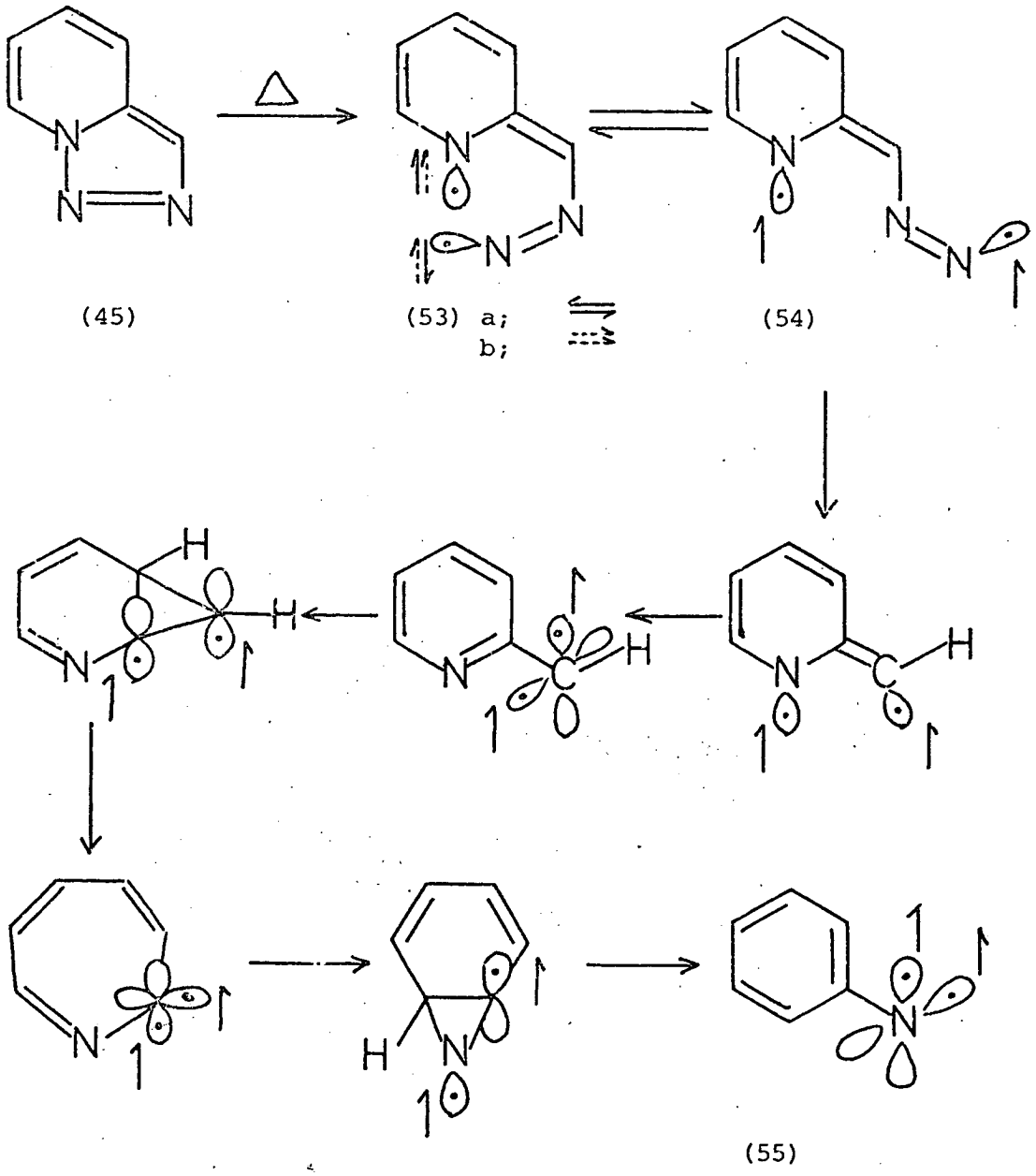
(48) (49) (50)



Scheme 2

mild pyrolysis of phenylazide (48). However, under more vigorous thermal conditions[35] it was found that phenylazide gives rise to 1-cyanocyclopentadiene (49) and pyridine (50).

The results obtained from the pyrolysis of phenylazide are explained[1] by the formation of an intermediate singlet nitrene which may undergo intramolecular insertion into an aromatic double bond leading, after rearrangement, to 1-cyanocyclopentadiene (49). It is suggested[1] that in the mild pyrolysis of phenylazide (48), the initially formed singlet nitrene decays by intersystem crossing to the triplet nitrene which may then undergo coupling or hydrogen capture to give azobenzene (46) and aniline (47) respectively. The apparently anomalous formation of pyridine (50) is explained[1,2] by a thermal interconversion of phenylnitrene (51) to 2-pyridylcarbene (52) (Scheme 2) and subsequent loss of carbon. The results[1] obtained from the pyrolysis of 1,2,3-triazolo[1,5-a]pyridine (45) lend support to the theory of a possible equilibrium between phenylnitrene and 2-pyridylcarbene [(51) $\rightleftharpoons$ (52)], but the notable absence of 1-cyanocyclopentadiene (49) as a product poses questions as to the nature of the intermediate involved in the pyrolysis. In his investigation Crow pyrolysed other 2-pyridylcarbene (52) generators[1] in a similar manner. The results obtained offered only one possible conclusion,[1] namely that of all the generators of phenyl nitrene, only 1,2,3-triazolo[1,5-a]pyridine (45) directly produces the triplet species capable of dimerization to give azobenzene (46) as the major product.

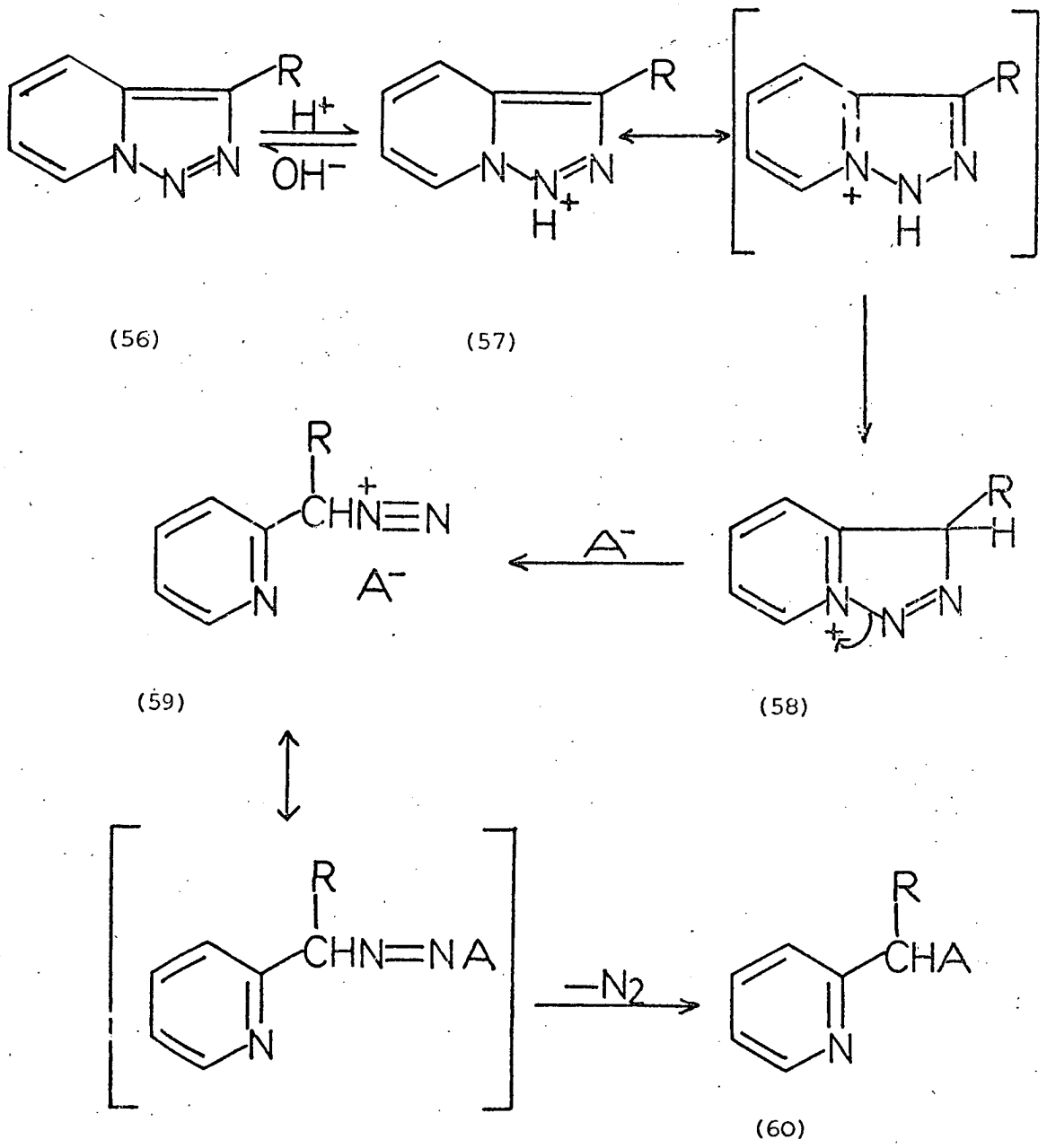


Scheme 3

Crow's explanation[1] of the course of the pyrolysis of 1,2,3-triazolo[1,5-a]pyridine (45) (Scheme 3) is based on the consideration of the spin state of the intermediate. He suggests that the stepwise elimination of nitrogen would entail the initial formation of a singlet biradical (53a) (i.e. conservation of spin state). However, rotational interconversion of the type [(53a) ⟹ (54)] would lead to separation of the lobes being so great as to render the distinction between singlet and triplet states meaningless. Subsequent loss of nitrogen from the now more likely triplet (53b) or (54) would lead eventually, with conservation of spin to triplet nitrene (55).

(b) Heterolytic Scission

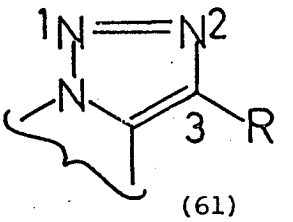
In 1958 Boyer and his co-workers observed[8] that 1,2,3-triazolo-[1,5-a]pyridine derivatives (56) underwent decomposition in acidic media, with loss of nitrogen, to give derivatives of α-pyridylmethanol (60). Thus, when 1,2,3-triazolo[1,5-a]pyridine (56; R = H), or its 3-phenyl derivative (56; R = Ph), was warmed in carboxylic acid or phenol solutions, the corresponding carboxylic acid esters (60; A = .OCOR) or the phenylether of α-pyridylmethanol (60; A = .OPh) were obtained. The mechanism suggested (Scheme 4)[8] for this acid catalysed scission of the triazole ring was founded on the results of studies by Boyer et.al. on the ultraviolet spectra of 1,2,3-triazolo[1,5-a]pyridine (56; R = H) in various media. These workers showed that triazolopyridine gave identical spectra in neutral or basic solution, whereas in acidic solution,



Scheme 4

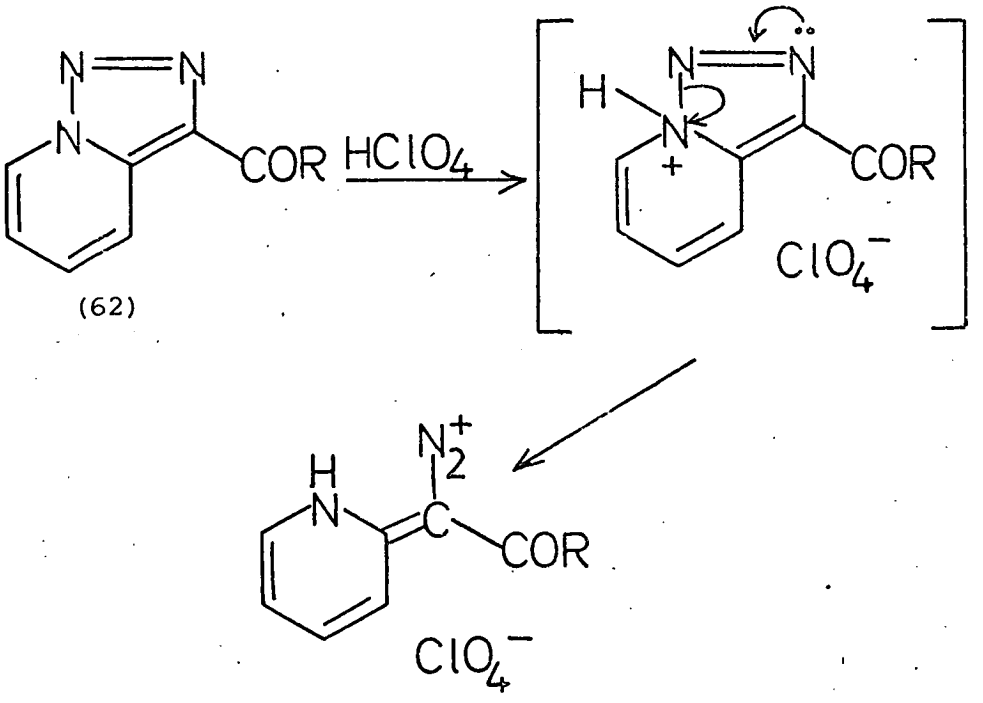
a different spectrum was obtained. The latter spectrum was assigned to the conjugate acid (57) of the triazolopyridine. When the acidic solution was neutralized, the spectrum reverted to that of the free triazolopyridine (56). The stability of the conjugate acid (57) was demonstrated[8] by the lack of change in the spectrum of a solution in 1.2 N-hydrochloric acid after keeping at room temperature for two weeks. At higher temperatures, a rearrangement of the tautomeric conjugate acid (58) followed by ring cleavage and a breakdown of the intermediate diazonium salt (59) resulted in the formation of the α-pyridylmethanol derivatives (60).

Heterolytic scission of this type has also been demonstrated in the 1,2,3-triazolo[1,5-a]quinazoline,[10a,12a] 1,2,3-triazolo-[5,1-c]-1,2,4-benzotriazine,[10b,c] and 1,2,3-triazolo[5,1-a]-pyrimidine[11b,12b,13] ring systems. However, a notable observation concerning acid-catalysed scission is the unwillingness[8,9,11b,13] of fused triazoles (61) to undergo cleavage with subsequent loss



(61)

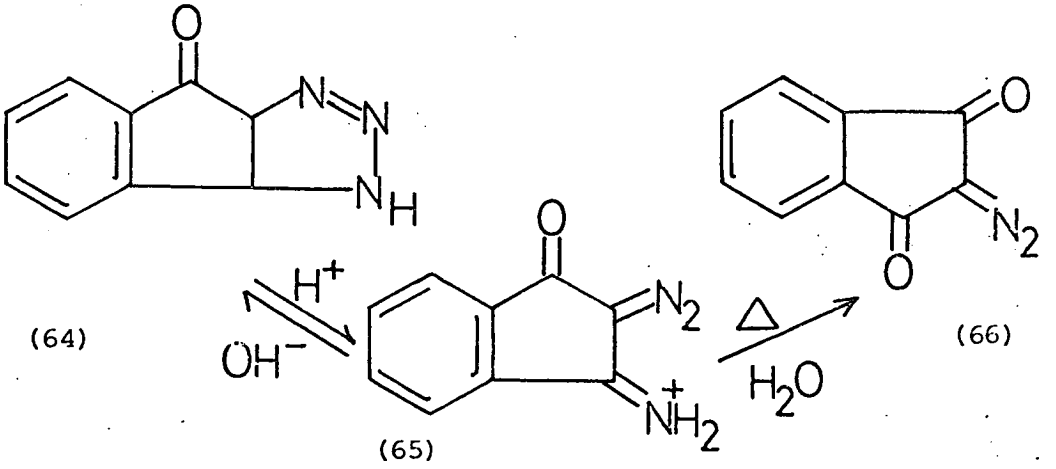
of nitrogen when the substituent at C-3 is electron withdrawing. Ring cleavage without loss of nitrogen has, however, been observed.[5,6] Treatment of 3-acyl-1,2,3-triazolo[1,5-a]pyridines (62) with perchloric acid affords[5] the solid diazonium perchlorates (63). Holt and Wall found[6] that the acid catalysed scission of



(62)

(63)

8-oxindeno[1,2-d]-1,2,3-triazole (64) gives the indene derivative (65) which was isolated as the acid salt. Treatment of the



(64)

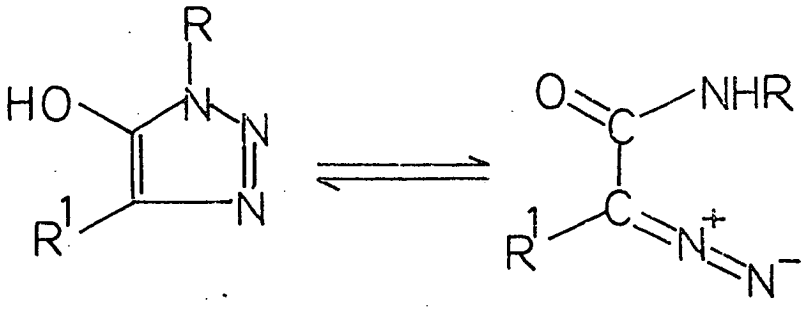
(65)

(66)

diazo compound (65) with base regenerated the oxindenotriazole (65). However, mild hydrolysis yielded the diazoindene derivative (66).

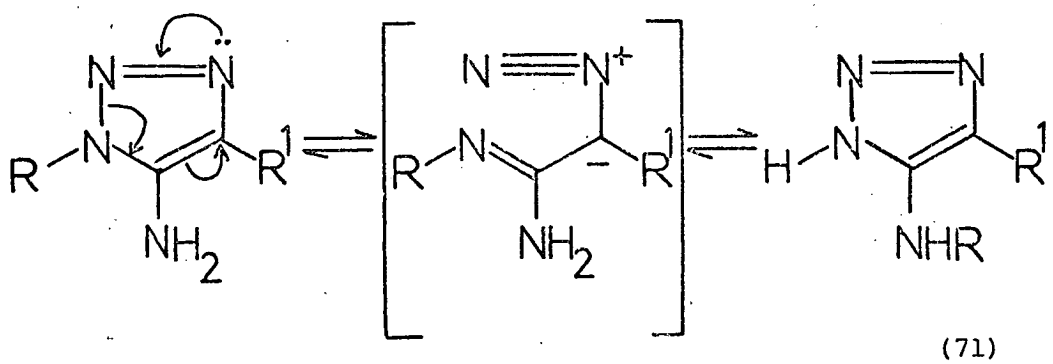
1.4. Diazoalkylideneamine-Triazole Equilibria and Related Processes

The tautomerism [(67) ⟹ (68)] has long been known[36-39] for simple hydroxy-1,2,3-triazoles. An intermediate (70) similar



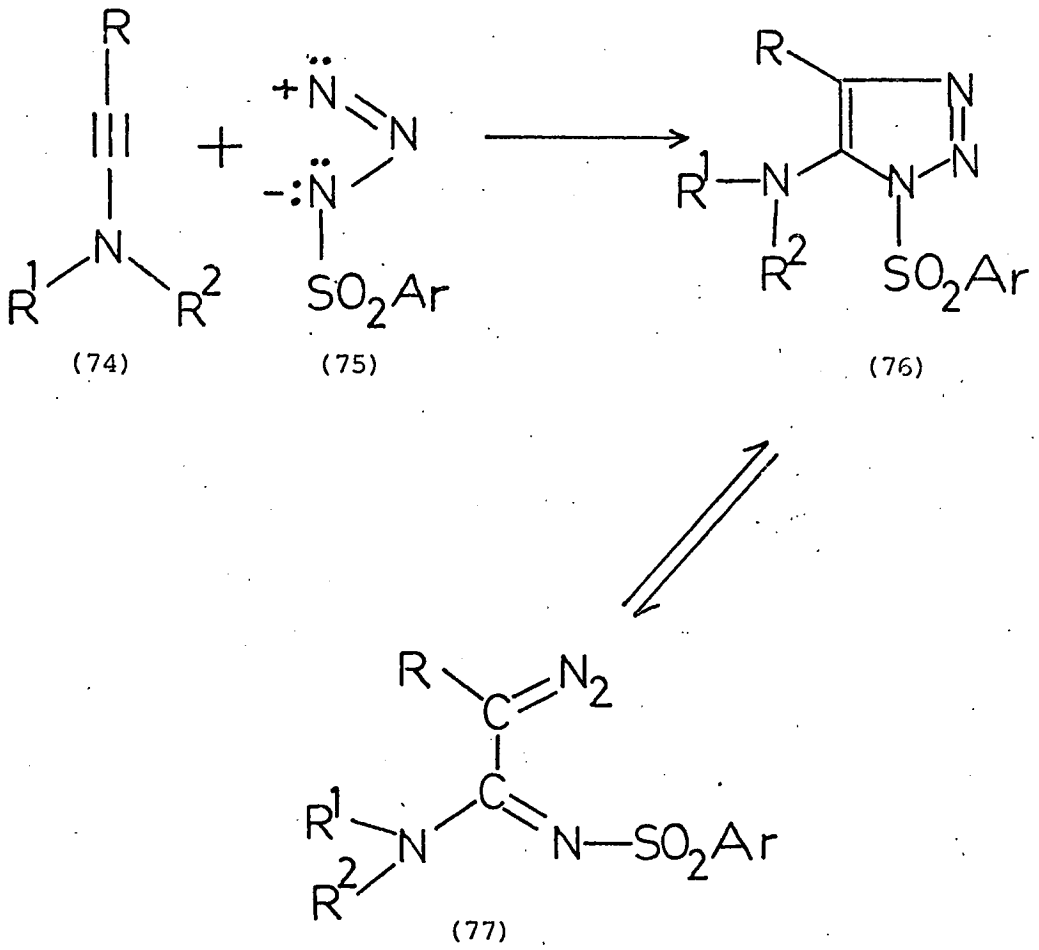
(67) (68)

to the diazo structure (68) has been thought[11a,40] for a number of years to be involved in the reversible isomerization[41] of 1-substituted-5-amino-1,2,3-triazoles [(69) ⟹ (71)].



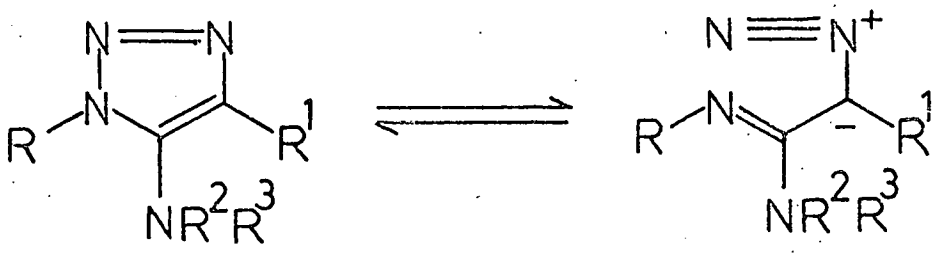
(69) (70) (71)

The effects of the substituents R and R^1[33,40,42,43] and the nature of the medium[33] in which the isomerization is carried out on the position of the equilibrium [(69) ⟹ (71)] have been investigated. Generally, the more electron withdrawing the substituent R, the further to the right the equilibrium will lie[11a,33,40] [i.e. the acidic tautomer (71) will predominate].



Scheme 5

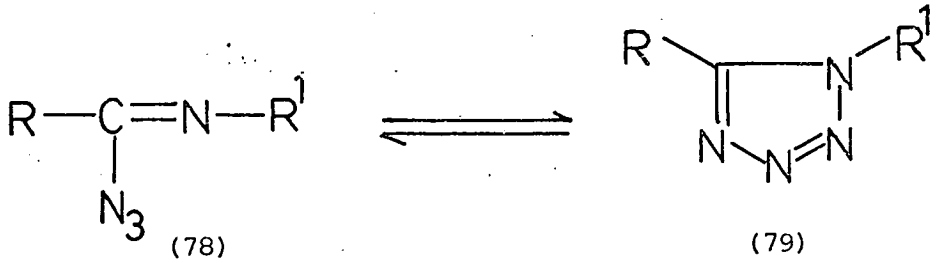
Solvents of high polarity also shift the equilibrium in the same direction.[33] The retrogressive rearrangement [(71) ⟶ (69)] has been observed to be promoted[11a,40] by electron donating substituents at C-4. The diazoalkylideneamine-triazole equilibrium [(72)⇌(73)], thought to be involved in such Dimroth rearrangements,[11a,40] has



(72) (73)

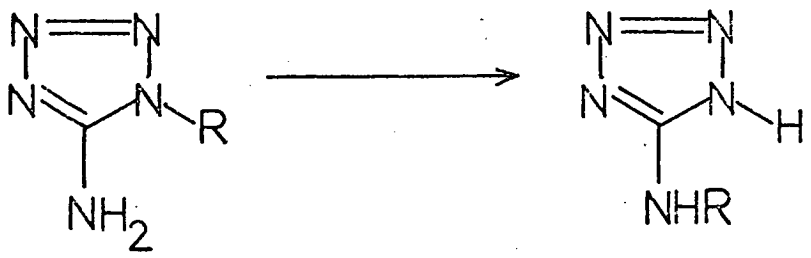
only recently been detected.[5,43-47] The existence of equilibria of the type [(72)⇌(73)] has been demonstrated simultaneously by Harmon and his co-workers,[43,46] and by Regitz and Himbert.[44,45] They have shown (Scheme 5) that the 1,3-dipolar addition of substituted benzenesulphonylazides (75) to ynamines (74) gives rise to equilibrium mixtures of the corresponding triazoles (76) and diazoamidines (77), the extent of the equilibrium [(76)⇌(77)] being dependent on the nature of the substituents. However, Regitz did observe[45] that when ynamines of the type (74; R = H) were used, the equilibrium lay heavily in favour of the diazo tautomer. This work stands in contrast to results obtained by Huisgen,[48] who found that the addition of aryl- and aroylazides to N,N-dimethyl-aminophenylacetylene gave only the corresponding 1,2,3-triazoles.

Analogous to the diazoalkylideneamine-triazole tautomerism [(72) ⇌ (73)] is the corresponding azidoazomethine-tetrazole isomerism [(78) ⇌ (79)].[20] The analogy between 1,2,3-triazoles



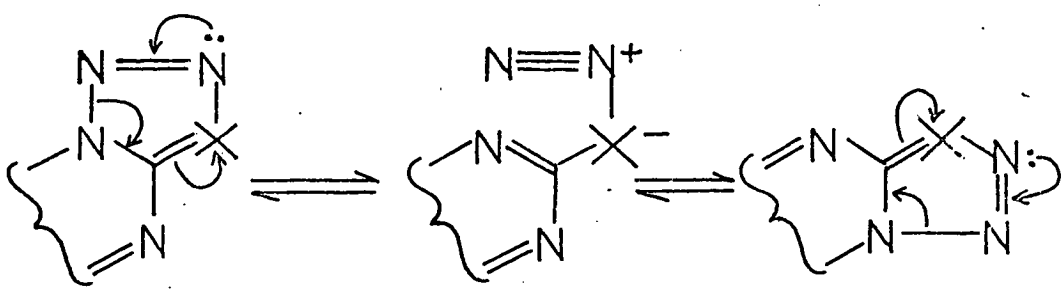
(78) (79)

and tetrazoles in such processes is further demonstrated by the facile thermal isomerization[49-51] of 1-substituted 5-aminotetrazoles (80) into substituted 5-aminotetrazoles (81). However, whereas

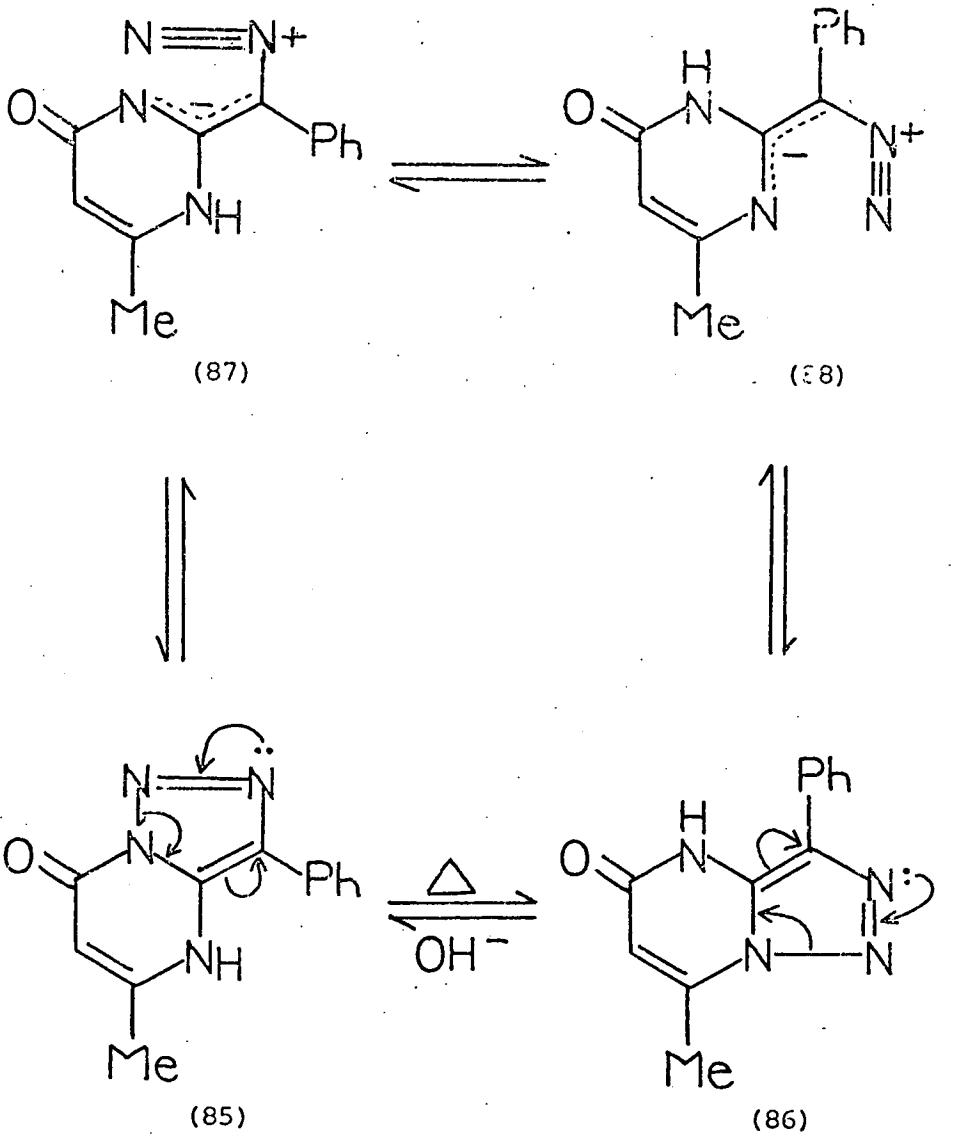


(80) (81)

azide-tetrazole tautomerism [(82) ⇌ (83); X = N] and the attendant Dimroth-type rearrangements [(82) ⇌ (83) ⇌ (84); X = N] of fused tetrazoloheterocycles have now been well documented,[21,22]

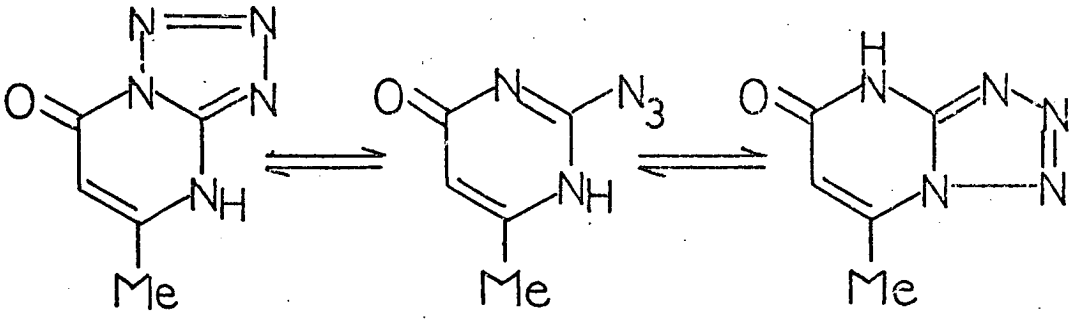


(82) (83) (84)



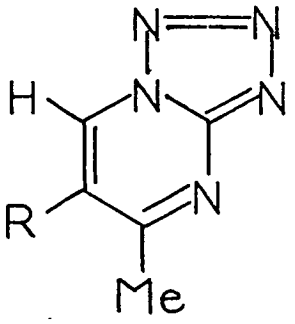
Scheme 6

only one example of the rearrangement of a fused 1,2,3-triazole [(82)⇌(83)⇌(84); X = CR] has been reported.[13] Condensation[13] of ethyl acetoacetate with 5-amino-4-phenyl-1H-1,2,3-triazole (Scheme 6) in the presence of piperidine gave a base stable product (85) which when crystallised or dried at elevated temperatures gave the thermally stable isomer (86), the proposed intermediates in this rearrangement being the open chain forms [(87)⇌(88)]. Reconversion of the isomer (86) into (85) was accomplished smoothly by warming in ethanolic piperidine. I.r. and ^{1}H n.m.r. investigation of the products failed to detect any of the intermediates [(87) or (88)]. This is in contrast to the corresponding tetrazolo[1,5-a]pyrimidone (89) which may be converted[21] into

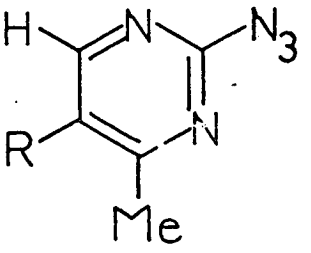


(89) (90) (91)

either the closed (91) or open-chain (90) isomeric structures depending on the conditions employed. Further insight into the subject of azide-tetrazole tautomerism [(82)⇌(83); X = N] in fused tetrazoloheterocycles has been obtained by Wentrup[52], and Huisgen and Fraunberg[53], in their studies of substituent effects in the tetrazolo[1,5-a]pyrimidine system. Huisgen observed[53] that when R is electron donating, the tetrazole form (92)



(92)



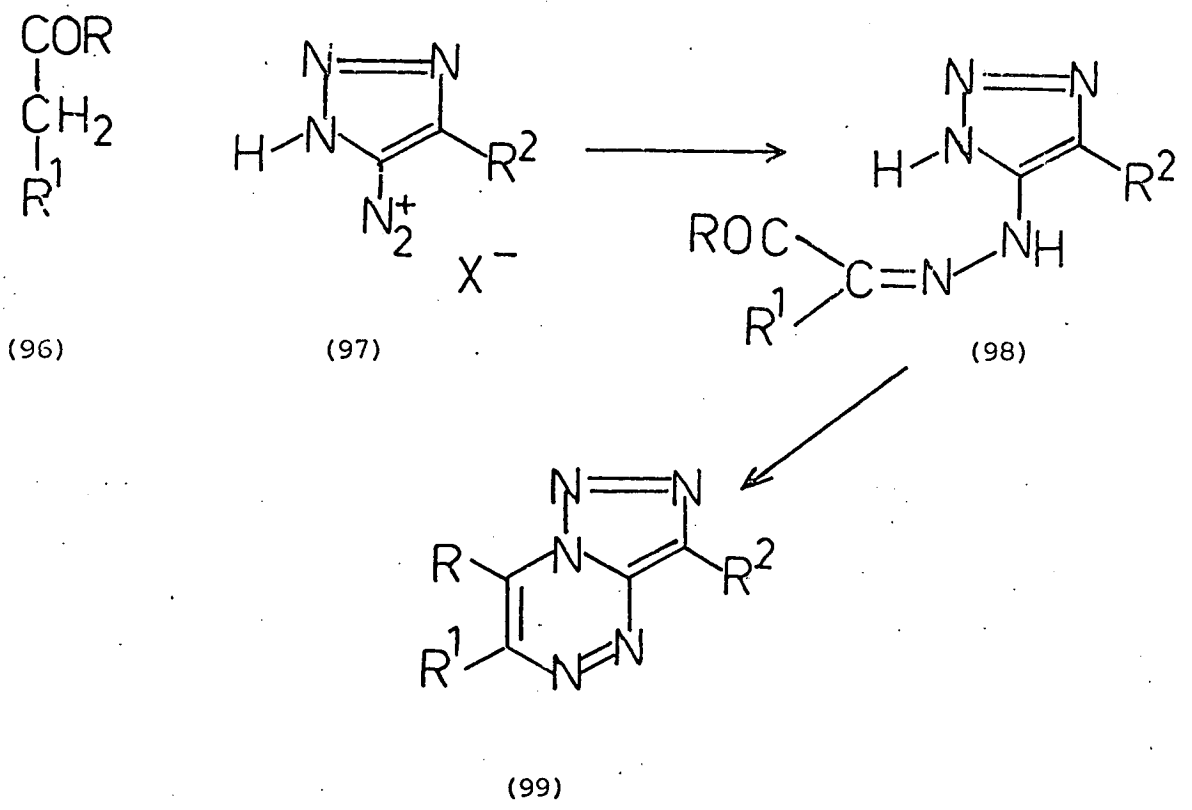
(93)

predominates, whereas if R is electron withdrawing, the azide form (93) is favoured.

The synthesis of new fused 1,2,3-triazole systems containing bridgehead nitrogen atoms, and the study of these and related heterocycles constitutes the subject material of the following thesis.

Chapter 2

The Diazotization of Amino-1,2,3- and Amino-1,2,4-triazoles - Synthetic Routes to the 1,2,3-Triazolo[5,1-c]-1,2,4-triazine and 1,2,4-Triazolo[5,1-c]-1,2,4-triazine Ring Systems



(96) (97) (98)

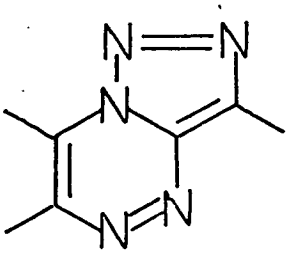
(99)

Scheme 7

Part One - Discussion

2.1 Introduction

The 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system (94) is of interest in relation to the question of the relative stabilities of the fused 1,2,3-triazole [e.g. (94)] and its diazo tautomer [e.g. (95)]. Thus it might be expected that the strongly electron-withdrawing character of the triazine ring would have the effect of destabilizing (94) relative to (95).



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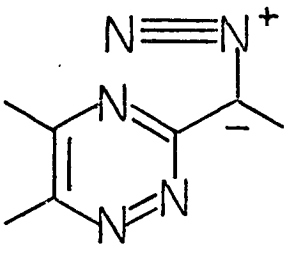
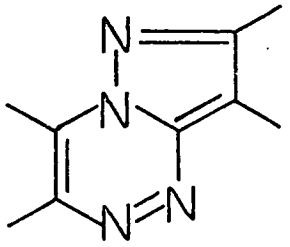


(95)

No examples of the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system (94) have as yet been reported. It was hoped to develop a suitable route to the ring system (94) by making use of the bifunctional reactivity of 1H-1,2,3-triazole diazonium salts (97). Thus coupling of such a salt with suitable active methylene compounds (96) should yield hydrazones (98) set up for cyclisation to 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives (99) (Scheme 7). Such a synthesis finds analogy in Partridge and Stevens'[54] study of the pyrazolo[5,1-c]-1,2,4-triazine ring system (100).

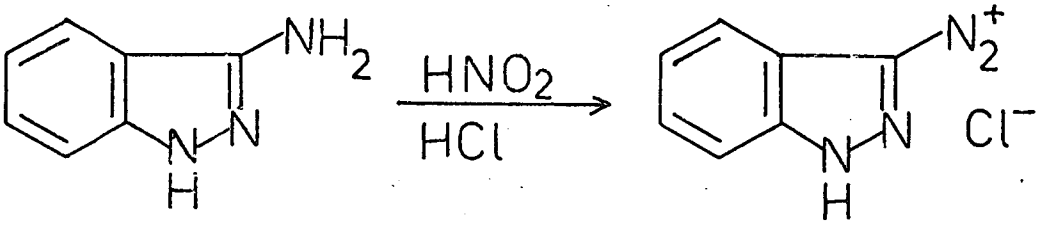


(100)

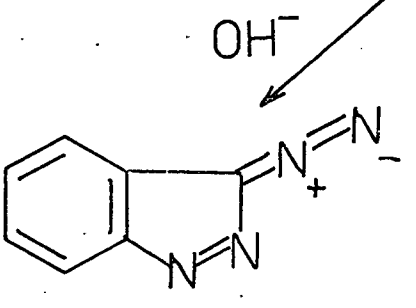
2.2. The Diazotization of 5-Membered Heterocycles

The diazotization of 5-membered amino heterocycles has not been as extensively studied as that of their benzenoid counterparts. The first example of a stable heterocyclic 5-membered diazonium salt was reported by Bamberger[55] in 1899. He found that treatment of a solution of 3-aminoindazole (101) in hydrochloric acid with sodium nitrite gave the diazonium salt (102), which, on treatment with alkali, lost a proton to yield the diazo compound (103). This last reaction is a general feature of diazonium salts,[56] and indeed, pyrrole and indole diazonium salts are so acidic that they give up a proton even in dilute acidic solution to afford the corresponding betaines.

The difficulty of introducing a suitably placed amino group in the 5-membered heterocycle is often a drawback in the formation of the required diazo compound. Other methods of synthesis must then be sought. Among the alternatives to diazotization is the method of direct introduction of the diazo group as used in the synthesis[57] of 3-diazo-2,4,5-triphenylpyrrole (105) from 2,4,5-triphenylpyrrole (104). This reaction, which is carried out under



(101) (102)



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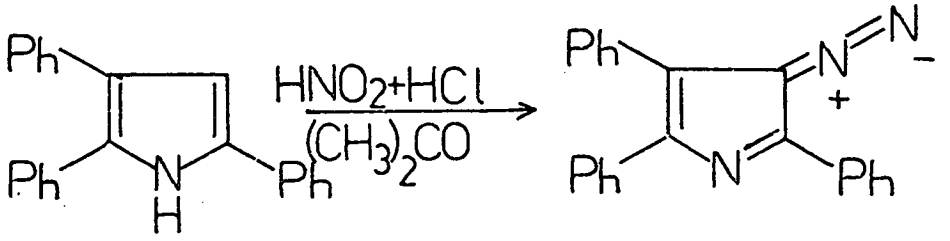
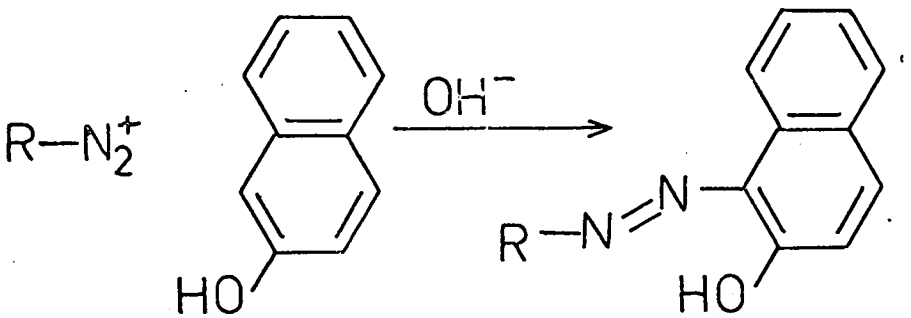


(104) (105)

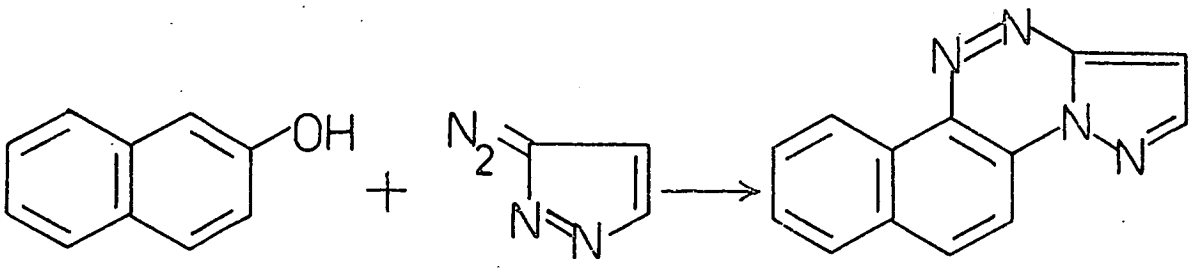
normal diazotization conditions, is thought[58] to proceed via a 3-nitroso intermediate which then reacts further with nitrous acid to give the diazo compound (105). This method has proved[59] to be the only suitable route to 2-diazopyrroles.

One of the most interesting reactions of diazonium salts and diazo compounds is their ability to couple with suitably acidic substrates. Although it is often difficult to determine which species actually undergoes coupling,[56] most diazo compounds and diazonium salts react with alkaline β-naphthol (107) to give highly coloured azo compounds [e.g. (106) → (108)]. However, Reimlinger and his co-workers[60] observed that when 3-diazopyrazole (109) was

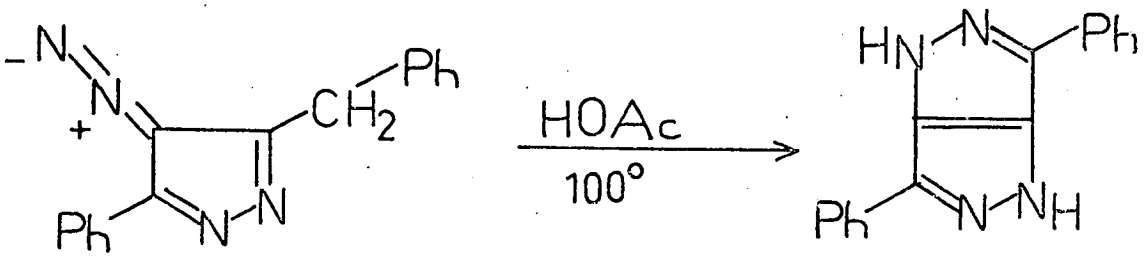


(106) (107) (108)

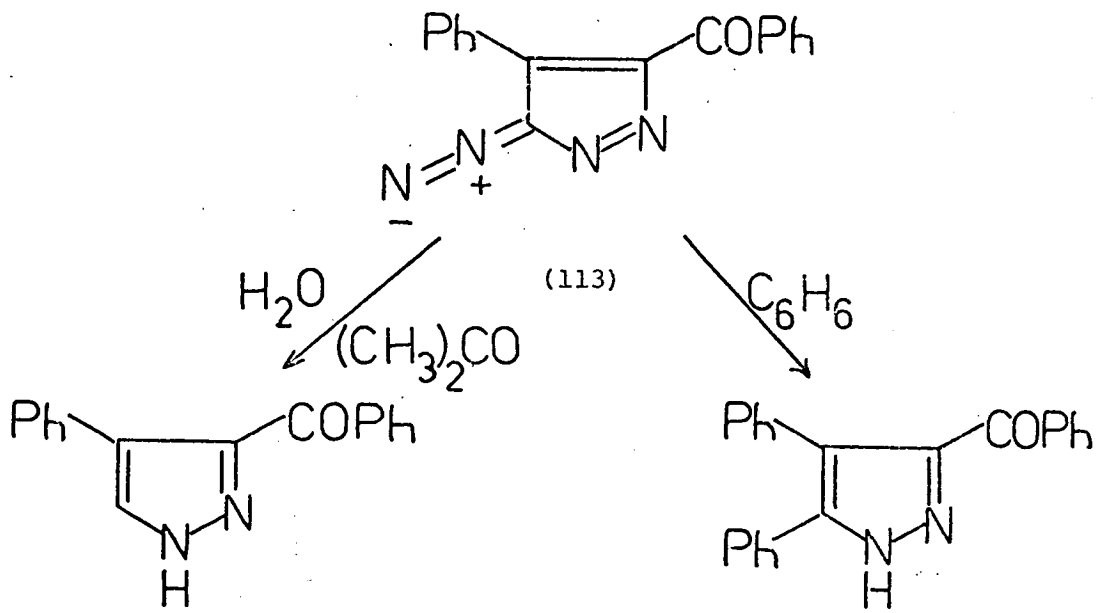
treated in this way, an intramolecular cyclization occurred, subsequent to coupling, to give the compound (110). Farnum and



(107) (109) (110)



(111) (112)

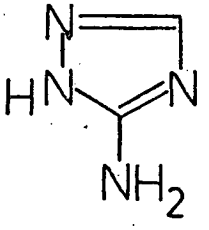


(114) (115)

Yates further observed[61] that when the diazopyrazole (111) was heated in acetic acid, intramolecular coupling occurred to give the pyrazolopyrazole (112).

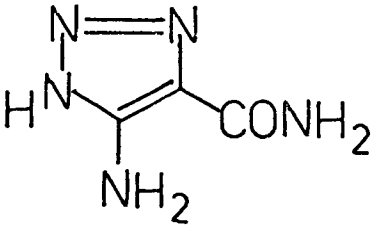
It has also been shown[61] that under some conditions, diazo compounds may lose nitrogen as exemplified by the photolytic conversion of the 3-diazopyrazole (113), in aqueous acetone or benzene, into the pyrazoles (114) and (115).

Information on the diazotization of aminotriazoles is even more scant than that relating to the diazotization of 5-membered heterocycles in general. Morgan and Reilly studied the diazotization of 3-amino-1,2,4-triazole (116) under varying sets of conditions,[62] and observed that a stable diazonium salt is formed only when an



(116)

oxy-acid (e.g. nitric acid) is used. When Shealy etal. diazotized 5-amino-1,2,3-triazole-4-carboxamide (117) with isoamyl nitrite in aqueous acetic acid solution, the diazo compound (118) was



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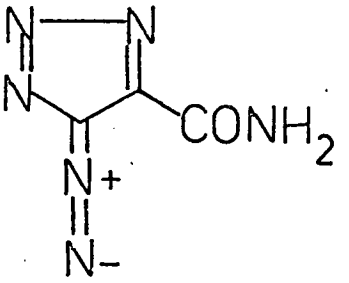

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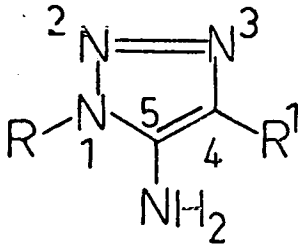

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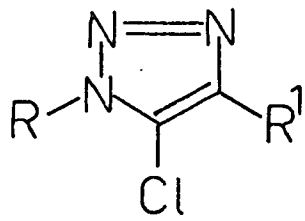

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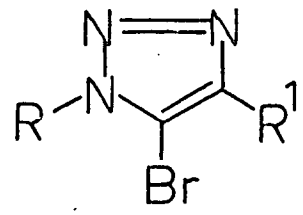
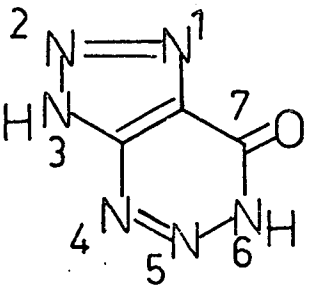


(122)

	R	R^1
a;	Ph	Ph
b;	$PhCH_2$	Ph
c;	$PhCH_2$	$CONH_2$
d;	Ph	CO_2Me



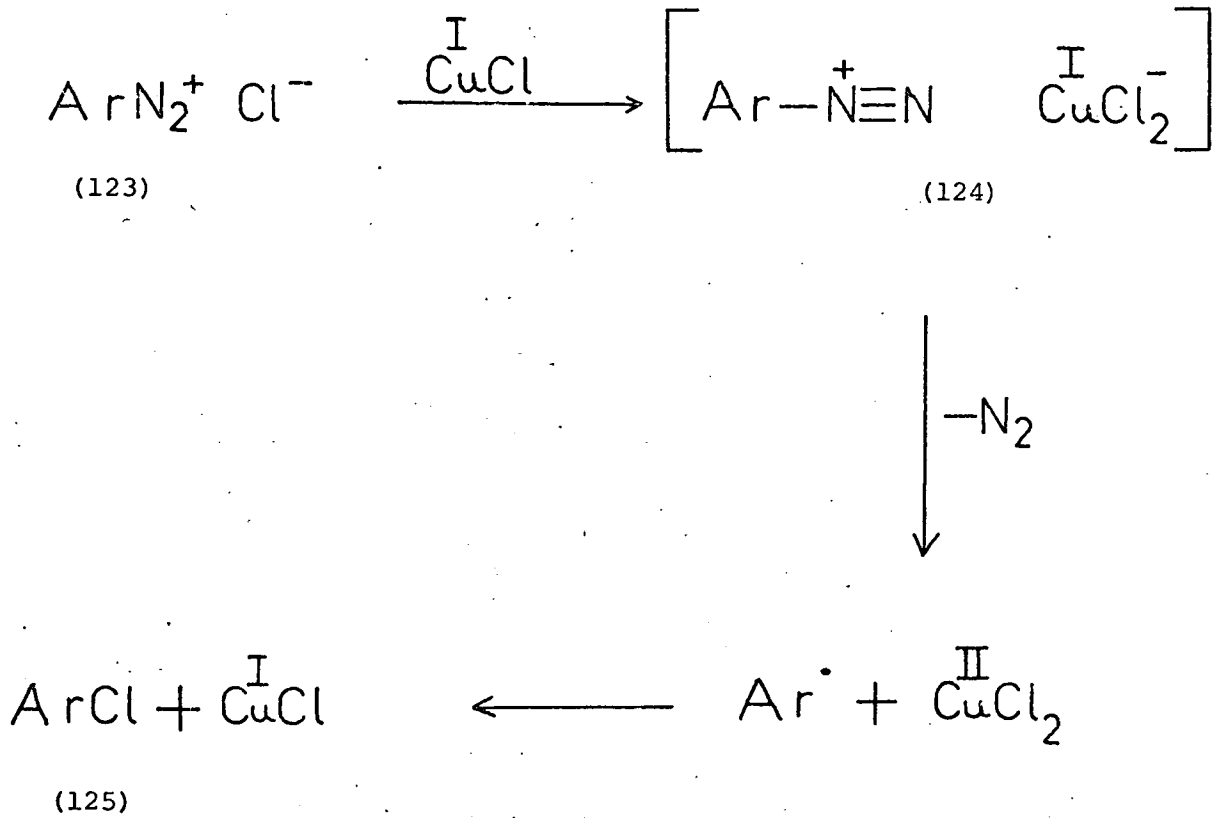
(119)

obtained,[63] but on standing in solution, slowly cyclized to 1,2,3-triazolo[4,5-d]-1,2,3-triazin-7(6H)-one (119) (2,8-diaza-hypoxanthine). This cyclization process [(118) → (119)] occurred much more rapidly in alkaline solution. Any use of the amino-triazole (117) as a starting material for the synthesis of the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system (94) must be made in such a way that the production of (119) does not become a complication.

As a prelude to the study of the coupling reactions of 1H-1,2,3-triazole diazonium salts with active methylene compounds, the diazotization of some simple 1,2,3-triazoles was investigated.

2.3. The Diazotization of Some 1,4-Disubstituted 5-Amino-1,2,3-triazoles

Work carried out in this department[64] has shown that when 5-amino-1,4-diphenyl-1,2,3-triazole[41] (120a) is stirred at 0° in aqueous hydrochloric acid or hydrobromic acid and treated with an aqueous solution of sodium nitrite, direct formation of the corresponding halogenotriazoles (121a) or(122a) occurs. These reactions contrast with the behaviour of benzendiazonium halides



(123) (124) (125)

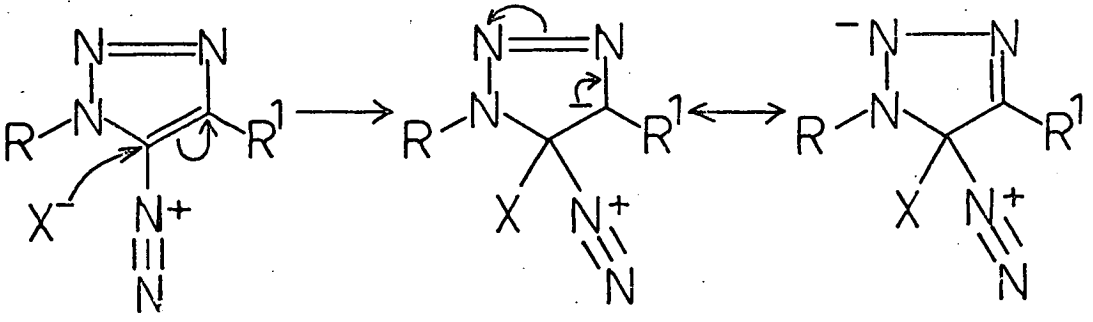
Scheme 8

which normally require the presence of cuprous halide (Sandmeyer reaction)[65] or of copper (Gattermann reaction)[65] for conversion into the corresponding halogenobenzenes. As a follow up to the previous work[64] the 5-aminotriazoles (120b)[66], (120c)[67], and (120d)[11a,41] were similarly diazotized to afford the 5-chloro- and 5-bromotriazoles (121b - d) and (122b - d). The halogenotriazoles (121b) and (122b) were purified by chromatography over alumina, and (121c) and (122c) were isolated from unreacted starting material (120c) by fractional crystallisation from ethanol. However, when the aminotriazole (120c) was diazotized in a mixture of aqueous hydrobromic acid and glacial acetic acid it gave 1-benzyl-5-bromo-1,2,3-triazole-4-carboxamide (122c) which required no further purification.

The halogenation reactions described are useful synthetically. The chlorotriazole[41] (121d) has been obtained previously by a two step synthesis involving the preformation of the hydroxytriazole followed by its reaction with phosphorus pentachloride. However, the overall yield of the synthesis is poor, and bromotriazoles are not easily accessible by this method.

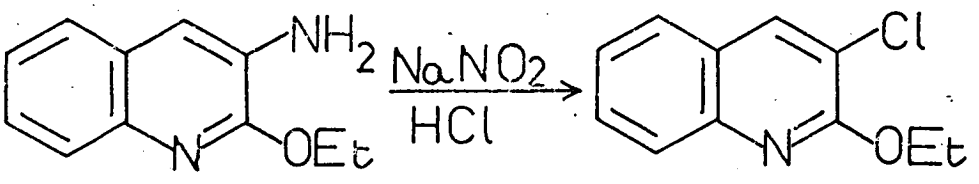
The question arises as to the mechanism involved in these halogenation reactions of 1,2,3-triazolediazonium salts. In the benzene series, replacement of the diazonium cation by a halogen atom is a relatively difficult process.[65] The mechanism now generally accepted for the Sandmeyer reaction (Scheme 8) involves the formation of an intermediate complex (124) between the diazonium salt (123) and cuprous chloride. Breakdown of the complex, probably by a process involving aryl radicals, gives rise to the aryl chloride (125). The direct halogenation reactions of

1,2,3-triazolediazonium salts presently described involve the formal substitution of diazonium cations by halide ions. Such processes may occur by way of a resonance stabilized intermediate of the type [(127)↔(128)] obtained by nucleophilic attack by the halide ion (X^-) on the diazonium salt (126). The structure (128) in which the negative charge resides on nitrogen will

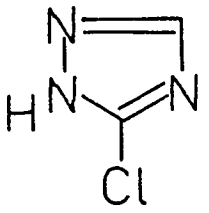


(126) (127) (128)

make the greater contribution to the stability of the hybrid. Formation of the intermediates [(127)↔(128)], the stability of which is not attainable in the benzene series, accounts for the ready displacement of 1,2,3-triazolediazonium cations compared with their benzene counterparts. The only apparent analogy in triazole chemistry is found in the work of Morgan and Reilly.[62] As already discussed (Chapter 2.2), diazotization of 3-amino-1,2,4-triazole (116) in nitric acid solution gives a stable solution of the diazonium salt which couples with β-naphthol. However, when diazotization is carried out in hydrochloric acid, the product is the chlorotriazole (129). Uncatalysed replacement of nitrogen by chloride ion has also been reported by Buchmann and Hamilton[68] in the diazotization of 3-amino-2-ethoxyquinoline (130) in hydrochloric acid to give the 3-chloro derivative (131).

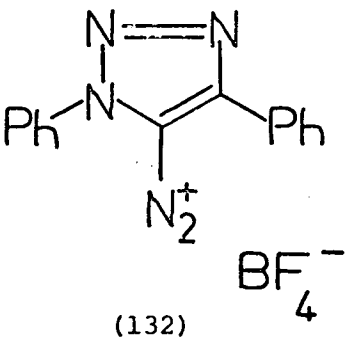


(130) (131)

(129) 

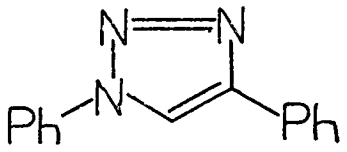
The fact that the (1,2,4-triazol-3-yl) diazonium cation is apparently stable[62] in nitric acid solution prompted the study of the diazotization of 5-amino-1,4-diphenyl-1,2,3-triazole (120a) in nitric acid. However, this reaction only resulted in the formation of a multicomponent oil.

The introduction of fluorine into a benzene ring is conveniently accomplished by the so-called Schiemann reaction.[69] This reaction involves the initial formation and pyrolytic decomposition of the stable benzenediazonium fluoroborate. In an attempt to develop a synthesis of fluoro-1,2,3-triazoles, 5-amino-1,4-diphenyl-1,2,3-triazole (120a) was diazotized in fluoroboric acid solution to give a yellow solid whose i.r. spectrum contained a sharp band at 2250 cm^{-1} consistent with the diazonium fluoroborate structure (132).



(132)

The solid (132) did not undergo nucleophilic attack by hydroxide ion when left in contact with dilute aqueous sodium hydroxide solution, but in accord with this structure, heating the salt (132) under reflux in ethanol gave a low yield of 1,4-diphenyl-1,2,3-triazole (133). The reductive deamination of diazonium salts in alcoholic

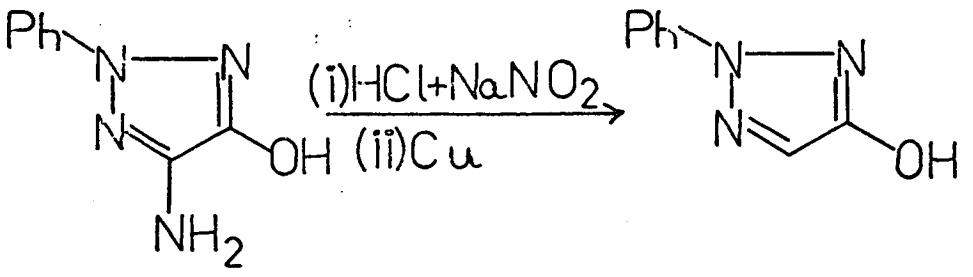


(133)

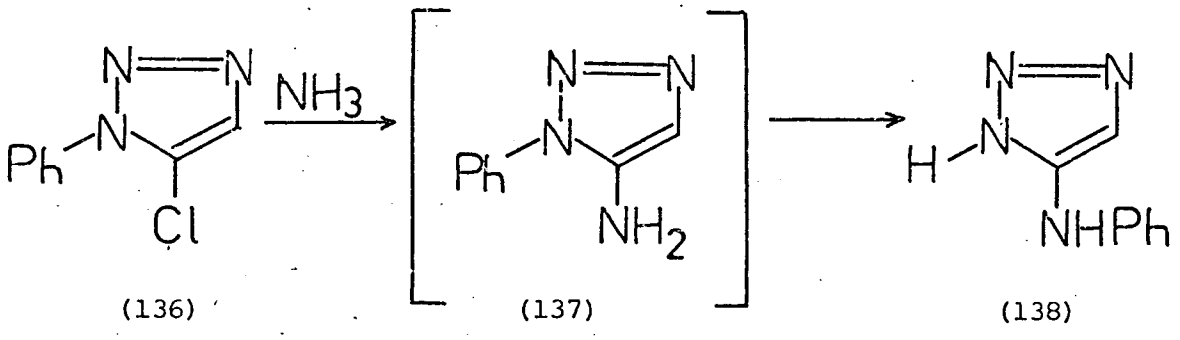
solution is a well-known process.[65] Cowdrey and Davies have suggested[65] that reactions of this type involve the permanent oxidation of a catalyst (e.g. copper) or some other species as exemplified by the equation:-

$$R\text{-}N_2^+ + C_2H_5OH \longrightarrow R\text{-}H + N_2 + H^+ + CH_3CHO.$$

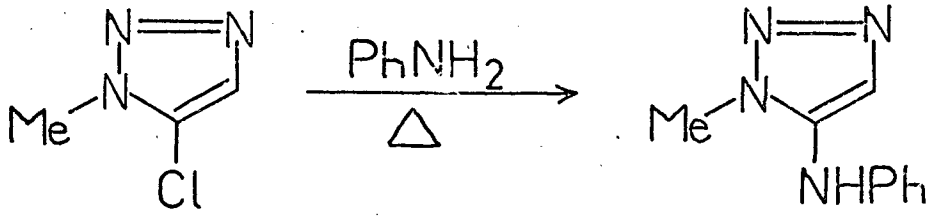
Replacement of the diazonium group from a 1,2,3-triazole by hydrogen has previously been observed by Thiele and Schleussner[70] in their work on the diazotization of 5-amino-4-hydroxy-2-phenyl-1,2,3-triazole (134). They observed that warming a solution of the diazonium salt



(134) (135)



(136) (137) (138)



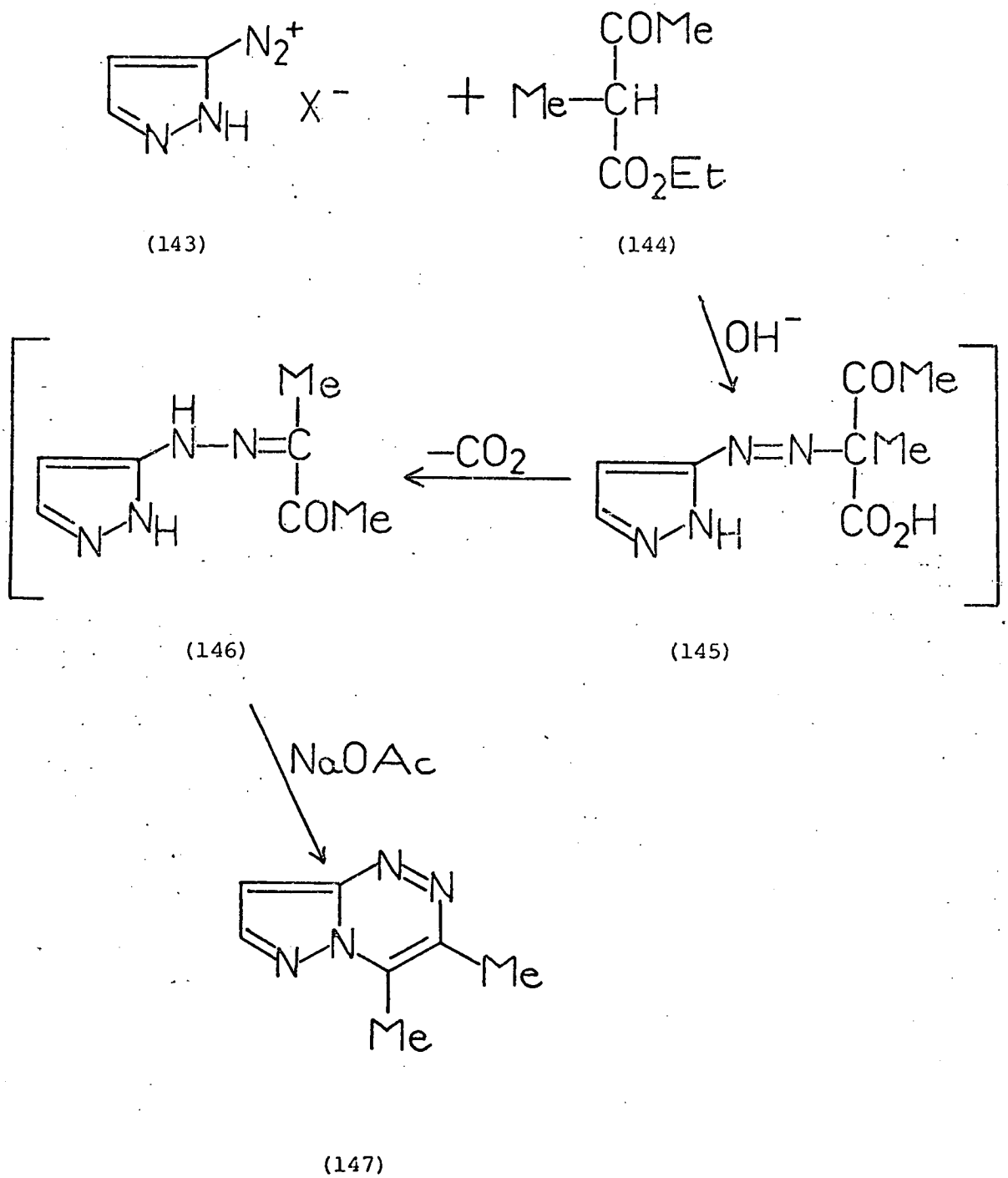
(139) (140)

derived from (134) with copper powder results in deamination to (135).

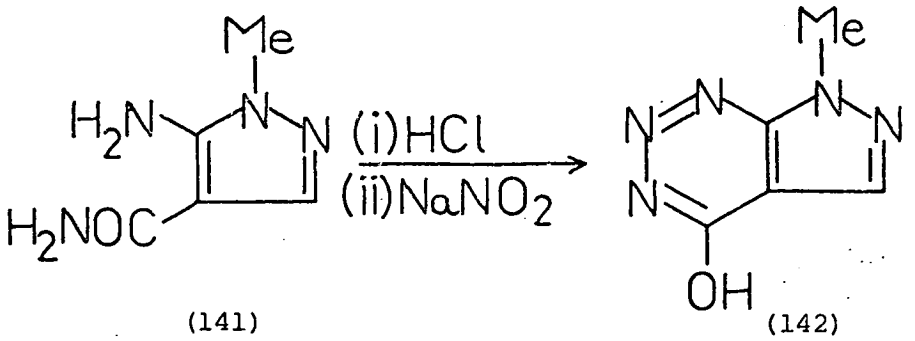
It was of interest to exploit the synthetic possibilities of the now readily available halogenotriazoles by studying their nucleophilic substitution reactions. It has previously been reported[41] that when 5-chloro-1-phenyl-1,2,3-triazole (136) is treated with ammonia, 5-anilino-1H-1,2,3-triazole (138) is obtained. The mechanism of this reaction probably involves the initial nucleophilic replacement of chloride ion by ammonia followed by Dimroth rearrangement[11a,33,40] [(137)⟶(138)] of the intermediate amine (137). A more straight forward example of such a nucleophilic displacement is the reaction of the 5-chlorotriazole (139) with aniline to give the 5-anilino compound (140).[41] 5-Chloro-1,4-diphenyl-1,2,3-triazole (121a) failed to react when similarly treated with aniline. The triazole (121a) also failed to react when it was heated under reflux with aqueous ethanolic sodium azide.

2.4. Some Coupling Reactions of 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride and the Synthesis and Reactivity of the 1,2,3-Triazolo [5,1-c] -1,2,4-triazine Ring System.

The ability of diazonium salts to couple with suitably activated aliphatic compounds has long been known and has been reviewed recently by Parmerter.[71] However, few examples have been reported on the use of diazo coupling in the formation of 6-membered heterocyclic compounds. Cheng has shown[72] recently that the diazotization of the 3-aminopyrazole (141) results in the isolation of the pyrazolotriazine (142). However, as has been

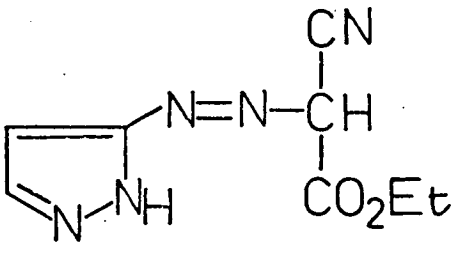

N2+
X-
NH
N
+ Me—CH
COMe
CO2Et
(143)
(144)
OH-
COMe
N=N—CMe
CO2H
NH
N
(145)
—CO2
Me
H
N—N=C
COMe
NH
N
(146)
NaOAc
N
N
N
Me
Me
(147)

Scheme 9

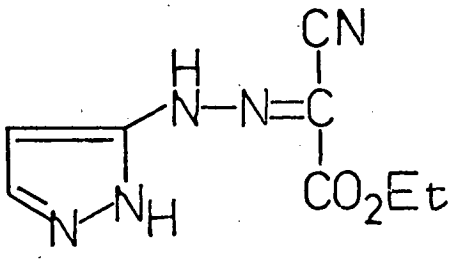


(141) (142)

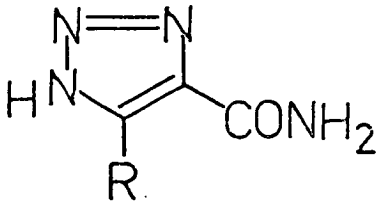
stated previously, the projected synthesis of the 1,2,3-triazolo-[5,1-c]-1,2,4-triazine ring system (94) finds more direct analogy in Partridge and Stevens' synthesis of the pyrazolo[5,1-c]-1,2,4-triazine ring system (100).[54] These workers found that when diazotized 3-aminopyrazole (143) was coupled with an active methylene compound [e.g. ethyl methylacetoacetate (144)] in the presence of base, and the resultant solution was buffered with sodium acetate, the dimethylpyrazolotriazine (147) was isolated. The course of this reaction (Scheme 9) probably involves a Japp-Klingemann[73,74] reaction [(143) + (144)⟶(145)⟶(146)] leading to the hydrazone (146) which then cyclizes <u>in situ</u> to the product (147). Supporting this mechanism is the fact that when ethyl cyanoacetate was used the hydrazone (149) was isolated.[54] The structure (149), as



(148)

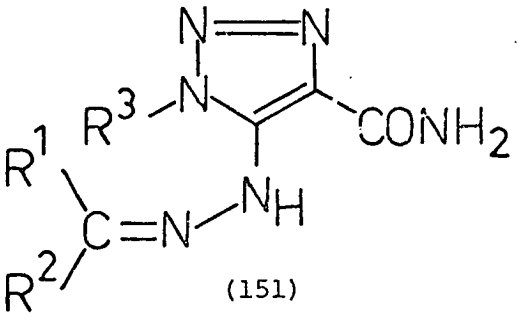


(149)



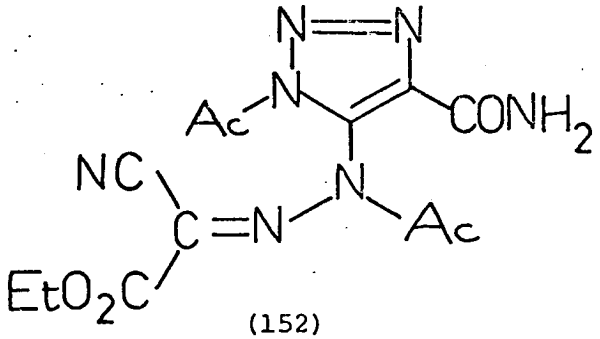
(150)

	R
a;	NH_2
b;	$NH_2.HCl$
c;	$N_2^+Cl^-$

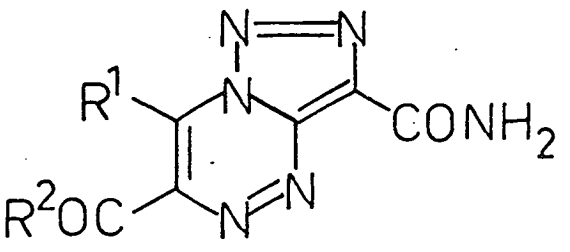


(151)

	R^1	R^2	R^3
a;	Ac	Ac	H
b;	Ac	CO_2Et	H
c;	Ac	COPh	H
d;	COPh	COPh	H
e;	CO_2Et	CO_2Et	H
f;	CO_2Et	COPh	H
g;	CO_2Et	CN	H
h;	$CONH_2$	CN	H
i;	CN	CN	H
j;	Ac	Ac	Ac
k;	Ac	CO_2Et	Ac
l;	Ac	COPh	Ac
m;	COPh	COPh	Ac
n;	CO_2Et	CO_2Et	Ac
o;	CO_2Et	COPh	Ac

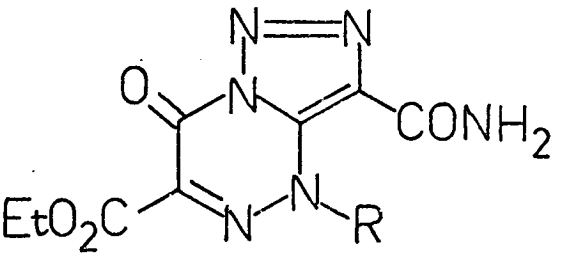


(152)



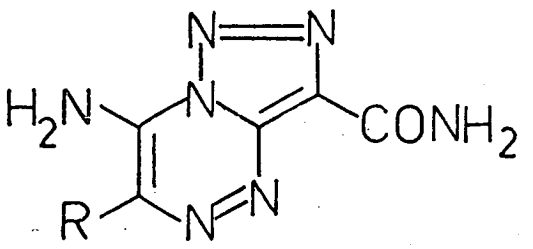
(153)

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



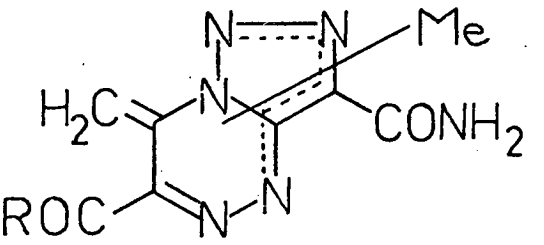
(154)

	R
a;	H
b;	Me



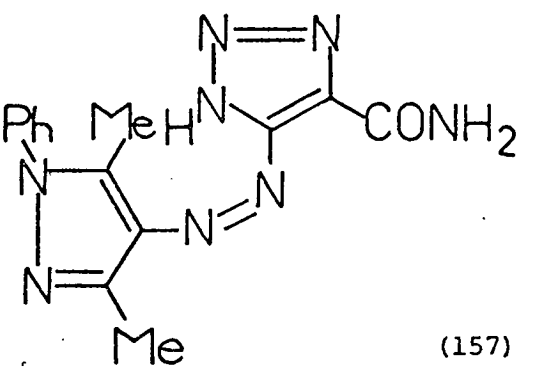
(155)

	R
a;	CO_2Et
b;	$CONH_2$
c;	CN



(156)

	R
a;	Me
b;	OEt



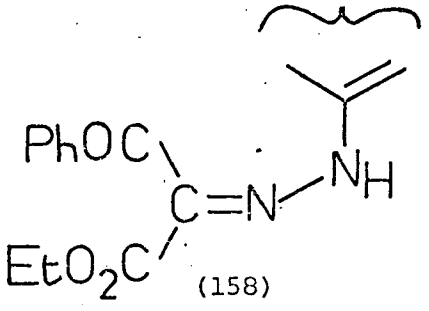
(157)

opposed to the azo tautomer (148) for such products is now well established.[71]

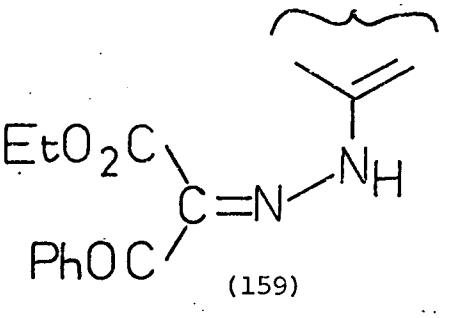
The diazotization of the amine hydrochloride (150 b) in methanolic solution using amyl nitrite gave the solid diazonium salt (150 c). The reason for supposing the product to be the diazonium salt (150 c) rather than the betaine (118) obtained by Shealy *etal.*[63] lies in the method of synthesis. Whereas Shealy used a weakly acidic medium (i.e. aqueous acetic acid) to make the diazo compound (118), the diazonium salt (150 c) was obtained from a strongly acidic solution. The diazonium chloride (150 c) remained stable when kept in a dark bottle and stored in a refridgerator prior to use.

When an aqueous ethanolic solution of the diazonium salt (150 c) was added to cooled solutions of the active methylene compounds (Table 1) in aqueous ethanolic sodium acetate, the hydrazones (151 a-g) were isolated. The products from diethyl malonate and ethyl cyanoacetate were obtained as a hydrate and an ethanol solvate respectively, as indicated by their i.r. and ^{1}H n.m.r. spectra. However, crystallisation or drying at an elevated temperature liberated the free compounds (151 e) and (151 g). When the diazonium salt (150 c) was coupled with cyanoacetamide, the hydrazone (151 h) was obtained. However, attempted crystallisation of this insoluble solid from aqueous dimethylsulphoxide resulted in the formation of its cyclic isomer, the triazolotriazine (155 b). When malononitrile was used as a substrate for coupling, the result was the direct isolation of a solid whose properties are consistent with the aminotriazolotriazine structure (155 c) (see later).

The ^{1}H n.m.r. spectrum of the hydrazone (151 f), which was obtained from ethyl benzoylacetate, indicated the presence of more than one species. This may be accounted for in terms of geometric isomers of the type (158) and (159). The hindered rotation



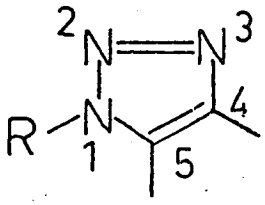
(158)



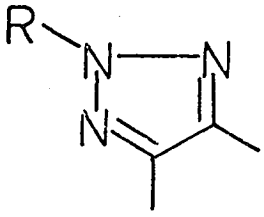
(159)

brought about by the azomethine double bond causes the protons of the ester groups in (158) and (159) to exhibit different chemical shifts.

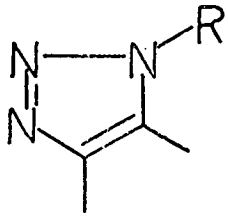
The evidence for the structures of the hydrazones (151 a-h) proved quite conclusive. ^{1}H n.m.r., i.r., and mass spectral data is consistent for the hydrazones (151 a-g), but some difficulty was encountered in obtaining correct analytical data (Table 1) for the hydrazones (151 c) and (151 g). The ketone hydrazones (151 a-d and f) all show ($M^+ - H_2O$) in their mass spectra, a result which indicates the formation of the corresponding triazolotriazines (153 a-e) in the probe. All of the hydrazones (151 a-h) are soluble on brief treatment with dilute aqueous sodium hydroxide solution and may be regenerated on acidification with dilute aqueous sulphuric acid. This behaviour is consistent with the acidity of the proton at N-1 on the triazole ring.



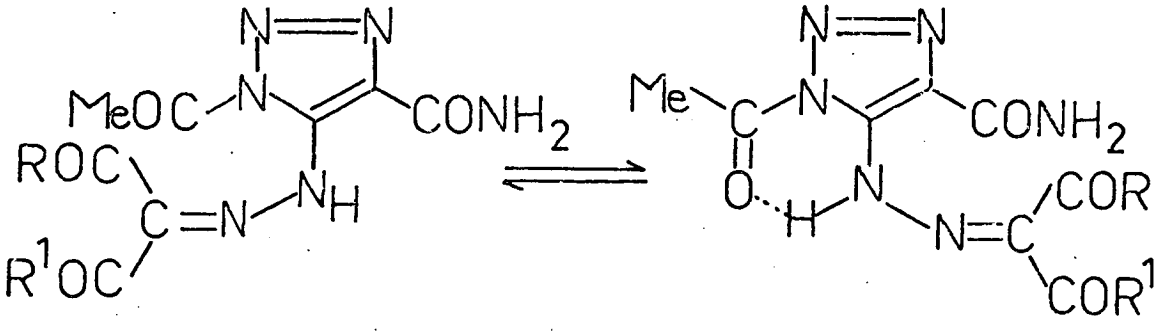
(160)



(161)



(162)



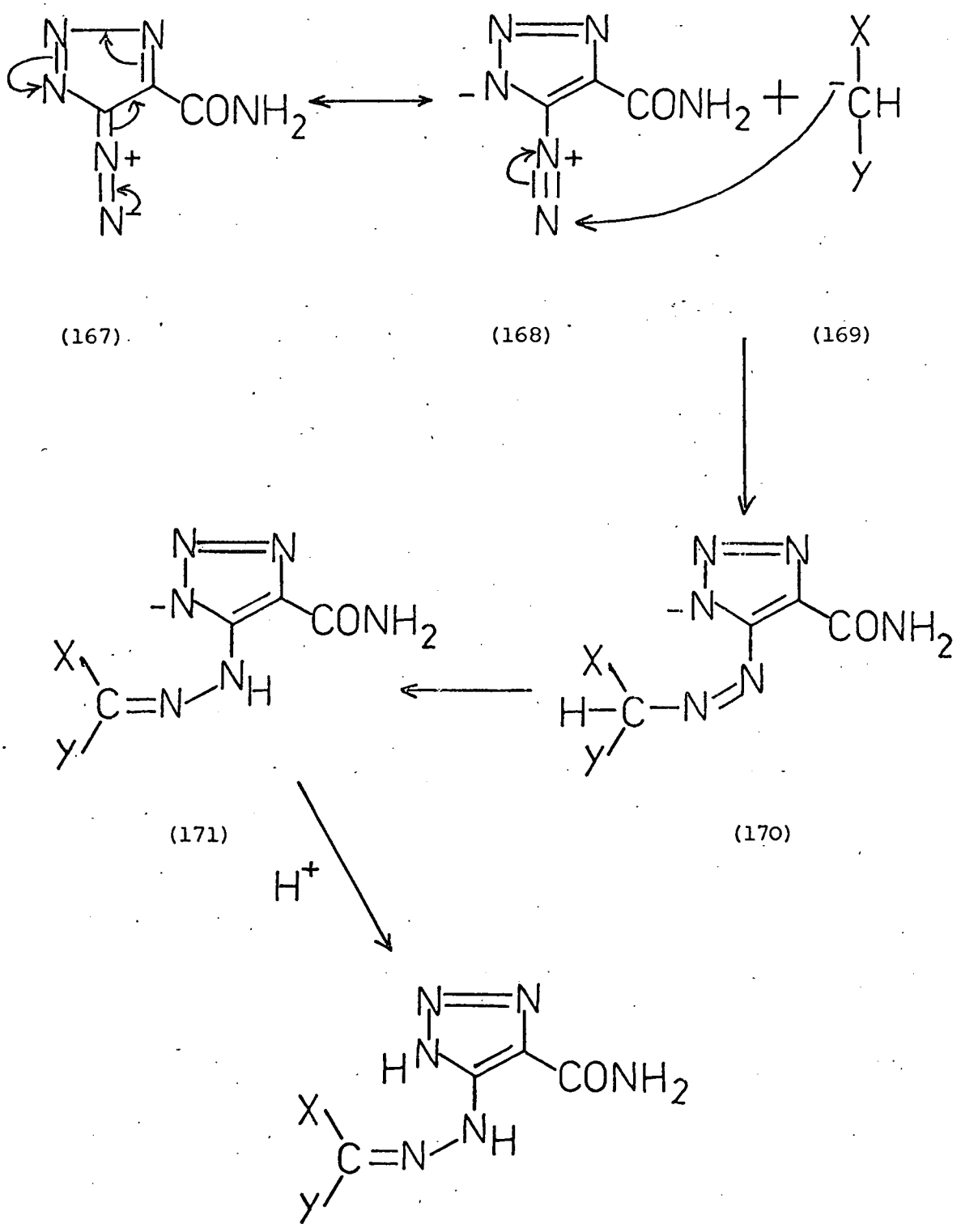
(163) (164)

It has been shown[11a] that acetylation of 1H-1,2,3-triazole derivatives results in the formation of the corresponding 1-acetyl compounds which exhibit characteristic i.r. and ^{1}H n.m.r. absorption. Correspondingly, acetylation of the hydrazones (151 a-f) was accomplished smoothly in warm acetic anhydride giving the 1-acetyltriazolylhydrazones(151 j-o), all of which show a characteristic signal at τ 7.20-7.35 in their ^{1}H n.m.r. spectra and a band at 1760-1750 cm^{-1} in their i.r. spectra. It is known[11a] that an acetyl group at N-1 on a triazole ring gives rise to such absorptions. As in the case of the parent hydrazones (151 a-h) the possibility of geometric isomerism [cf. (158) and (159)] also exists in the acetyl derivatives (151 j-o) and is indicated by the multiplicity in the ^{1}H n.m.r. spectra of (151 k,l, and o). The compounds (151 k and o) appear to consist of more than one species as shown by irregular multiplets attributable to the ethyl protons of the ester groups. In the case of (151 l), signals at τ 7.25 and 7.33, attributable to .N.COMe, and τ 7.48 and 7.56, attributable to .COMe, were observed. However, as well as geometric isomerism, other factors may exist which can account for this multiplicity. Although N- unsubstituted 1,2,3-triazoles are generally written as in structure (160; R=H), the structures (161; R=H) and (162; R=H) are equally likely. Correspondingly the acetyl derivatives (161; R=Ac) and (162; R=Ac) may be formed as well as (160; R=Ac). Another factor which may account for the observed multiplicity is the possible existence of hydrogen - bonded structures, of the type (164), in equilibrium with non-bonded structures of the type (163).

The possibility of diacetylation in the case of the hydrazone (151c), is excluded on the basis of analysis and mass spectral evidence. Although more than one signal attributable to .N.COMe is observed in the case of (151 l), the fact that the sum of the integrals at τ 7.25 and 7.33 is equal to the sum of the integrals at τ 7.48 and 7.56, provides additional evidence against the possibility of diacetylation. However, diacetylation of the hydrazone (151 h) was achieved under standard monoacetylation conditions. The position of this second acetyl group has been assigned as in (152). The possibility of acetylation of the amide group is excluded on the basis of the ^{1}H n.m.r. spectrum of (152) which shows signals at τ 1.54 and 2.00 attributable to an intact primary amide. Attempted acetylation of the hydrazone (151 h) obtained from cyanoacetamide, resulted in the formation of a highly insoluble, black, intractable solid which could not be characterised.

When an attempt was made to hydrolyse the acetyl derivatives (151 j) and (151 k) by heating under reflux in aqueous acetic acid, the products were the corresponding triazolotriazines (153 a) and (153 b).

As has been previously stated (Chapter 2.2), when a diazonium salt is introduced into a basic medium and coupled with an acidic substrate, it is difficult to detect whether deprotonation of the diazonium cation to give the corresponding betaine has occurred prior to coupling. Consequently, the mechanism of the coupling reaction between the diazonium salt (150 c) and the active methylene compounds listed in Table 1 depends on whether



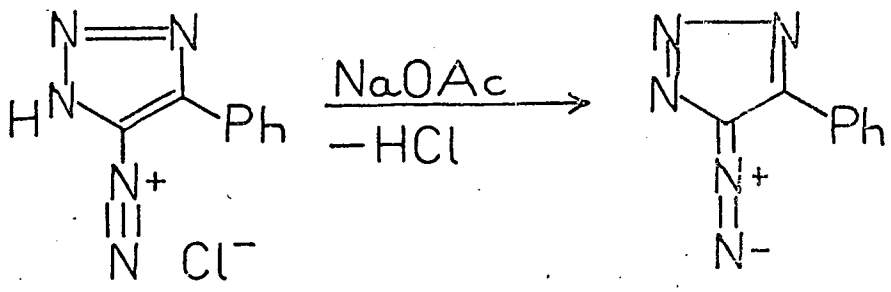
(167) (168) (169)

(170) (171)

(172)

Scheme 10

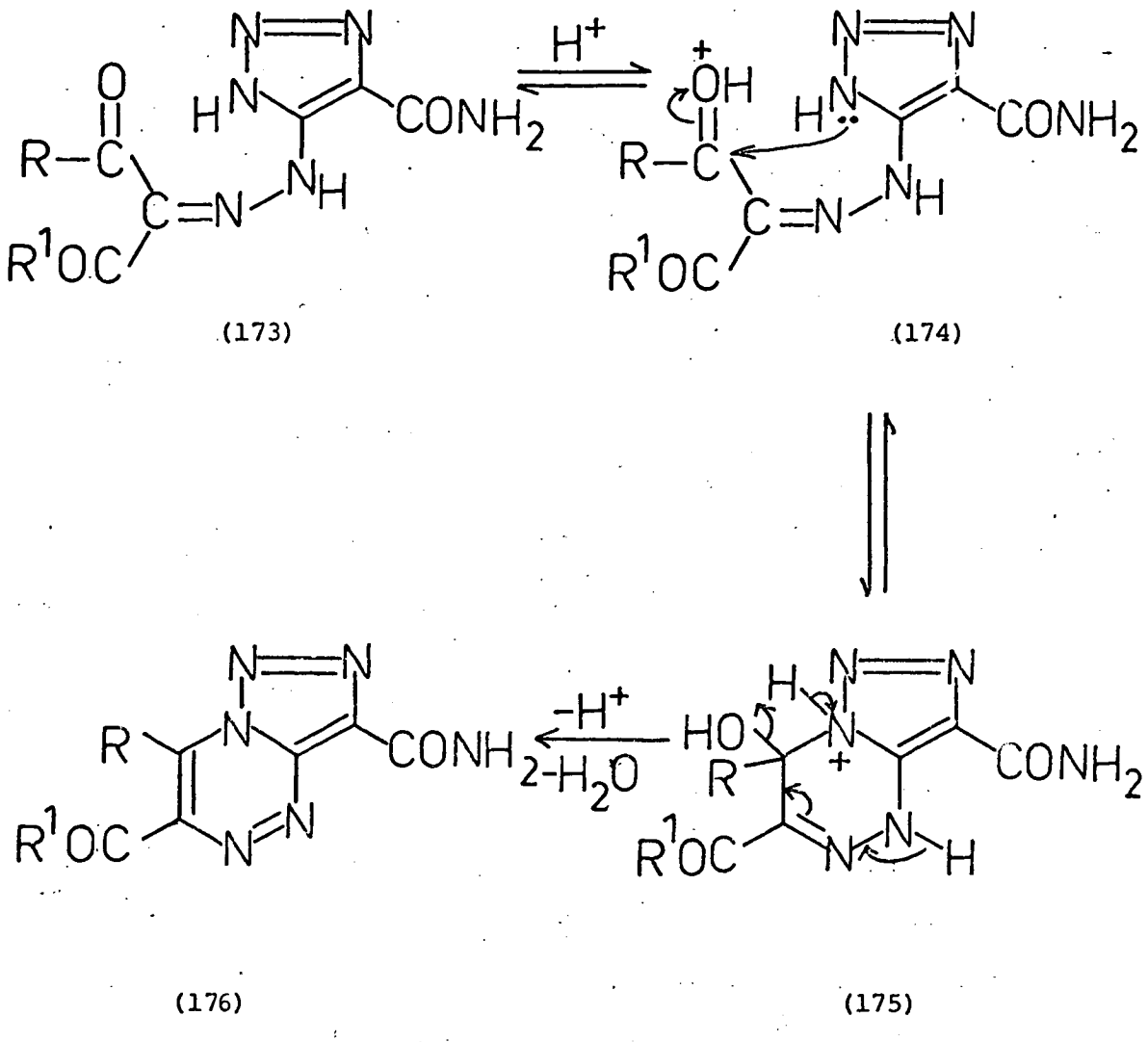
the triazole (150 c) is deprotonated when introduced into a solution containing sodium acetate. Although no investigation has been carried out as to whether or not this happens in the case of (150 c), results have been obtained[75] which show that the corresponding 4-phenyltriazolediazonium chloride (165) is converted



(165) (166)

into the betaine (166) on treatment with an aqueous ethanolic solution of sodium acetate. By analogy, a mechanism thus exists for coupling between the betaine [(167)⟷(168)] and the ionized active methylene compound (169) (Scheme 10) leading eventually to the hydrazone (172). Since no acidification is required to obtain the free hydrazones (151 a-h), the acidity of the aqueous ethanolic medium must be sufficient to carry out the protonation [(171)⟶(172)]. A slightly modified mechanism involving reaction of the betaine [(167)⟷(168)] with the enolized active methylene compound may also be possible.

When the hydrazones (151 a-g) were heated under reflux in glacial acetic acid, the corresponding triazolotriazines (153 a-e), (154 a) and (155 a) were formed. In the last case a considerable amount of starting hydrazone (151 g) was recovered on work up of the



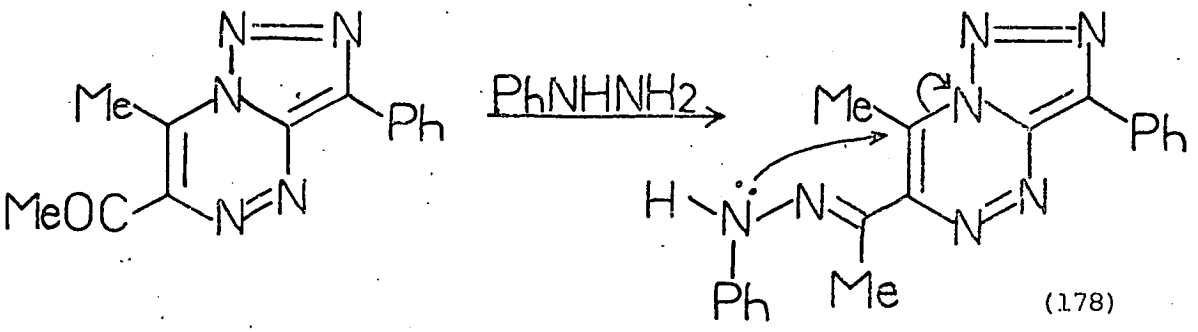
(173) (174) (175) (176)

Scheme 11

reaction mother liquor. The cyclization of the hydrazone (151 a), from acetylacetone, resulted in the isolation of a solid whose i.r. spectrum changed on crystallisation but whose ^{1}H n.m.r. and mass spectrum remained unaltered. Such a feature may possibly be explained in terms of an alteration in crystal structure having occurred during the crystallisation process. The triazolotriazine (153 a) was also obtained by heating the hydrazone (151 a) in aqueous ethanol or aqueous sulphuric acid, the product from both reactions being isolated as a hydrate as shown by the i.r. spectrum. Liberation of the free triazolotriazine (153 a) was achieved by drying the hydrate in vacuo at an elevated temperature. The mechanism involved in the acid catalysed cyclization of the hydrazones (151 a-g) may be as outlined in Scheme 11 [(173)⟶(176)].

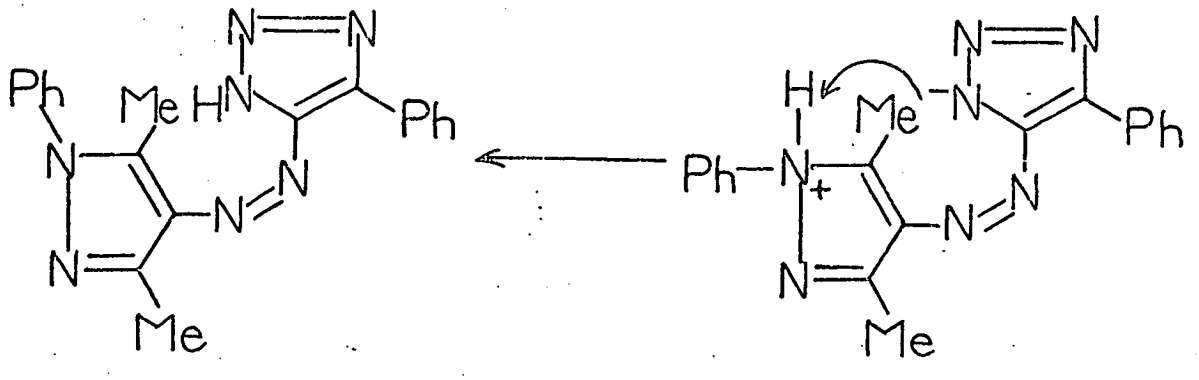
When the hydrazones (151 e) and (151 h), from diethyl malonate and cyanoacetamide respectively, were heated in aqueous ethanolic sodium acetate solution, they gave rise to the corresponding triazolotriazines (154 a) and (155 b), isolation of the former requiring the acidification of the reaction mixture with dilute aqueous sulphuric acid solution. A combination of the sodium acetate catalysed coupling of the diazonium salt (150 c) with ethyl cyanoacetate followed, without isolation of the hydrazone (151 g), by base-catalysed cyclisation, was applied successfully to give a good yield of the aminotriazolotriazine (155 a).

The structures of the triazolo[5,1-c]triazine-3-carboxamides (153 a-e), (154 a) and (155 a and b) were supported in each case by i.r., ^{1}H n.m.r. (where relevant) and mass spectra, and by analytical



(177)

(178)



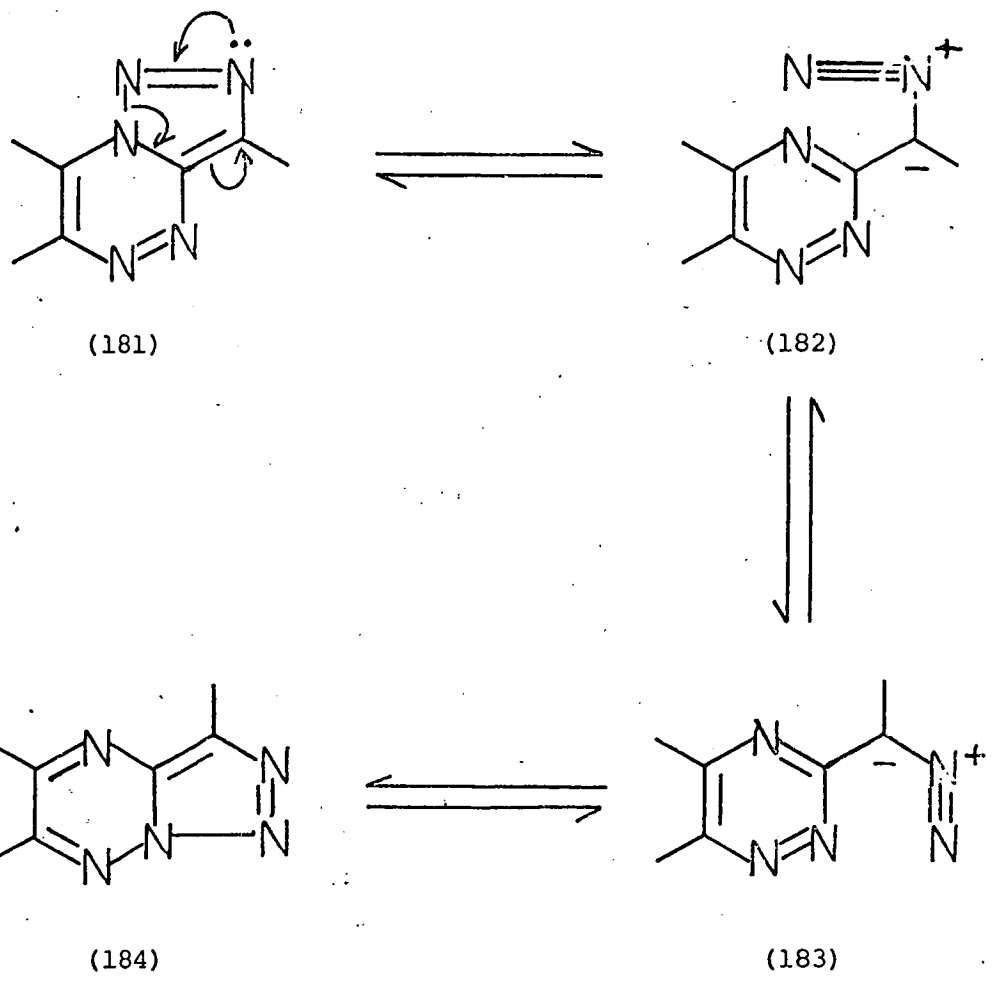
(180)

(179)

Scheme 12

data. However, no ^1H n.m.r. spectrum of the aminotriazolotriazine (155 a) was obtained due to its insolubility in [$^2H_6$] dimethylsulphoxide. In each case the mass spectrum showed a peak at (M^+-83), a feature common to the analogous 1,2,3-triazolo[1,5-a] pyrimidine-3-carboxamides described in Chapter 4 (see later). Other work carried out in this department has shown conclusively[76] that 6-acetyl-7-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (177) reacts with phenylhydrazine to give the azo compound (180). The probable mechanism of this reaction is outlined in Scheme 12. The existence of the triazolo[5,1-c]-1,2,4-triazine nucleus (181) in the compounds (153 a-e), (154 a), and (150 a and b) has further been confirmed by the reaction of the triazolotriazine (151 a) with phenylhydrazine to give a product whose i.r., ^1H n.m.r., and mass spectra and analysis are consistent with the corresponding azotriazole structure (157). The result of this reaction excludes the possibility that the triazolo[1,5-b]-1,2,4-triazine nucleus (184) is present in the compounds (153 a-e), (154 a) and (150 a and b) rather than the triazolo[5,1-c]-1,2,4-triazine nucleus (181). Such a possibility arises due to the potential Dimroth rearrangement (Scheme 13) [(181)$\rightleftharpoons$(184)] of the triazolo[5,1-c]triazine system (181) subsequent to its formation as described (Scheme 11).

As has been stated previously, malononitrile reacted with the diazonium salt (150c) to give the triazolotriazine (155 c) rather than the expected, isomeric hydrazone (151 i). Although no confirmation of this structure is possible on the basis of i.r., ^1H n.m.r., and mass spectral or analytical data, the solid obtained from the



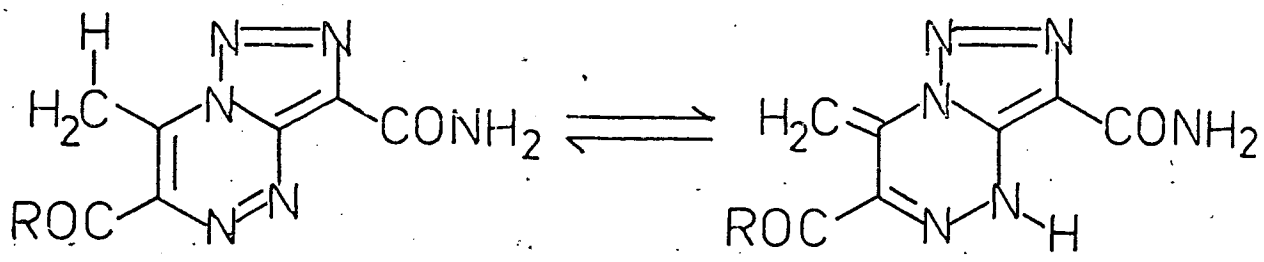
(181) (182)

(184) (183)

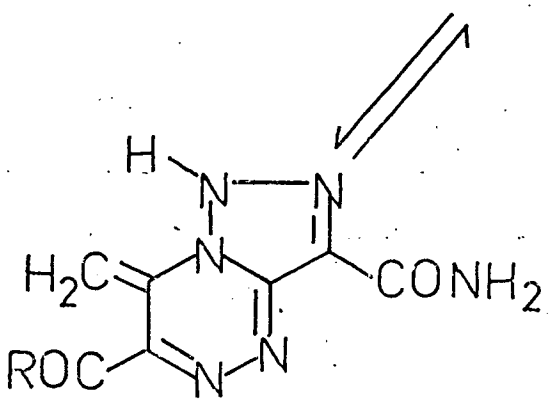
Scheme 13

coupling reaction could not be changed by heating under reflux in either glacial acetic acid or dimethylsulphoxide, save for the formation of an acetic acid solvate which quickly liberated the free compound (155 c) on treatment with a saturated aqueous solution of sodium hydrogen carbonate. These results showed that the coupling product does not change under standard 'cyclization' conditions thus suggesting that it already exists in the cyclized form (155 c). Although i.r. and mass spectral data were consistent with a structure of the type (155 c), the compound failed to give correct analytical data. When an attempt was made to characterise the aminonitrile (155 c) by its conversion into the aminoamide (155 b) of established structure using polyphosphoric acid, no isolable material was obtained. Similarly, attempted acetylation of (155 c) in order to obtain a simple derivative, resulted in the formation of a mixture which was not readily separable.

As expected, the triazolotriazine (154 a) was found to be acidic, giving a red solution on brief treatment with dilute aqueous sodium hydroxide solution from which the lactam (154 a) was regenerated on re-acidification with dilute aqueous sulphuric acid solution. However, when the triazolotriazines (153 a and b) and (155 c) were similarly treated with dilute aqueous sodium hydroxide, they unexpectedly gave red solutions which gave no isolable material on re-acidification. The decomposition of the aminonitrile (155 c) was indicated by the evolution of hydrogen cyanide which occurred on acidifcation of its alkaline solution. On contact with base, the aminoester (155 a) gave insoluble solid which behaved as a sodium salt. However, re-acidification of the



(185) (186)



(187)

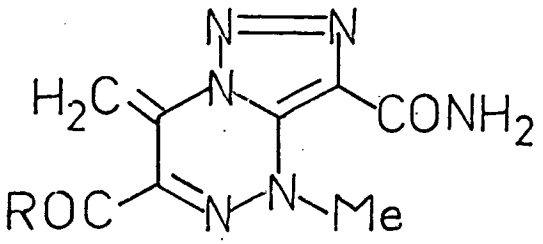
R = Me or OEt

Scheme 14

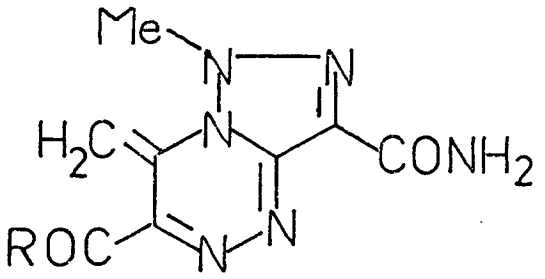
solid did not afford the unchanged aminoester (155 a), but gave instead a product (W) which had a markedly different i.r. spectrum from (155 a) but whose mass spectrum was identical. No ^{1}H n.m.r. spectrum of (W) was obtained due to its insolubility in $[^{2}H_{6}]$-dimethylsulphoxide. The highly insoluble (W) was crystallised from aqueous dimethylformamide to afford a solid whose i.r. spectrum showed it to be a solvate. An attempt to drive off the solvent of crystallisation by heating in vacuo at 100° resulted in the decomposition of (W) to a char. No further attempt was made to characterise (W). The remainder of the triazolotriazines (153 c-e) and (155 b) did not react with alkali under such conditions.

As a result of the described reactivity of the triazolotriazines (153 a and b), (154 a), and (155 a) with alkali, attempts were made to methylate them using methyl iodide or dimethyl sulphate in the presence of potassium carbonate. Low yields of the monomethyl derivatives were obtained from (153 a and b) and (154 a), but (155 a) gave unchanged starting material. Since the methyl derivative of (154 a) shows three carbonyl bands in its i.r. spectrum, the possibility of O- methylation is excluded in favour of the formation of the N- methyl structure (154 b). The methylation of (153 a and b) may best be explained in terms of tautomerism (Scheme 14) of the type [(185) ⇌ (186) ⇌ (187)] existing in the parent systems (153 a and b). Evidence for this is obtained in the ^{1}H n.m.r. spectra of the monomethyl derivatives (156 a and b) which distinctly indicate the presence of a terminal methylene group. Although no conclusive evidence has been obtained for the exact structure of (156a and b) and (154 b), comparison of their u.v. spectra shows that of (154 b)

to be markedly different from those of (156 a and b). If (156 b) had the form of (188; R=OEt) its u.v. spectrum would be expected to be largely the same as that of (154 b). Since similarities also exist between the u.v. spectra of (154 b) and the parent lactam



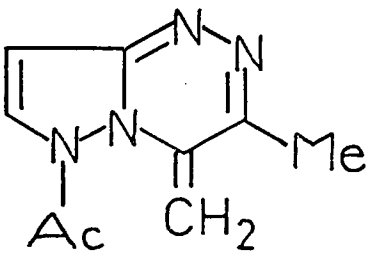
(188)



(189)

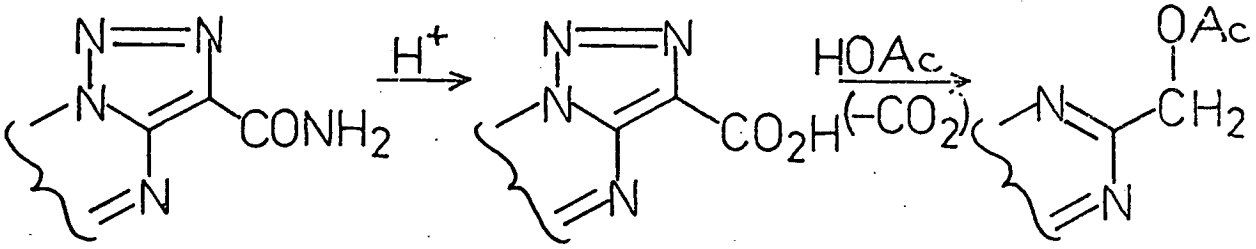
(154 a), the evidence suggests that the monomethyl compounds (156 a and b) have the form (189) rather than (188).

Although no peculiar behaviour with base has been reported for the pyrazolo[5,1-c]-1,2,4-triazine ring system (100), Partridge and Stevens have shown that the dimethyl compound (147), described previously, forms an acetyl derivative[54] on warming in acetic anhydride, the structure of which is given as (190). However, the attempted acetylation of the triazolotriazine (153 a) gave a black intractable tar.



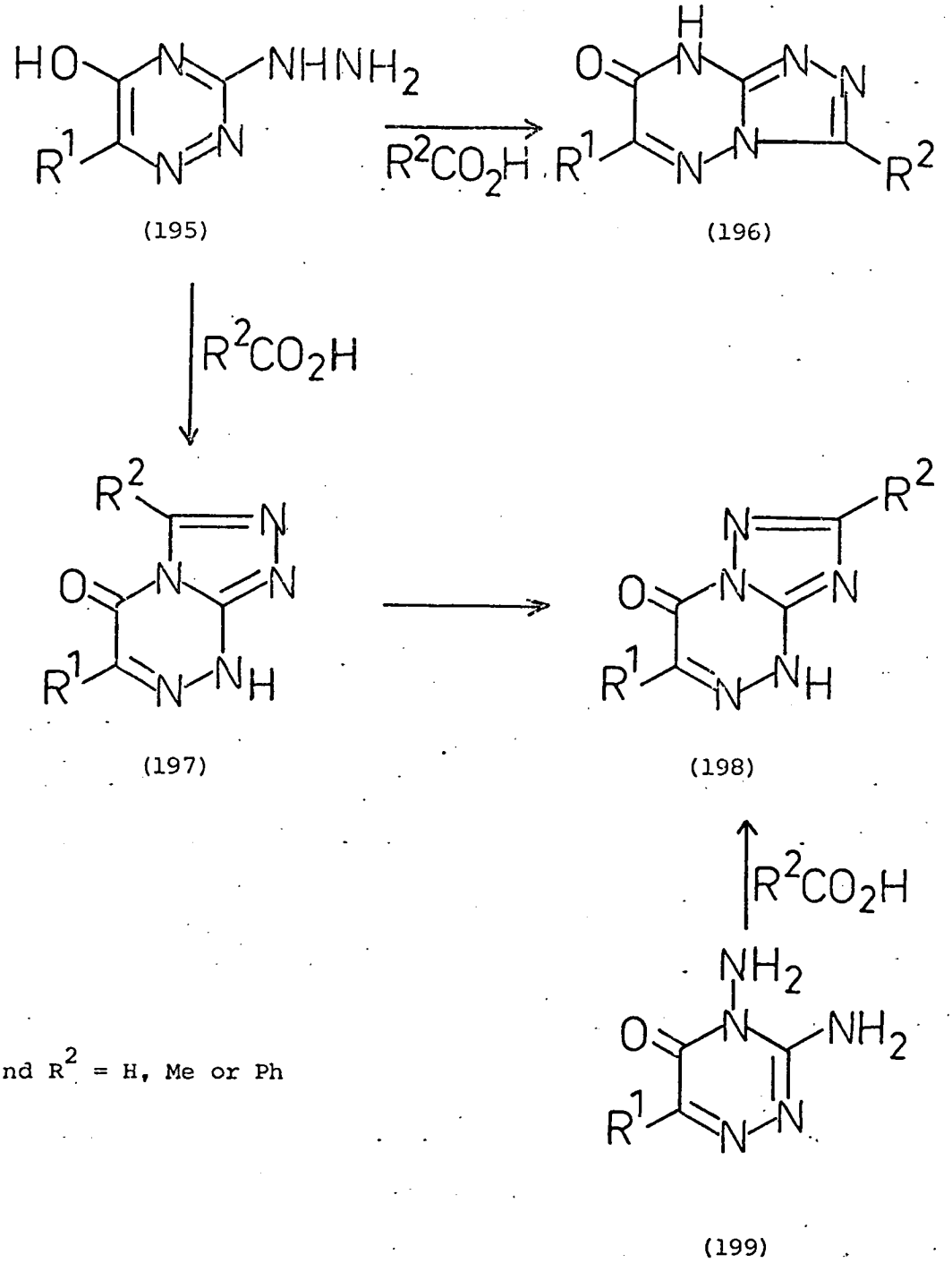
(190)

Attempts to alter the functional groups in the aminoester (155 a) proved unsuccessful. When this compound was subjected to hydrolytic conditions such as refluxing ethanolic sulphuric acid, sodium carbonate or dimethylformamide-sulphuric acid, unchanged starting material or the unidentified solid (W) was recovered. Thus, no ester or amide hydrolysis or conversion of the 7-amino group into a 7-oxo group was observed. Similarly, the attempted hydrolysis of the ester (153 b) proved unsuccessful. An attempt to hydrolyse the amide group of (153 a) or (155 a) under conditions, such that the resultant acid (191) might undergo decarboxylation followed by heterolytic ring scission[8] (cf. Chapter 1.3b) to the acetoxy compound (192), namely by heating under reflux in sulphuric acid - glacial acetic acid, failed to give any identifiable material.



(191) (192)

The attempted hydrolysis of the 3-carboxamide group of the triazolotriazines (153 b) and (155 a) using the technique of diazotizing their hydrochloric acid solutions[77] gave unchanged starting material.

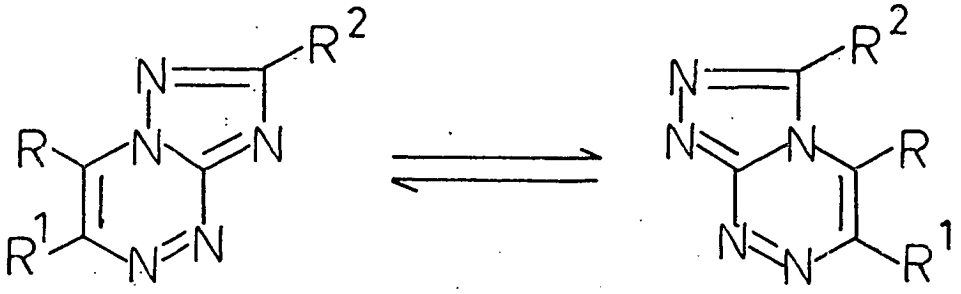


R^1 and R^2 = H, Me or Ph

Scheme 15

2.5 The Synthesis and Reactivity of the 1,2,4-Triazolo[5,1-c]-1,2,4-triazine and 1,2,4-Triazolo[3,4-c]-1,2,4-triazine Ring Systems—the Rearrangement of Fused 1,2,4-Triazines

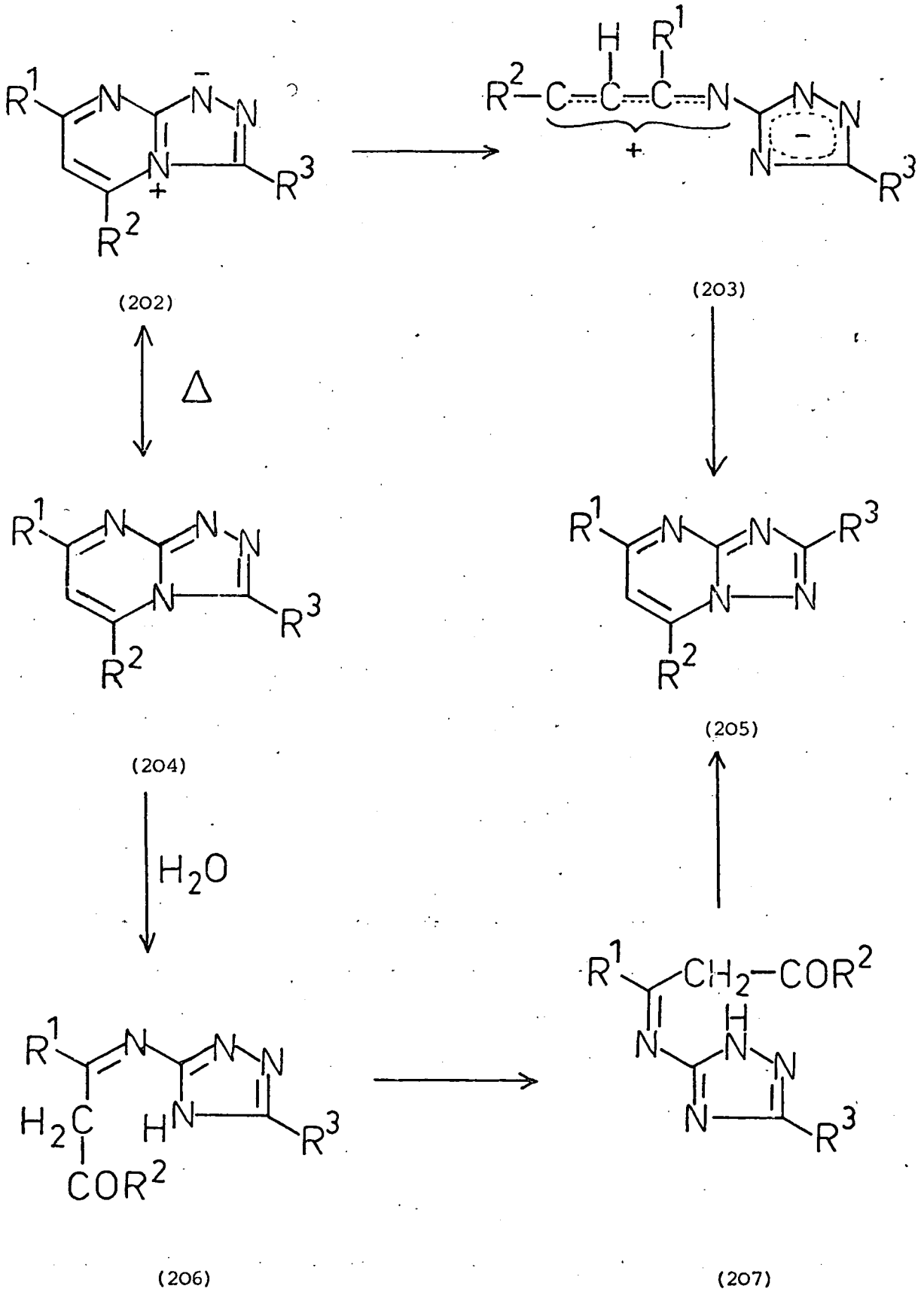
The successful synthesis of the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system (94) by the method outlined in Chapter 2.4 prompted an analogous investigation into the synthesis of the 1,2,4-triazolo-[5,1-c]-1,2,4-triazine ring system (193). This previously reported[78,79,80] ring system (193) has been obtained in one instance by rearrangement[80]



(193) (194)

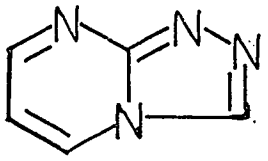
of the 1,2,4-triazolo[3,4-c]-1,2,4-triazine ring system (194) [(194)⟶ (193)]. Thus, derivatives of (193) are of potential interest with respect to a possible equilibrium of the type [(193)⇌(194)].

The system (198) has been synthesized by Jacquier[80] *etal*.by the methods broadly outlined in Scheme 15. However, the route [(195)→ (197) → (198)] is complicated by the simultaneous formation of the 1,2,4-triazolo[4,3-b]-1,2,4-triazine ring system (196). In order to eliminate any doubt as to the assignment of structures (196) and (198), the latter was synthesized unambiguously by the method employed previously by Dornow and his co-workers[78,79] in their synthesis of (198; R^1=Me,R^2=H).

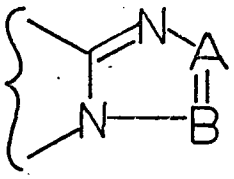


Scheme 16

The Dimroth-type rearrangement [(193)⇌(194)] of the fused 1,2,4-triazine nucleus finds analogy in other systems such as 1,2,4-triazolo[4,3-a]pyrimidine [81-85] (200), and has also been observed in azines[86] suitably fused to tetrazoles (201; A=B=N) or



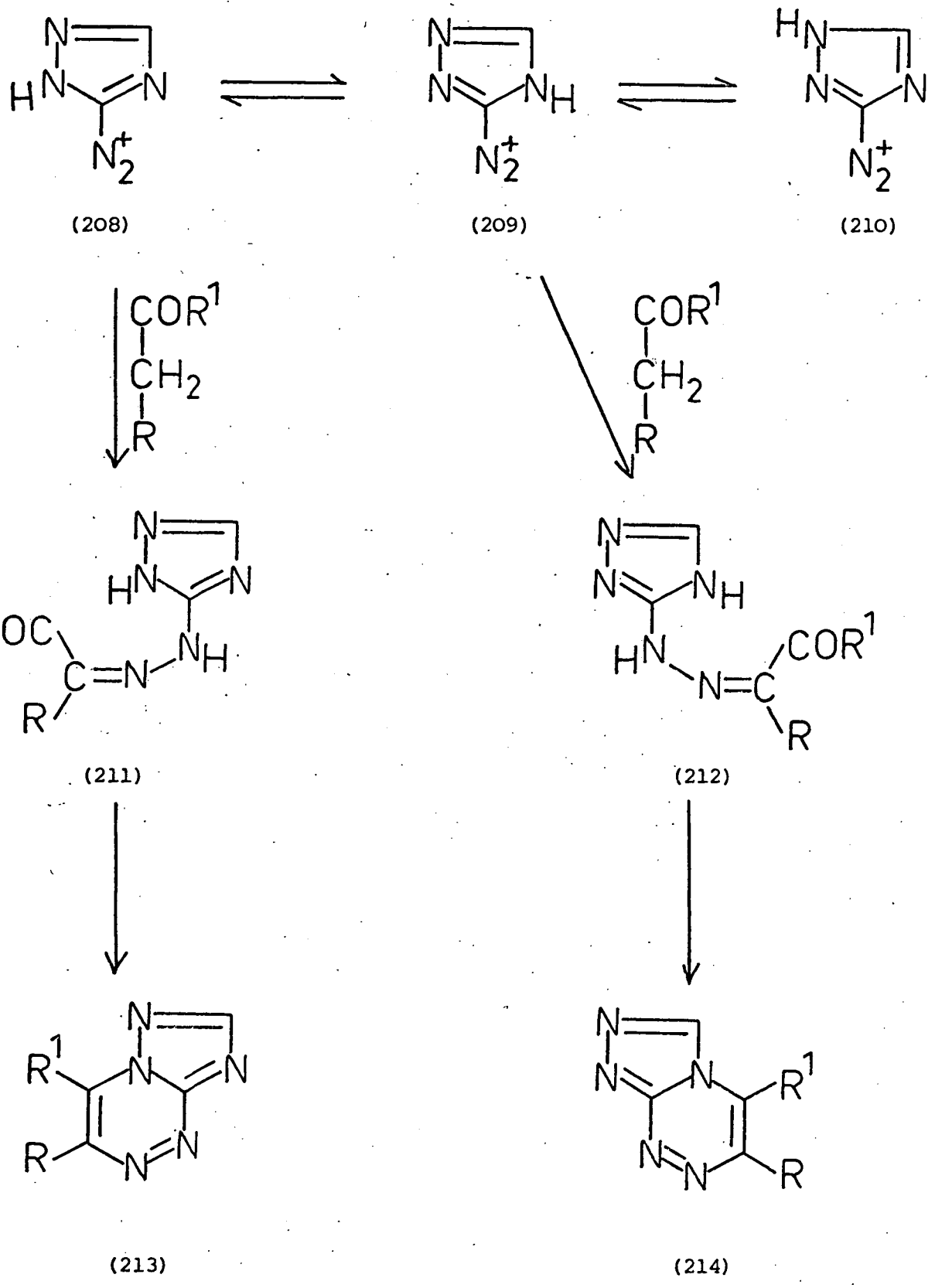
(200)



(201)

imidazoles (201; A=.CR,B=.CR[1]). Bee and Rose have discussed[82] the mechanism of such a rearrangement (Scheme 16) and their work on the 1,2,4-triazolo[4,3-a]pyrimidine (204) system lends support to mechanisms possible in aqueous and non-aqueous conditions. It was found[82] that when compounds of the type (204) were subjected to dry heat, the isomeric 1,2,4-triazolo[1,5-a]pyrimidines (205) were isolated. The pathway for such a reaction probably involves zwitterionic forms such as (202) and (203). The conversion of (204) into (205) was found[82] to proceed much more rapidly under aqueous alkaline or acidic conditions. The mechanism in this case probably involves the addition of water to the C(4)-N bond leading to the cleavage of this bond and formation of (206) and (207) and subsequent recyclisation.

As has previously been stated (section 2.2),amino-1,2,4-triazole (116) gives a stable diazonium cation when the diazotization

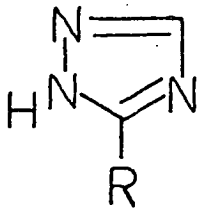


Scheme 17

is carried out[62] in nitric acid solution. Thus a route (Scheme 17) is available to the 1,2,4-triazolo[5,1-c]-1,2,4-triazine ring system (193) (cf. Section 2.1). As described earlier, the possibility of rearrangement to the [3,4-c] system (194) exists. However, due to the projected route to the system (213) [Scheme 17; (208)⟶(211)⟶(213)], the system (194) may be formed more directly. As in 1,2,3-triazole chemistry, tautomerism of the type [(208)⟹(209)⟹(210)] may occur, and the diazonium salts (208) and (209) may couple to give hydrazones of the type (211) and (212) which could cyclize as described (Scheme 17) to give the isomeric triazolotriazines (213) and (214).

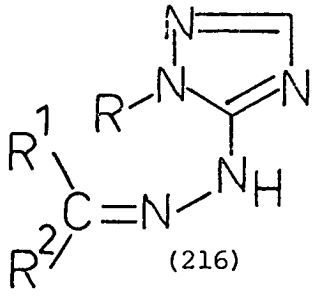
2.6 Some Coupling Reactions of 2H-1,2,4-Triazole-3-diazonium Nitrate and the Synthesis and Reactivity of the 1,2,4-Triazolo[5,1-c]-1,2,4-triazine Ring System.

When a freshly prepared solution of 2H-1,2,4-triazole-3-diazonium nitrate (215 b) was introduced into an aqueous ethanolic solution of a suitable active methylene compound, which contained sodium acetate, the hydrazones (216 a, c-g, i, and j) were obtained. The hydrazone (216 e) was isolated as an ethanol solvate contaminated with a trace of an unidentified solid. Liberation of the free compound (216 e) was effected by fractional crystallisation followed by drying at an elevated temperature. The reactions leading to the isolation of (216 c-e and i) also afforded varying amounts of the unreacted active methylene compounds. Diethyl malonate, as well as giving the hydrazone (216 j), afforded a solid, which when acidified, gave a product whose properties were consistent with it being the



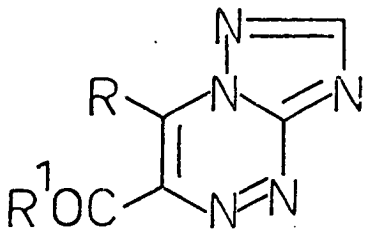
(215)

	R
a;	NH_2
b;	$N_2^+ NO_3^-$



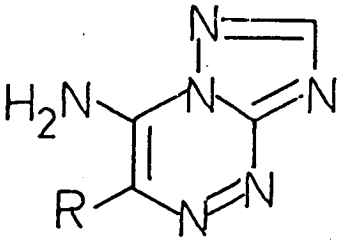
(216)

	R	R^1	R^2
a;	H	Ac	Ac
b;	H	Ac	$.CO_2Et$
c;	H	Ac	.COPh
d;	H	.COPh	.COPh
e;	H	CN	.COPh
f;	H	CN	$.CO_2Et$
g;	H	CN	CN
h;	H	CN	$.CONH_2$
i;	H	.COPh	$.CO_2Et$
j;	H	$.CO_2Et$	$.CO_2Et$
k;	Ac	Ac	Ac
l;	Ac	$.CO_2Et$	$.CO_2Et$



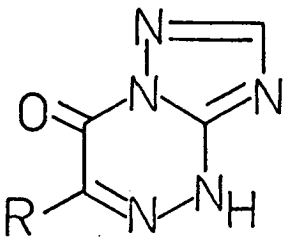
(217)

	R	R^1
a;	Me	Me
b;	Me	.OEt
c;	Me	Ph
d;	Ph	Ph



(218)

	R
a;	.COPh
b;	$.CO_2Et$
c;	CN
d;	$.CONH_2$



(219)

	R
a;	.COPh
b;	$.CO_2Et$
c;	.CN
d;	$.CO_2H$

hydrate of the triazolotriazine (219 b) (see later). Cyanoacetamide gave a mixture of the triazolotriazine (218 d) and a resinous material which behaved as a polymer, showing high molecular weight fragments in its mass spectrum. The triazolotriazine (218 d) was separated from the insoluble resin by fractional crystallisation from water.

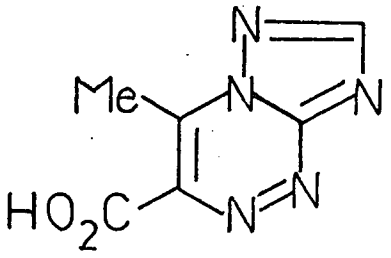
The products (216 a, c-g, i and j) gave i.r., ^{1}H n.m.r. and mass spectral and analytical data which was consistent with hydrazone structures. However, crystallisation of the hydrazones (216 f and g) resulted in the formation of the corresponding triazolotriazines (218 b and c). As in the case of the (1,2,3-triazol-5-yl)hydrazones (Chapter 2.4), geometrical isomerism is possible [cf. (158) and (159)]. This isomerism is detected in the ^{1}H n.m.r. spectra of (216 c) and (216 i). The hydrazone (216 c) shows two signals which may be attributed to methyl protons, and the hydrazone (216 i) shows irregular multiplets attributable to the protons of the ethyl group. Attempts to further characterise the hydrazones (216 a and j) by converting them, in hot acetic anhydride, into the (2-acetyl-1,2,4-triazol-3-yl)hydrazones (216 k and l), resulted in the formation of multicomponent oils or in the isolation of the unreacted hydrazone.

When the hydrazones (216 a, c-f, i and j) were treated briefly with dilute aqueous sodium hydroxide solution they gave red solutions. The hydrazone (216 g) when similarly treated gave a sparingly soluble sodium salt. This behaviour is consistent with the presence of a 2H-1,2,4-triazole nucleus. When the

alkaline solutions from (216 d-f) or the insoluble salt from (216 g) were re-acidified using dilute aqueous sulphuric acid, the parent hydrazones were regenerated. Similar acidification of the alkaline solutions of (216 i and j) afforded the triazolotriazines (219 a and b) (see later). Re-acidification of the alkaline solutions from (216 a and c) gave rise to amorphous solids (A) and (C). These solids had previously been isolated as by-products in the synthesis of (216 a and c).

The behaviour of the solids (A) and (C) was very similar to that of the amorphous solid (B), which is the sole product isolated from the coupling reaction between the diazonium salt (215 b) and ethyl acetoacetate. When (A), (B) and (C) were treated with dilute aqueous sodium hydroxide, they gave red solutions, acidification of which, regenerated the starting materials. Although the mass spectra of the solids exhibited parent ions consistent with the triazolotriazines (217 a-c), their i.r. and ^{1}H n.m.r. spectra were indefinite and indicative of polymeric substances. The analytical data obtained for (A), (B) and (C) was consistent in each case with the hemi-hydrate of the triazolotriazines (217 a-c), but the u.v. spectrum of (A) was very similar, but not identical, to that of the hydrazone (216 a). In attempts to gain more information about the nature of the solids (A), (B), and (C), the solid (A) was subjected to attempted benzoylation, hydrogenation, oxidation (with activated manganese dioxide), acid hydrolysis and reaction with hydrazine, but each reaction gave unreacted starting material. The solid (A) recovered from these reactions had variable melting point

but its i.r. spectrum did not change. An attempt to methylate the solid (A) resulted in the isolation of a froth. The froth, which was insoluble in base, showed high molecular weight fragments in its mass spectrum, and its ^1H n.m.r. spectrum consisted of a multitude of unassigned peaks. The mass spectral properties of the froth, suggest that it is polymeric. When the solid (B) was heated under reflux in aqueous ethanolic sodium carbonate, the i.r., ^1H n.m.r., and mass spectral and analytical data of the product were consistent with the triazolotriazine structure (220).



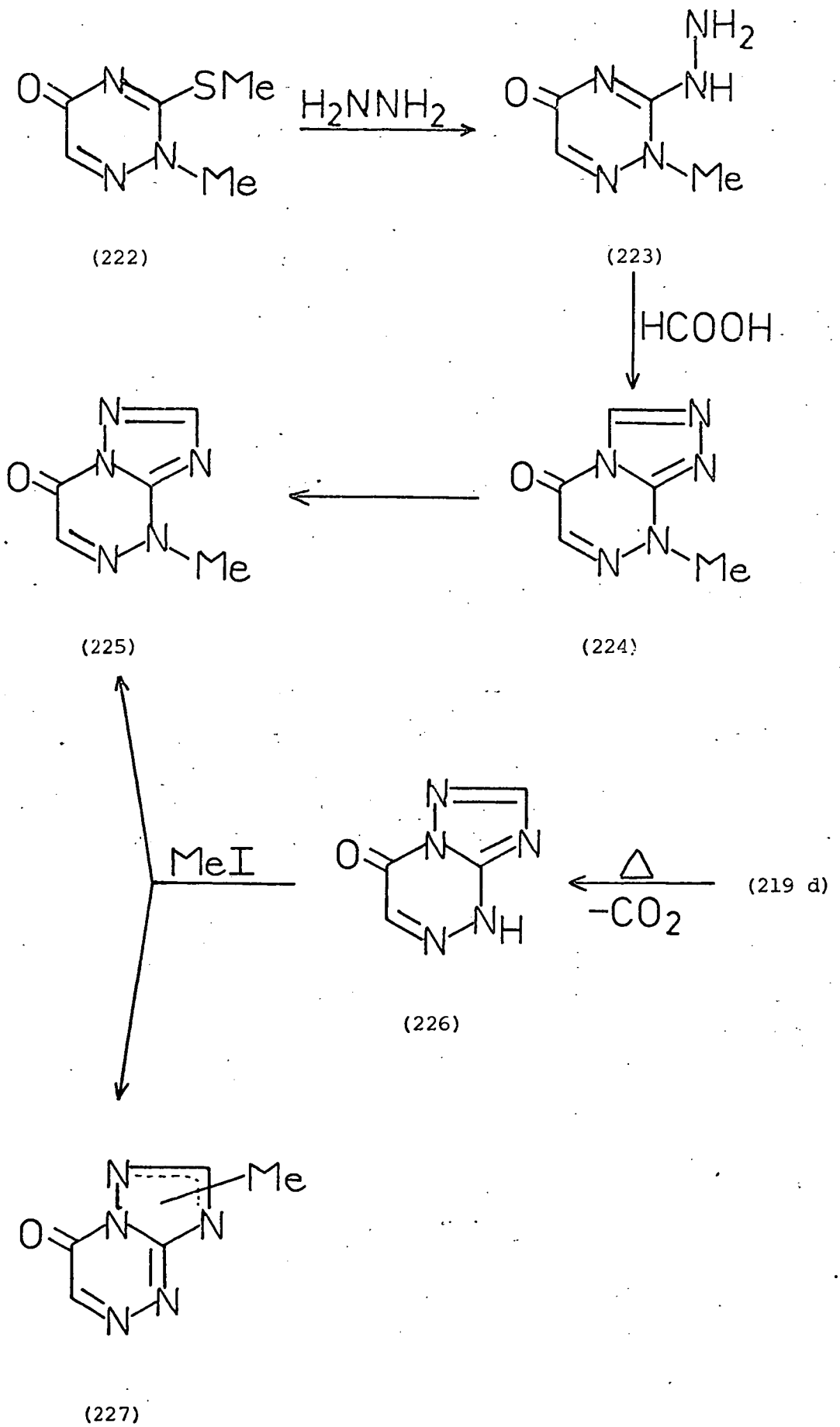
(220)

When the hydrazones (216 d-g, i and j) were heated under reflux in glacial acetic acid, the triazolotriazines (217 d), (218 a-c) and (219 a and b) were formed. When (216 a and c) were similarly treated, the solids (A) and (C) were obtained. Cyclization of the hydrazones (216 f and j) was also effected by heating under reflux in aqueous ethanolic sodium acetate. However, under such conditions the hydrazone (216 f), gave rise to two products. As well as affording the aminoester (218 b), the lactam (219 c), which was not formed in the reaction of (216 f) with acetic acid, was obtained. The triazolotriazine (219 c) was isolated by acidification as a hydrate, as indicated by its i.r. spectrum. The free compound (219c) was obtained by heating the hydrate at an elevated temperature. The

attempted base-catalysed cyclization of (216 a) resulted, as in the acid-catalysed case, in the formation of the solid (A).

When the diazonium salt (215 b) was coupled with the appropriate active methylene compounds, and the reaction mixtures were subjected to the described base catalysed cyclization conditions, the triazolotriazines (218 a,b and d) and (219 a-c) were obtained. The compounds (218 b) and (219 c) were the products obtained from the reaction with ethyl cyanoacetate. As in the low temperature reaction with cyanoacetamide, the product (218 d) was isolated together with a red resinous solid. The reaction with ethyl benzoylacetate gave the product (219 a), as well as some unreacted active methylene compound. The products (218 a) and (219 b) were isolated as solvates, but crystallisation or drying at an elevated temperature gave the free triazolotriazines (218 a) and (219 b). Work up of the reaction mixture which afforded the product (218 a) gave a solid multi-component mixture from which no identifiable material could be obtained. The attempt to synthesize the triazolotriazines (217d) and (218c) by coupling, followed by base-catalysed cyclization, resulted in the isolation of the respective hydrazones (216 d and g), some unreacted dibenzoylmethane also being recovered from the former reaction.

When the diazonium salt (215 b) was coupled with diethyl malonate in aqueous ethanolic sodium carbonate and the resultant reaction mixture was heated under reflux, a mixture of the ester (219 b) and the corresponding carboxylic acid (219 d) was obtained. The acid, which was isolated as a hydrate, was also


SMe
H_2NNH_2
NH_2
NH
Me
(222)
(223)
HCOOH
(225)
(224)
MeI
(226)
Δ
$-CO_2$
(219 d)
(227)

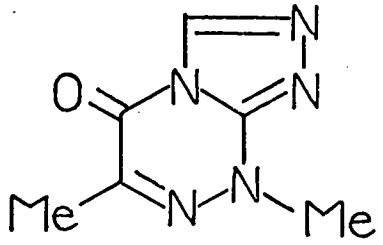
Scheme 18

formed when the ester (219 b) was hydrolysed with hot aqueous ethanolic sodium carbonate. Isolation of the free acid (219 d) was effected by crystallisation from ethanol-glacial acetic acid.

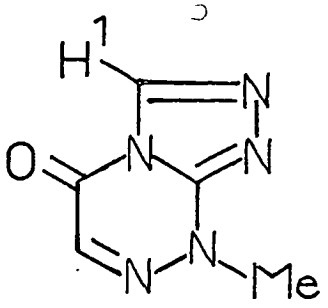
Due to the manner in which the hydrazones (216 a, c-g, i and j) and the triazolotriazines (217 d), (218 a-d), and (219 a-c) were formed and isolated, it seems reasonable to suggest that the mechanisms involved in their syntheses are similar to those postulated for the 1,2,3-triazole series (Chapter 2.4) (cf. Schemes 10 and 11).

The i.r., ^{1}H n.m.r., and mass spectral data obtained from the products (217 d), (218 a-d), and (219 a-d) were consistent with the assigned triazolotriazine structures, but (218 c and d) did not give correct analyses. The H-2 signal in the ^{1}H n.m.r. spectra of the 7-amino series (218 a-d) occurs at τ 1.10-1.24 whereas the corresponding signal for the lactam series (219 a-d) occurs at τ 1.46-1.60.

Any doubt as to the exact nature of the heterocyclic nucleus existing in the compound (219 b) was removed (Scheme 18) by the unambiguous synthesis of the triazolo[3,4-c]triazine (224) by a method used by Dornow *etal*[78] in their synthesis of the dimethyl compound (221). The 3-methylmercaptotriazine[87] (222), when treated

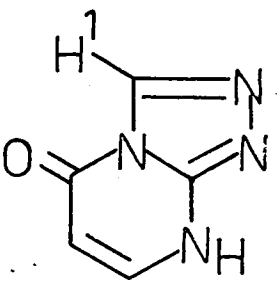


(221)



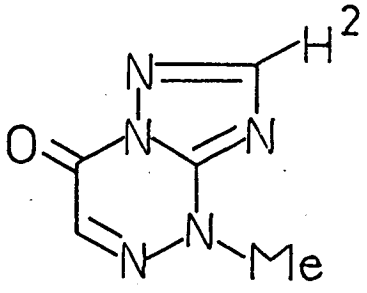
$H^1 = \tau\ 0{\cdot}76$

(224)



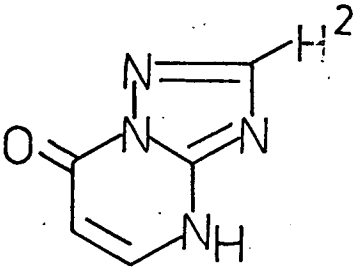
$H^1 = \tau\ 0{\cdot}76$

(230)



$H^2 = \tau\ 1{\cdot}63$

(225)

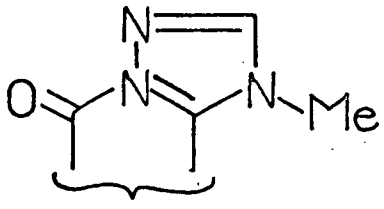


$H^2 = \tau\ 1{\cdot}16$

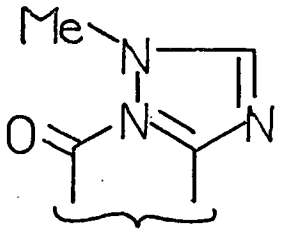
(231)

Scheme 19

with hydrazine hydrate at ambient temperature, gave the corresponding hydrazino compound (223) (characterised by its ability to form a benzylidene adduct), which cyclized to the triazolo[3,4-c]triazine (224) on heating under reflux briefly in formic acid. Prolonged treatment of the hydrazino compound (223) with formic acid, or treatment of the triazolotriazine (224) with hot aqueous ethanolic sodium acetate, resulted in the isolation of the triazolo[5,1-c]triazine (225). When the hydrate of the acid (219 d) (which was known to decarboxylate readily as indicated by its mass spectrum) was heated in vacuo the triazolotriazine (226) was formed. Methylation of the product (226) gave a mixture of two monomethyl derivatives which were readily separated by chromatography to give the previously obtained 4-methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one (225), and another N-methyl product (227). Due to the presence of a carbonyl band in the i.r. spectrum of (227), the possibility of O-methylation

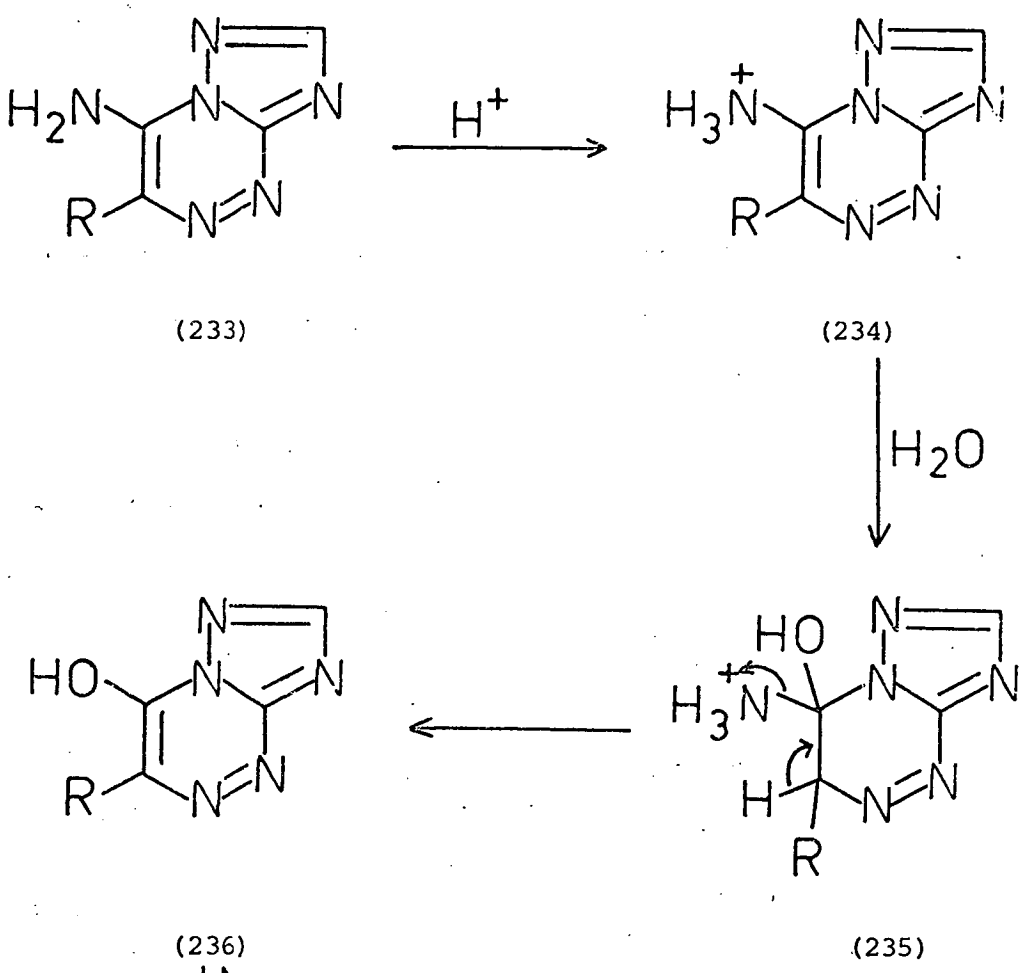


(228)



(229)

was excluded in favour of a structure of the type (228) or (229). Further evidence for the structure of (225) was obtained on comparison of the chemical shifts of the H-1 and H-2 signals of (224) and (225) with those of the corresponding triazolopyrimidines[88] (230) and (231) (Scheme 19). The corresponding protons of (230) and (231)



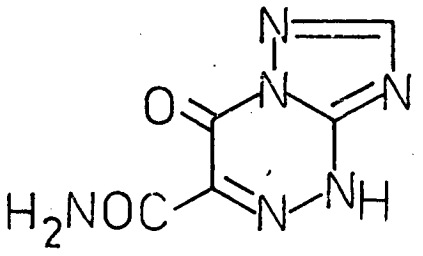
(233) (234) (235) (236) (237)

Scheme 20

have effectively the same environment as their triazolotriazine counterparts, and it can be observed that the H-1 signals of (224) and (230) appear at lower field than those of (225) and (231).

As has been previously stated (see page 49), the lactam series (219) exhibits a characteristic signal for H-2 in the ^1H n.m.r. spectrum. This, coupled with the inter-relation reactions to be described, helps establish the structures of the triazolo[5,1-c]-triazines (218 a-d), and (219 a-c).

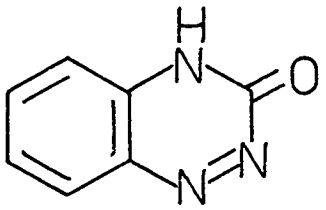
The 7-aminotriazolotriazines (218 a-c) were converted into their 7-oxo counterparts (219 a-c) by acid catalysed hydrolysis. When the aminoamide (218 d) was similarly treated, the triazolo-triazine (232) was formed. The mechanism for such a hydrolysis



(232)

(Scheme 20) probably involves the protonation of the 7-amino system to give the intermediate (234) followed by the addition of water and finally the elimination of ammonia. The i.r. spectra of the compounds (219 a-d) and the decarboxylated triazolotriazine (226) suggest that they prefer to exist in the lactam form (237) rather than the tautomeric 7-hydroxy form (236). This result

finds analogy[89] in the benzo-1,2,4-triazinone system (238).

(238) 

In a further investigation of the reactivity of the 7-amino group of the compounds (218 a-d), the attempted acetylation of (218 b) resulted in the isolation of unreacted starting material (218 b) or the lactam (219 b). The latter product was isolated in low yield and was probably formed as a result of the acid catalysed hydrolysis of the 7-amino group of (218 b), since water was involved in the work up. Similarly the attempted diazotization of the aminotriazolotriazine (218 a) resulted largely in the recovery of starting material. The isolation of a trace of the lactam (219 a) may once again be interpreted in terms of the acid catalysed hydrolysis of (218 a). When the diazotization of (218 a) was carried out under non-aqueous conditions, only starting material was recovered.

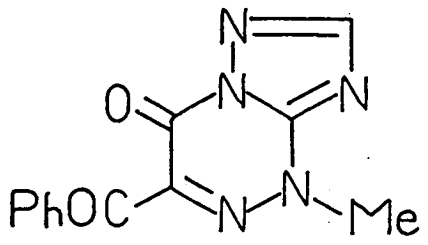
Attempts to hydrolyse the cyano group of (219 c) using aqueous sodium carbonate or concentrated sulphuric acid proved unsuccessful, and the action of concentrated sulphuric acid on the aminonitrile (218 c) effected the formation of the hydrazone (216 g). However, the cyano compounds (218 c) and(219 c) were smoothly converted into the corresponding amides (218 d) and(232) using polyphosphoric acid.

The conversion of the esters (218 b) and (219 b) into the corresponding amides (218 d) and (232) was effected by saturating their ethanolic solutions with ammonia. The amides (218 d) and

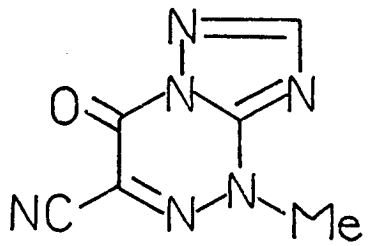
(232) were separated from the unreacted starting materials (218 b) and (219 b) by fractional crystallisation.

As well as establishing the exact structure of the triazolo-[5,1-c]triazines (218 a-d) and (219 a-c), the inter-relation reactions described have also cleared any doubt as to the gross structures of the compounds (218 c and d). Neither of these compounds have afforded correct analytical data.

The attempted methylation of the compounds (219 a and c) using methyl iodide resulted in the recovery of unreacted starting materials and the isolation of multicomponent gums. However, when dimethyl sulphate was used as a methylating agent, the mono-methyl derivatives (239) and (240) were obtained. The structures



(239)



(240)

of (239) and (240) followed from their i.r. spectra, which in the case of (240) excluded the possibility of O-methylation. In addition their u.v. spectra were similar to that of (225) of established structure.

Part Two - Experimental

(For general experimental procedures, see Appendix)

2.7 The Diazotization of Some 1,4-Disubstituted 5-Amino-1,2,3-triazoles and Related Reactions

The Preparation of the 1,4-Disbustituted 5-Amino-1,2,3-triazoles (120 a-d)

5-Amino-1,4-diphenyl-1,2,3-triazole[41] (120 a) m.p. 173° (lit.,[41] 179°), 5-amino-1-benzyl-4-phenyl-1,2,3-triazole[66] (120 b) m.p. 157° (lit.,[66] 158°), 5-amino-1-benzyl-1,2,3-triazole-4-carboxamide[67] (120 c) m.p. 232° (lit.,[67] 235°), and methyl 5-amino-1-phenyl-1,2,3-triazole-4-carboxylate[11a] (120 d) m.p. 169° (lit.,[41] 173°) were prepared as described in the literature.

The Diazotization of the Triazoles (120 b-d) in Aqueous Hydrochloric Acid

A solution of sodium nitrite (1.50g) in water(30 ml) was added dropwise, over a period of 5 min, at 0° (ice-bath) to stirred solutions (or suspensions) of the triazoles (120 b-d) (0.0045 mol) in concentrated hydrochloric acid (30 ml). The mixtures were stirred for a further 5 min at 0°, and then for 10 min at room temperature.

(a) The triazole (120 d) afforded methyl 5-chloro-1-phenyl-1,2,3-triazole-4-carboxylate[41] (121 d) which was filtered off from the

reaction mixture, washed with water and dried (0.87g) (82%), m.p. 83° (from aqueous ethanol) (lit.,[41] 88°), $\nu_{max.}$ 1720 (CO) cm^{-1}, m/e 239, and 237 (M, 237.45).

Found: C, 50.5; H, 3.4; N, 17.2%

$C_{10}H_8ClN_3O_2$ requires: C, 50.5; H, 3.4; N, 17.7%

(b) The triazole (120 c) gave a solid (0.79g), m.p. 199-213°, which was leached with hot ethanol (5.0 ml) leaving the starting amine (120 c) insoluble (0.51g), m.p. 230-4°, identical (m.p. and i.r. spectrum) with an authentic[67] sample.

1-Benzyl-5-chloro-1,2,3-triazole-4-carboxamide (121 c) crystallised from the ethanol extract, and was combined with a second crop obtained by evaporating the ethanol mother liquor and triturating the resultant gum with ether (total 0.21g), m.p. 169° (from aqueous ethanol), $\nu_{max.}$ 3350 and 3150 (NH), and 1670 (CO) cm^{-1}, m/e 238, and 236 (M, 236.45).

Found : C, 50.7; H, 3.8; N, 23.7%.

$C_{10}H_9ClN_4O$ requires: C, 50.8; H, 3.9; N, 24.2%.

(c) The diazotization of the triazole (120 b) (5.0g; 0.02 mol) was carried out as described before. The reaction mixture (containing a solid) was extracted with chloroform to give a gum (4.92g) which was chromatographed over alumina. Elution with ether gave 1-benzyl-5-chloro-4-phenyl-1,2,3-triazole (121 b) (1.59g) (30%), m.p. 67° (from ethanol), m/e 271, and 269 (M, 269.45).

Found: C, 67.0; H, 4.5; N, 15.4%.

$C_{15}H_{12}ClN_3$ requires: C, 66.8; H, 4.5; N, 15.6%.

Further elution with more polar solvents gave gums which were shown by t.l.c. in (1:1) benzene-ether to be multicomponent mixtures.

The Diazotization of the Triazoles (120 b-d) in Aqueous Hydrobromic Acid.

A solution of sodium nitrite (0.50g) in water (10 ml) was added dropwise, over a period of 5 min, at 0° (ice-bath) to stirred solutions (or suspensions) of the triazoles (120 b-d) (0.0015 mol) in 50% w/v aqueous hydrobromic acid (10 ml). The mixtures (containing solids) were stirred for a further 10 min at 0°, and then for 90 min at room temperature.

(a) The triazole (120 d) afforded methyl 5-bromo-1-phenyl-1,2,3-triazole-4-carboxylate (122 d), which was filtered off from the reaction mixture, washed with a saturated aqueous solution of sodium hydrogen carbonate, then water and dried (0.35g) (83%), m.p. 162-6°. After three crystallisations from ethanol, the crude product gave colourless needles which showed the same i.r., ^{1}H n.m.r. and mass spectra, but had m.p. 96°; $\nu_{max.}$ 1720 (CO)cm^{-1}, τ ($CDCl_3$) 2.45(5H,s,ArH), and 6.00(3H,s,Me), m/e 283, and 281 (M, 281.91)

Found : C, 42.2; H, 2.8; N, 14.8%.

$C_{10}H_8BrN_3O_2$ requires: C, 42.6; H, 2.8; N, 14.9%.

(b) The triazole (120 c) gave a solid (0.29 g), m.p. 170-85° (decomp.) whose i.r. spectrum [$\nu_{max.}$ 3450,3300,3200(NH), 1680sh and 1660 (CO)cm^{-1}] suggested a mixture which contained starting material. Fractional crystallisation of the solid from ethanol gave pure samples of the starting material (120 c), m.p. > 230° (decomp.), and 1-benzyl-5-bromo-1,2,3-triazole-4-carboxamide (122 c), m.p. 175° which was identical (m.p. and i.r. spectrum) with a sample prepared as described later.

(c) The diazotization of the triazole (120 b) (2.50g; 0.01 mol) was carried out as described before. The mixture (containing a solid) was extracted with chloroform to give a gum (3.03g) which was chromatographed over alumina. Elution with benzene afforded 1-benzyl-5-bromo-4-phenyl-1,2,3-triazole (122 b) (2.10g) (67%), m.p. 82° (from ethanol), m/e 315, and 313 (M, 314.91).

Found: C, 57.4; H, 3.7; N, 13.9%.

$C_{15}H_{12}BrN_3$ requires: C, 57.3; H, 3.8; N, 13.4%.

Further elution with more polar solvents gave gums, shown by t.l.c. to be multicomponent mixtures.

The Diazotization of the Triazole (120 c) Using Hydrobromic Acid in Glacial Acetic Acid.

A solution of sodium nitrite (0.50g) in water (10ml) was added dropwise, over a period of 5 min, at 0° (ice-bath) to a stirred solution of the triazole (120 c) (0.0015 mol) in 50% w/v aqueous hydrobromic acid (10 ml) and glacial acetic acid (25 ml). The solution was stirred for a further 10 min at 0°, and then for 90 min at room temperature. The solution was then diluted with an equal volume of water, extracted with chloroform and then washed with saturated aqueous sodium hydrogen carbonate solution to give 1-benzyl-5-bromo-1,2,3-triazole-4-carboxamide (122 c) (0.26g) (60%), m.p. 187° (from ethanol), $\nu_{max.}$ 3350, 3250w, and 3100(NH), and 1670(CO) cm^{-1}, m/e 282, and 280 (M, 281.91)

Found: C, 42.8; H, 3.3; N, 19.7%.

$C_{10}H_9BrN_4O$ requires: C, 42.7; H, 3.2; N, 19.9%.

The Attempted Diazotization of 5-Amino-1,4-diphenyl-1,2,3-triazole (120a) in Nitric Acid Solution.

A solution of the aminotriazole[41] (120 a) (0.35g; 0.0015 mol) in concentrated nitric acid (10 ml) was cooled to 0° (ice-bath)

and treated dropwise with stirring over 10 min with a solution of sodium nitrite (0.50g) in water (10 ml). Stirring was continued at 0° for a further 30 min, and then at room temperature for 1h. The reaction mixture was extracted with chloroform to give a red oil (0.27g) which was shown by t.l.c. to be a multicomponent mixture.

The Attempted Diazotization of the Triazole (120 a) in Fluoroboric Acid Solution

A solution of the aminotriazole[41] (120 a) (1.18g; 0.005 mol) in 40% w/v aqueous fluoroboric acid (50 ml) was cooled to 0° (ice-bath) and treated dropwise with stirring over 5 min with a solution of sodium nitrite (2.5g) in water (50 ml). Stirring at 0° was continued for a further 10 min and then at room temperature for 10 min. The resultant yellow solid was collected, washed thoroughly with water and dried (2.19g). The solid, which remained unchanged on standing in dilute aqueous sodium hydroxide solution for 2h, showed an intense absorption at 2250 cm^{-1} in its i.r. spectrum. It was heated under reflux in ethanol (40 ml) for 3h, leaving an insoluble solid (0.72g) whose featureless i.r. spectrum showed it to be inorganic material. Evaporation of the ethanol mother liquor afforded an oil (1.36g), shown by t.l.c. (in toluene over silica) to be a multicomponent mixture. Chromatography of the oil over alumina gave, on elution with (9:1) toluene-ether, a single identifiable solid, namely 1,4-diphenyl-1,2,3-triazole[90] (133) (0.19g), m.p. 184° (from ethanol) (lit.,[90] 185°), m/e 221 (M^{+}) (M,221).

Found: C, 76.0; H, 5.1; N, 19.1%.

$C_{14}H_{11}N_3$ requires: C, 76.0; H, 5.0; N, 19.0%.

Elution with more polar solvents gave gums which on t.l.c. examination (in toluene over silica) proved to be multicomponent mixtures.

The Attempted Nucleophilic Substitution Reactions of the Chlorotriazole (121 a)

The Attempted Reaction of the Triazole (121 a) with Aniline.

Solutions of the chlorotriazole[64] (121 a) (0.51g; 0.002 mol) in redistilled aniline (0.60g) were heated at 100°, 120° and 150°. On cooling, the solutions were triturated with dilute hydrochloric acid, the resultant solids were collected, washed with water and dried to afford starting material (92-98%), m.p. 123-9° (lit., 137°) (identical i.r. spectrum).

The Attempted Reaction of the Triazole (121 a) with Sodium Azide.

Solutions of the chlorotriazole[64] (121 a) (0.25g; 0.001 mol) in ethanol (4.0 ml) and sodium azide (0.25g) in water (2.0 ml) were mixed and heated under reflux for 2h. The reaction mixture was evaporated and the residue was triturated with water to afford starting material (0.20g), m.p. 130-3°, which was identified by its m.p. and i.r. spectrum.

2.8 Some Coupling Reactions of 4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride and the Synthesis of the 1,2,3-Triazolo-[5,1-c]-1,2,4-triazine Ring System.

5-Amino-1H-1,2,3-triazole-4-carboxamide (150 a)

The amide (150 a) was prepared by the method of Hoover and Day[67], m.p. 223° (from water)(lit.,[67] 225°), $\nu_{max.}$ 3350,3200 and 2700 br(NH), 1680(CO), and 1650(NH def.) cm^{-1}.

5-Amino-4-carbamoyl-1H-1,2,3-triazole Hydrochloride (150 b)

The amide (150 a)(16.0g) was dissolved with gentle heating in a mixture of methanol (500 ml) and glacial acetic acid (35 ml). The solution was cooled in an ice-bath and saturated with dry hydrogen chloride to give the insoluble hydrochloride (150 b) which was filtered off, washed with a little methanol, dried and combined with a second crop obtained by concentrating the mother liquor to ca 30 ml and collecting the precipitated solid (total 17.0g), $\nu_{max.}$ 3400-2300br(NH,NH_3^+), 2000-1860(NH_3^+), and 1690-1660(CO) cm^{-1}.

4-Carbamoyl-1H-1,2,3-triazole-5-diazonium Chloride (150 c)

A suspension of the hydrochloride (150 b)(17.0g) in methanol (250 ml) was saturated with dry hydrogen chloride, cooled to 0° (ice-bath) and treated dropwise with stirring with amyl nitrite (21.5 ml). The mixture was stirred for a further 2h in the melting

ice-bath and the diazonium salt (150 c) was collected, washed with a little methanol and dried (15.2g), $\nu_{max.}$ 3300 and 3150(NH), 2500-2100br and 1840-1760br($\overset{+}{N} \equiv N$), and 1700-1660br(CO) cm^{-1}. The salt was kept in a dark bottle and stored in a refrigerator prior to use as described later.

Coupling Reactions of the Diazonium Salt (150 c) with Active Methylene Compounds

(a) A freshly prepared solution of the diazonium salt (150 c) (1.2g; 0.0069 mol) in water (25 ml) and ethanol (25 ml) was added dropwise, with stirring, to solutions of the active methylene compounds (Table 1) (0.0069 mol), and anhydrous sodium acetate (0.80g) in water (2.0 ml), and ethanol (5.0 ml), which were cooled in an ice-bath. Stirring was continued in the melting ice-bath for 2h. The resultant solids were collected, washed with water, and dried to give the triazolylhydrazones (151 a-h). Analytical data is collected in Table 1.

Pentane-2,3,4-trione 3-(4-carbamoyl-1H-1,2,3-triazol-5yl)hydrazone (151 a) (97%) had m.p. 181° (decomp.) (from methanol), $\nu_{max.}$ 3400 and 3350-3250br(NH), and 1690 and 1660(CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.15br (1H,s,NH), 2.44br(1H,s,NH), 7.64(3H,s,Me), and 7.74(3H,s,Me), m/e 238(M^+) and 220(M^+-H_2O) (M,238).

Ethyl 2,3-dioxobutyrate 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl) hydrazone (151 b) (85%) had m.p. 150° (from ethanol), $\nu_{max.}$ 3350 and 3200(NH), and 1700 and 1670(CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.17br(1H,s,NH), 2.28br(1H,s,NH), 2.59br(1H,s,NH), 5.76(2H,q,J7Hz,CH_2), 7.76(3H,s,Me) and 8.74(3H,t,J7Hz,Me), m/e 268(M^+) and 250(M^+-H_2O) (M,268).

1-Phenylbutane-1,2,3-trione 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl) hydrazone (151 c) (58%) had m.p. > 145° (decomp.) (from ethyl acetate-light petroleum), $\nu_{max.}$ 3550w,3450 and 3350-3200br(NH), and 1660br and 1630(CO)cm^{-1}, τ [$(CD_3)_2SO$] 2.10-2.76(8H,m,ArH,NH) and 7.73(3H,s,Me), m/e 300 (M^+) and 282 (M^+-H_2O) (M,300).

1,3-Diphenylpropane-1,2,3-trione 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (151 d) (69%) after crystallisation of the crude solid from ethanol, had m.p. 154° (from ethanol), $\nu_{max.}$ 3450-3000br (NH), and 1660-1640br and 1630(CO)cm^{-1}, m/e 362(M^+) and 344(M^+-H_2O) (M,362).

Diethyl mesoxalate 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (151 e) was isolated as a hydrate (1.31g), $\nu_{max.}$ 3450,3300 and 3200 (NH), 2800-2100br and 1960-1840(H_2O), and 1700 and 1670br(CO)cm^{-1}, which on crystallisation from ethanol gave the free hydrazone (151 e) m.p. 173°, $\nu_{max.}$ 3450,3300w and 3200br(NH), and 1700 and 1670br (CO)cm^{-1}, τ [$(CD_3)_2SO$] 2.01br(1H,s,NH), 2.34br(1H,s,NH), 5.67(2H,q, J7Hz,CH_2),5.73(2H,q,J7Hz,CH_2),8.70(3H,t,J7Hz,Me), and 8.72(3H,t,J7Hz, Me), m/e 298(M^+) (M,298).

Ethyl benzoylglyoxalate 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl) hydrazone (151 f) (82%) had m.p. 176° (from ethanol), $\nu_{max.}$ 3400, 3300br, and 3100(NH), and 1700 and 1660(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.60br (1H,s,NH),2.00-2.76(7H,m,ArH,NH),5.60-6.12(2H,m,CH_2), and 8.62-9.04(3H,m,Me), m/e 330(M^+) and 312(M^+-H_2O) (M,330).

Ethyl cyanoglyoxalate 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (151g) (1.24g) was isolated as its ethanol solvate τ [$(CD_3)_2SO$] 1.80br(s,NH),2.12br(s,NH),5.68(q,J7Hz,CH_2),6.57(q,J7Hz,CH_2),

8.71(t,J7Hz,Me), and 8.96(t,J7Hz,Me), which when crystallised from glacial acetic acid-ethanol and dried in vacuo at 80° gave the free hydrazone (151g), m.p. 180° (decomp.), $\nu_{max.}$ 3450-3300br(NH), 2250(.C ≡ N), and 1720 and 1680(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.80br(1H,s,NH), 2.12br(1H,s,NH),5.68(2H,q,J7Hz,CH_2), and 8.71(3H,t,J7Hz,Me), m/e 251(M^+) (M,251).

(b) Cyanoacetamide (0.59g; 0.0069 mol) coupled with the diazonium salt (150 c) as described in (a) to give 2-oxocyanoacetamide 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (151h)(0.96g)(63%), m.p. > 200°(decomp.) $\nu_{max.}$ 3400-3100br(NH),2250(.C ≡ N), and 1680br (CO)cm^{-1}, which when crystallised from aqueous dimethylsulphoxide gave 7-amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3,6-dicarboxamide (155 b) m.p. > 280°(decomp.) which was identical (m.p. and i.r. spectrum) with a sample obtained later.

The hydrazones(151 a-h)were readily soluble in dilute aqueous sodium hydroxide solution giving red solutions, from which they were regenerated, unchanged, by acidification with dilute aqueous sulphuric acid.

(c) Malononitrile (0.53g; 0.0069 mol), when reacted with the diazonium salt (150 c), as described in (a) above, gave 7-amino-6-cyano-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (155 c) (1.12g)(80%), m.p. 255° (from aqueous dimethylformamide), $\nu_{max.}$ 3450-3000br(NH), and 1660br(CO)cm^{-1}, m/e 204 (M^+) and 121(M^+-83) (M 204). Analytical data is collected in Table 3. No u.v. data was obtained for (155 c) due to its insolubility in absolute ethanol.

The Reactions of the Hydrazones (151 a-h) with Acetic Anhydride.

The hydrazones (151 a-h) (0.002 mol) were heated under reflux in acetic anhydride (5-10 ml) for 2-5 min. In each case the reaction mixture was allowed to cool and any solid was collected and combined with a second crop obtained by evaporating the mother liquor and triturating the residue with ether, to give the monoacetyl derivatives (151 j-o) of the hydrazones (151 a-f) (75-93%). Analytical data is collected in Table 2.

Pentane-2,3,4-trione 3-(1-acetyl-4-carbamoyl-1,2,3-triazol-5-yl) hydrazone (151 j) had m.p. 163° (from ethyl acetate), $\nu_{max.}$ 3400,3300w, and 3200(NH), 1760(.N.COMe), and 1690,1680sh and 1650sh(CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.59br(1H,s,NH), 1.96br(1H,s,NH), 7.25(3H,s,.N.COMe), 7.53(3H,s,Me), and 7.60(3H,s,Me), m/e 280(M^+)(M,280).

Ethyl 2,3-dioxobutyrate 2-(1-acetyl-4-carbamoyl-1,2,3-triazol-5-yl) hydrazone (151 k) had m.p. 185°(decomp.)(from acetic anhydride), $\nu_{max.}$ 3450,3250 and 3300(NH), 1760(.N.COMe), and 1700br and 1660(CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.58br(1H,s,NH), 1.95br(1H,s,NH), 5.55-5.76(2H,m,CH_2), 7.24(3H,s,N.COMe), 7.60(3H,s,Me) and 8.68(3H,q,J7Hz,Me), m/e 310 (M^+)(M,310).

1-Phenylbutane-1,2,3-trione 2-(1-acetyl-4-carbamoyl-1,2,3-triazol-5-yl) hydrazone (151 l) had m.p. 185° (from acetic anhydride), $\nu_{max.}$ 3400, 3300w and 3200(NH), 1760(.N.COMe), and 1690br and 1660(CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.61br(1H,s,NH), 1.97br(1H,s,NH), 2.03-2.49(5H,m,ArH), 7.25 and 7.33(3H,s,.N.COMe), and 7.48 and 7.56(3H,s,Me), m/e 342 (M^+)(M,342).

1,3-Diphenylpropane-1,2,3-trione 2-(1-acetyl-4-carbamoyl-1,2,3-triazol-5-yl)hydrazone (151 m) had m.p. 184° (from ethyl acetate), $\nu_{max.}$ 3500, 3400, and 3300(NH), 1750(.N.COMe), and 1680br and 1660sh(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.58-2.51(12H,m,ArH,NH), and 7.29(3H,s,.N.COMe), m/e 404 (M^+)(M,404).

Diethyl mesoxalate 2-(1-acetyl-4-carbamoyl-1,2,3-triazol-5-yl)hydrazone (151 n) had m.p. 171°(from ethyl acetate-light petroleum), $\nu_{max.}$ 3450, 3250 and 3200sh(NH), 1760(.N.COMe), and 1720, 1690sh and 1670(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.60br (1H,s,NH),1.97br(1H,s,NH), 5.65(2H,q,J7Hz,CH_2), 5.72(2H,q,J7Hz,CH_2), 7.25(3H,s,.N.COMe), 8.69(3H,t,J7Hz,Me), and 8.73(3H,t,J7Hz,Me), m/e 340(M^+)(M,340).

Ethyl benzoylglyoxalate 2-(1-acetyl-4-carbamoyl-1,2,3-triazol-5-yl) hydrazone (151 o) had m.p. 170° (from acetic anhydride), $\nu_{max.}$ 3450, 3300 and 3200(NH), 1760(.N.COMe), and 1700 and 1680(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.60br(1H,s,NH), 1.98-2.55(7H,m,ArH,NH), 5.58-5.84(2H,m,CH_2) 7.32(3H,s,.N.COMe), and 8.71-8.92(3H,m,Me), m/e 372(M^+)(M,372).

The hydrazone (151 g) afforded the diacetyl derivative (152) (0.52 g)(78%), m.p. 153°(from ethyl acetate), $\nu_{max.}$ 3400,3300 and 3200(NH), 1780(.N.COMe), and 1730sh, 1710 and 1680(CO)cm^{-1},τ [$(CD_3)_2SO$] 1.54br(1H,s,NH), 2.00br(1H,s,NH), 5.67(2H,q,J7Hz,CH_2),7.17(3H,s,.N.COMe), 7.48(3H,s,.N.COMe), and 8.72(3H,t,J7Hz,Me), m/e 335(M^+)(M,335).

Found:	C, 43.2;	H, 3.9;	N, 29.0%.
$C_{12}H_{13}N_7O_5$ requires:	C, 43.0;	H, 3.9;	N, 29.2%.

The attempted acetylation of the hydrazone (151 h) from cyanoacetamide gave an intractable, black solid (0.59g) which proved very insoluble on attempted crystallisation from dimethylformamide and dimethylsulphoxide and showed an indefinite and smeared out i.r. spectrum.

The Hydrolysis of the N-Acetyl-hydrazones (151 j and k).

The N-acetyl-hydrazones (151 j and k) (0.20g) were heated under reflux in 50% aqueous acetic acid solution (10 ml) for 10-15 min. Evaporation of the reaction mixtures and treatment of the resultant gums with water afforded the hydrate of 6-acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 a) (0.15g), m.p. 160° and ethyl 3-carbamoyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (153b) (0.16g), m.p. 160°, which were identical (m.p. and i.r. spectrum) with samples obtained later.

The Cyclization of the Hydrazones (151 a-g) to the 1,2,3-Triazolo [5,1-c]-1,2,4-triazines (153 a-e), (154 a), and (155 a) Using Glacial Acetic Acid.

(a) The hydrazones (151 a-f) (0.002 mol) were heated under reflux in glacial acetic acid (10 ml) for 30 min [2h in the case of the hydrazone (151 e)]. The reaction mixtures were evaporated and the residues were triturated with ether to afford the triazolotriazines (153 a-e) and (154 a) (89-97%). Analytical data is collected in Table 3.

6-Acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 a) had m.p. 160-70° (decomp.) (from aqueous ethanol). The crude solid had $\nu_{max.}$ 3450,3300w and 3150(NH), and 1700 and 1680(CO) cm^{-1}, but after crystallisation and drying at 80° in vacuo it showed $\nu_{max.}$ 3450,3300,3250sh, and 3200sh(NH), and 1700 and 1680(CO) cm^{-1}, $\lambda_{max.}$ 210,236 and 332nm (log ε 4.15,4.40 and 3.27). The ^1H n.m.r. and mass spectra run before and after crystallisation were identical, τ [$(CD_3)_2SO$] 2.07br(1H,s,NH), 2.24br(1H,s,NH), 7.18(3H,s,Me), and 7.29(3H,s,Me), m/e 220(M^+), and 137(M^+-83) (M,220).

Ethyl 3-Carbamoyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (153 b) had m.p. 162° (from ethanol-glacial acetic acid), $\nu_{max.}$ 3450,3250w, and 3200(NH), and 1720, and 1680(CO)cm^{-1}, $\lambda_{max.}$ 210sh, 239 and 333nm(log ε 4.11,4.40 and 3.19), τ [$(CD_3)_2SO$] 2.07br(1H,s,NH), 2.15br(1H,s,NH), 5.52(2H,q,J7Hz,CH_2), 7.15(3H,s,Me), and 8.61(3H,t, J7Hz,Me), m/e 250(M^+) and 167(M^+-83)(M,250).

6-Benzoyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 c) had m.p. 196°(decomp.)(from ethanol-glacial acetic acid), $\nu_{max.}$ 3450,3350, and 3200(NH), and 1680br(CO)cm^{-1}, $\lambda_{max.}$ 213sh,226, 246,263sh and 338nm (log ε 4.31,4.33,4.31,4.13 and 3.28), τ [$(CD_3)_2SO$] 1.81-2.43(7H,m,ArH and NH), and 7.27(3H,s,Me), m/e 282 (M^+), and 199 (M^+-83)(M,282).

6-Benzoyl-7-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 d) had m.p. 232° (from ethanol-glacial acetic acid), $\nu_{max.}$ 3450, 3300w, and 3200br(NH), and 1670br(CO)cm^{-1}, m/e 344(M^+), and 261 (M^+-83)(M,344). No u.v. data was obtained due to the insolubility of (153 d) in absolute ethanol.

Ethyl 3-Carbamoyl-7-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (153 e) had m.p. 193° (from glacial acetic acid-ethanol), $\nu_{max.}$ 3400,3300w, and 3200(NH), and 1740, and 1680(CO)cm^{-1}, $\lambda_{max.}$ 208 infl.,226,240sh,282 and 258nm(log ε 4.20,4.24,4.18,4.06 and 3.52), τ [$(CD_3)_2SO$] 2.00(1H,s,NH), 2.20-2.43(6H,m,ArH and NH), 5.63(2H,q, J7Hz,CH_2), and 8.83(3H,t,J7Hz,Me), m/e 312(M^+), and 229(M^+-83)(M,312).

Ethyl 3-Carbamoyl-4,7-dihydro-7-oxo-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (154 a) had m.p. > 192°(decomp.) (from benzene-glacial acetic acid) $\nu_{max.}$ 3450,3300 and 3200(NH), and 1740 and 1670br (CO),

$\lambda_{max.}$ 207,245,266sh,308 infl. and 351nm(log ε 4.03,4.33,4.04,3.19 and 3.51), τ [$(CD_3)_2SO$] 1.74-2.48br(2H,m,NH),5.48-5.74(2H,m,CH_2), and 8.67(3H,t,J7Hz, Me), m/e 252(M^+)(M,252).

(b) The hydrazone (151g)(0.50g; 0.002 mol) was heated under reflux in glacial acetic acid (10 ml) for 2h. The reaction mixture was allowed to cool, giving ethyl 7-amino-3-carbamoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (155 a) (0.25g)(50%) m.p. 270°(decomp.) (from dimethylformamide-glacial acetic acid), $\nu_{max.}$ 3400, and 3250-3050br (NH), and 1710, and 1680(CO)cm^{-1}, m/e 251(M^+), and 168(M^+-83)(M,251). [No u.v. data was obtained due to the insolubility of (155 a) in absolute ethanol, and no ^1H n.m.r. data was obtained due to its insolubility in dimethylsulphoxide.] Evaporation of the mother liquor and trituration of the residue with ether afforded a solid (0.21g) m.p. > 180° (decomp.) $\nu_{max.}$ 3400, and 3250-3050br(NH), 2200(CN), and 1710, and 1670br(CO), τ [$(CD_3)_2SO$] 1.74-2.57br(2H,m,NH), 5.49-5.86 (2H,m,CH_2), and 8.54-8.82(3H,m,Me), m/e 251. Treatment of the solid (0.05g) with dilute aqueous sodium hydroxide solution gave an orange solution, which, when acidified with dilute aqueous sulphuric acid, afforded the starting hydrazone (151g)(0.043g), m.p. > 180°(decomp.), which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

6-Acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 a)

(a) The hydrazone (151 a) (0.48g; 0.002 mol) was heated under reflux in 50% aqueous ethanol (15 ml) for 15 min. The reaction mixture was allowed to cool and the resultant insoluble triazolotriazine (153 a)

was collected and combined with a further crop obtained by evaporating the mother liquor (total 0.38g), m.p. > 156°(decomp.).

(b) The hydrazone (151 a)(0.48g; 0.002 mol) was heated under reflux in 20% w/v sulphuric acid (5 ml) and ethanol (10 ml) for 1h. The reaction mixture was allowed to cool and the triazolotriazine (153 a) was collected and combined with a further crop obtained by concentrating the mother liquor to 5 ml and diluting it with water (total 0.38g), m.p. > 155°(decomp.).

In (a) and (b) the triazolotriazine (153 a) was isolated as the hydrate $\nu_{max.}$ 3550,3400, and 3300-3200br(NH,H_2O), and 1710, and 1680 (CO)cm^{-1} which on drying in vacuo at 100° for 15h gave the free triazolotriazine (153 a).

The Cyclization of the Hydrazones (151 e and h) to the Triazolotriazines (154 a) and (155 b) Using Aqueous Ethanolic Sodium Acetate

The hydrazones (151 e and h)(0.002 mol) and anhydrous sodium acetate (0.16g) were heated under reflux in water (5.0 ml) and ethanol (10 ml) for 1h. The reaction mixtures were evaporated under reduced pressure.

Trituration of the residue from the hydrazone (151 e) with dilute aqueous sulphuric acid afforded, after washing with water, the triazolotriazine (154 a)(0.37g)(74%), m.p. > 180°(decomp.), which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

Trituration of the residue from the hydrazone (151 h) with water gave 7-amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3,6-dicarboxamide (155 b)(0.34g)(77%), m.p. 292°(decomp.), $\nu_{max.}$ 3400-3100br(NH), and 1680, and 1660(CO)cm^{-1}, m/e 222(M^+) and 139(M^+-83)(M,222).

No u.v. data was obtained due to the insolubility of (155 b) in absolute ethanol. Analytical data is collected in Table 3.

Ethyl 7-Amino-3-carbamoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (155 a).

A freshly prepared solution of the diazonium salt (150 c) (1.2g; 0.0069 mol) in water (25 ml) and ethanol (25 ml) was added dropwise, with stirring to a solution of ethyl cyanoacetate (0.79g; 0.0069 mol), and anhydrous sodium acetate (0.80g) in water (2.0 ml), and ethanol (5.0 ml), which was cooled in an ice bath. Stirring was continued in the melting ice-bath for 2h. The reaction mixture was then heated under reflux for 1h and the resultant solid was collected, washed with water and dried *in vacuo* at room temperature to give the triazolotriazine (155 a) (1.45g) (84%), m.p. > 250°(decomp.), which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

The Thermal Cyclization of the Hydrazone (151 h)

The hydrazone (151 h) (0.22g; 0.001 mol) was heated under reflux in dimethylsulphoxide (2.0 ml) for 1 min. The reaction mixture was allowed to cool and then diluted with water. The resultant solid was collected and washed with a little methanol to give 7-amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3,6-dicarboxamide (155 b) (0.14g) (64%), m.p. > 290°(decomp.), which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

The Behaviour of the Triazolotriazines (153 a-e), (154 a), and (155 a-c) with Sodium Hydroxide

The triazolotriazines (153 a-e), (154 a), and (155 a-c) were treated briefly with dilute aqueous sodium hydroxide solution.

(i) The compounds (153 a and b) gave dark red solutions, which, when acidified with dilute sulphuric acid, gave red solutions, without the recovery of the starting material.

(ii) The compounds (153 c-e) and (155 b) were insoluble and were recovered unchanged (i.r. spectra) after filtering off the solid and washing it with water.

(iii) The compound (154 a) gave a red solution, which, when acidified with dilute aqueous sulphuric acid afforded unchanged triazolotriazine which was identical (i.r. spectrum) with starting material.

(iv) The compound (155 a) gave an insoluble sodium salt $\nu_{max.}$ 3350br, and 3200(NH), and 1680, and 1650(CO) cm^{-1} which burned leaving a residue. Acidification of the salt with dilute aqueous sulphuric acid gave an unidentified solid (W), m.p. > 200° (decomp.), $\nu_{max.}$ 3400, and 3300(NH), and 1780-1700br, 1670, 1650, and 1630(CO and NH deformation) cm^{-1}, m/e 251(M^+). Crystallisation of (W) from aqueous dimethylformamide gave a solvate $\nu_{max.}$ 3450w, 3400 and 3150(NH), and 1700w and 1680, and 1630(NH def.) cm^{-1}. An attempt to drive off the solvent of crystallisation by drying the solvate in vacuo at 100° resulted in the decomposition of (W) to a char.

(v) The compound (155 c) gave a red solution which when acidified with dilute sulphuric acid gave a yellow, non-filterable, gelatinous precipitate accompanied by the evolution of hydrogen cyanide.

The Attempted Methylation of the Triazolotriazines (153 a and b), (154 a), and (155 a)

(i) The triazolotriazines (153 a and b) (0.009 mol), anhydrous potassium carbonate (9.6g), and methyl iodide (6.0 ml) were heated under reflux in anhydrous acetone (300 ml) for 3h.

After filtering off the insoluble inorganic material, and evaporating the filtrates, the residues were treated with water and extracted with chloroform.

(a) The extract from the acetyltriazolotriazine (153 a) gave a gummy solid (2.06g), which, on trituration with ethanol, yielded a solid (1.52g), m.p.> 170°(decomp.), which was chromatographed over alumina. Elution with ether-toluene (3:1) afforded a monomethyl derivative (156 a) of the triazolotriazine (153 a)(0.42g) m.p. > 200°(decomp.) (from ethanol-glacial acetic acid), $\nu_{max.}$ 3450,3300, and 3250(NH), and 1690(CO) cm^{-1}, $\lambda_{max.}$ 215,244,283sh,294,302sh and 363nm(log ε 3.79, 3.96,3.92,3.98,3.90 and 3.84), τ [$(CD_3)_2SO$] 1.93br(1H,s,NH), 2.34br (1H,s,NH), 4.03(1H,s,olefinic CH), 4.32(1H,s,olefinic CH), 5.91(3H, s,Me), and 7.55(3H,s,.COMe), m/e234(M^+)(M,234).

Found: C,46.0; H,4.3; N,36.1%.

$C_9H_{10}N_6O_2$ requires: C,46.2; H,4.3; N,35.9%.

Elution with more polar solvents mainly afforded dark intractable oils. However, trituration of the residue obtained by elution with chloroform-methanol (9:1) with a little methanol, gave a yellow solid (0.22g) m.p. 231-40°(decomp.), $\nu_{max.}$ 3600w,3500,3400, and 3300br and 1690-1670br(CO) cm^{-1}, and τ [$(CD_3)_2SO$] 2.01(s,NH), 2.22 (s,NH), 2.42(s,NH), 2.59(s,NH), 2.73(s), 5.89(s,Me), 6.02(s,Me), 7.73 (s,Me), and 8.01(s,Me), and which moved as a single spot on t.l.c. examination.

(b) The extract from the triazolotriazine (153 b) gave an oil (2.22g) which when triturated with ethanol afforded a monomethyl derivative (156 b) of the triazolotriazine (153 b)(0.66g) m.p. > 145°(decomp.). Crystallisation of the solid from ethanol-glacial acetic acid raised the m.p. to 201°, $\nu_{max.}$ 3350-3150br(NH), and 1700, and 1680

(CO)cm^{-1}, $\lambda_{max.}$ 234,241,281sh,295,301sh, and 356nm(log ε 3.95,4.02, 3.83,3.93,3.88 and 3.82), τ($CDCl_3$)4.08(2H,s,olefinic CH_2), 5.57 (2H,q,J7Hz,CH_2),5.77(3H,s,Me), and 8.58(3H,t,J7Hz,Me),m/e 264(M^+) (M,264).

Found: C,45.5; H,4.7; N,31.9%.

$C_{10}H_{12}N_6O_3$ requires: C,45.4; H,4.5; N,31.8%.

Examination of the ethanol mother liquor by t.l.c. showed it to contain a multicomponent mixture.

(ii) The triazolotriazines (154 a) and (155 a)(0.0015 mol), anhydrous potassium carbonate (1.6g), and dimethyl sulphate (0.9 ml) were heated under reflux in anhydrous acetone (50 ml) for 4h. After filtering off the insoluble inorganic material, the acetone filtrates were evaporated under reduced pressure and the residues were treated with water and extracted with chloroform.

(a) The extract from the triazolotriazinone (154 a) gave an oil (0.35g) which on trituration with ethanol afforded a monomethyl derivative (154 b) of the triazolotriazine (154 a)(0.09g) m.p. 233° (from ethanol-glacial acetic acid), $\nu_{max.}$ 3400,3250w, and 3150(NH), and 1720,1680sh, and 1670(CO)cm^{-1}, λ_{max} 240,270 infl., and 338nm(log ε 4.37,3.50, and 2.88), m/e 266(M^+)(M,266).

Found: C,40.8; H,3.8; N,31.6%.

$C_9H_{10}N_6O_4$ requires: C,40.6; H,3.8; N,31.6%.

T.l.c. examination of the oil (0.24g) obtained by evaporating the trituration mother liquor showed it to be a multicomponent mixture.

(b) The solid, obtained by hot filtration of the reaction mixture from (155 a), when washed with water, gave unreacted aminotriazolotriazine (155 a) (0.33g), m.p. > 230°(decomp.), which was identical (i.r. spectrum) with an authentic sample. The chloroform extract gave no solid on trituration of the resultant oil (0.08g) with ethanol.

The Attempted Hydrolysis of Ethyl 7-Amino-3-carbamoyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxylate (155 a) with Dilute Aqueous Sulphuric Acid.

The aminotriazolotriazine (155 a) (0.75g; 0.003 mol) was heated under reflux with 4N aqueous sulphuric acid (7.5 ml) in ethanol (20 ml) or dimethylformamide (20 ml) for 2h.

(i) Unreacted starting material (155 a) (0.73g), m.p. > 250°(decomp.) which was identical (m.p. and i.r. spectrum) with an authentic sample, was filtered off from the hot ethanolic solution.

(ii) The dimethylformamide solution was concentrated to ca.15 ml and compound (W) was collected and combined with a second crop obtained by further concentration of the mother liquor to ca. 5 ml and dilution with water (total 0.67g) m.p. > 190°(decomp.), identical (m.p. and i.r. spectrum) with a sample obtained before.

The Attempted Hydrolysis of the Triazolotriazine Esters (153 b) and (155 a).

(i) The triazolotriazine (153 b) (0.50g; 0.002 mol) was heated under reflux in ethanol (20 ml) with 20% w/v sulphuric acid (5 ml) for 5h. The reaction mixture was concentrated to ca. 5 ml, treated with a little water, made just basic with solid sodium hydrogen carbonate and then readjusted to pH 6 using

dilute aqueous sulphuric acid. Extraction of the reaction mixture with chloroform afforded a gummy solid (0.23g), which on trituration with ethanol-ether gave unreacted triazolotriazine (153 b) (0.11g), m.p. 155-9°, which was identical (m.p. and i.r. spectrum) with an authentic sample. T.l.c. examination of the ethanol-ether mother liquor indicated it to contain a multicomponent mixture.

(ii) The aminotriazolotriazine (155 a) (1.0g; 0.004 mol) was heated under reflux in ethanol (20 ml) with N aqueous sodium carbonate solution (10 ml) for 1h. The solid collected on cooling was stirred in dilute aqueous sulphuric acid to give compound (W) (0.89g), m.p. > 200° (decomp.), which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

The Attempted Hydrolysis of the Triazolotriazine-3-carboxamides (153 a and b) and (155 a)

(i) The triazolotriazines (153 a) and (155 a) (0.004 mol) were heated under reflux in glacial acetic acid (20 ml) with 20% w/v sulphuric acid (10 ml) for 1-3h giving black solutions.

(a) Concentration of the reaction mixture from the acetyltriazolotriazine (153 a) to ca. 10 ml and extraction of the mother liquor with chloroform gave a black intractable tar (0.12 g).

(b) Concentration of the reaction mixture from the aminotriazolotriazine (155 a) to ca. 10 ml, and neutralisation with solid sodium hydrogen carbonate, gave no material after extraction with chloroform.

(ii) Solutions of the triazolotriazines (153 b) and (155 a) (0.002 mol) in 90% w/v sulphuric acid (3.0 ml) were stirred and cooled to 0° (ice-bath), and treated dropwise with a solution of 0.5N aqueous

sodium nitrite (3.2 ml). After the additions were complete, the reaction mixtures were stirred for a further 5 min and were then diluted with water (10 ml).

(a) The resultant solid obtained from the triazolotriazine (153 b) was filtered off and washed with water to give unreacted starting material (153 b) (0.20g), m.p. 155-9°, which was identified by its m.p. and i.r. spectrum. Extraction of the mother liquor with chloroform after neutralizing with solid sodium hydrogen carbonate afforded no material.

(b) The triazolotriazine (155 a) afforded unreacted starting material (0.38g), m.p. > 250°C (decomp.), which was identified by its m.p. and i.r. spectrum.

The Attempted Reaction of 6-Acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 a) with Acetic Anhydride.

The triazolotriazine (153 a) (0.55g; 0.0025 mol) was heated under reflux in acetic anhydride (3.0 ml) for 30 min. Evaporation of the resultant black reaction mixture using toluene to azeotrope off any remaining acetic anhydride gave a black intractable tar (0.57g).

The Reaction of 6-Acetyl-7-methyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (153 a) with Phenylhydrazine.

The triazolotriazine (153 a) (0.44g; 0.002 mol) and phenylhydrazine (0.22g) were heated under reflux in methanol (20 ml) for 3h. The azo compound (157), was deposited on cooling and was combined with a second crop which was obtained by evaporating the mother liquor and triturating the residue with a little methanol (total 0.54g) (87%), (from glacial acetic acid-dimethylformamide),

$\nu_{max.}$ 3400,3300, and 3100(NH), and 1680(CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.07-2.74 (7H,m,ArH and NH), 7.39(3H,s,Me) and 7.53(3H,s,Me),m/e 310(M^+)(M,310).

Found: C,53.8; H,4.7; N,35.7%.

$C_{14}H_{14}N_8O$ requires: C,54.2; H,4.5; N,36.1%.

Experiments with 7-Amino-6-cyano-1,2,3-triazolo[5,1-c]-1,2,4-triazine-3-carboxamide (155 c).

(i) Reaction with Glacial Acetic Acid

The triazolotriazine (155 c)(0.25g) was heated under reflux in glacial acetic acid (5.0 ml) for 30 min. Evaporation of the reaction mixture and trituration of the residue with ether gave an acetic acid solvate of the triazolotriazine (155 c)(0.25g), $\nu_{max.}$ 3450-3150br(NH), 2900-2350br(acetic acid), 2300w, and 2200(CN), and 1700(CO), and 1650br(NH deformation) cm^{-1}. Treatment of the solvate with saturated aqueous sodium hydrogen carbonate solution caused effervescence and resulted in the formation of the free triazolotriazine (155 c) which was identified by its i.r. spectrum.

(ii) Attempted Reaction in Dimethylsulphoxide.

The triazolotriazine (155 c)(0.25g) was heated under reflux in dimethylsulphoxide (1.0 ml) for 1 min. Dilution with water gave unchanged triazolotriazine (155 c)(0.25g) which was identified by its i.r. spectrum.

(iii) Attempted Reaction with Polyphosphoric Acid

The triazolotriazine (155 c)(0.41g; 0.002 mol) was stirred in polyphosphoric acid (ca. 3 ml) for 3h at 80°. The reaction mixture was diluted with water and scratched but no solid was deposited. The reaction mixture was made just alkaline with

solid sodium hydrogen carbonate and scratched. No solid was obtained and extraction with chloroform afforded no material.

(iv) Reaction with Acetic Anhydride

The triazolotriazine (155 c) (0.21g; 0.001 mol) was heated under reflux in acetic anhydride (5.0 ml) for 5 min. The solid deposited on cooling was combined with a second crop obtained by evaporating the mother liquor and triturating the residue with ether (total, 0.25g), m.p. 154-9°(decomp.). T.l.c. examination of the solid showed it to be a mixture containing at least five components. Crystallisation of a sample of the solid from ethanol-glacial acetic acid did not purify the solid.

Table 1

Analytical Data for the (1,2,3-Triazol-5-yl)hydrazones (151 a-g)

Active methylene compd.	Hydrazone	Mol.Formula	Found(%)			Required(%)		
			C	H	N	C	H	N
acetylacetone	151 a	$C_8H_{10}N_6O_3$	40.5	4.4	35.5	40.4	4.2	35.3
ethyl acetoacetate	151 b	$C_{11}H_{14}N_6O_5$	42.9	4.5	26.7	42.6	4.5	27.1
benzoylacetone	151 c	$C_{13}H_{12}N_6O_3$	52.3	4.6	26.4	52.0	4.0	28.0
dibenzoylmethane	151 d	$C_{18}H_{14}N_6O_3$	59.2	4.1	22.9	59.6	3.9	23.2
diethyl malonate	151 e	$C_{10}H_{14}N_6O_5$	40.6	4.7	28.2	40.3	4.7	28.0
ethyl benzoylacetate	151 f	$C_{14}H_{14}N_6O_4$	50.9	4.2	25.1	50.9	4.2	25.5
ethyl cyanoacetate	151 g	$C_8H_9N_7O_3$	38.8	4.0	38.1	38.2	3.6	39.1

Table 2

Analytical Data for the Monoacetyl Derivatives of the (1,2,3-Triazol-5-yl)hydrazones (151 a-f).

Hydrazone	Monoacetyl Derivative	Mol.Formula	Found(%)			Required(%)		
			C	H	N	C	H	N
151 a	151 j	$C_{10}H_{12}N_6O_4$	43.2	4.1	29.6	42.9	4.3	30.0
151 b	151 k	$C_{11}H_{14}N_6O_5$	42.9	4.5	26.7	42.6	4.5	27.1
151 c	151 l	$C_{15}H_{14}N_6O_4$	53.0	4.1	25.0	52.6	4.1	24.6
151 d	151 m	$C_{20}H_{16}N_6O_4$	59.2	4.0	21.0	59.4	4.0	20.8
151 e	151 n	$C_{12}H_{16}N_6O_6$	42.5	4.8	24.4	42.3	4.7	24.7
151 f	151 o	$C_{16}H_{16}N_6O_5$	51.1	4.2	22.4	51.6	4.3	22.6

Table 3

Analytical Data for the 1,2,3-Triazolo[5,1-c]-1,2,4-triazines (153 a-e), (154 a), and (155 a-c)

Triazolotriazine	Mol.Formula	Found(%)			Required(%)		
		C	H	N	C	H	N
153 a	$C_8H_8N_6O_2$	43.6	3.6	38.0	43.7	3.6	38.2
153 b	$C_9H_{10}N_6O_3$	43.4	4.0	33.0	43.2	4.0	33.6
153 c	$C_{13}H_{10}N_6O_2$	55.6	3.5	29.5	55.4	3.5	29.8
153 d	$C_{18}H_{12}N_6O_2$	62.5	3.6	24.0	62.8	3.5	24.4
153 e	$C_{14}H_{12}N_6O_3$	54.2	4.0	26.5	53.8	3.9	26.9
154 a	$C_8H_8N_6O_4$	37.6	3.1	33.2	38.1	3.2	33.3
155 a	$C_8H_9N_7O_4$	38.5	3.6	39.1	38.2	3.6	39.1
155 b	$C_6H_6N_8O_2$	32.1	2.7	50.8	32.4	2.7	50.5
155 c	$C_6H_4N_8O$	33.9	2.3	52.7	35.3	2.0	54.9

2.9 Some Coupling Reactions of 2H-1,2,4-Triazole-3-diazonium Nitrate and the Synthesis and Reactivity of the 1,2,4-Triazolo[5,1-c]-1,2,4-triazine Ring System.

2H-1,2,4-Triazole-3-diazonium Nitrate (215 b)

A solution of sodium nitrite (0.9g) in the minimum volume of water was added dropwise at 0°(ice-bath) to a stirred suspension of 3-amino-2H-1,2,4-triazole(215 a)(1.26g; 0.015 mol) in a mixture of concentrated nitric acid (1.5 ml) and water (3.5 ml). Stirring was continued for a further 15 min at 0° and the resulting diazonium salt solution was used directly in the coupling reactions described below.

Coupling Reactions of the Diazonium Salt (215 b) with Some Active Methylene Compounds.

A freshly prepared solution of the diazonium salt (215 b) (0.015 mol) was added dropwise, with stirring, to a solution of an active methylene compound (0.015 mol) and anhydrous sodium acetate (1.6 g) in water (4.0 ml) and ethanol (10 ml). Stirring in the melting ice-bath was continued for 2h.

(a) Acetylacetone afforded pentane-2,3,4-trione 3-(2H-1,2,4-triazol-3-yl)hydrazone (216 a) which was filtered off from the reaction mixture and washed with water (63%), m.p. 158°(from ethanol), $\nu_{max.}$ 3300 and 3100br(NH), and 1690(CO) cm^{-1}, $\lambda_{max.}$ 207,230sh and 306nm(log ε 3.92, 3.68, and 3.95) τ[$(CD_3)_2SO$] 2.17(1H,s,H-5), 2.84br(1H,s,NH), 7.65 (3H,s,Me) and 7.91(3H,s,Me), m/e 195(M^+), and 177(M^+-H_2O) (M,195).

Found: C,43.0; H,4.7; N,35.9%.

$C_7H_9N_5O_2$ requires: C,43.1; H,4.6; N,35.9%.

The mother liquor was concentrated to ca. 20ml and the amorphous solid (A) was collected and combined with a second crop, obtained by extracting the mother liquor with chloroform and triturating the resultant gum with ether (total 0.37g), m.p. 196°(decomp.) (from ethanol), $\nu_{max.}$ 3500-3100br(NH), and 1690br(CO) cm^{-1}, $\lambda_{max.}$ 208 and 319nm(log ε 3.72 and 3.77), m/e 177. The ^1H n.m.r. spectrum of (A) in $[^2H_6]$ dimethylsulphoxide is broad and unresolved.

Found: C,45.4; H,4.2; N,37.1%.

Calculated for $C_7H_7N_5O.\frac{1}{2}H_2O$; C,45.1; H,4.3; N,37.6%.

(b) Ethyl acetoacetate afforded an amorphous solid (B) which was washed with dilute hydrochloric acid, then water and combined with a second crop obtained by diluting the acidic washings with water (total 0.43g), m.p. 200-3°, $\nu_{max.}$ 3500-3000br(NH), and 1720 cm^{-1}, m/e 207. The ^1H n.m.r. spectrum of (B) in $[^2H_6]$ dimethylsulphoxide is broad and unresolved. Concentration of the mother liquor to ca. 20 ml gave a further crop of solid (0.92g), m.p. 178-80°, which has identical i.r., ^1H n.m.r., and mass spectral properties to those described for (B) above. Crystallisation of this solid from ethanol-glacial acetic acid raised its m.p. to 189°.

Found: C,44.7; H,4.4; N,32.2%.

Calculated for $C_8H_9N_5O_2.\frac{1}{2}H_2O$: C,44.5; H,4.6; N,32.4%.

Extraction of the remaining aqueous solution with chloroform gave no further material.

(c) Benzoylacetone afforded a solid (2.75g), which after washing, with water, was leached with boiling light petroleum leaving the insoluble 1-phenylbutane-1,2,3-trione 2-(2H-1,2,4-triazol-3-yl) hydrazone (216 c) (2.34g), m.p. 137° (from ethyl acetate), $\nu_{max.}$ 3300-3100br(NH), and 1640(CO)cm^{-1}, τ [$(CD_3)_2SO$] 2.11(1H,s,H-5), 2.14-2.61 (5H,m,ArH), 2.71br(1H,s,NH), 7.72(s,Me), and 7.84(s,Me), m/e 257 (M^+), and 239(M^+-H_2O) (M,257).

Found: C,55.9; H,4.3; N,27.4%.

$C_{12}H_{11}N_5O_2$ requires: C,56.0; H,4.3; N,27.2%.

The mother liquor was concentrated to ca. 20 ml and the solid (0.73g) was collected and leached with boiling light petroleum, leaving an insoluble amorphous solid (C) (0.69g), m.p. 157° (from ethanol-light petroleum), $\nu_{max.}$ 3400-3000br(NH), and 1650br(CO)cm^{-1}, m/e 239. The ^1H n.m.r. spectrum of (C) in [$^2H_6$] dimethylsulphoxide was broad and unresolved.

Found: C,58.3; H,3.9; N,28.4%.

Calculated for $C_{12}H_9N_5O.\frac{1}{2}H_2O$: C,58.1; H,4.0; N,28.2%.

Evaporation of the combined light petroleum mother liquors gave benzoylacetone (0.45g). Extraction of the remaining aqueous solution with chloroform gave no further material.

(d) Dibenzoylmethane gave a solid, which was collected and combined with a second crop obtained by concentration of the mother liquor (total 3.31g). The solid was leached with boiling light petroleum leaving the insoluble 1,3-diphenylpropane-1,2,3-trione 2-(2H-1,2,4-triazol-3-yl)hydrazone (216 d) (1.66g), m.p. 184° (from aqueous ethanol), $\nu_{max.}$ 3300 and 3100br(NH), and 1650(CO)cm^{-1}, τ [$(CD_3)_2SO$]

2.22(1H,s,H-5), and 1.96-2.72(11H,m,ArH and NH), m/e 319(M^+) and 301(M^+-H_2O) (M,319).

Found: C,63.8; H,4.1; N,22.0%.

$C_{17}H_{13}N_5O_2$ requires: C,64.0; H,4.1; N,21.9%.

Evaporation of the light petroleum mother liquor gave dibenzoylmethane (1.60g). Extraction of the remaining aqueous solution with chloroform gave no further material.

(e) Benzoylacetonitrile afforded a solid which was combined with a further crop, obtained by concentrating the mother liquor to ca. 20 ml(total 2.66g). This solid was stirred in cold benzene leaving an insoluble solid (1.24g), which was crystallised from ethanol leaving an insoluble unidentified solid (0.21g).

Phenylglyoxalonitrile 1-(2H-1,2,4-triazol-3-yl)hydrazone(216 e) crystallised from the ethanol as the ethanol solvate (1.03g), τ[$(CD_3)_2SO$] 1.30br(1H,s,NH), 2.09(1H,s,H-5), 2.56(5H,s,ArH), 6.54 (q,J7Hz,CH_2), and 8.94(t,J7Hz,Me). Drying at 80° for 17h liberated the free hydrazone (216 e), m.p. 168°(from ethanol), $\nu_{max.}$ 3300-3100br (NH), 2250(.C ≡ N), and 1600(CO)cm^{-1}, τ[$(CD_3)_2SO$] 1.30br(1H,s,NH), 2.09(1H,s,H-5), and 2.56(5H,s,ArH), m/e 240(M^+) (M,240).

Found: C,55.0; H,3.4; N,35.0%.

$C_{11}H_8N_6O$ requires: C,55.0; H,3.3; N,35.0%.

Evaporation of the benzene mother liquor gave benzoylacetonitrile (1.13g). Extraction of the remaining aqueous solution with chloroform gave an intractable red gum (0.32g).

(f) Ethyl cyanoacetate and malononitrile gave ethyl cyanoglyoxalate 2-(2H-1,2,4-triazol-3-yl)hydrazone (216 f) (99%), m.p. 150-5°, $\nu_{max.}$ 3650,3400, and 3200(NH),2250(.C ≡ N), and 1720(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.63 (1H,s,H-5), 5.75(2H,q,J7Hz,CH_2), and 8.73(3H,t,J7Hz,Me), m/e 208(M^+)(M,208), and mesoxalonitrile 2-(2H-1,2,4-triazol-3-yl) hydrazone(216g)(76%), m.p. > 190°(decomp.), $\nu_{max.}$ 3500,3400 and 3200-3000br(NH), and 1690(NH def.)cm^{-1}, τ [$(CD_3)_2SO$] 1.10(s,NH), m/e 161(M^+)(M,161). The attempted crystallisation of the hydrazones (216 f and g) from ethanol, glacial acetic acid or dimethylformamide gave the triazolotriazines (218 b and c) which were identical with samples obtained later.

(g) Cyanoacetamide afforded a red resinous solid (1.16g), m.p. > 200° (decomp.). The resin was crystallised from dimethylformamide, m.p. 250°(decomp.), to give a solid which showed ill-defined i.r. and ^1H n.m.r. spectra. The mass spectrum contained peaks due to high molecular weight fragments up to, and greater than 400 mass units. Concentration of the mother liquor to ca. 20 ml afforded a solid (0.39g), m.p. > 200°(decomp.), which was leached with boiling water leaving a further crop of red resinous material (0.28g), m.p. > 200° (decomp.). Evaporation of the aqueous extract afforded 7-amino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide(218 d)(0.11g), m.p. > 220°(decomp.)(from water), $\nu_{max.}$ 3400,3250br and 3100br(NH), and 1680br(CO)cm^{-1}, τ [$(CD_3)_2SO$] 0.4-0.8br(2H,s,NH), 1.24(1H,s,H-2), 1.44br(1H,s,NH) and 2.16br(1H,s,NH), m/e 179(M^+)(M,179). No u.v. data was obtained due to the insolubility of (218 d) in ethanol.

Found: C,32.4; H,2.8; N,52.3%.

$C_5H_5N_7O$ requires: C,33.6; H,2.8; N,54.7%.

(h) Ethyl benzoylacetate afforded the insoluble ethyl 2-benzoylglyoxylate 2-(2H-1,2,4-triazol-3-yl)hydrazone(216 i). A further crop was obtained by concentrating the mother liquor to ca. 20 ml. The solids were combined (2.95g), m.p. 139-44° (from ethyl acetate), $\nu_{max.}$ 3400, and 3250-3000br(NH), and 1700 and 1690sh(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.99(1H,s,NH),2.16(1H,s,H-5),2.66(5H,s,ArH),6.00(q, J7Hz,CH_2)6.02(q,J7Hz,CH_2), and 8.98(3H,t,J7Hz,Me), m/e 287 (M^+)(M, 287).

Found: C,54.6; H,4.5; N,24.4%.

$C_{13}H_{13}N_5O_3$ requires: C,54.4; H,4.5; N,24.4%.

Extraction of the mother liquor with chloroform afforded ethyl benzoylacetate (0.56g).

(i) Diethyl malonate gave diethyl mesoxalate 2-(2H,1,2,4-triazol-3-yl)hydrazone(216 j)(1.84g), m.p. 140°(from ethanol), $\nu_{max.}$ 3200-2700br(NH), and 1720 and 1690(CO)cm^{-1},τ [$(CD_3)_2SO$] 1.69(1H,s,H-5), 5.68(2H,q,J7Hz,CH_2),5.75(2H,q,J7Hz,CH_2), 8.72(3H,t,J7Hz,Me), and 8.73(3H,t,J7Hz,Me), m/e 255(M^+)(M^+,255).

Found: C,42.5; H,5.0; N,27.7%.

$C_9H_{13}N_5O_4$ requires: C,42.4; H,5.1; N,27.5%.

Concentration of the mother liquor to ca. 20 ml afforded a solid, which when acidified with dilute aqueous sulphuric acid gave the hydrate of ethyl 4,7-dihydro-7-oxo-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (219 b),$\nu_{max.}$ 3100-2400br(NH,OH) and 1740br and 1700sh(CO)cm^{-1}. The solvent of crystallisation was driven off by drying at 80° for 4h, and the solid was combined with a

further crop obtained by extracting the mother liquor with chloroform and triturating the resultant gummy residue with ether (total 0.42g), m.p. 204°. The triazolotriazine(219 b) was identical (m.p. and i.r. spectrum) with a sample obtained later.

Reactions of the (1,2,4-Triazol-3-yl)hydrazones(216 a, c-g, i and j)

Action of Dilute Aqueous Sodium Hydroxide Solution

The hydrazones (216 a, c-f, i and j) were immediately soluble in dilute aqueous sodium hydroxide solution giving red, orange or yellow solutions. The hydrazone (216g) gave a colourless, sparingly soluble salt which gave a yellow solution with hot water.

Immediate acidification of the alkaline solutions of (216 a and c) with dilute aqueous hydrochloric acid gave the amorphous solids (A) and (C) respectively, which were identical (m.p. and i.r. spectrum) with samples obtained as described before.

Similar acidification of the alkaline solutions of (216 d-f) or of the sodium salt derived from (216 g) regenerated the unchanged hydrazones, which were identified by m.p. and i.r. spectrum.

Acidification of the alkaline solutions obtained from (216 i and j) afforded the triazolotriazines (219 a and b) which were identical (m.p. and i.r. spectrum) with samples obtained later.

The Attempted Acetylation of the Hydrazones (216 a and j)

(i) The hydrazone (216 a)(0.39g; 0.002 mol) was warmed in acetic anhydride (1.5 ml) until the suspended solid dissolved. The excess of acetic anhydride was evaporated under reduced pressure, using toluene to remove the last traces, to give a gum (0.38g), which was shown by t.l.c. to be a multicomponent mixture.

(ii) Treatment of the hydrazone (216 j) (0.51g; 0.002 mol) with acetic anhydride as described in (i) above, gave a gum which was treated with ether to afford starting material (82%), identified by i.r. spectrum.

(iii) Heating the hydrazone (216j) (0.51g; 0.002 mol) under reflux in acetic anhydride (1.5 ml) for 0.75h, and the mixture worked up as in (i) above, gave starting material (48%) which was identified by its i.r. spectrum. Examination of the mother liquor by t.l.c. showed a multicomponent mixture.

The Cyclization of (1,2,4-Triazol-3-yl)hydrazones to 1,2,4-Triazolo-[5,1-c]-1,2,4-triazines

(a) The hydrazones (216 d-g, i and j) (0.002 mol) were heated under reflux in glacial acetic acid (10 ml) for 2h. The reaction mixtures were allowed to cool and any solid was collected, washed with ether, and dried with suction. Further crops were obtained by evaporating the filtrates under reduced pressure and triturating the gummy residues with ether. Both crops were combined and crystallised to give the triazolotriazines (217 d), (218 a-c) and (219 a and b) (57-70%).

6-Benzoyl-7-phenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (217 d) had m.p. 194° (from benzene), $\nu_{max.}$ 1680 (CO) cm^{-1}, $\lambda_{max.}$ 213,258, and 331nm (log ε 4.32,4.29, and 3.91), τ [$(CD_3)_2SO$] 0.90 (1H,s,H-2), and 1.96-2.64 (10H,m,ArH), m/e 301 (M^+) (M,301).

Found:	C,68.2;	H,3.7;	N,23.4%.
$C_{17}H_{11}N_5O$ requires:	C,67.8;	H,3.7;	N,23.2%.

7-Amino-6-benzoyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine(218 a) had m.p. 224°(from benzene-glacial acetic acid), $\nu_{max.}$ 3400 and 3100 (NH), and 1640(CO)cm^{-1}, $\lambda_{max.}$ 216,243 infl.,300, and 331 nm(log ε 4.23,3.87,4.08, and 4.15),τ [$(CD_3)_2SO$] 0.40br(2H,s,NH),1.10(1H,s,H-2), and 2.00-2.56(5H,m,ArH), m/e 240(M^+)(M,240).

Found: C,55.3; H,3.5; N,35.4%.

$C_{11}H_8N_6O$ requires: C,55.0; H,3.3; N,35.0%.

Ethyl 7-amino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (218 b) had m.p. 210°(from ethanol-glacial acetic acid), $\nu_{max.}$ 3400 and 3250-3100br(NH), and 1710(CO)cm^{-1}, $\lambda_{max.}$ 215,229,282 and 325nm (log ε 4.04,4.07,3.90 and 4.02), τ [$(CD_3)_2SO$] 1.23(1H,s,H-2),5.55 (2H,q,J7Hz,CH_2), and 8.61(3H,t,J7Hz,Me), m/e 208(M^+)(M,208).

Found: C,40.4; H,4.0; N,40.4%.

$C_7H_8N_6O_2$ requires: C,40.4; H,3.8; N,39.8%.

7-Amino-6-cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazine(218 c) had m.p. > 240°(decomp.)(from ethanol-glacial acetic acid), $\nu_{max.}$ 3400 (NH), 2250(.C ≡ N), and 1660(NH def.)cm^{-1}, $\lambda_{max.}$ 210,228,279,284sh, and 332nm(log ε 4.19,4.10,3.88,3.85, and 3.98),τ [$(CD_3)_2SO$] 0.25br (2H,s,NH) and 1.10(1H,s,H-2), m/e 161(M^+)(M,161).

Found: C,36.1; H,1.9; N,58.7%.

$C_5H_3N_7$ requires: C,37.2; H,1.9; N,60.9%.

6-Benzoyl-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(219 a) had m.p. 255°(from glacial acetic acid), $\nu_{max.}$ 3200 and 3150(NH), and 1720 and 1670(CO)cm^{-1}, $\lambda_{max.}$ 210,257 and 310nm(log ε 4.19, 4.06 and 3.97),τ [$(CD_3)_2SO$] 1.51(1H,s,H-2), and 1.90-2.53(5H,m,ArH), m/e 241(M^+)(M,241).

Found: C,54.6; H,3.0; N,29.3%.

$C_{11}H_7N_5O_2$ requires: C,54.8; H,2.9; N,29.0%.

Ethyl 4,7-dihydro-7-oxo-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (219 b) had m.p. 204°(from ethanol), $\nu_{max.}$ 3100-2600br (NH), and 1750 and 1690(CO) cm^{-1}, $\lambda_{max.}$ 208,220sh,261sh,269 infl.,273 and 318nm(log ε 4.07,3.94,3.64,3.68,3.70 and 4.00), τ $[(CD_3)_2SO]$ 1.56 (1H,s,H-2), 5.64(2H,q,J7Hz,CH_2), and 8.68(3H,t,J7Hz,Me), m/e 209 (M^+) (M,209).

Found: C,40.1; H,3.3; N,33.7%.

$C_7H_7N_5O_3$ requires: C,40.2; H,3.3; N,33.5%.

(b) The hydrazones (216 a and c) (0.005 mol) were heated under reflux in glacial acetic acid (20 ml) for 1-2h. Evaporation of the solvent and trituration of the resultant gums with ether afforded the solids (A) (0.97g) and (C) (1.15g) which were identical (i.r. spectrum) with samples obtained previously.

(c) The hydrazones (216 a, f and j) (0.0015 mol) in ethanol (5.0 ml) and water (2.0 ml) were heated under reflux with anhydrous sodium acetate (0.12g) for 1h.

(i) In the case of (216 a), evaporation of the mixture and trituration of the resultant solid residue with water afforded the solid (A) (0.29g), identical [m.p.196°(decomp.) and i.r. spectrum] with a sample obtained previously.

(ii) Evaporation of the mixture from the hydrazone (216 f) and trituration of the gummy residue with water gave the aminoester (218 b) (0.14g), identical (m.p. 210° and i.r. spectrum) with a sample obtained previously. The aqueous mother liquors were evaporated and the resultant cake was leached with hot methanol.

Evaporation of the methanol gave a solid (0.12g), which was separated by extraction with hot chloroform (50 ml) into the soluble amino-ester (218 b)(0.04g) and the sodium salt of the ketonitrile (219 c). Acidification of the latter with dilute aqueous hydrochloric acid gave the hydrate of 6-cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(219 c)(0.05g), $\nu_{max.}$ 3500, and 3400-2400br(NH,OH), and 1700br(CO) cm^{-1}, which when heated at 80° for 4h gave the free triazolotriazine (219 c), sublimes at 240°(from ethanol), $\nu_{max.}$ 3000-2600br(NH), 2300sh (.C ≡ N), and 1720(CO) cm^{-1}, $\lambda_{max.}$ 213,217sh, 253,257sh, 275, and 319nm(log ε 3.93,3.93, 3.64, 3.63, 3.52 and 3.98), τ $[(CD_3)_2SO]$ 1.46(1H,s,H-2), m/e 162(M^+)(M,162).

Found: C,37.2; H,1.4; N,51.9%.

$C_5H_2N_6O$ requires: C,37.0; H,1.2; N,51.9%.

(iii) Evaporation of the mixture from the hydrazone (216 j) and acidification of the residue with dilute aqueous sulphuric acid gave a solid, which when dried at 80° for 4h, afforded the triazolo-triazine (219 b)(77%), identical (m.p. 204° and i.r. spectrum) with a sample obtained previously.

The Direct Synthesis of 1,2,4-Triazolo[5,1-c]-1,2,4-triazines from 2H-1,2,4-Triazole-3-diazonium Nitrate (215 b)

A freshly prepared solution of the diazonium salt (215 b) (0.015 mol) was added dropwise to a cooled (ice-bath), stirred solution of the appropriate active methylene compound (0.015 mol), and anhydrous sodium acetate (1.6g) in water (4.0 ml) and ethanol (10 ml). The reaction mixture was stirred in the melting ice-bath

for 1h, and was then heated under reflux for a further 1h(0.5h in the case of malononitrile.

(a) The cooled mixture from dibenzoylmethane afforded a solid which was washed with water and combined with a second crop obtained by evaporating the mother liquor and treating the residue with a little water. The crude solid product was extracted with hot light petroleum to give the hydrazone (216 d)(2.02g), identical(m.p. 184° and i.r. spectrum) with a sample obtained as described previously. Evaporation of the light petroleum extract afforded dibenzoylmethane (1.59g). Extraction of the remaining aqueous solution with chloroform gave no more material.

(b) Benzoylacetonitrile gave the ethanol solvate of the triazolotriazine (218 a), τ [$(CD_3)_2SO$] 0.36br(2H,s,NH), 1.10(1H,s,H-2), 2.00–2.27(5H,m,ArH),6.55(q,J7Hz,CH_2), and 8.96(t,J7Hz,Me). The free triazolotriazine (218 a)(2.05 g)(57%),[identical (m.p.224° and i.r. spectrum) with a sample obtained previously] was obtained by drying the solvate at 80° for 4h. Concentration of the mother liquor to ca. 20 ml gave a solid (1.06g), m.p. 76-135°, which was shown by t.l.c. to be a mixture of at least five components, and did not give any recognisable material on crystallisation from ethanol-glacial acetic acid. Acidification of the remaining aqueous solution followed by extraction with chloroform gave no more material.

(c) Evaporation of the reaction mixture from ethyl cyanoacetate afforded a solid cake which was leached with hot water (25 ml) leaving the insoluble triazolotriazine (218 b), more of which was obtained by evaporating the aqueous extract and re-extracting with hot water (total 0.57g).

The aqueous mother liquor was made up to 25 ml with water and subjected to a constant chloroform extraction for 60h. The chloroform extract gave a solid, which was crystallised from a mixture of ethanol (10 ml) and glacial acetic acid (5.0 ml), to give more of the triazolotriazine (218 b)(0.35 g) which was identical (m.p. 210° and i.r. spectrum) with a sample obtained previously.

Acidification of the aqueous mother liquor, remaining after constant chloroform extraction, with dilute aqueous hydrochloric acid gave a solid which was crystallised from ethanol to afford the triazolotriazine (219 c)(0.33g) which was identical (m.p. 240° and i.r. spectrum) with a sample obtained previously. Extraction of the acidic mother liquor with chloroform gave no more material.

(d) Malononitrile afforded the hydrazone (216g)(1.15g)(48%), identical [m.p. 240°(decomp.) and i.r. spectrum] with a sample prepared as described previously. Concentration of the mother liquor to ca. 20 ml gave a black intractable solid (0.30g). No material was obtained on acidification of the aqueous mother liquor and extraction with chloroform.

(e) Cyanoacetamide gave a resinous red solid which was combined with a second crop, obtained by concentrating the mother liquor to ca. 20 ml. The solid, when warmed with water, left the insoluble aminoamide (218 d)(0.78g)(29%), which was identical (m.p. > 220° and i.r. spectrum) with a sample obtained previously. Evaporation of the aqueous extract gave a resinous red solid (0.72g) which showed ill-defined i.r. and ^{1}H n.m.r. spectra, identical with those of the resinous solid obtained in the reaction between the

diazonium salt (215 b) and cyanoacetamide, at low temperature described before.

(f) The mixture obtained from ethyl benzoylacetate was concentrated to ca. 20 ml and extracted with chloroform to give a gum (0.88g) which was shown by t.l.c. to be a multicomponent mixture. Acidification of the aqueous solution with dilute sulphuric acid gave the triazolotriazine (219 a)(1.74g)(48%) which was identical (m.p. 255° and i.r. spectrum) with a sample obtained as described previously. Extraction of the remaining aqueous solution with chloroform gave no further material.

(g) Diethyl malonate gave a solid which was combined with a second crop obtained by concentrating the mother liquor to ca. 20 ml. Acidification of the solid with dilute hydrochloric acid gave the hydrate of the triazolotriazine (219 b)(1.51g) which was identical (m.p. 204° and i.r. spectrum) with a sample obtained previously.

4,7-Dihydro-7-oxo-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylic Acid (219 d)

(a) A freshly prepared solution of the diazonium salt (215 b) (0.06 mol) was added dropwise to a cooled solution of diethyl malonate(0.06 mol) and sodium carbonate (8.4g) in water (16 ml) and ethanol (40 ml). Stirring was continued for 1h, and the mixture was then heated under reflux for a further 2h. The solid was collected on cooling and acidified with dilute hydrochloric acid to give a hydrated form of the acid (219 d)(7.0g), $\nu_{max.}$ 3500-3100br, and 2700-2300br(NH,OH and H_2O), 1940-1820(H_2O) and 1740-1680br(CO)cm^{-1}, which was crystallised from ethanol glacial acetic acid to give the free acid (219 d), m.p. 194°(decomp.),

$\nu_{max.}$ 3200-2600br(NH,OH), and 1750 and 1690br(CO), $\lambda_{max.}$ 216,247 infl., 380sh, and 312nm(log ε 4.15,3.64,3.73, and 3.98), τ [$(CD_3)_2SO$] 1.60(1H, s,H-2), m/e 181(M^+) and 137(M^+-CO_2) (M,181).

Found: C,33.2; H,1.8; N,38.5%

$C_5H_3N_5O_3$ requires: C,33.2; H,1.7; N,38.6%.

Concentration of the mother liquor to ca. 20 ml afforded a solid, which when acidified with dilute hydrochloric acid, gave the hydrate of the triazolotriazine (219 b)(1.40g) which was identical (m.p. 204° and i.r. spectrum) with a sample prepared before.

(b) The acid (219 d) was also obtained when the ester (219 b)(0.42g; 0.002 mol) was heated under reflux with 2N aqueous sodium carbonate solution (5.0 ml) in ethanol (10 ml) for 1h. The solid which separated on cooling was collected and acidified with dilute aqueous hydrochloric acid to give the hydrate of the acid (219 d)(0.35g) m.p. 201-4°.

When the hydrate of the acid (219 d) was prepared, by the methods described, and crystallised from water, a second hydrated form was obtained, $\nu_{max.}$ 3600,3500,3100,2800-2300br(NH,OH, H_2O), 1940-1820br(H_2O), and 1720-1680br(CO)cm^{-1}. The m.p. and ^1H n.m.r. spectra of the free acid (219 d) and both of its hydrated forms were identical.

Investigation of the Solids (A,B and C)

(a) The Action of Aqueous Alkali

The solids (A,B and C) were all immediately soluble in dilute aqueous sodium hydroxide solution giving red solutions, acidification of which with dilute aqueous sulphuric acid regenerated the solids,

identical (m.p. and i.r. spectrum), with authentic samples.

(b) The Attempted Methylation of the Solid (A)

The solid (A) (0.37g), suspended in methanol (3.0 ml) was treated with 4% w/v aqueous sodium hydroxide solution (3.0 ml). The resulting solution was treated with methyl iodide (0.6 ml) and the reaction mixture was shaken at room temperature for 5h. Evaporation of the methanol followed by extraction of the remaining aqueous solution with chloroform gave a froth (0.34g), which was insoluble in dilute aqueous sodium hydroxide solution. T.l.c. examination of the froth was inconclusive. The ^{1}H n.m.r. spectrum of the froth (in $CDCl_3$) contained a multitude of unassignable peaks. Mass spectra of the froth, run at 180°, 220° and 240°, showed no apparent parent ion and contained peaks due to many high molecular weight fragments.

(c) The Attempted Benzoylation of the Solid (A)

The solid (A) (0.93g) was shaken with 10% w/v aqueous sodium hydroxide solution (5.0 ml) and benzoyl chloride (0.64 ml) for 15 min. The resultant insoluble solid was combined with a second crop which precipitated on extraction of the mother liquor with chloroform. After being washed with water, the solid burned leaving a residue. After washing with a little dilute hydrochloric acid, followed by water, the solid (0.54g) had m.p. > 200° (decomp.), did not leave a residue on burning, and was identical (i.r. spectrum) with starting material. The chloroform extract gave no material. Acidification of the remaining aqueous mother liquor with dilute hydrochloric acid gave benzoic acid (0.57g), m.p. 117-20°,

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

(d) The Attempted Hydrogenolysis of the Solid (A)

No uptake of hydrogen was observed after 2h when hydrogenation of the solid (A) (0.37g) was attempted in ethanol (100 ml) over 10% palladium-charcoal. Evaporation of the filtered mixture gave a quantitative recovery of starting material which was identified by its m.p. 175-84°, and i.r. spectrum.

(e) The Attempted Oxidation of the Solid (A)

The solid (A) (0.37g) was heated under reflux with activated manganese dioxide (1.0g) in dry acetone (150 ml) on a boiling water bath for 4h. The reaction mixture was filtered and evaporated, and the solid obtained was combined with a second crop, which was isolated by extracting the solid, from the hot filtration, with hot ethanol. The resultant dark olive-green solid (0.24g) had m.p. > 150° (decomp.), i.r. spectrum identical with that of the solid (A).

(f) The Attempted Acidic Hydrolysis of the Solid (A)

The solid (A) (1.0g) was heated under reflux with 5N aqueous sulphuric acid solution (3.0 ml) for 90 min. The solid which precipitated on cooling and dilution of the reaction mixture with water, was washed with water and combined with a second crop which separated, on extraction of the aqueous mother liquor with chloroform (total 0.75g), m.p. 250° (decomp.), i.r. spectrum identical with that of the solid (A). The chloroform extract afforded no material.

(g) The Attempted Reaction of the Solid (A) with Hydrazine.

The solid (A) (0.93g) and 98% hydrazine monohydrate (0.25g; 0.24 ml) were heated under reflux in methanol (50 ml) for 1h. The solid which separated on cooling was combined with a second crop, obtained by evaporating the mother liquor and triturating the residue with ether, (total 0.91g), m.p. > 200°(decomp.), i.r. spectrum identical with that of unreacted starting material (A).

(h) The Hydrolysis of the Solid (B)

The solid (B) (0.86g) was heated under reflux with 2N aqueous sodium carbonate solution (10 ml) in ethanol (20 ml) for 2h. Concentration of the reaction mixture to ca. 10 ml and acidification with dilute aqueous hydrochloric acid gave a solid, which was combined with a second crop, which precipitated on extraction of the aqueous mother liquor with chloroform (total 0.28g), m.p. > 220°(decomp.), i.r. spectrum identical with that of starting material (B).

Constant chloroform extraction of the aqueous mother liquor for 48h afforded 7-methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylic acid (220) (0.19g), m.p. > 165°(from ethyl acetate-light petroleum), $\nu_{max.}$ 3100(OH), 1720(CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.57(1H,s,H-2), and 7.45(3H,s,Me), m/e 179(M^+)(M,179).

Found:	C,40.2;	H,2.9;	N,38.6%.
$C_6H_5N_5O_2$ requires:	C,40.2;	H,2.8;	N,39.1%.

Proof of the Structure of the 1,2,4-Triazolo[5,1-c]-1,2,4-triazine (219 b)

2-Methyl-3-thiomethyl-1,2,4-triazin-5-one (222) was synthesized by the method of F. Sorm etal.[87] The crude solid (90%), m.p. 154-9° (lit.,[87] 159°) was used without further purification.

2-Methyl-3-hydrazino-1,2,4-triazin-5-one (223)

The thiomethyltriazine (222) (0.63g; 0.004 mol) was dissolved in isopropanol (15 ml) with gentle warming, 98% hydrazine monohydrate (1.0 ml) was added and the solution was left at room temperature for 48h. The yellow, light sensitive, hydrazinotriazine (223) was filtered off (98%), m.p. 231° (decomp.) (from dimethylformamide), $\nu_{max.}$ 3100, 2700-2500br (NH), and 1640-1600br (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.88 (1H, s, H-6), and 6.51 (3H, s, Me), m/e 141 (M^+) (M, 141).

Found: C, 34.5; H, 5.0; N, 49.6%

$C_4H_3N_5O$ requires: C, 34.0; H, 5.0; N, 49.6%.

The hydrazino compound (223) gave the bisulphate salt of a benzylidene derivative when treated with benzaldehyde in methanolic concentrated sulphuric acid, m.p. 251° (from glacial acetic acid), $\nu_{max.}$ 3100-2500br (NH), and 1710 (CO) cm^{-1}.

Found: C, 40.3; H, 3.9; N, 21.4%.

$C_{11}H_{11}N_5O.H_2SO_4$ requires: C, 40.4; H, 4.0; N, 21.3%.

The free benzylidene derivative was liberated from its bisulphate salt by treatment with an aqueous solution of sodium hydrogen carbonate. It had m.p. 188° (from ethanol), $\nu_{max.}$ 3200-2600br (NH) and 1680 (CO) cm^{-1}.

Found: C, 57.8; H, 4.9; N, 30.7%.

$C_{11}H_{11}N_5O$ requires: C, 57.6; H, 4.8; N, 30.6%.

The Reaction of the Hydrazinotriazine (223) with Formic Acid.

The hydrazinotriazine (223) (0.21g; 0.0015 mol) was heated under reflux with 99% formic acid (4.0 ml) for 10 min-5lh. The excess of formic acid was removed under reduced pressure, the residue was triturated with a little water and the solid product was collected.

(i) After 10 min, examination of the reaction mixture by t.l.c. showed only one spot. Work up of the reaction mixture as described before afforded 4-methyl-1,2,4-triazolo[3,4-c]-1,2,4- triazin-7(4H)-one (224) (0.14g), m.p. 166° (sealed tube) (from ethanol), $\nu_{max.}$ 1710(CO) cm^{-1}, $\lambda_{max.}$ 217,222sh,238, and 319nm(log ε 3.95,3.91,3.81, and 3.85), τ [$(CD_3)_2SO$] 0.76(1H,s,H-1),2.38(1H,s,H-6), and 6.03(3H,s,Me), m/e 151(M^+) (M,151).

Found: C,39.5; H,3.3; N,46.2%.

$C_5H_5N_5O$ requires: C,39.8; H,3.3; N,46.4%.

(ii) After 30 min, t.l.c. showed the appearance of a second spot, and after 5lh, the first spot had disappeared and only the second spot remained. Work up of the reaction mixture after 5lh gave 4-methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(225) (0.14g), m.p. 174° (sealed tube) (from ethanol), $\nu_{max.}$ 1710 and 1690sh(CO) cm^{-1}, $\lambda_{max.}$ 211,244,250sh and 300nm(log ε 3.89,3.71,3.62 and 3.93), τ [$(CD_3)_2SO$] 1.63(1H,s,H-2),2.18(1H,s,H-6) and 6.02(3H,s,Me), m/e 151 (M^+) (M,151).

Found: C,40.0; H,3.4; N,46.6%.

$C_5H_5N_5O$ requires: C,39.8; H,3.3; N,46.4%.

(iii) Work up of the reaction mixture after 8h gave a solid (0.10g), m.p. 140-155°, whose ^1H n.m.r. spectrum indicated a mixture of the

isomeric triazolotriazines (224) and (225), having the composition (225)(80%) and (224)(20%) as estimated from the integrated ratio of the Me-4 signals.

Conversion of the Triazolotriazine (224) into the Isomeric Compound (225)

The compound (224)(0.10g; 0.0066 mol) and anhydrous sodium acetate (0.06g) were heated under reflux in ethanol (2.0 ml) and water (1.0 ml) for 90 min. Evaporation of the reaction mixture, and trituration of the residue with a little water, afforded the isomeric compound (225)(0.09g), which was identical (m.p. 174°, i.r. and ^{1}H n.m.r. spectra) with a sample prepared as described before.

1,2,4-Triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(226)

The hydrate of the acid (219d)(2.16g), which was obtained prior to crystallisation from water, was heated in vacuo (water pump) at 215° (oil bath). The sublimate, which collected on a cold finger condenser, proved to be the decarboxylated triazolotriazine (226) (1.32g), sublimes at 204° (from ethanol)(lit.[80] m.p. 240°), $\nu_{max.}$ 3200-3000br(NH), and 1690(CO) cm^{-1}, $\lambda_{max.}$ 213,241,246sh,269 infl., and 298 nm(log ε 3.83,3.56,3.53,3.53 and 3.81), τ[$(CD_3)_2SO$] 1.63(1H,s,H-2), and 2.19(1H,s,H-6), m/e 137(M^+)(M,137).

Found: C,35.1; H,2.1; N,51.2%.

$C_4H_3N_5O$ requires: C,35.0; H,2.2; N,51.1%.

4-Methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(225)

The triazolotriazine(226)(1.1g; 0.008 mol) was suspended in methanol (12 ml) and treated with 4% w/v aqueous sodium hydroxide

solution (12 ml). The resultant solution was shaken with methyl iodide (2.4 ml) at room temperature for 17h. The volatile material was evaporated under reduced pressure from the mixture and the remaining aqueous solution was extracted with chloroform. The chloroform extract afforded a solid (0.56g), m.p. 120-36°, whose t.l.c. and ^{1}H n.m.r. spectrum, τ [$(CD_3)_2SO$] 1.47(s), 1.50(s), 1.63(s), 2.18(s), 5.70(s) and 6.02(s), showed it to be a mixture of two methylated derivatives of (226). Chromatography of the solid (0.55g) over silica and elution with chloroform gave the triazolotriazine (225) (0.34g), m.p. 174°, which was identical (m.p., mixed m.p. and i.r. and ^{1}H n.m.r. spectra) with a sample prepared previously. Further elution with methanol afforded the isomeric monomethyl derivative (227) (0.21g), m.p. 207° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1690(CO) cm^{-1}, $\lambda_{max.}$ 221,255,260 infl., 268sh, and 342nm(log ε 4.20, 3.50,3.49,3.33, and 3.94), τ [$(CD_3)_2SO$] 1.47(1H,s,H-2 or H-6), 1.50 (1H,s,H-6 or H-2), and 5.70(3H,s,Me), m/e 151(M^+) (M,151).

Found: C,40.1; H,3.4; N,46.4%.

$C_5H_5N_5O$ requires: C,39.8; H,3.3; N,46.4%.

The Reactions of 1,2,4-Triazolo[5,1-c]-1,2,4-triazines

(a) The Methylation of the Triazolotriazines (219 a and c)

(i) The lactams (219 a and c) (0.002 mol), suspended in methanol (3.0 ml), were treated with 4% w/v aqueous sodium hydroxide solution (3.0 ml) and shaken with methyl iodide (0.6 ml) for 17h. Evaporation of the reaction mixtures under reduced pressure and extraction of the remaining aqueous solutions with chloroform gave gums (0.11-0.13g), t.l.c. examination of which, showed them to be multicomponent mixtures.

Acidification of the remaining aqueous solutions with dilute aqueous sulphuric acid gave the unchanged starting materials (219 a and c)(30-45%), which were identified by m.p., i.r. spectrum and t.l.c.

(ii) The triazolotriazines (219 a and c)(0.0015 mol) were heated under reflux with anhydrous potassium carbonate (1.6g) and dimethyl sulphate (0.9 ml) in dry acetone (50 ml) for 4h. The reaction mixtures were filtered hot to remove insoluble inorganic material. The acetone filtrates were evaporated under reduced pressure and the residual oils were treated with water, and extracted with chloroform to give gums. Trituration of the gum from (219 a) with methanol-ether gave

6-benzoyl-4-methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(239) (60%), m.p. 166° (from ethanol), $\nu_{max.}$ 1730(CO)cm^{-1}, $\lambda_{max.}$ 209, 259, and 312nm(log ε 4.21, 4.08, and 4.04), τ [$(CD_3)_2SO$] 1.48(1H,s,H-2),1.90-2.53(5H,m,ArH), and 5.96(3H,s,Me), m/e 255(M^+)(M,255).

Found: C,56.7; H,3.7; N,27.3%.

$C_{12}H_9N_5O_2$ requires: C,56.5; H,3.5; N,27.4%.

Trituration of the gum from (219 c) with methanol-ether gave

6-cyano-4-methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one(240) (61%), m.p. 169° (from ethanol), $\nu_{max.}$ 2250(.C ≡ N) and 1710(CO)cm^{-1}, $\lambda_{max.}$ 215,253,261sh, and 320nm(log ε 3.94,3.70,3.60, and 4.01), τ [$(CD_3)_2SO$] 1.39(1H,s,H-2) and 5.90(3H,s,Me), m/e 176(M^+)(M,176).

Found: C,40.7; H,2.3; N,47.7%.

$C_6H_4N_6O$ requires: C,40.9; H,2.3; N,47.7%.

(b) The Hydrolysis of the 7-Aminotriazolotriazines (218 a-d) to the Triazolotriazinones (219 a-c) and (232)

The triazolotriazines (218 a-d)(0.003 mol) in ethanol (20 ml) were heated under reflux with 4N aqueous sulphuric acid (7.5 ml)

for 1-3h. The reaction mixtures were cooled and any insoluble solid was combined with a second crop, obtained by concentrating the mother liquors to ca. 10 ml, and a third crop obtained by extracting the remaining aqueous solution with chloroform. The combined solids were washed with water, dried in vacuo, and crystallised to give the triazolotriazinones (219 a)(66%), (219 b)(42%) and (219 c)(28%), which were identical (m.p. and i.r. spectrum) with samples prepared previously, and 4,7-dihydro-7-oxo-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (232)(50%), m.p. > 310° (from dimethylformamide), $\nu_{max.}$ 3350,3200 and 3000-2300br(NH), and 1740 and 1670(CO)cm^{-1},τ [$(CD_3)_2SO$] 1.60(1H,s,H-2), and 2.00-2.30br(2H,s,NH), m/e 180(M^+)(M,180). No u.v. data was obtained due to the insolubility of (232) in ethanol.

Found: C,34.0; H,2.3; N,46.2%.

$C_5H_4N_6O_2$ requires: C,33.3; H,2.2; N,46.7%.

(c) The Hydrolysis of the 6-Cyanotriazolotriazines (218 c) and (219 c) to the Amides (218 d) and (232)

(i) The triazolotriazines (218 c) and (219 c)(0.004 mol) were stirred in concentrated sulphuric acid (3.0 ml) at room temperature for 30 min. The reaction mixtures were poured onto ice and scratched, and any solid which separated was collected and washed with water, to give [from (218 c)] the hydrazone (216 g)(72%), identical (m.p.> 190° and i.r. spectrum) with an authentic sample, and in the case of (219 c), the starting material (66%), identified by m.p. > 240° and i.r. spectrum.

(ii) The triazolotriazine (219 c)(0.40g; 0.0025mol) was heated under reflux in ethanol (25 ml) with N aqueous sodium carbonate solution (10 ml) for 2.5h. Evaporation of the reaction mixture and treatment

of the resultant residue with dilute aqueous hydrochloric acid gave a solid, which when washed with water and dried at 80° for 4h gave unchanged starting material (219 c)(83%), identified by m.p. > 240° and i.r. spectrum.

(iii) The triazolotriazines (218 c) and(219 c)(0.004 mol) were stirred in polyphosphoric acid (ca. 5.0 ml) for 3h at 80°. The reaction mixtures were allowed to cool, diluted with water, and any resultant solid was collected and combined with a second crop, obtained by neutralising the mother liquors with solid sodium hydrogen carbonate. Crystallisation of the crude solids gave the triazolotriazines (218 d) (74%) and (232)(60%) which were identical (m.p. and i.r. spectrum) with authentic samples.

(d) The Ammonolysis of the Triazolotriazine Esters (218 b) and (219 b) to the Amides (218 d) and (232)

Solutions of the triazolotriazines (218 b) and (219 b)(0.003 mol) in ethanol (100 ml) were cooled in ice-water and saturated with ammonia gas. The reaction mixtures were stoppered and allowed to stand at room temperature for 16-24h. The ethanol was then evaporated under reduced pressure.

(i) The solid residue from (218 b) was shown by its i.r. spectrum, $\nu_{max.}$ 3400-3150br(NH), and 1700 and 1680(CO)cm^{-1}, to be a mixture of starting material (218 b) and the amide (218 d). Examination of the mixture by t.l.c. showed chromatographic separation to be impractical. Fractional crystallisation of the solid from ethanol gave pure samples of the two components (218 b) and 218 d) which were

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

(ii) The product from (219 b) was acidified with dilute aqueous sulphuric acid to give a solid which was combined with a second crop obtained by extracting the aqueous solution with chloroform. The crude product was leached with hot ethanol to leave the insoluble amide (232) (0.08g) which was identical (m.p. > 310° and i.r. spectrum) with a sample obtained previously. Evaporation of the ethanol extract gave unchanged starting material (219 b) (0.33g), m.p. 200-4°.

(e) The Attempted Acetylation of the Triazolotriazine (218 b)

(i) The triazolotriazine (218 b) (0.32g; 0.0015 mol) was heated under reflux in acetic anhydride (3.0 ml) for 1 min. The reaction mixture was allowed to cool and the solid was collected and washed with ether to give unchanged starting material (recovery 84%).

(ii) Reaction (i) was repeated but heating under reflux was continued for 1h. The solid was collected from the cooled mixture to give starting material (16%) (identified by m.p. 205-8° and i.r. spectrum). Evaporation of the filtrate gave an oil which did not solidify on trituration with organic solvents. When the oil was allowed to stand in contact with water for 24h, a solid was obtained (0.08g), m.p. 186-99°, which on crystallisation yielded the triazolotriazine (219 b) (0.04g), m.p. 201-3°, which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

(iii) The triazolotriazine (218 b) (0.64g; 0.003 mol) was stirred in acetic anhydride (5.0 ml) containing concentrated sulphuric acid (0.5 ml) at room temperature for 1h. Unreacted starting material was removed by filtration (0.06g) and the resultant reaction mixture

was diluted with water and allowed to stand at room temperature overnight. Chloroform extraction of the solution gave a solid, which was crystallised to afford the triazolotriazine (219 b) (0.33g) (52%), m.p. 198-201° (ethanol-glacial acetic acid), identical (i.r. spectrum) with an authentic sample.

(f) The Attempted Diazotization of the Aminotriazolotriazine (218 a)

(i) The amino compound (218 a) (0.72g; 0.003 mol), dissolved in glacial acetic acid (10 ml) containing 90% w/v aqueous sulphuric acid (5.0 ml), was stirred and cooled to < 5°. A 0.5N aqueous solution of sodium nitrite (10 ml) was added dropwise and stirring was continued at 0-5° for 15 min. The reaction mixture was diluted with water and the resultant solid was dried at 80° for 4h to give unreacted starting material (recovery 82%) (identified by m.p. and i.r. spectrum). Concentration of the mother liquor to ca. 10 ml, and extraction with chloroform, gave a gum, which on trituration with ether afforded the triazolotriazinone (219 a) (0.06g), m.p. 211-7°, identical (i.r. spectrum) with an authentic sample.

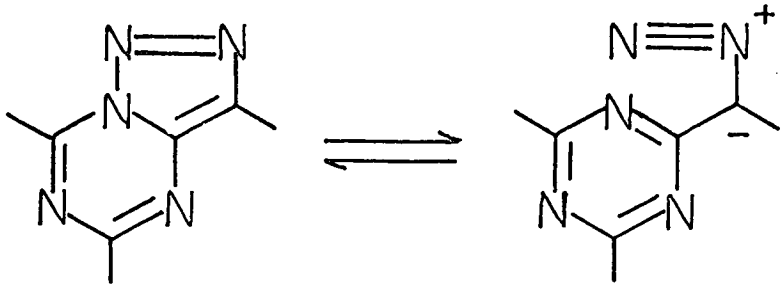
(ii) A suspension of the triazolotriazine (218 a) (0.24g; 0.001 mol) in dimethoxyethane (3.0 ml), cooled to < 5°, was stirred and treated dropwise with amyl nitrite (0.12g; 0.14 ml; 0.001 mol), and stirring was continued for 45 min. Glacial acetic acid (3.0 ml) was added and stirring was continued for a further 17h. The insoluble solid was collected and combined with a second crop, obtained by evaporating the mother liquor under reduced pressure, and triturating the residue with benzene. The solid (0.17g) was identical (m.p. 224° and i.r. spectrum) with unreacted starting material (218 a).

Chapter 3

An Investigation of Some Synthetic Routes to, and the Reactivity of, the 1,2,3-Triazolo[1,5-a]-1,3,5-triazine Ring System

3.1 Introduction

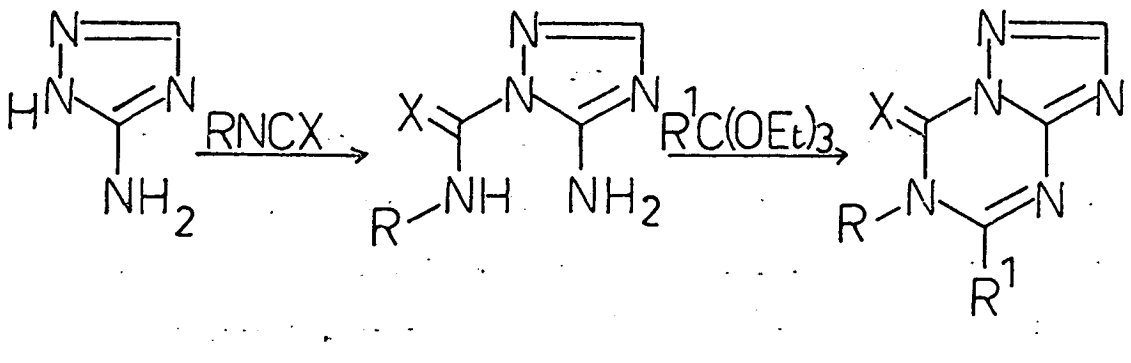
No examples of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system (241) have as yet been reported. As in the case of the 1,2,3-



(241) (242)

triazolo[5,1-c]-1,2,4-triazine ring system (94) (Chapter 2.1), the possibility of the tautomerism [(241)⇌(242)] exists. Due to the strongly electron-withdrawing character of the 1,3,5-triazine ring, the possible instability of (241), with respect to (242), is potentially greater than that which may be expected for the triazolo[5,1-c]-1,2,4-triazine ring system (94).

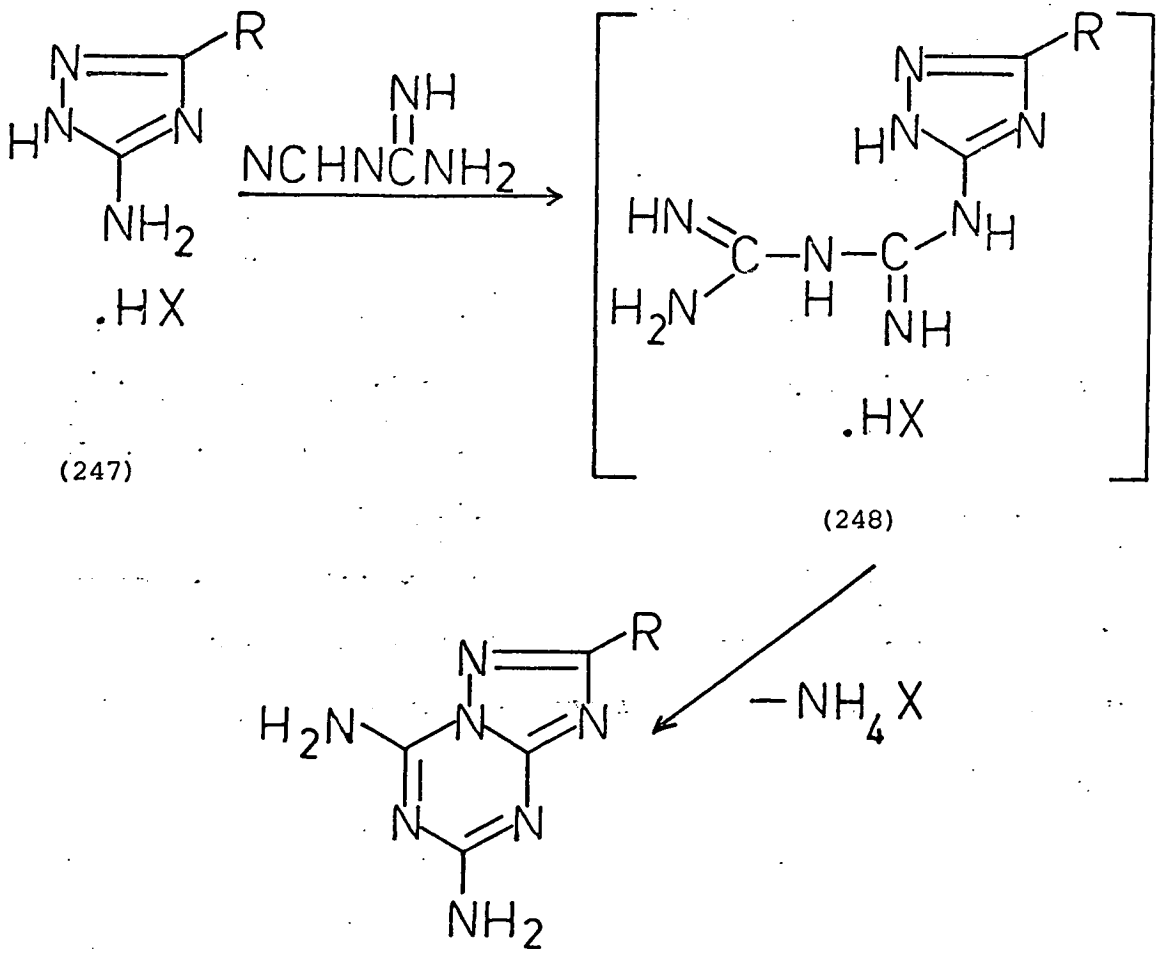
Some well documented[91-94] routes to fused 1,3,5-triazines suggest methods which may be employed in an attempt to synthesize the system (241) starting with an intact triazole nucleus. Molecules of the type (244) may be cyclized[91-93] to the 1,2,4-triazolo[1,5-a]-1,3,5-triazine ring system (245) on suitable treatment with an orthoester (Scheme 21). The substrate for such a synthesis has been obtained[92,93] by reacting the amino-1,2,4-triazole (243) with a suitable isocyanate or isothiocyanate. Taylor has also synthesized[91] the system (245) by the method described, [(244) ⟶ (245); X = O] having obtained the triazolecarboxamide (244; X = O) by reacting (243) with potassium cyanate in an acidic medium.



(243) (244) (245)

Scheme 21

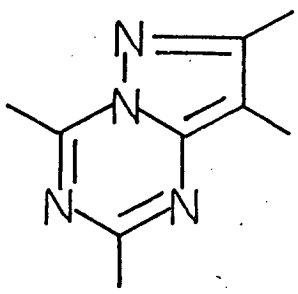
X = O or S



(247) (248) (249)

Scheme 22

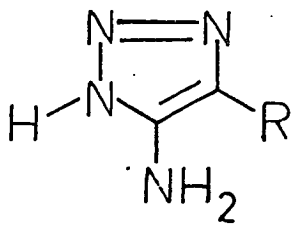
A modification of the synthesis [(243) ⟶ (244) ⟶ (245)] has been carried out by Capuano *et al.*[93] - namely, when R = .COR[1], the adduct (244) was cyclized intramolecularly to the triazolotriazine (245). The pyrazolo[1,5-a]-1,3,5-triazine ring system (246) has also been obtained[93] by this method.



(246)

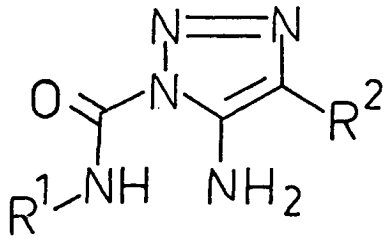
The knowledge that dicyandiamide reacts with the salts of aromatic amines has also been utilised in a synthesis[94] of the 1,2,4-triazolo[1,5-a]-1,3,5-triazine ring system (249) (Scheme 22). The intermediate involved in the addition of dicyandiamide to amino-1,2,4-triazoles (247) probably has the form (248).

In the present work, attempts have been made to synthesize the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system (241) by methods analogous to those outlined in Schemes 21 and 22.



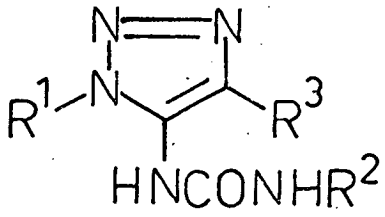
(250)

	R
a;	Ph
b;	.$CONH_2$



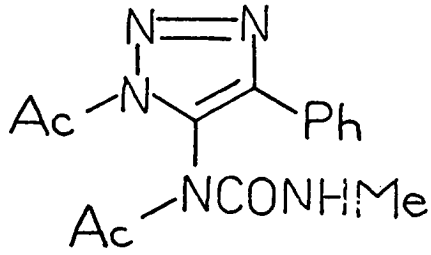
(251)

	R^1	R^2
a;	Me	Ph
b;	Me	.$CONH_2$
c;	Ph	Ph
d;	Ph	.$CONH_2$

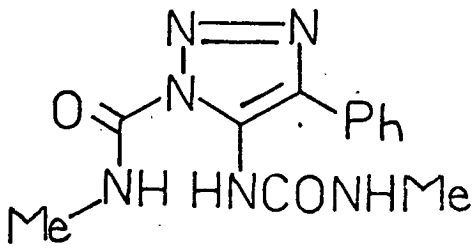


(252)

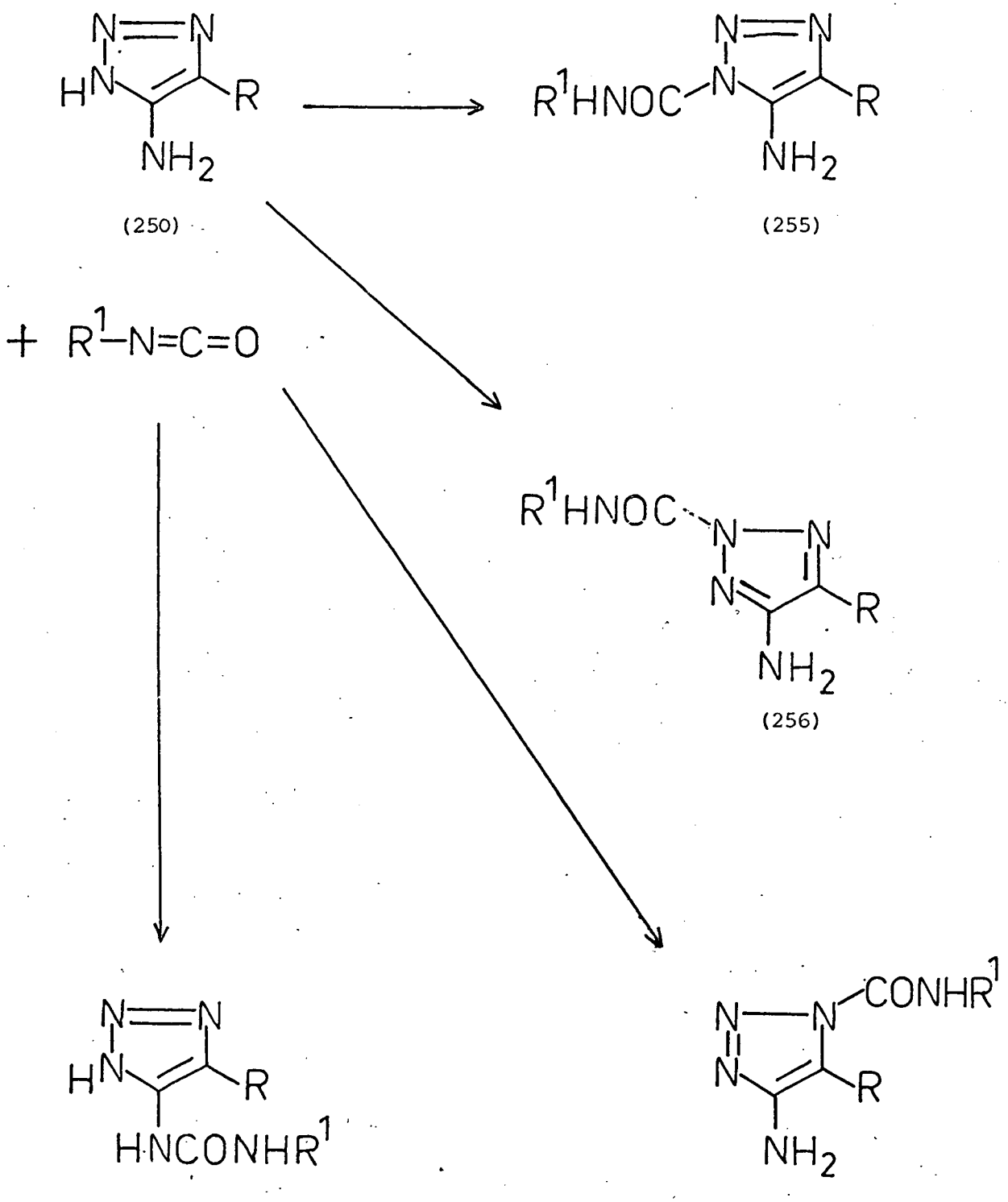
	R^1	R^2	R^3
a;	H	Me	Ph
b;	H	Me	.$CONH_2$
c;	H	Ph	Ph
d;	H	Ph	.$CONH_2$
e;	Ac	Me	Ph
f;	Ac	Me	.$CONH_2$
g;	Ac	Ph	Ph
h;	Ac	Ph	.$CONH_2$
i;	H	H	.$CONH_2$



(253)



(254)

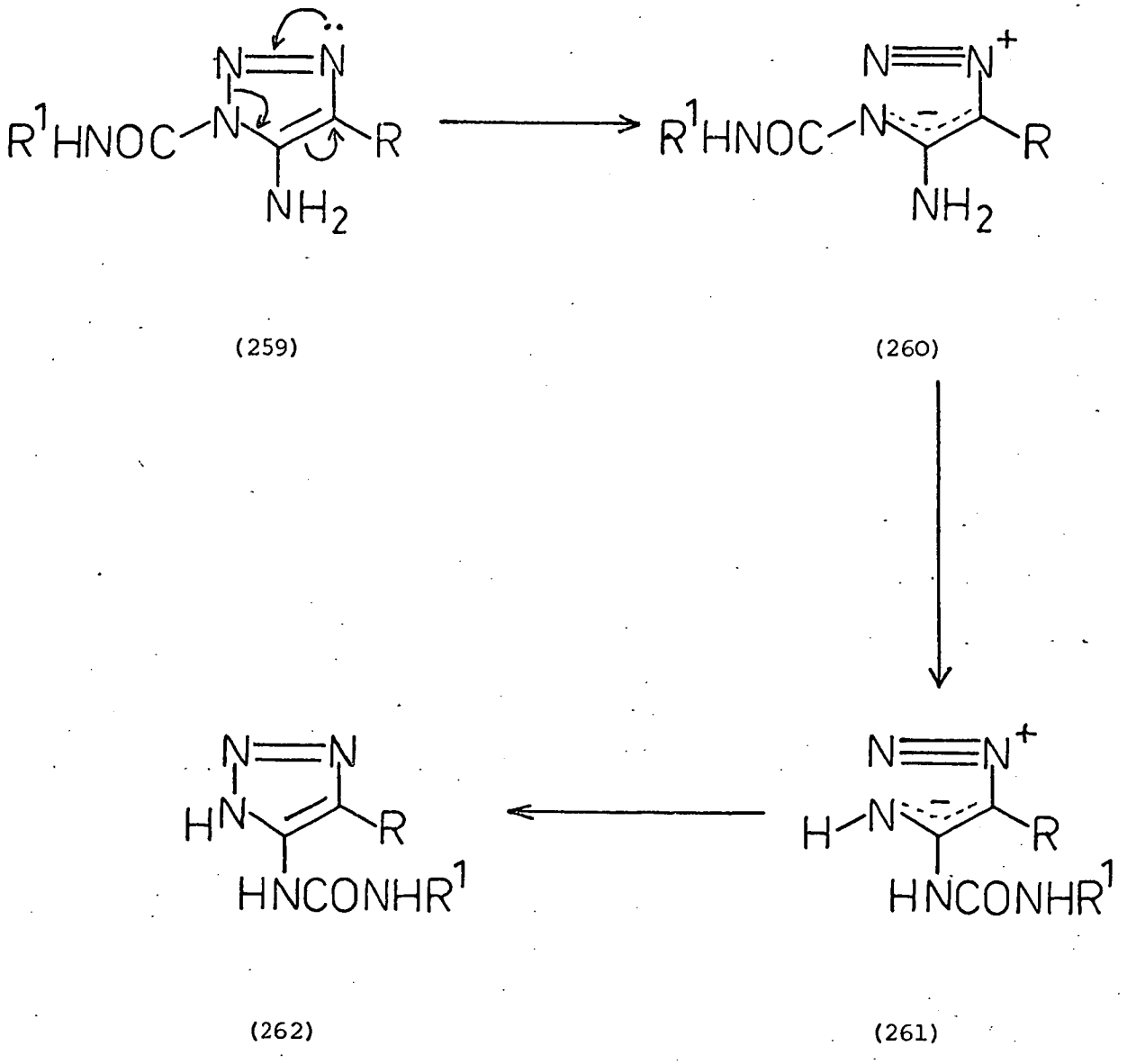


Scheme 23

3.2 The Reactions of 5-Amino-1H-1,2,3-triazoles with Isocyanates and Isothiocyanates and the Synthesis and Reactivity of the 1,2,3-Triazolo[1,5-a]-1,3,5-triazine Ring System

In an attempt to form substrates which were suitable for the formation of the 1,2,3-triazolo[1,5-a]-1,3,5-triazine ring system (241) (cf. Scheme 21), the aminotriazoles (250 a and b) were treated with methylisocyanate and phenylisocyanate. The products initially formed showed properties consistent with the N-substituted carboxamide structures (251 a-d). However, when an isocyanate adds to an amino-1H-1,2,3-triazole (e.g. 250) there are four possible structures for the adduct, [(255) - (258)]. The structures (255 - 257) arise as a result of the tautomerism exhibited by 1H-1,2,3-triazoles (see Chapter 2.4, page 33). The structure (258) may be obtained from (250) by the addition of the isocyanate to the primary amino group rather than at a ring nitrogen atom. Adducts of the type (255-258) have been formed by Hirata *etal*.[92] in their analogous study of the additions of isocyanates to amino-1,2,4-triazole (243).

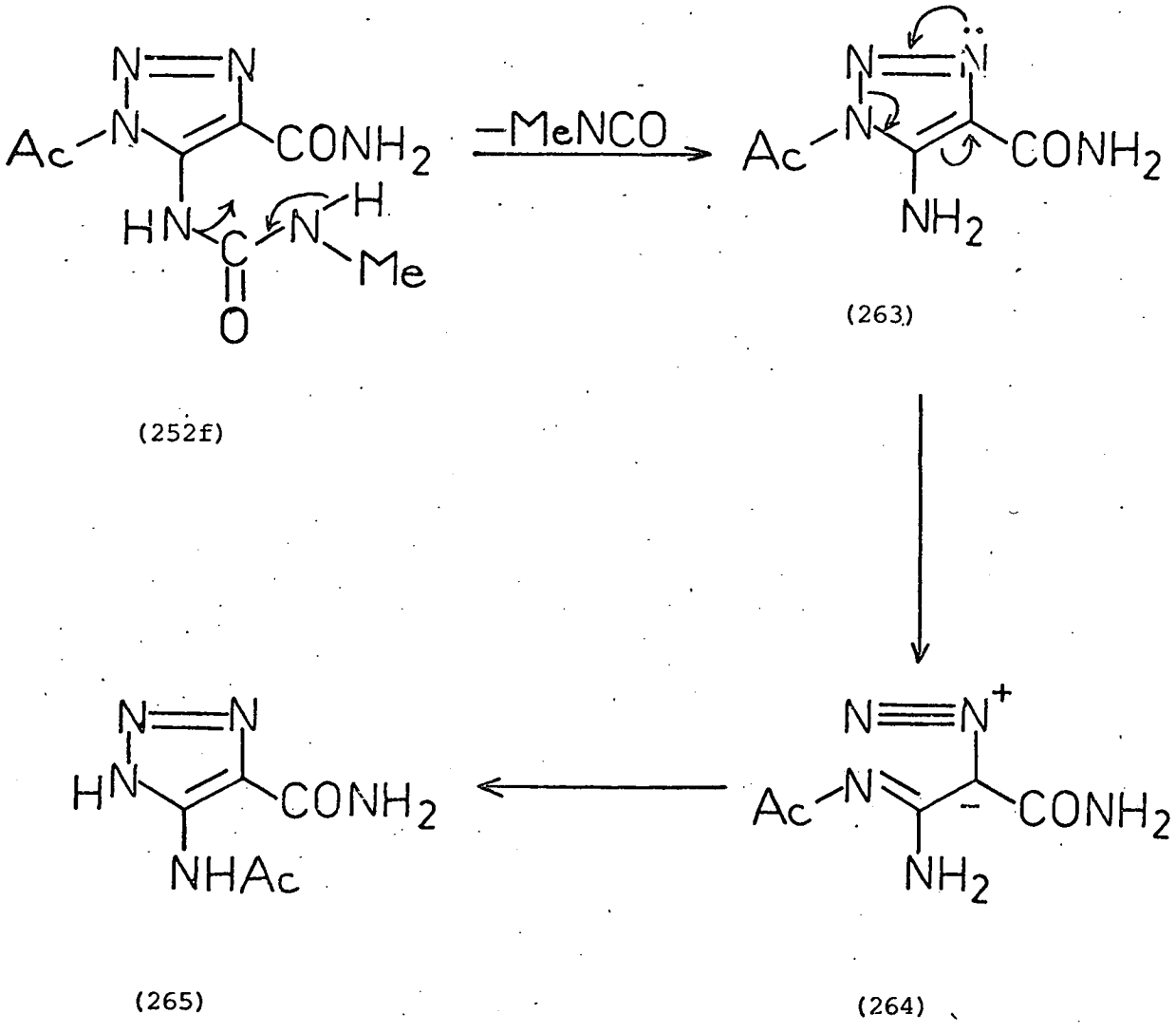
The formation of structures of the type (258) may be excluded due to the inability of the compounds (251 a-d) to form salts with dilute aqueous sodium hydroxide solution. Compounds of the type (258) would be expected to exhibit acidic behaviour due to the presence of a 1H-1,2,3-triazole nucleus. When the compounds (251 a and b) were treated, for a prolonged period, with base, the amino-1H-1,2,3-triazoles (250 a and b) were formed. However, the 4-substituted triazolecarboxamides (251 a,b and d) may all be converted into the corresponding ureas (252 a,b and d) by heating under reflux in



(259) (260) (261) (262)

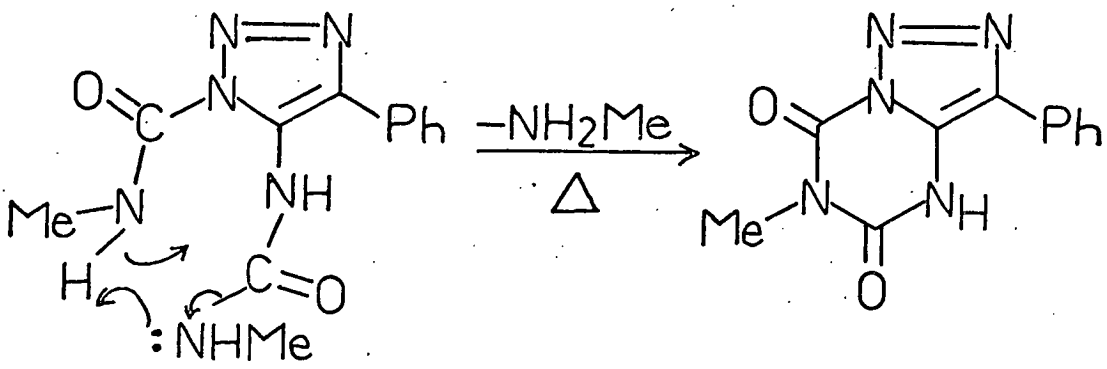
Scheme 24

dimethylformamide, the reactions [(251 b and d) → (252 b and d)] taking place on attempted crystallisation. The conversion [(251 a) → (252 a)] was also achieved in the melt. The compounds (252 b and d) were also formed by the prolonged treatment of (250 b) with methylisocyanate or phenylisocyanate. The attempted conversion of (251 c) into (252 c) in hot dimethylformamide resulted in the isolation of a multicomponent mixture. However, the conversion [(251 c) → (252 c)] was carried out smoothly by heating under reflux in toluene. The formation of the ureas (252 a-d) from the compounds (251 a-d) may best be interpreted in terms of a Dimroth rearrangement[11a] (Scheme 24) [(259) → (260) → (261) → (262)], the observed results being consistent with the assertion[11a] that strongly electron-withdrawing groups prefer to be situated on the exocyclic nitrogen atom (e.g. 262) rather than the ring nitrogen atom (e.g. 259). The rearrangement of the compounds (251 b and d) goes much more easily than that of (251 a and c). This may be accounted for in terms of the greater stabilizing effect of an amide group, as opposed to a benzene ring, on a negative charge. Hence the ability to form the intermediates (e.g. 260 or 261) in the case of (251 b and d) is greater than that in (251 a and c). The conversion of (251 a) into (252 a), in dimethylformamide, also resulted in the formation of an unidentified by-product (X). The compound (X), which was acidic, gave a ^{1}H n.m.r. spectrum which showed only absorptions attributable to NH and aromatic protons. The mass spectral and analytical data obtained from (X) did not suggest a readily assignable structure.



Scheme 25

The conversion of the compounds (251 a-d) into the ureas (252 a-d) helps confirm the structure of the adducts as being of the type (255) rather than (256) or (257)(Scheme 23). The structures (251 a-d) and (252 a-d) may be differentiated in several ways. The compounds (251 a-d) exhibit bands at 1730-1720 cm^{-1} in their i.r. spectra which are characteristic[11a] for a carbonyl group attached to a triazole ring nitrogen atom. In comparison, the compounds (252 a-d) show no absorption above 1700cm^{-1}. As has previously been stated, compounds of the type (262) are expected to exhibit acidic properties. The compounds (252 a-d) are soluble in dilute aqueous sodium hydroxide solution and are regenerated unchanged on acidification, whereas the Dimroth isomers (251 a-d) remain insoluble in base. As was observed in the case of the (1H-1,2,3-triazol-5-yl)hydrazones (see Chapter 2.4), the ureas (252 a-d) were readily acetylateable, monoacetyl derivatives (252 f-h) being obtained except in the case of (252 a) which gave a diacetyl compound (253). The result of such acetylations was the appearance of signals of τ7.19-7.26 and bands at 1770-1740cm^{-1} in the ^{1}H n.m.r. and i.r. spectra of the compounds (252 f-h) and (253) [cf. the (1-acetyl-1,2,3-triazol-5-yl)hydrazones, Chapter 2.4]. The 4-substituted triazolecarboxamide (251 a) failed to give a readily accessible acetyl derivative. When the acetyl compound (252 f) was crystallised from aqueous dimethylformamide, hydrolysis to the parent urea (252 b) occurred. However, when crystallisation from dimethylformamide-benzene was attempted, the result was the formation of the acetamidotriazole (265).



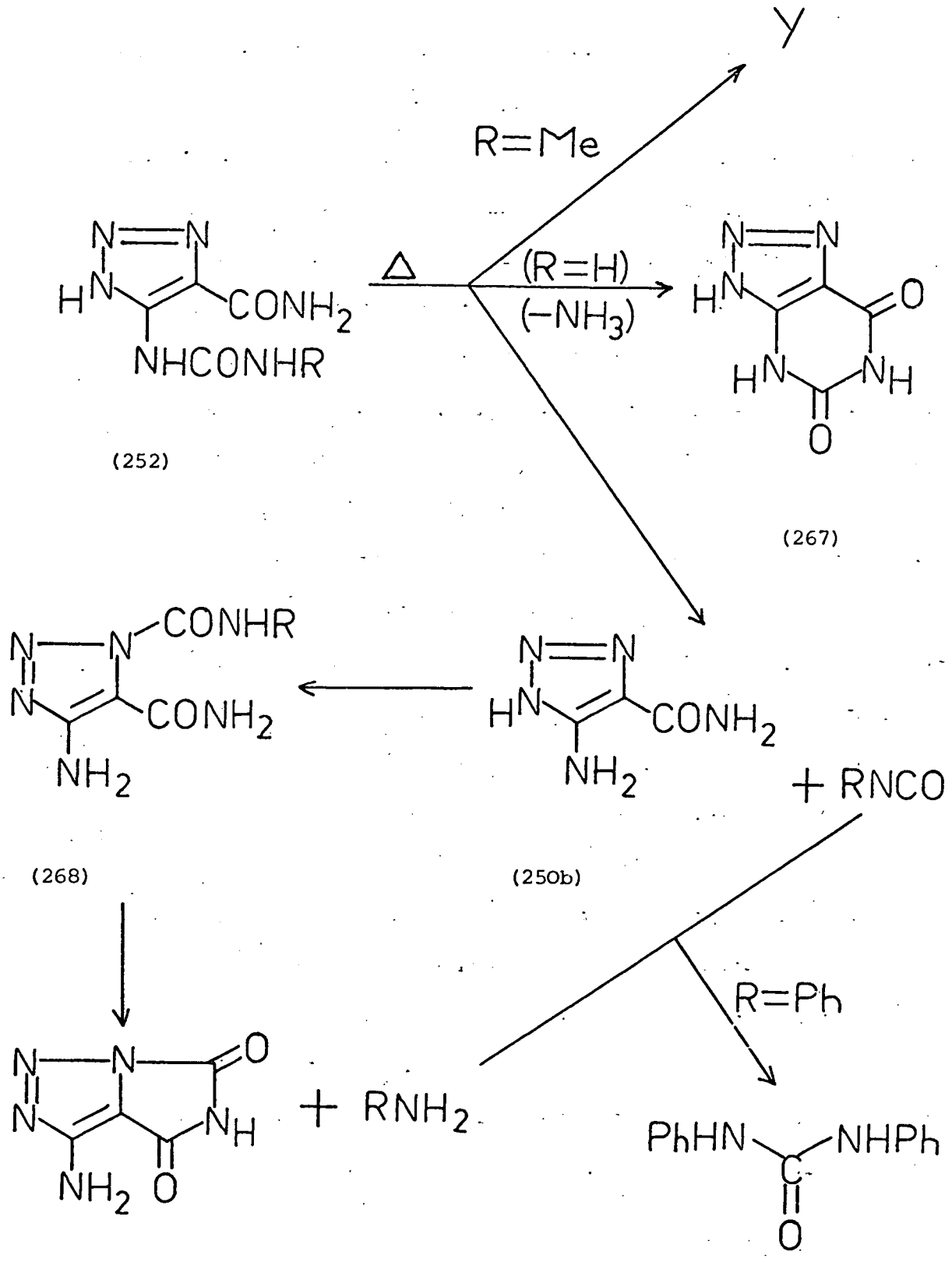
(254) (266)

Scheme 26

The mechanism of this reaction (Scheme 25) probably involves the initial thermolytic loss of methylisocyanate, followed by the Dimroth rearrangement [(263) ⟶ (264) ⟶ (265)]. This result is explicable[11a] in terms of the preference of electron-withdrawing groups to be situated on the exocyclic nitrogen atom (cf. Scheme 24).

Additional evidence for the site of addition of the isocyanates to the aminotriazoles (250 a and b), has been obtained from the reaction of the urea (252 a) with methylisocyanate. A product was obtained whose ^{1}H n.m.r., i.r. and mass spectral and analytical data were consistent with a structure of the type (254). When the triazole-carboxamide (251 a) was similarly treated with methylisocyanate, a quantitative recovery of the starting material was obtained. These results reinforce the evidence which suggests that the isocyanates add to the aminotriazoles (250 a and b) at N-1. In an attempt to carry out the reaction outlined in Scheme 26, the compound (254) was heated under reflux in dimethylformamide. However, instead of the formation of the triazolotriazine (266), the reaction gave rise to the production of the urea (252 a) and the unidentified solid (X).

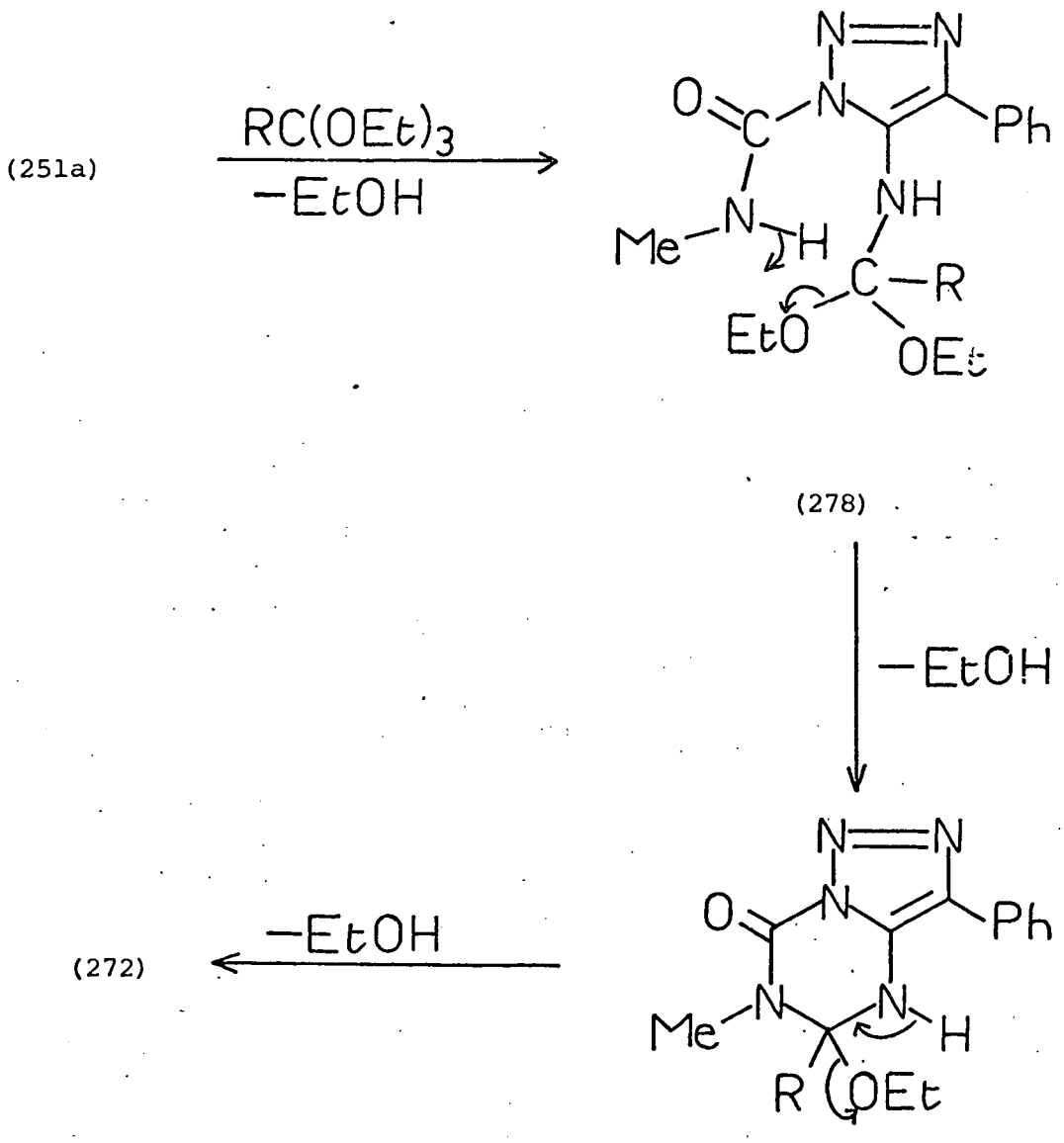
When reactions [Scheme 27; (252 b and d) ⟶ (267)], similar to that outlined in Scheme 26, using the ureas (252b and d) were attempted, the result in each case was the isolation of a product (Z). The reaction involving the urea (252 b) also gave rise to an unidentified product (Y) whose i.r. and mass spectra did not suggest a plausible structure. The urea (252 d) also gave 1,3-diphenylurea[95] (270) and the aminotriazole (250 b), from this reaction. The product (Z) was thought initially to be the expected triazolopyrimidine (267)[96].



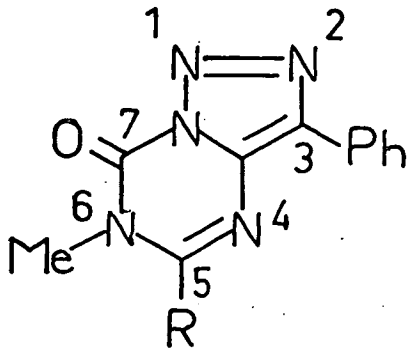
R = H, Me, Ph

Scheme 27

I.r. and mass spectral data obtained from (Z) were consistent with this structure, but it was not supported by results obtained from the combustion analysis of (Z). However, an attempt to confirm the structure of (Z),by synthesizing the triazolopyrimidine (267), by fusing the triazolecarboxamide (250 b) with urea resulted in the formation of the compound (252 i) whose structure was confirmed by its solubility in alkali. When the urea (252 i) was heated under reflux in the presence of base it gave rise to (Z) and a solid whose structure was suggested, by its i.r., mass spectrum and analysis, to be the dihydrate of the triazolopyrimidine (267). The last named product is assigned the structure (267) on the basis of its m.p. being identical with that previously reported[96] for the triazolopyrimidine (267). The question as to the structure of (Z) now arises. The mass spectrum of (Z) shows it to be isomeric with the triazolopyrimidine (267). On the basis of the various products obtained from the thermal reactions of (252 b and d), Scheme 27 is suggested. As has been described, the triazolopyrimidine (267) is only obtained from the urea (252 i). However, the product (Z) may arise from the initial thermolytic loss of the isocyanate, followed by its readdition onto the triazole (250 b) at N-3 to give (268)(cf. Scheme 23). The product (Z) is tentatively assigned the structure (269) which is consistent with the spectral data already found for (Z). The isolation of the triazole (250 b) and 1,3-diphenylurea (270) from the reaction involving the urea (252 d) is also consistent with such a mechanism, (270) being obtained by the addition of aniline to phenylisocyanate.


(251a)
RC(OEt)3
−EtOH
Ph
Me
NH
R
EtO
OEt
(278)
−EtOH
(272)
−EtOH
Ph
Me
H
R
OEt
(279)

Scheme 28



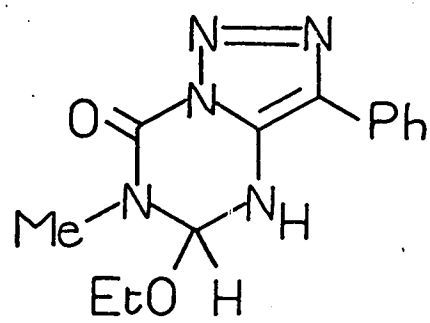
(272)

R

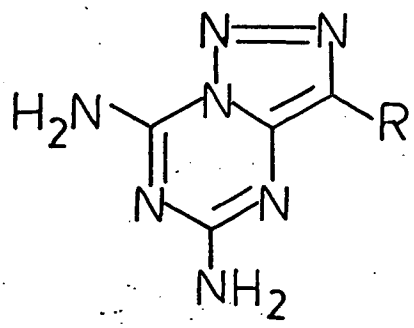
a; H

b; Me

c; Et



(273)

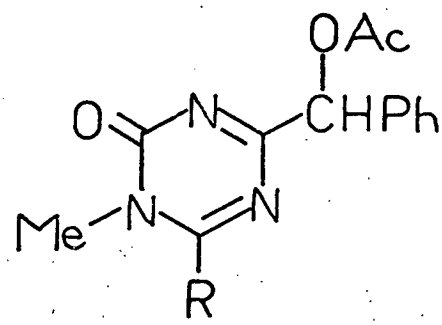


(274)

R

a; Ph

b; $CONH_2$



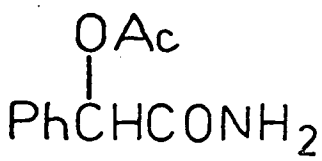
(275)

R

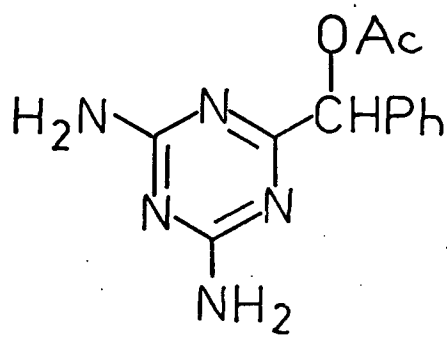
a; H

b; Me

c; Et

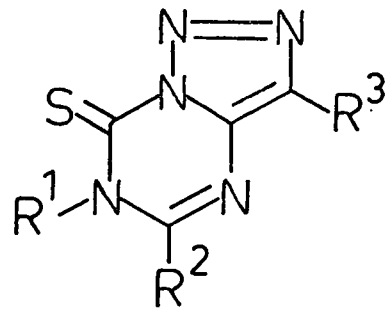


(276)



(277)

In order to obtain a route to triazolotriazines of the type (271), an attempt was made to add methylisothiocyanate to the



(271)

aminotriazole (250 a), as in the cases of the isocyanate additions already discussed. However, unreacted triazole (250 a) or a multi-component oil was recovered under a variety of conditions. This is in contrast to the successful results obtained[92,93] from amino-1,2,4-triazoles.

When the 4-phenyltriazolecarboxamide (251 a) was treated with triethylorthoformate, triethylorthoacetate, or triethylorthopropionate in dimethylformamide at an elevated temperature, it gave low yields of the triazolotriazines (272 a-c). The mechanism involved in such reactions (Scheme 28) probably involves the intermediates (278) and (279). Evidence for such a mechanism was provided by the isolation of the adduct (273) from the reaction involving triethyl-orthoformate. When (273) was heated under reflux in dimethylforma-mide the triazolotriazine (272 a) was obtained.

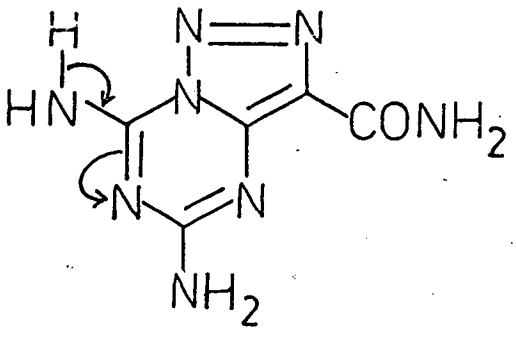
Attempts were made to improve the yield of the triazolotriazine (272 a) by carrying out the reaction under various sets of conditions. However, no increase in yield was observed when the reaction was carried out in neat triethylorthoformate, and no identifiable material

was isolated when the reaction was carried out in the presence of acetic anhydride. When the triazolecarboxamide (251 a) was treated with neat triethylorthoformate at a lower temperature, the result was the production of a mixture of the triazolotriazine (272 a) and the previously obtained bis-urea (254). The last named product (254) was probably formed by the initial thermolytic elimination of methyl-isocyanate from the urea (251 a), followed by its addition to a molecule of (252 a) which was formed by the Dimroth rearrangement of (251 a) (cf. Schemes 24, 25 and 27).

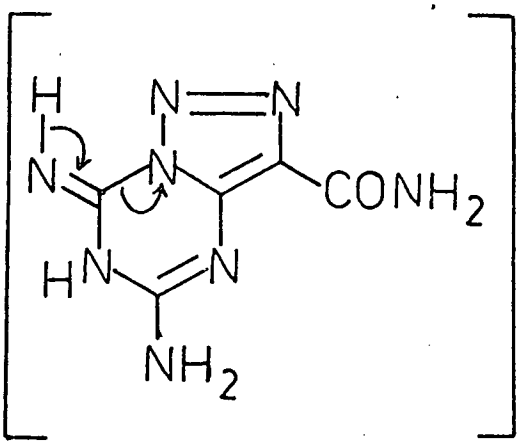
When attempts were made to react the carboxamides (251 b and c) with triethylorthoformate, the result in each case was the production of a gross mixture. These results and also the low yields of the triazolotriazines (272 a-c) may be explained readily in terms of the Dimroth rearrangement, previously observed, (cf. Scheme 24) of the triazolecarboxamides (251 a-d). The production of the ureas (252 a-d) prior to reaction with the orthoester would not result in the formation of a triazolotriazine.

The reaction of the aminotriazoles (250 a and b) with dicyandiamide in aqueous hydrochloric acid resulted in the formation of the triazolotriazines (274 a and b) (cf. Scheme 22).

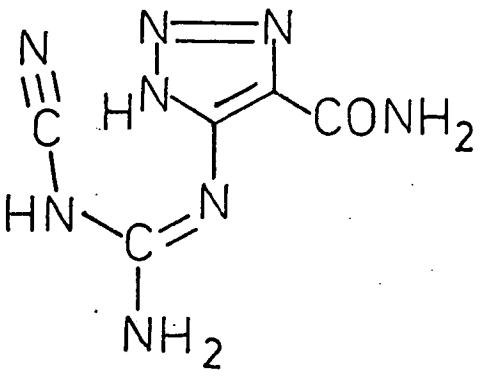
Confirmatory evidence for the triazolotriazine structures (272 a-c) and (274 a and b) was obtained from their properties, i.r., ^1H n.m.r. (where relevant) and mass spectral and combustion analysis. However, some doubt may exist in the assignment of the structures (274 a and b) due to the data obtained from these products also being consistent with structures of the type (280) (cf. Scheme 22).



(274b)

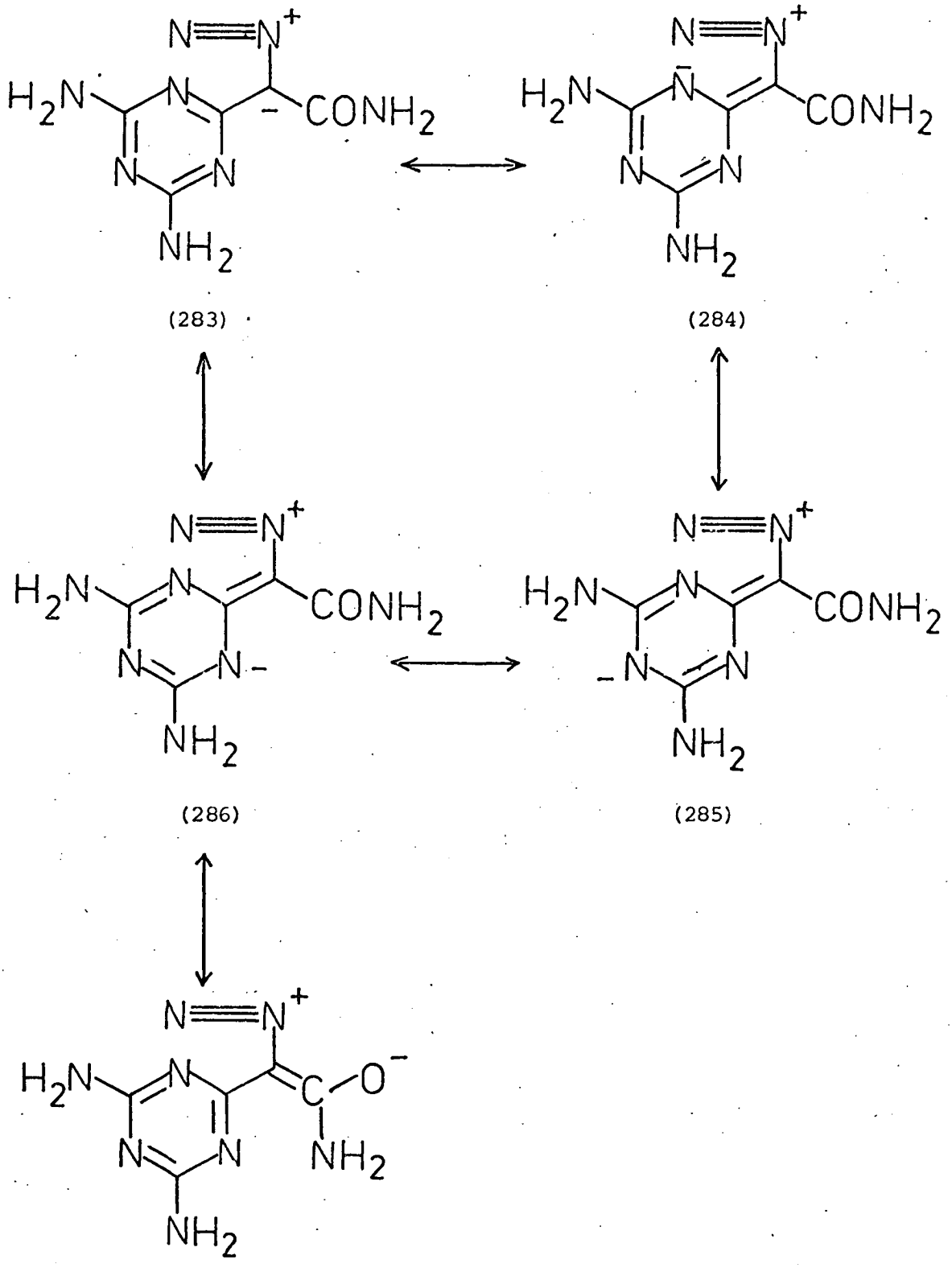


(281)



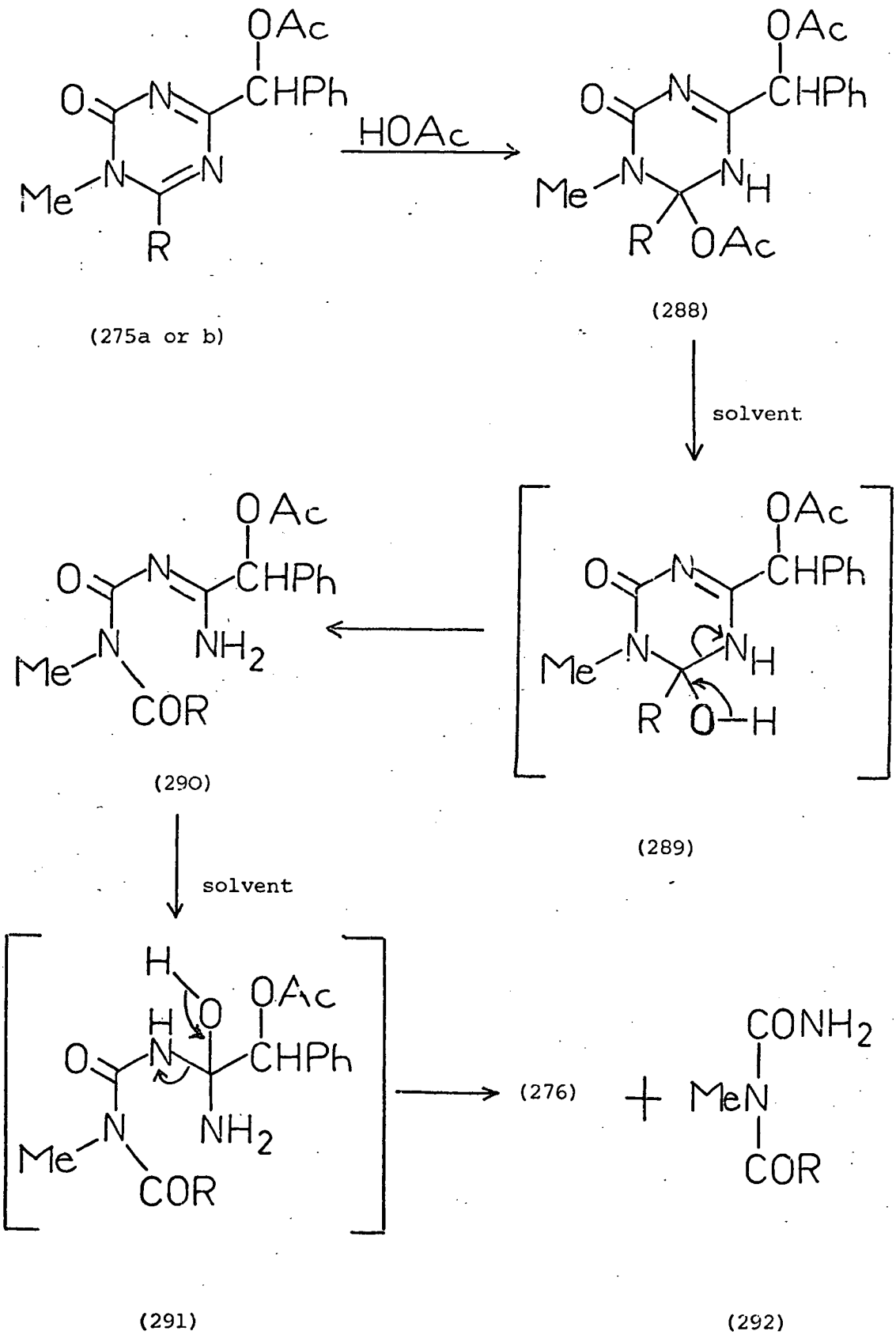
(282)

Scheme 29

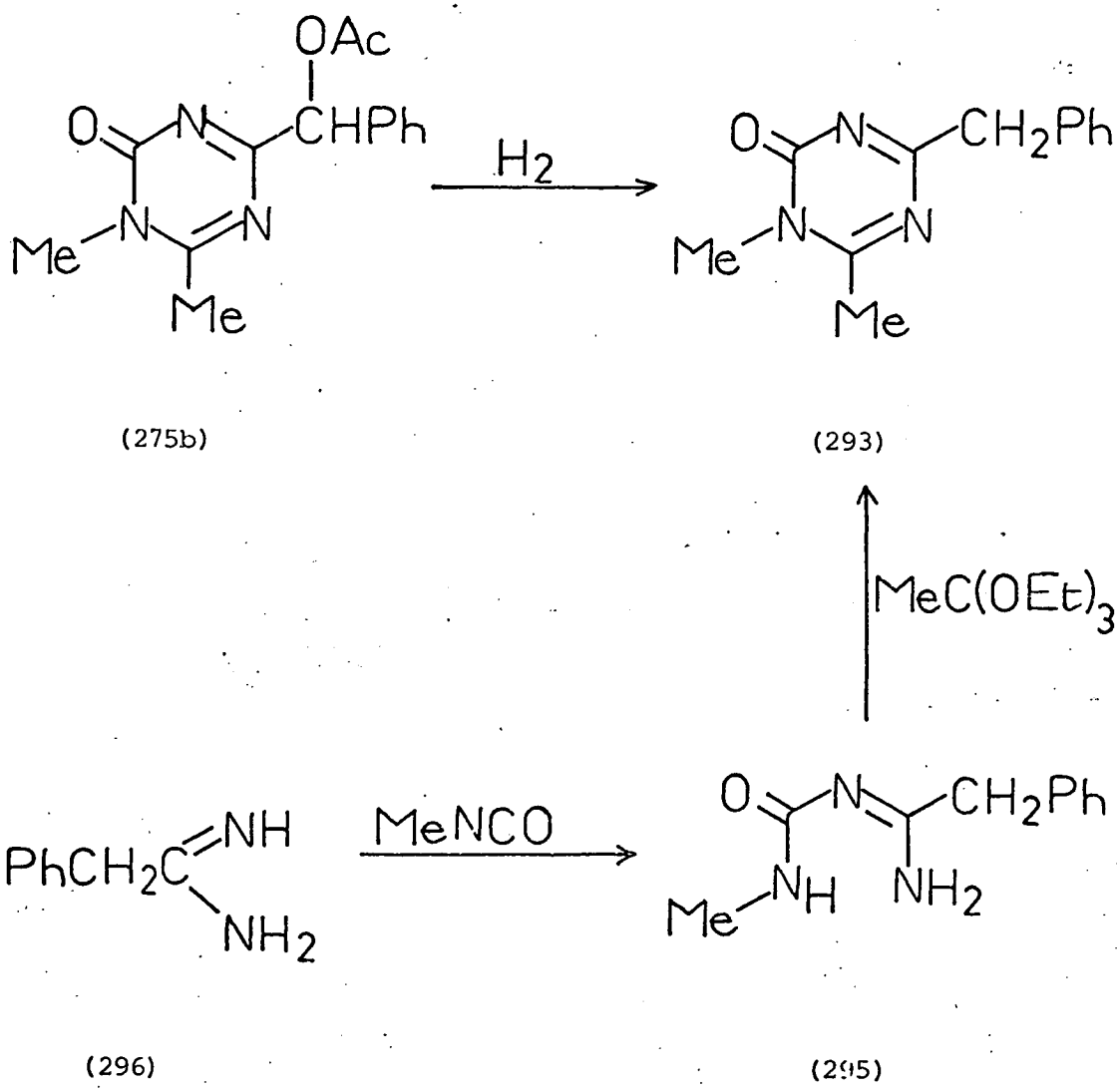


(283) (284) (286) (285) (287)

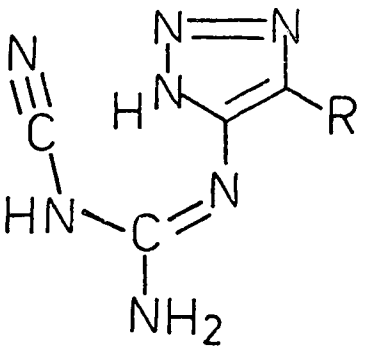
Scheme 30


OAc
CHPh
HOAc
Me
R
(275a or b)
(288)
solvent
NH2
COR
(290)
(289)
solvent
(291)
(276)
CONH2
MeN
(292)

Scheme 31


OAc
CHPh
O
N
Me
N
N
Me
H2
CH2Ph
(275b)
(293)
MeC(OEt)3
PhCH2C
NH
NH2
MeNCO
CH2Ph
NH
NH2
(296)
(295)

Scheme 32



(280)

In an attempt to crystallise the product (274 b), it was observed that marked differences had occurred in its i.r. spectrum during crystallisation. The most noteworthy difference being the appearance of a sharp band at 2150 cm^{-1}. Such a difference may be explained in terms of the opening-up of the triazole ring as postulated in Chapter 3.1, or alternatively by the opening-up of the triazine ring (Scheme 29). The latter of these alternatives would result in the formation of a structure of the type (282) which contains a nitrile group. However, as has been stated previously the electron-withdrawing character of the triazine ring may promote the opening of the triazole ring. This, coupled with the electron-withdrawing nature of an amide group, helps stabilize the negative charge (Scheme 30) of the open chain form of (274 b). If this is the case, the diazo group of (283-287) would give rise to the observed absorption at 2150 cm^{-1} in the i.r. spectrum of (274 b).

Further evidence for the structures (272 a-c) and (274 a) has been obtained from their heterolytic scission (see Chapter 1.3) in glacial acetic acid to yield the acetoxytriazines (275 a-c) and (277).

When the treatment of (272 a and b) in acetic acid was prolonged, this resulted in the formation of α-acetoxyphenylacetamide[97] (276). Although the mechanism of this cleavage is not clear, a process similar to that outlined in Scheme 31 probably operates subsequent to the formation of (275 a and b).

When the acetoxytriazine (275 b) was hydrogenated it gave the benzyltriazine (293) which was unambiguously synthesized by adding methylisocyanate to phenylacetamidine[98] (294), and reacting the product (295) with triethylorthoacetate (Scheme 32). The intermediate (295) decomposed to phenylacetamidine on attempted crystallisation. In the final cyclization step [(295) ⟶ (293)], some phenylacetamide was also produced. This synthesis helps to establish the existence of a 1,3,5-triazine nucleus in the compounds (272 a-c).

3.3 Experimental. (For general experimental procedures, see Appendix).

5-Amino-1H-1,2,3-triazoles (250 a and b)

5-Amino-4-phenyl-1H-1,2,3-triazole (250a) was prepared as described in the literature[11b]. 5-Amino-1H-1,2,3-triazole-4-carboxamide (250 b) was prepared as described previously[67] (cf. page 60).

The Synthesis and Reactivity of Some 5-Amino-1,2,3-triazole-1-carboxamides (251 a-d) and the Isomeric Ureas (252 a-d)

5-Amino-4-phenyl-1,2,3-triazole-1-carboxamides (251 a and c)

The triazolecarboxamides (251 a and c) were obtained (80-85%) by dissolving the aminotriazole (250 a)(0.80g; 0.005 mol) and methylisocyanate or phenylisocyanate (0.005 mol) in benzene (50 ml) and allowing the solution to stand for 12-14h at room temperature. The resultant solid was collected and combined with a second crop isolated by evaporating the mother liquor and triturating the residue with a little benzene to give the triazolecarboxamides (251 a and c), which were insoluble on brief treatment with dilute aqueous sodium hydroxide solution.

5-Amino-4-phenyl-1,2,3-triazole-1-(N-methylcarboxamide)(251 a) had m.p. 124° (from benzene), $\nu_{max.}$ 3450w, and 3350(NH), and 1720(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.18br(1H,q,J4.5Hz,NH), 2.10-2.28(2H,m,ArH), 2.47-2.75 (3H,m,ArH),3.30br(2H,s,NH), and 7.15(3H,d,J4.5Hz,Me), m/e 217(M^+) (M,217).

Found:	C,55.8;	H,5.0;	N,32.6%.
$C_{10}H_{11}N_5O$ requires:	C,55.2;	H,5.1;	N,32.3%.

5-Amino-4-phenyl-1,2,3-triazole-1-(N-phenylcarboxamide) (251 c) had m.p. 142° (from benzene), $\nu_{max.}$ 3400(NH) and 1720(CO)cm^{-1}, m/e 279 (M^+) (M,279).

Found: C,64.4; H,4.6; N,25.1%.

$C_{15}H_{13}N_5O$ requires: C,64.5; H,4.7; N,25.1%.

The N-methylcarboxamide (251 a) was also obtained (85%) by dissolving the aminotriazole (250 a) (0.005 mol) and methylisocyanate (0.005 mol) in dimethylformamide (2.0 ml) and leaving the resultant solution at room temperature for 18h before precipitating the product (251 a) with water.

5-Amino-4-carbamoyl-1,2,3-triazole-1-carboxamides (251 b and d)

A solution of the aminotriazolecarboxamide (250 b) (0.64g; 0.005 mol) and methylisocyanate or phenylisocyanate (0.005 mol) in dimethylformamide (2.0 ml) was left at room temperature for 3h (15 min in the case of the reaction with phenylisocyanate) then diluted with water to afford 5-amino-4-carbamoyl-1,2,3-triazole-1-(N-methylcarboxamide) (251 b) (0.34g) (37%), m.p. 248-50°, $\nu_{max.}$ 3500, 3400, and 3200(NH), and 1730, and 1670(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.26br (1H,q,J4.5Hz,NH), 2.43br(1H,s,amide NH), 2.75br(1H,s,amide NH), 3.12br(2H,s,NH), and 7.17(3H,d,J4.5Hz,Me), m/e 184(M^+) (M,184), or 5-amino-4-carbamoyl-1,2,3-triazole-1-(N-phenylcarboxamide) (251 d) (1.28g) (97%), m.p. > 230°(decomp.), $\nu_{max.}$ 3450w,3400, and 3200(NH), and 1730, and 1670(CO)cm^{-1}, m/e 246(M^+) (M,246). The N-substituted carboxamides (251 b and d) were insoluble on brief treatment with dilute aqueous sodium hydroxide solution and on crystallisation

from aqueous dimethylformamide gave the corresponding ureas (252 b and d) which were identical (m.p. and i.r. spectrum) with samples obtained later.

Evaporation of the mother liquor from the reaction with methylisocyanate gave a solid (0.47g), m.p. 223-31°, whose ^{1}H n.m.r. spectrum, τ [$(CD_3)_2SO$] 0.81br(s,NH),1.70br(s,NH),2.25br(s,NH),2.43br(q,J4.5Hz,NH), 2.60br(s,NH),4.06br(s,NH),7.07(d,J4.5Hz,Me), and 7.30(d,J4.5Hz,Me), is consistent with a mixture of the isomers (251 b) and (252 b) having the composition (251 b)(16%),(252 b)(84%) as estimated from the integrated ratio of the ^{1}H n.m.r. signals due to the N.Me groups.

When the N-methylcarboxamides (251 a and b)(0.001 mol) were suspended in aqueous dilute sodium hydroxide solution (2.0 ml), gradual solution took place. Acidification with dilute aqueous sulphuric acid gave the aminotriazoles (250 a and b)(55-70%) which were identified by m.p. and i.r. spectra.

The Attempted Acetylation of 5-Amino-4-phenyl-1,2,3-triazole-1-(N-methylcarboxamide)(251 a)

(a) The N-methylcarboxamide(251a)(0.33g; 0.0015 mol) was heated under reflux briefly in acetic anhydride (3.0 ml) until complete solution was attained. The reaction mixture was evaporated under reduced pressure and any remaining acetic anhydride azeotroped with toluene to give an oil. Trituration of the oil with ether gave a solid (0.11g), m.p. 128-52°, which was shown by t.l.c. to be a three component mixture. Evaporation of the ether mother liquor gave an oil (0.24g) which was proved by t.l.c. to be a multicomponent mixture.

(b) The N-methylcarboxamide(251 a) (0.33g; 0.0015 mol) was stirred at room temperature with acetyl chloride (5.0 ml) in benzene (20 ml) for 4h. The resultant solid was collected, washed with a cold aqueous solution of sodium hydrogen carbonate, then water, and dried in vacuo at room temperature to give unchanged starting material (251 a)(0.20g), m.p. 122°, which was identified by m.p. and i.r. spectrum.

The Attempted Reaction of 5-Amino-4-phenyl-1,2,3-triazole-1-(N-methylcarboxamide(251 a) with Methylisocyanate

The N-methylcarboxamide (251 a)(0.44g; 0.002 mol) and methylisocyanate (0.11g; 0.15 ml; 0.002 mol) were dissolved in benzene (50 ml) and the solution was left at room temperature for 16h. Evaporation of the reaction mixture gave unchanged N-methylcarboxamide (251 a) (100%) which was identified by m.p. and i.r. spectrum.

N-Substituted N^1-(4-Phenyl-1H-1,2,3-triazol-5-yl)ureas (252 a and c)

(a) N-Methyl-N^1-(4-phenyl-1H-1,2,3-triazol-5-yl) urea (252 a) was obtained (50-60%) by:-

(i) melting the N-methylcarboxamide (251 a)(0.44g; 0.002 mol) using a heated oil bath, holding at the melt for 5 min, dissolving the resultant solid in dilute aqueous sodium hydroxide solution and acidifying with dilute aqueous sulphuric acid solution.

(ii) heating the N-methylcarboxamide (251 a)(1.32g; 0.006 mol) in dimethylformamide (5.0 ml) under reflux for 30 min, filtering off any insoluble solid (after dilution with water), and collecting the product which was deposited on standing.

The urea (252 a) had m.p. 213° (from ethanol), $\nu_{max.}$ 3350w, and 3200br(NH), and 1650(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.76 br(1H,s,NH), 2.19-2.29

(2H,m,ArH), 2.46-2.67(3H,m,ArH),3.70br(1H,q,J4.5Hz,NH), and 7.38 (3H,d,J4.5Hz,Me), m/e 217(M^+)(M,217).

Found: C,55.3; H,5.2; N,31.9%.

$C_{10}H_{11}N_5O$ requires: C,55.3; H,5.1; N,32.2%.

The insoluble solid obtained, in case (ii), by dilution with water was combined with a second crop obtained by evaporating the mother liquor and triturating the residue with aqueous ethanol (total, 0.23g). The solid (X), which was unidentified, had m.p. 236° (from aqueous dimethylformamide), $\nu_{max.}$ 3450w, and 3300(NH), and 1640(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.35br(1H,s,NH), 2.16-2.31(2H,m,ArH), and 2.53-2.69(3H,m,ArH),m/e 186 (M^+).

Found: C,56.4; H,4.4; N,31.1%.

The solid (X) was readily soluble in dilute aqueous sodium hydroxide solution and was regenerated on acidification with dilute aqueous sulphuric acid.

(b)(i) N-Phenyl-N^1-(4-phenyl-1H-1,2,3-triazol-5-yl)urea(252 c) was obtained (97%) by heating the N-phenylcarboxamide (251 c)(0.56g; 0.002 mol) under reflux in toluene (15 ml) for 5h and evaporating off the solvent. The urea (252 c) had m.p. 173° (from aqueous ethanol), $\nu_{max.}$ 3250-3050br(NH), and 1650(CO)cm^{-1}, m/e 279(M^+)(M,279).

Found: C,63.0; H,4.9; N,25.2%.

$C_{15}H_{13}N_5O$ requires: C,64.5; H,4.7; N,25.1%.

(ii) When the N-phenylcarboxamide (251 c)(0.56g; 0.002 mol) was heated under reflux in dimethylformamide (3.0 ml) for 30 min and the solution diluted with water, a solid (0.47g), m.p. 129-51°, was

obtained whose t.l.c. showed it to be a multicomponent mixture.

N-Substituted N^1-(4-Carbamoyl-1H-1,2,3-triazol-5-yl)ureas (252 b and d)

The aminotriazolecarboxamide (250 b)(0.64g; 0.005 mol) and methylisocyanate or phenylisocyanate (0.005 mol) were dissolved in dimethylformamide (3.5 ml) and the solution was set aside at room temperature for 18h (3h in the case of phenylisocyanate). Dilution of the reaction mixture with water gave the ureas (252 b and d).

N-(4-Carbamoyl-1H-1,2,3-triazol-5-yl)-N^1-methylurea (252 b) (0.41g) had m.p. > 250°(decomp.), $\nu_{max.}$ 3450w,3400, and 3250(NH), and 1690, and 1650(CO) cm^{-1}, τ [$(CD_3)_2SO$] 0.80br(1H,s,NH), 2.24br(1H,s,NH), 2.42br (1H,q,J4.5Hz,NH), 2.58br(1H,s,NH) and 7.29(3H,d,J4.5Hz,Me), m/e 184 (M^+)(M,184).

Found:	C,32.3;	H,4.4;	N,45.5%.
$C_5H_8N_6O_2$ requires:	C,32.6;	H,4.4;	N,45.6%.

N-(4-Carbamoyl-1H-1,2,3-triazol-5-yl)-N^1-phenylurea (252 d) (1.30g)(84%), had m.p. > 245°(decomp.)(from benzene-dimethylformamide), $\nu_{max.}$ 3500w, and 3400-3200(NH), and 1680, and 1640(CO) cm^{-1}, m/e 246(M^+)(M,246).

Found:	C,47.7;	H,4.2;	N,33.8%.
$C_{10}H_{10}N_6O_2$ requires:	C,48.8;	H,4.1;	N,34.1%.

Evaporation of the mother liquor from the reaction with methylisocyanate gave a solid (0.44g), m.p. 221-35°, whose ^1H n.m.r. spectrum, τ [$(CD_3)_2SO$] 0.73br(s,NH), 1.72br(q,J4.5Hz,NH), 2.20br(s,NH), 2.44br (s,NH), 2.60br(s,NH), 4.07br(s,NH), 7.07(d,J4.5Hz,Me), and 7.30(d,J4.5Hz, Me), was consistent with a mixture of the isomers (251 b) and (252 b), which had the composition (251 b)(66%), (252 b)(34%) as estimated

from the integrated ratio of the ^1H n.m.r. signals due to the .N.Me groups.

The ureas (252 a-d) were readily soluble in aqueous dilute sodium hydroxide solution and were regenerated on acidification with aqueous dilute sulphuric acid.

The Acetylation of the Ureas (252 a-d)

The ureas (252 a-d)(0.0015 mol) were heated briefly under reflux in acetic anhydride (3.0 ml) until complete solution was obtained. The acetylated ureas (253)(51%) and (252 f-h)(73-85%) were isolated by collecting the insoluble solid and combining it with a second crop obtained by evaporating the mother liquor and azeotroping off any remaining acetic anhydride with toluene.

N-Acetyl-N-(1-acetyl-4-phenyl-1,2,3-triazol-5-yl)-N^1-methylurea(253) had m.p. 152°(from ethanol), $\nu_{max.}$ 3350(NH), and 1760, 1720, and 1680(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.63br(1H,q,J4.5Hz,NH), 2.22-2.50(5H,m,ArH), 7.20(3H,s,Ac), 7.26(3H,d,J4.5Hz,Me), and 7.90(3H,s,Ac), m/e 301(M^+) (M,301).

Found:	C,56.1;	H,5.0;	N,23.1%.
$C_{14}H_{15}N_5O_3$ requires:	C,55.8;	H,5.0;	N,23.2%.

N-(1-Acetyl-4-carbamoyl-1,2,3-triazol-5-yl)-N^1-methylurea(252 f) had m.p. 189°, $\nu_{max.}$ 3450w, and 3250br(NH), and 1760,1740, and 1670br(CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.26br(1H,s,NH), 1.68br(1H,s,NH), 2.03(1H,s,NH), 2.67(1H,q,J4.5Hz,NH), 7.26(3H,s,Ac), and 7.27(3H,d,J4.5Hz,Me), m/e 226(M^+)(M,226), and when crystallised from dimethylformamide-benzene, and aqueous dimethylformamide gave the acetamidotriazolecarboxamide (265) and the urea (252 b) respectively (identified by i.r. spectrum).

N-(1-Acetyl-4-phenyl-1,2,3-triazol-5-yl)-N^1-phenylurea (252g) had m.p. 173°(from ethanol-dimethylformamide), $\nu_{max.}$ 3300, and 3100w(NH); and 1740, and 1680(CO)cm^{-1},τ (CD Cl_3) 0.11br(1H,s,NH), 2.30-2.98 (10H,m,ArH), and 7.19(3H,s,Ac), m/e 321(M^+)(M,321).

Found: C,63.2; H,4.8; N,22.0%.

$C_{17}H_{15}N_5O_2$ requires: C,63.5; H,4.7; N,21.8%.

N-(1-Acetyl-4-carbamoyl-1,2,3-triazol-5-yl)-N^1-phenylurea (252h) had m.p. 202° (from dimethylformamide-benzene), $\nu_{max.}$ 3500w,3350, and 3300br(NH), and 1770, 1700 and 1680(CO)cm^{-1},τ [$(CD_3)_2SO$] 0.14br (1H, s,NH), 0.78br(1H,s,NH),1.66br(1H,s,NH),2.02br(1H,s,NH),2.45-3.03(5H,m, ArH), and 7.24(3H,s,Ac), m/e 288(M^+)(M,288).

Found: C,50.3; H,4.3; N,29.2%.

$C_{12}H_{12}N_6O_3$ requires: C,50.0; H,4.2; N,29.2%.

The Reaction of the Urea (252 a) with Methylisocyanate

The urea (252 a)(0.33g; 0.0015 mol) and methylisocyanate (0.09g; 0.11 ml; 0.0015 mol) were dissolved in dimethylformamide (2.0 ml) and the solution was left at room temperature for 16 h. Dilution with water afforded N-methyl-N^1-[1-(N-methylcarbamoyl)-4-phenyl-1,2,3-triazol-5-yl] urea (254)(0.31g)(76%), m.p. 165° (from ethanol-benzene), $\nu_{max.}$ 3350(NH), and 1740w, 1720w, and 1690(CO)cm^{-1}, τ [$(CD_3)_2SO$] 1.33br(1H,q,J4.5Hz,NH),1.39(1H,s,NH), 2.13-2.23(2H,m, ArH),2.49-2.64(3H,m,ArH), 3.37br(1H,q,J4.5Hz,NH), 7.12(3H,d,J4.5Hz, Me), and 7.36(3H,d,J4.5Hz,Me), m/e 274(M^+)(M,274).

Found: C,53.5; H,5.3; N,30.5%.

$C_{12}H_{14}N_6O_2$ requires: C,52.5; H, 5.2; N,30.6%.

When the urea (254) (0.21g) was heated under reflux in dimethylformamide (2.0 ml) for 2h and the reaction mixture was evaporated and treated with water, compound (X) was obtained (0.02g) m.p. 229-34° (decomp.), identical (m.p. and i.r. spectrum) with a sample obtained previously. Evaporation of the aqueous mother liquor and trituration of the resultant gum with aqueous ethanol gave the N-(1H-triazolyl)-N^1-methylurea (252 a) (0.05g), m.p. 203-7°, which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

The Attempted Reaction of the Aminotriazole (250 a) with Methylisothiocyanate

(a) The aminotriazole (250 a) (0.80g; 0.005 mol) and methylisothiocyanate (0.37g; 0.35 ml; 0.005 mol) were dissolved in benzene (50 ml) and the solution was left for 12h at room temperature, or heated under reflux for 3h. Any insoluble material was combined with a second crop obtained by evaporating the mother liquor, and treating the residue with a little benzene to give unchanged triazole (250 a) (79-83%) m.p. 122°, which was identified by its m.p. and i.r. spectrum.

(b) The aminotriazole (250 a) (0.80g; 0.005 mol) and methylisothiocyanate (0.37g; 0.005 mol) were dissolved in dimethylformamide (2.0 ml) and the solution was left at room temperature for 12h. Evaporation of the reaction mixture gave an oil (1.15g) whose t.l.c. showed it to be a multicomponent mixture.

The Synthesis of Some 1,2,3-Triazolo[1,5-a]-1,3,5-triazines.

6-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7(6H)-one (272 a)

(a) The N-methylcarboxamide (251 a) (4.4g; 0.02 mol) was stirred in triethylorthoformate (15 ml) at 100° for 17h. The resultant solid was collected, washed with a little methanol, then ether, and dried *in vacuo* at room temperature to give the triazolotriazine (272 a) (0.74g) (16%), m.p. 242° (from aqueous dimethylformamide), $\nu_{max.}$ 1750(CO)cm^{-1}, $\lambda_{max.}$ 214,236,245 infl., 254 infl., and 297nm(log ε 3.91,3.94,3.89,3.79 and 4.16), τ [$(CD_3)_2SO$] 1.50(1H,s,H-5), 1.74-1.84 (2H,m,ArH), 2.39-2.62(3H,m,ArH), and 6.42(3H,s,Me-6), m/e 227(M^+), (M,227).

Found: C,58.1; H,3.9; N,30.7%.

$C_{11}H_9N_5O$ requires: C,58.1; H,4.0; N,30.8%.

Evaporation of the triethylorthoformate mother liquor under reduced pressure gave an oil (4.21g) whose t.l.c. showed it to be a multicomponent mixture.

(b) The N-methylcarboxamide (251 a) (0.44g; 0.002 mol) was heated under reflux in triethylorthoformate (3.0 ml) containing acetic anhydride (3.0 ml) for 1h. Evaporation of the reaction mixture under reduced pressure gave an oil (0.43g) which did not crystallise and was shown to be a multicomponent mixture by t.l.c. in ether over silica.

(c) The N-methylcarboxamide (251 a) (1.32g; 0.006 mol) was stirred in triethylorthoformate (8.4 ml) at 70° for 20h. The resultant solid was collected, washed with a little ether, and dried *in vacuo* at room temperature. The solid (0.29g) had m.p. 251-66°,

$\nu_{max.}$ 3350(NH), and 1750w,1740w,1720w, and 1690(CO)cm^{-1}, and the ^1H n.m.r. spectrum,τ [$(CD_3)_2SO$] 1.33br(q,J4.5Hz,NH), 1.39br(s,NH), 1.50[s,H-5(272a)] ,1.70-1.82(m,ArH), 2.13-2.23(m,ArH), 2.49-2.64(m,ArH), 3.37br(q,J4.5Hz,NH), 6.42 [s,Me-6(272 a)] , 7.12(d,J4.5Hz,Me), and 7.36 (d,J4.5Hz,Me), was consistent with a mixture of the triazolotriazine (272 a)(12%) and the urea (254)(88%), the composition being estimated from the integrated ratio of the ^1H n.m.r. signals due to the Me-6 (272 a) and .N.Me(254) groups. No attempt was made to separate the mixture. Evaporation of the mother liquor afforded an oil, which was triturated with a little methanol, to give the triazolotriazine (272 a)(0.02g) m.p. 240°, identical (m.p. and i.r. spectrum) with a sample prepared before. Evaporation of the trituration liquor gave an oil (1.06g) which was shown by t.l.c. to be a multicomponent mixture.

(d) The N-methylcarboxamide (251 a)(4.4g; 0.02 mol.) and triethyl-orthoformate (8.9g; 9.9 ml; 0.06 mol) were stirred in dimethyl-formamide (10.0 ml) at 100° for 16h. Dilution of the reaction mixture with methanol gave the triazolotriazine (272 a), which was combined with a second crop obtained by evaporating the mother liquor and triturating the resultant oil (3.77g) with methanol (total, 0.69g) (15%), m.p. 239°, identical (m.p. and i.r. spectrum) with a sample prepared previously. The trituration liquor slowly deposited 4,5-dihydro-5-ethoxy-6-methyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7-one (273)(0.90g), m.p. 117° (from ethanol), $\nu_{max.}$ 3250(NH), and 1690(CO)cm^{-1}, τ ($CDCl_3$)0.77(1H,s,H-5),1.89-1.98(2H,m,ArH),

2.57-2.65(3H,m,ArH),5.67(2H,q,J7Hz,CH_2),6.62(3H,s,Me-6), and 8.66 (3H,t,J7Hz,Me), m/e 273(M^+)(M,273).

Found: C,57.6; H,5.7; N,25.6%.

$C_{13}H_{15}N_5O_2$ requires: C,57.1; H,5.5; N,25.8%.

Evaporation of the mother liquor afforded an oil (2.81g) which was shown by t.l.c. to be a multicomponent mixture.

The ethoxy compound (273)(0.27g; 0.001 mol) was heated under reflux in dimethylformamide (2.0 ml) for 2h, and the reaction mixture was diluted with methanol to give the triazolotriazine (272 a)(0.11g) (48%), m.p. 242°, which was identified with an authentic sample by its m.p. and i.r. spectrum. Evaporation of the mother liquor gave an oil (0.13g) whose t.l.c. showed it to be a multicomponent mixture.

5,6-Dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7(6H)-one (272 b) and 5-Ethyl-6-methyl-3-phenyl-1,2,3-triazolo[1,5-a]-1,3,5-triazin-7(6H)-one(272 c)

The N-methylcarboxamide (251 a)(1.76g; 0.008 mol) and triethylorthoacetate or triethylorthopropionate (0.024 mol) were stirred in dimethylformamide (4.0 ml) at 100° for 16h. Dilution of the reaction mixture with methanol gave a solid, which was combined with a second crop, obtained by evaporating the mother liquor and triturating the resultant oil with methanol to give the dimethyltriazolotriazine (272 b)(0.99g)(51%) m.p. 220°(decomp.)(from aqueous dimethylformamide), $\nu_{max.}$ 1740(CO)cm^{-1}, $\lambda_{max.}$ 214,235,246,255 and 295nm(log ε 3.96,3.91, 3.88,3.83 and 4.23),τ [$(CD_3)_2SO$] 1.74-1.86(2H,m,ArH), 2.41-2.66 (3H,m,ArH), 6.44(3H,s,Me-6), and 7.39(3H,s,Me-5), m/e 241(M^+) (M,241),

Found: C,59.6; H,4.6; N,29.0%,

$C_{12}H_{11}N_5O$ requires: C,59.7; H,4.6; N,29.0%,

or, the ethylmethyltriazolotriazine (272 c)(0.97g)(48%), m.p. 211° (from aqueous dimethylformamide), $\nu_{max.}$ 1740(CO) cm^{-1}, $\lambda_{max.}$ 215,235, 245,254 and 296nm(log ε 3.95,3.90,3.85,3.81 and 4.22), τ [$(CD_3)_2SO$] 1.70-1.84(2H,m,ArH), 2.38-2.70(3H,m,ArH),6.44(3H,s,Me), 7.08(2H,q, J7Hz,CH_2), and 8.68(3H,t,J7Hz,Me), m/e 255(M^+) (M,255).

Found: C,61.0; H,5.2; N,27.3%.

$C_{13}H_{13}N_5O$ requires: C,61.2; H,5.1; N,27.5%.

Evaporation of the mother liquor from both reactions gave oils (0.96-1.08g) which were shown by t.l.c. to be multicomponent mixtures.

The Reactions of the N-Substituted Carboxamides (251 b and c) with Triethylorthoformate

(a) The N-methylcarboxamide (251 b)(0.37g; 0.002 mol) and triethylorthoformate (0.89g; 0.99 ml; 0.006 mol) were stirred in dimethylformamide (2.0 ml) at 100° for 15 h. Evaporation of the reaction mixture and trituration of the residue with ether gave a solid (0.35g) m.p. > 175° (decomp.), which had an ill-defined i.r. spectrum and which was shown by t.l.c. to be a gross mixture.

(b) The N-phenylcarboxamide (251 c)(0.56g; 0.002 mol) was stirred in triethylorthoformate (2.8 ml) at 100° for 19h. Evaporation of the reaction mixture afforded an oil (0.49g) which did not crystallise and which was shown by t.l.c. to be a multicomponent mixture.

The Reactions of the Triazoles (250 a and b) with Dicyandiamide

The aminotriazole (250 a or b)(0.0125 mol) and dicyandiamide (1.26g; 0.0150 mol) were heated under reflux in water (5.0 ml) containing concentrated hydrochloric acid (1.1 ml) for 20-30 min. The resultant solid was filtered off from the hot reaction mixture and washed with water.

(a) The aminophenyltriazole (250 a) gave 5,7-diamino-3-phenyl-1,2,3-triazole[1,5-a]-1,3,5-triazine (274 a)(0.29g)(10%), m.p. > 227°(decomp.) (from aqueous dimethylformamide), $\nu_{max.}$ 3350-3100br(NH), and 1680 (NH def.) cm^{-1}, $\lambda_{max.}$ 215,287,295sh, and 318sh nm(log ε 4.18,4.16,4.13 and 3.64), m/e 227(M^+)(M,227).

Found:	C,52.9;	H,4.0;	N,43.4%.
$C_{10}H_9N_7$ requires:	C,52.9;	H,4.0;	N,43.1%.

The mother liquor was allowed to cool and an oil, which was insoluble in chloroform, separated out. The supernatant liquid was decanted from the oil, which on contact with dilute aqueous ammonia solution gave an amorphous solid (0.55g) m.p. 85-107°, having an ill-defined i.r. spectrum and shown by t.l.c. examination to be a multi-component mixture. No material was obtained from the supernatant mother liquor, on extraction with chloroform, before or after adjustment to pH8 with dilute aqueous ammonia solution.

(b) The aminotriazolecarboxamide (250 b) gave a solid which was combined with a second crop which separated from the cooled mother liquor (total, 1.44g). The crude solid had m.p. > 280°(decomp.), $\nu_{max.}$ 3450w,3350, and 3250br(NH), 1680(CO), and 1660 (NH def.) cm^{-1}, and on crystallisation from aqueous dimethylsulphoxide had m.p.> 240° (decomp.), $\nu_{max.}$ 3350, and 3200(NH), 2150(.C ≡ N or .$\overset{+}{N}$ ≡ N), and 1660br(CO) cm^{-1}, m/e 194 (M^+)(M,194).

Found: C,30.8; H,3.1; N,57.3%.

Calculated for $C_5H_6N_8O$: C,30.9; H,3.1; N,57.7%.

The Synthesis of Some 4-Substituted 1,3,5-Triazines.

The Reactions of the Triazolotriazines (272 a-c) with Hot Glacial Acetic Acid

The 1,2,3-triazolo-1,3,5-triazines (272 a and b)(0.003 mol) were heated under reflux in glacial acetic acid (35 ml) for 16h. Evaporation of the reaction mixtures left oils which were washed with a saturated aqueous solution of sodium hydrogen carbonate and extracted with chloroform.

(i) The triazolotriazine (272 a) gave an oil which on trituration with methanol-ether yielded α-acetoxyphenylacetamide (276) (0.27g), m.p. 112°(lit.,[97], 112°) (from ethanol-light petroleum), $\nu_{max.}$ 3400, and 3200(NH), and 1740, and 1660(CO) cm^{-1}, τ ($CDCl_3$) 2.54-2.72(5H,m, ArH), 3.64br(2H,s,NH), 3.97(1H,s,CH), and 7.87(3H,s,Me), m/e 193 (M^+) (M,193).

Found: C,62.1; H,5.8; N,7.2%

$C_{10}H_{11}NO_3$ requires: C,62.2; H,5.7; N,7.3%.

(ii) The 5-methyltriazolotriazine (272 b) gave a solid (0.64g), m.p. 105-68°, which when fractionally crystallised from ethanol gave 4- (α-acetoxybenzyl)-1,6-dimethyl-1,3,5-triazin-2(1H)-one (275 b) (0.45g), m.p. 202°(from ethanol), $\nu_{max.}$ 1730, and 1700(CO) cm^{-1}, τ($CDCl_3$) 2.34-2.46(2H,m,ArH), 2.61-2.70(3H,m,ArH), 3.78(1H,s,benzylic H), 6.54(3H,s,Me-1), 7.53(3H,s,Me-6), and 7.80(3H,s,OAc), m/e 273 (M^+) (M,273),

Found: C,61.3; H,5.5; N,15.2%,

$C_{14}H_{15}N_3O_3$ requires: C,61.5; H,5.5; N,15.4%,

and α-acetoxyphenylacetamide (276) (0.03g), m.p. 111°, which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

(iii) The triazolotriazines (272 a and c) (0.003 mol) were heated under reflux in glacial acetic acid (35 ml) for 6h and 9h respectively. The reaction mixtures were evaporated and the resultant oils were washed with a saturated aqueous solution of sodium hydrogen carbonate and extracted into chloroform.

(a) The triazolotriazine (272 a) gave an oil (0.62g), which when triturated with methanol-ether gave 4-(α-acetoxybenzyl)-1-methyl-1,3,5-triazin-2(1H)-one (275 a) (0.06g), m.p. 173° (from ethanol-light petroleum), $\nu_{max.}$ 1740, and 1690 (CO) cm^{-1}, τ ($CDCl_3$) 1.82 (1H,s,H-6), 2.35-2.49 (2H,m,ArH), 2.55-2.71 (3H,m,ArH), 3.72 (1H,s,benzylic H), 6.57 (3H,s,Me-1), and 7.80 (3H,s,OAc), m/e 259 (M^+) (M,259).

Found: C,60.0; H,4.9; N,16.1%.

$C_{13}H_{13}N_3O_3$ requires: C,60.2; H,5.1; N,16.2%.

Evaporation of the trituration liquor gave an oil, which when retriturated with methanol-ether gave α-acetoxyphenylacetamide (276) (0.08), m.p. 111° (from ethanol-light petroleum), which was identical (m.p. and i.r. spectrum) with a sample obtained previously. T.l.c. examination of the trituration liquor showed it to contain a multicomponent mixture.

(b) The 5-ethyltriazolotriazine (272 c) gave 4-(α-acetoxybenzyl)-6-ethyl-1-methyl-1,3,5-triazin-2(1H)-one (275 c) (0.76g) (89%), m.p. 168° (from ethanol), $\nu_{max.}$ 1730, and 1690 (CO) cm^{-1}, τ ($CDCl_3$) 2.33-2.46 (2H, m,ArH), 2.59-2.75 (3H,m,ArH), 3.75 (1H,s,benzylic H), 6.57 (3H,s,Me-1), 7.30 (2H,q,J7Hz,CH_2), 7.81 (3H,s,OAc), and 8.73 (3H,t,J7Hz,Me), m/e 287 (M^+) (M,287).

Found: C,62.6; H,5.9; N,14.6%.

$C_{15}H_{17}N_3O_3$ requires: C,62.7; H,5.9; N,14.6%.

4-(α-Acetoxybenzyl)-2,6-diamino-1,3,5-triazine (277)

The diaminotriazolotriazine (274 a) (0.56g; 0.0025 mol) was heated under reflux in glacial acetic acid (20 ml) for 9h. The reaction mixture was evaporated and the resultant oil was washed

with a saturated aqueous solution of sodium hydrogen carbonate, and extracted into chloroform to give a solid, which was crystallised from ethanol to give the acetoxybenzyltriazine (277)(0.31g)(50%), m.p. 212°, $\nu_{max.}$ 3500,3400, and 3150(NH), 1730(CO), and 1680w(NH def.), τ ($CDCl_3$) 2.52-2.74(5H,m,ArH),3.75(1H,s,benzylic H),4.27br(4H,s,NH), and 7.84(3H,s,OAc), m/e 259(M^+)(M,259).

Found: C,55.6; H,5.2; N,27.0%.

$C_{12}H_{13}N_5O_2$ requires: C,55.6; H,5.1; N,27.0%.

4-Benzyl-1,6-dimethyl-1,3,5-triazin-2(1H)-one(293)

(a) The acetoxybenzyltriazine (275 b)(0.11g) was hydrogenated in ethanol (50 ml) over 10% palladium-charcoal. Evaporation of the filtered reaction mixture and trituration of the resultant oil with ether gave the benzyltriazinone (293)(0.08g), m.p. 130° (from ethanol), $\nu_{max.}$ 1680(CO)cm^{-1}, τ ($CDCl_3$)2.52-2.84(5H,m,ArH), 6.10(2H, s,benzylic CH_2), 6.52(3H,s,Me-1), and 7.53(3H,s,Me-6),m/e 215(M^+) (M,215).

Found: C,67.4; H,6.2; N,19.4%.

$C_{12}H_{13}N_3O$ requires: C,67.0; H,6.1; N,19.5%.

(b) Phenylacetamidine[98] (2.43g; 0.018 mol) and methylisocyanate (1.05g; 1.35 ml; 0.018 mol) were dissolved in benzene (200 ml) and the solution was left at room temperature for 2h. The resultant solid was collected to give N-(N-methylcarbamoyl)phenylacetamidine(295)(1.92g), m.p. 143-7°, $\nu_{max.}$ 3350, and 3200br(NH), 1700(CO), and 1640(NH def.) cm^{-1}, m/e 191(M^+)(M,191), which on crystallisation from benzene gave phenylacetamide,[99] m.p. 148° (lit.[99], 155°) $\nu_{max.}$ 3350, and 3150(NH), and 1640(CO)cm^{-1}, identical (i.r. spectrum) with an authentic sample.

The crude N-(N-methylcarbamoyl)phenylacetamidine (295)(1.43g; 0.0075 mol) was stirred in triethylorthoacetate (15 ml) at 100° under nitrogen for 17h. The reaction mixture was filtered hot to remove unreacted starting material (295)(0.35g) m.p. 141-8° which was identified by its m.p. and i.r. spectrum. On cooling, the filtrate deposited phenylacetamide (0.23g), m.p. 155°, which was identical (m.p. and i.r. spectrum) with an authentic sample[99]. Evaporation of the remaining mother liquor gave an oil, which was triturated with ethanol-ether to give the benzyltriazinone (293)(0.33g), m.p. 127-29° (from ethanol), which was identical (m.p., mixed m.p., and i.r. spectrum) with a sample obtained previously.

The Thermal Reactions of the N-Methyl and N-Phenylureas (252 b and d)

The N-substituted urea (252 b or d)(0.0015 mol) was heated under reflux in dimethylformamide (5.0 ml) for 3h. The reaction mixture was evaporated and the resultant solid product was collected.

(a) The product from the N-methylurea (252 b) was treated with water to give a solid (Y)(0.10g), m.p. 268°(decomp.)(from water), $\nu_{max.}$ 3450-3200br(NH), and 1700br(CO) cm^{-1}, m/e 198(M^+). The mother liquor slowly deposited a solid (Z)(0.07g), m.p. 238°(from ethanol-glacial acetic acid), $\nu_{max.}$ 3200-3100br(NH), and 1710br(CO) cm^{-1}, m/e 153(M^+).

Found: C,33.4; H,3.3; N,44.1%.

(b) The product from the N-phenylurea (252 d), when leached with boiling water, gave the insoluble 1,3-diphenylurea[95] (270) which was combined with a second crop obtained as described later.

Evaporation of the mother liquor gave a solid (0.24g), m.p.> 190° (decomp.), $\nu_{max.}$ 3200-2700br(NH), and 1710-1660br(CO)cm^{-1}, which was subjected to preparative t.l.c. in 25% methanol-chloroform over silica to give 1,3-diphenylurea[95] (270)(total, 0.07g), m.p. 239°(from ethanol), (lit.,[95] 239°), $\nu_{max.}$ 3300(NH), and 1650(CO)cm^{-1}, m/e 212(M^+)(M,212), and 5-amino-1H-1,2,3-triazole-4-carboxamide[67] (250 b)(0.03g)m.p. 218°, (lit.,[67]225°)(identified by its i.r. spectrum), and the solid (Z) (0.03g), m.p. 236°, which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

The Reaction of 5-Amino-1H-1,2,3-triazole-4-carboxamide (250 b) with Urea

The aminotriazole (250 b)(0.64g; 0.005 mol) and urea (0.30g; 0.005 mol) were mixed intimately and heated at 200° (oil-bath) for 30 min. The resultant solid (0.79g), which was collected on cooling, had m.p. > 290°(decomp.)(from aqueous dimethylformamide), and showed spectral properties consistent with the urea (252 i). The product, which was soluble on brief treatment with dilute aqueous sodium hydroxide solution and regenerated on acidification of the solution with dilute aqueous sulphuric acid, had $\nu_{max.}$ 3450-3200br(NH), and 1740, and 1680(CO)cm^{-1}, m/e 170(M^+)(M,170).

Found:	C,28.8;	H,3.6;	N,48.9%.
$C_4H_6N_6O_2$ requires:	C,28.2;	H,3.6;	N,49.4%.

When this solid (0.34g; 0.001 mol) was heated under reflux in 10% aqueous sodium hydroxide solution (5.0 ml) for 30 min, and the cooled reaction mixture acidified with dilute aqueous sulphuric acid, the solid (Z)(0.17g), m.p. 220°(decomp.) was obtained, which

was identical (m.p. and i.r. spectrum) with a sample obtained previously. The aqueous mother liquor slowly deposited the dihydrate of 3H-1,2,3-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione[96] (267) (0.10g), m.p. > 320° (from aqueous dimethylformamide) (lit.,[96] > 320°), $\nu_{max.}$ 3500, 3400, 3350, and 3300 (NH,OH), 2750-2200br, and 1960-1860br (OH), and 1690, and 1670 (CO) cm^{-1}, m/e 153 (M^+) (M,153).

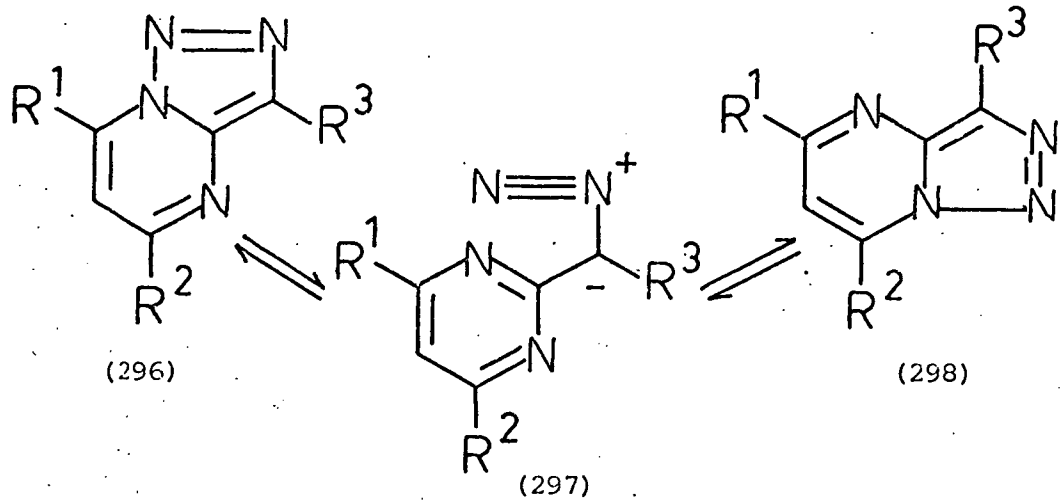
Found:	C,25.7;	H,3.6;	N,37.6%.
$C_4H_3N_5O_2.2H_2O$ requires:	C,25.4;	H,3.7;	N,37.1%.

Chapter 4

The Synthesis and Reactivity of the 1,2,3-Triazolo[1,5-a]-pyrimidine Ring System - Diazoalkylideneamine - -Triazole Equilibria

4.1 Introduction

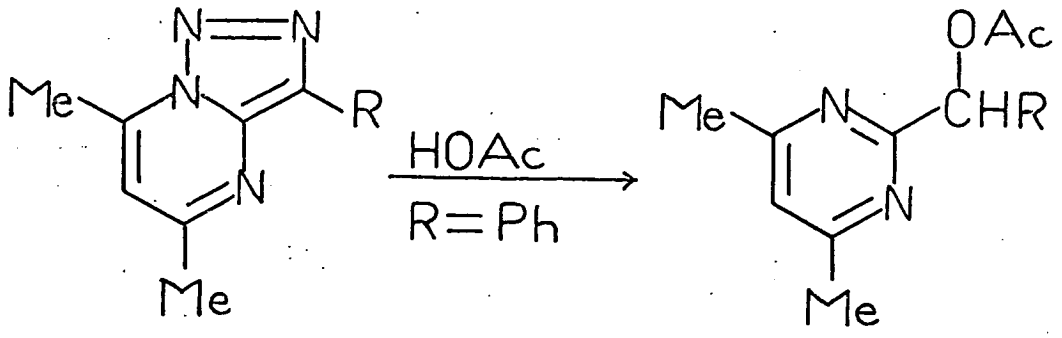
As has already been discussed (Chapter 1.4) the 1,2,3-triazolo-[1,5-a]pyrimidine ring system (e.g. 296) has been shown[13] to undergo Dimroth rearrangement [(296)⇌(297)⇌(298)]. As in the



(296) (297) (298)

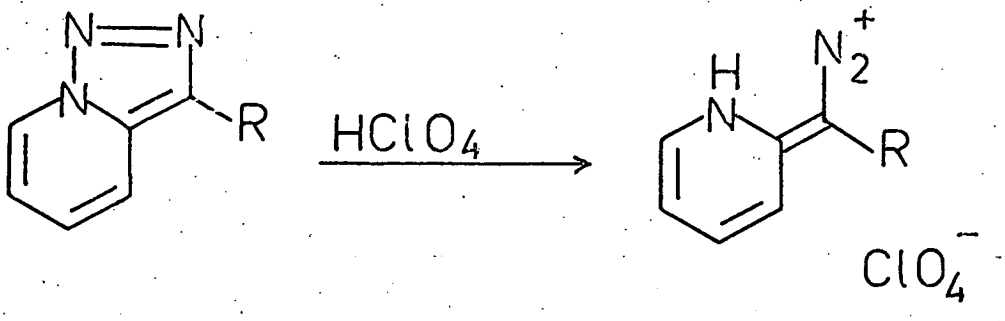
1,2,3-triazolo[5,1-c]-1,2,4-triazine (Chapter 2.1) and 1,2,3-triazolo-[1,5-a]-1,3,5-triazine (Chapter 3.1) ring systems, the electron-withdrawing character of the azine ring of (296) may have the effect of destabilizing (296) (relative to (297). However, attempts to detect an intermediate of the type (297) in the rearrangement [(296)⇌(298)] have as yet proved[11b] unsuccessful.

Previous studies[11b,13] of the ring system (296) have shown that when R^3=Ph, the triazole ring of (296) is susceptible,in acidic media, to heterolytic scission (see Chapter 1.3). Molecules such as (299; R=Ph), when suitably treated with glacial acetic acid, (Scheme 33) gave pyrimidine derivatives[11b,13](e.g. 300; R=Ph)(cf. Chapter 1.3; Scheme 4). However, the system has shown no tendency to react when R = .$CONH_2$.[11b,13] This result is consistent(see Chapter 1.3) with the observation that the 1,2,3-triazolopyridine system (301)



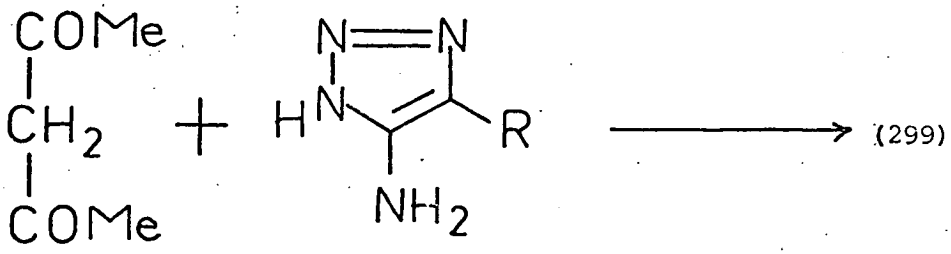
(299) (300)

Scheme 33



(301) (302)

Scheme 34



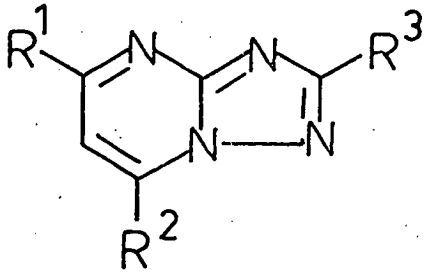
(303)

R = Ph, $CONH_2$

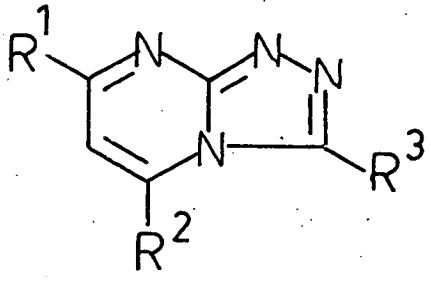
Scheme 35

does not undergo triazole scission, in carboxylic acid solution, when the substituent R is electron-withdrawing.[8,9] The electron-withdrawing nature of R does not, however, prevent the formation[5] of stable diazonium perchlorates (302) when (301) is treated with perchloric acid (Scheme 34). Thus, the behaviour of the triazolopyrimidines (296) and the triazolopyridines (301), in glacial acetic acid, may best be interpreted in terms of the inability of the triazole ring to undergo protonation, when the triazole substituent is electron withdrawing (see Chapter 1.3; Scheme 4).

The methods used to date in the synthesis of the 1,2,3-triazolo-[1,5-a]pyrimidine ring system (296) have been based[11b,13] on the bifunctional reactivity of the amino-1,2,3-triazoles (303). Molecules such as (299) have been prepared by the acid or base catalysed condensation of (303) (Scheme 35) with for example acetyl-acetone. Reactions of this type are analogous[86,88] to syntheses of the corresponding 1,2,4-triazolopyrimidines (304) and (305).

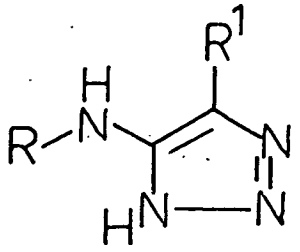


(304)



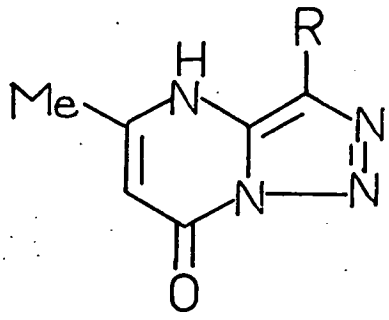
(305)

The following study was undertaken with a view to extending the synthetic routes to the 1,2,3-triazolo[1,5-a]pyrimidine ring system (296) and further to study the acid catalysed scission of the system (296). Experiments have been devised in an attempt to detect the



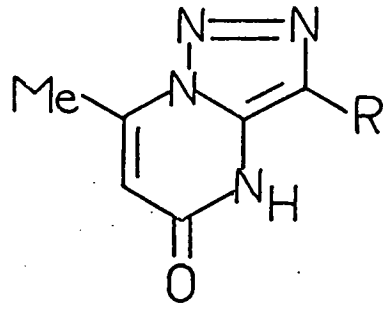
(306)

	R	R^1
a;	H	.$CONH_2$
b;	Ac	.$CONH_2$
c;	H	Ph

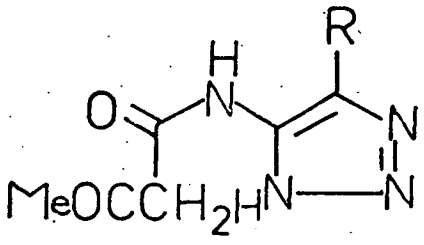


(307)

	R
a;	Ph
b;	.$CONH_2$

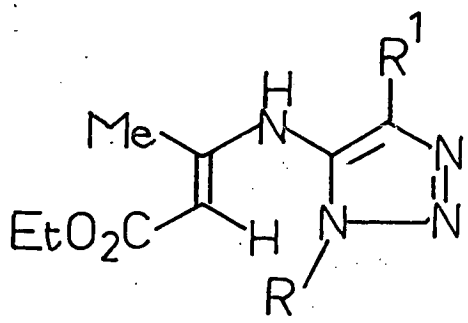


(308)



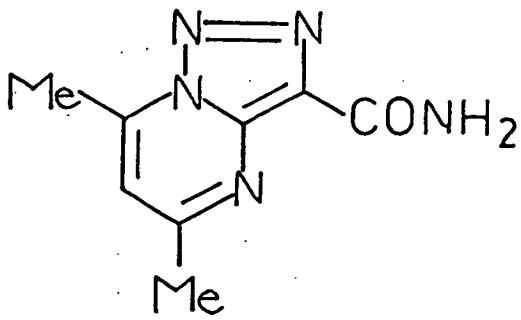
(309)

	R
a;	Ph
b;	.$CONH_2$



(310)

	R	R^1
a;	H	Ph
b;	H	.$CONH_2$
c;	Ac	.$CONH_2$



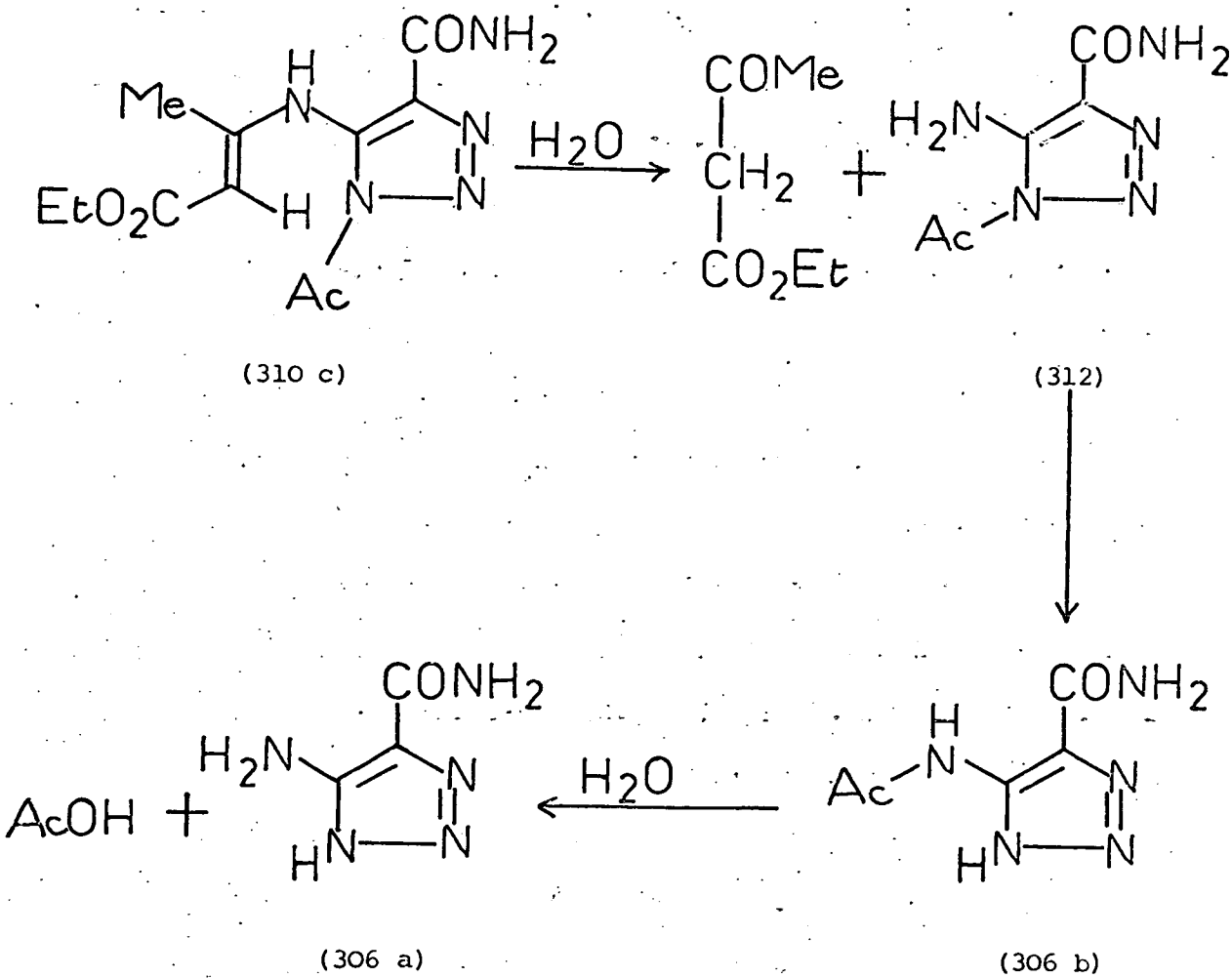
(311)

diazoalkylideneamine-triazole tautomerism [(296)⟹(297)].

4.2 The Synthesis and Reactivity of the 1,2,3-Triazolo[1,5-a]-pyrimidine Ring System

Work in this department[13] (see Chapter 1.4) has shown that the triazolopyrimidines (307a) and(307b) may undergo a reversible interconversion. As previously described, this Dimroth rearrangement is catalysed in one direction by the presence of base, and the converse rearrangement is promoted thermally. When the aminotriazole (306 a) was condensed with ethyl acetoacetate under thermal, or base or acid catalysed conditions, the product was the isomer mixture [(307 b) + (308 b)]. In each case, the proportions of (307 b) and (308 b) were identical, and attempts to separate the mixture by fractional crystallisation, chromatography and preferential salt formation proved unsuccessful. A by-product in the acetic acid catalysed reaction was the acetamidotriazole (306 b).

By analogy with the investigation of the structures (307 a) and (308 a), attempts were made to synthesise the compounds (309 b) and (310b) with a view to their subsequent conversion to the single isomers (308 b) and (307 b) respectively. However, the conditions which proved successful for the synthesis of (309 a) - namely, heating the aminotriazole (306 c) and ethyl acetoacetate under reflux in toluene - did not give (309 b) when the triazolecarboxamide (306 a) was used. Instead, a quantitative recovery of the starting triazole (306 a) was obtained. When the triazole (306 a) and ethyl acetoacetate were heated under reflux in toluene or benzene which contained


CONH2
Me
H
N
N
N
EtO2C
H
N
Ac
H2O
COMe
CH2
CO2Et
+
CONH2
H2N
N
N
Ac
N
(310 c)
(312)
CONH2
H
N
Ac
N
N
H
N
CONH2
H2N
N
N
AcOH +
H
N
H2O
(306 b)
(306 a)

Scheme 36

a catalytic amount of glacial acetic acid, the result was the recovery of the triazole (306 a) and the isolation of a small amount of the isomer mixture [(307 b) + (308 b)]. This last set of conditions had proved successful[13] in obtaining (310 a) from (306 c). However, when the triazole (306 a) and ethyl acetoacetate were stirred in dimethylformamide, containing glacial acetic acid, at an ambient temperature, the result was the formation of the monohydrate of the vinylaminotriazole (310 b).

The adduct (310 b) was characterised by its i.r., ^{1}H n.m.r. and mass spectrum. The analytical data obtained from the product remained (after crystallisation from ethanol) consistent with the monohydrate of (310 b). The presence of a 1H-1,2,3-triazole nucleus in (310 b) was confirmed by its ability to form a sodium salt and also by the formation of a 1-acetyl derivative (310 c). This derivative (310 c) had a band at 1770 cm^{-1} in its i.r. spectrum and a signal at τ7.29 in its ^{1}H n.m.r. spectrum. Both of these features are attributable to the presence of a triazole N-acetyl group.[11a]

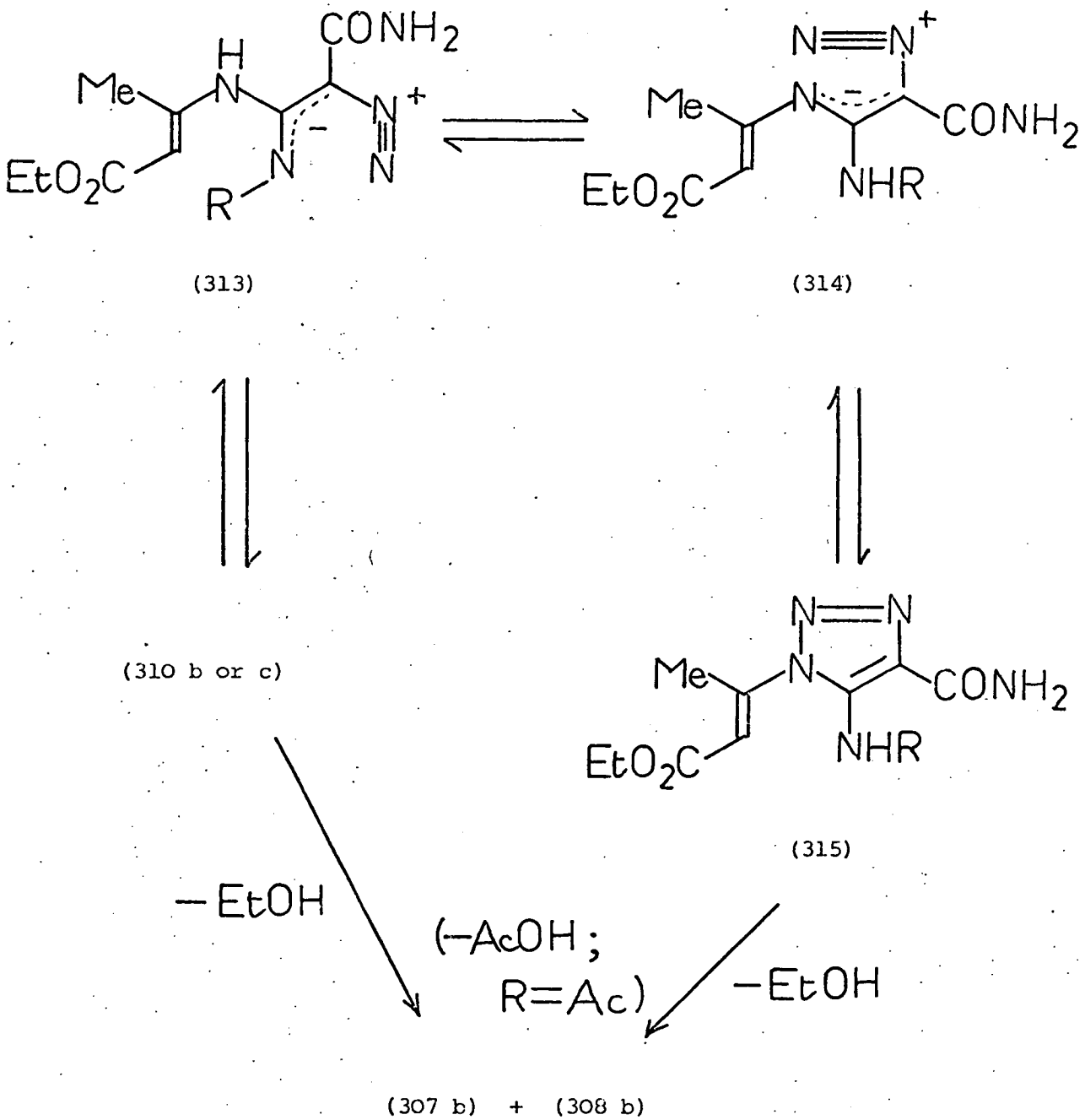
Attempts to regenerate the vinylaminotriazole (310 b) by hydrolysing the acetyl derivative (310 c) proved unsuccessful. When (310 c) was heated under reflux in aqueous ethanolic sulphuric acid, the triazole (306 a) was the sole product. When (310 c) was simply heated under reflux in aqueous ethanol, the triazole (306 a) and the acetamidotriazole (306 b) were isolated. The mechanism of this hydrolysis (Scheme 36) probably involves the initial hydrolysis of the vinyl group leading to the formation of ethyl acetoacetate and the acetamidotriazole (306 b). Hydrolysis of the acetyl group,

subsequent to the Dimroth rearrangement [(312) ⟶ (306 b)] (cf. Chapter 3.2, Scheme 25), thus explains the isolation of the triazole (306 a).

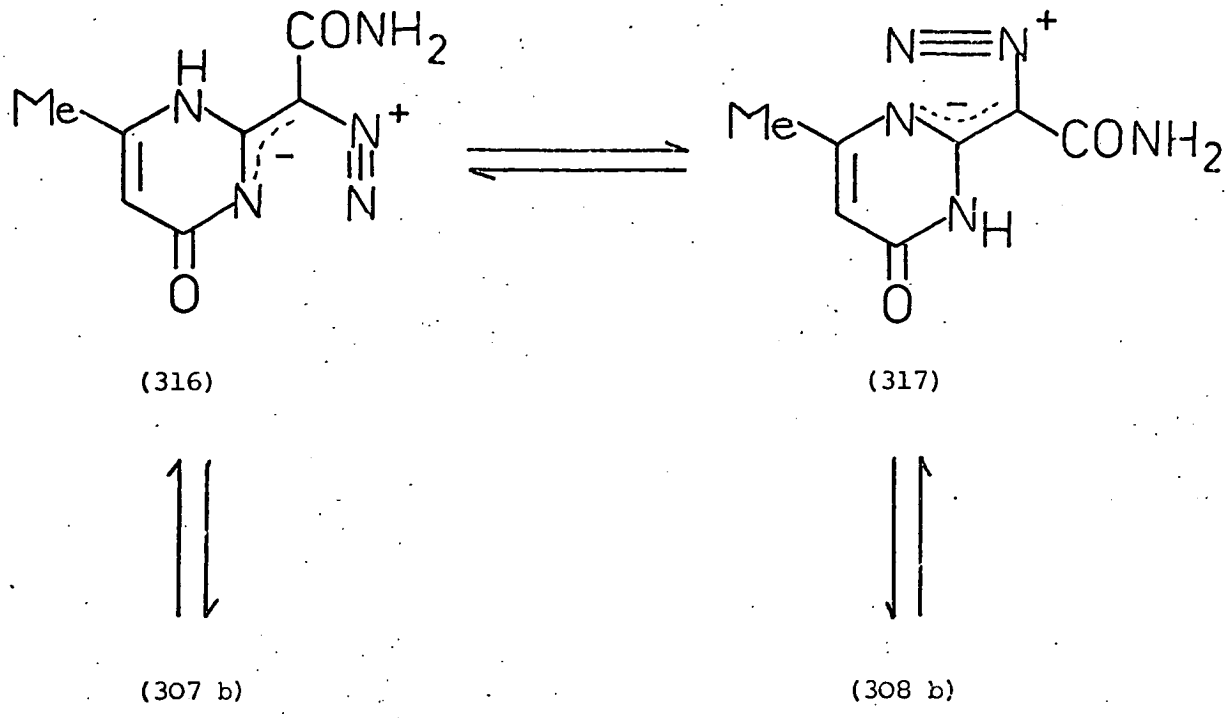
In an attempt to determine at which site ethyl acetoacetate attacks the aminotriazole (306 a), the acetamidotriazole (306 b) was subjected to exactly the same conditions which led to (310 b) - namely stirring with ethyl acetoacetate in dimethylformamide containing glacial acetic acid. The result was the recovery of unchanged starting material. From this result, it may be concluded that ethyl acetoacetate condenses with the primary amino group of (306 a) rather than with the ring nitrogen atom.

In an attempt to synthesize the single triazolopyrimidine isomer (307 b), the vinylaminotriazole (310 b) was subjected to heating under reflux in ethanolic piperidine and glacial acetic acid. Similarly, the acetyl derivative (310 c) was heated in glacial acetic acid. The result in each case was the formation of the isomer mixture [(307 b) + (308 b)]. When (310 c) was treated as described, the acetamidotriazole (306 b) was also formed. The isomer mixture was also formed when the vinylaminotriazoles (310 b) and (310 c) were treated briefly with dilute aqueous sodium hydroxide solution and the resultant solutions were acidified with dilute aqueous sulphuric acid. When the vinylaminotriazole (310 b) was melted on the Kofler block and the melt allowed to re-solidify, the result was the formation of the isomer mixture [(307 b) + (308 b)].

The results described above, all pose questions as to the mechanism of the formation of the isomer mixture. Three plausible possibilities exist. Firstly, the vinylaminotriazole (310 b or c)


CONH2
H
N
Me
N+
EtO2C
N
N
R
(313)
N≡N+
Me
N
CONH2
EtO2C
NHR
(314)
(310 b or c)
N=N
Me
N
CONH2
EtO2C
NHR
(315)
-EtOH
(-AcOH;
R=Ac)
-EtOH
(307 b) + (308 b)

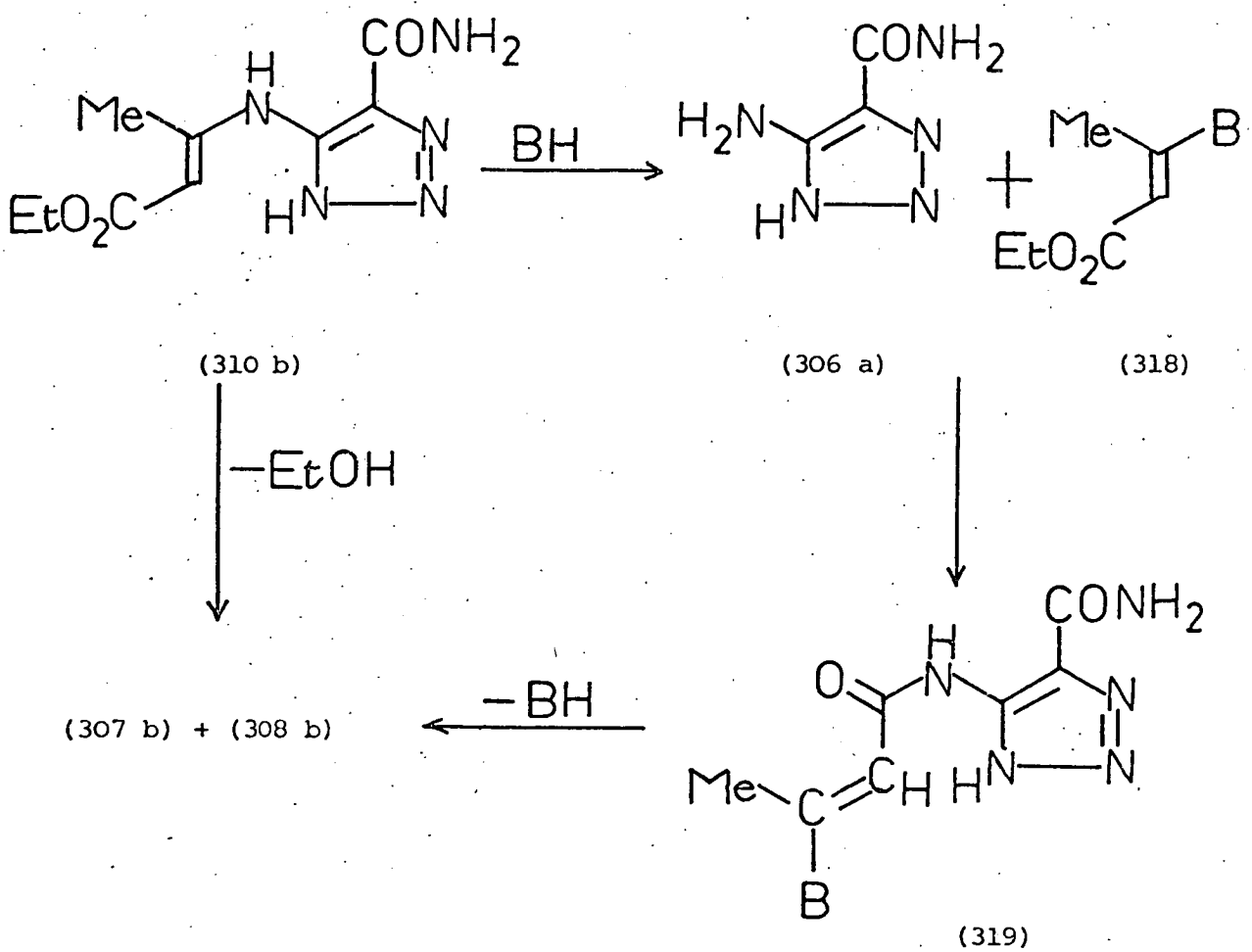
Scheme 37



(316) (317)

(307 b) (308 b)

Scheme 38



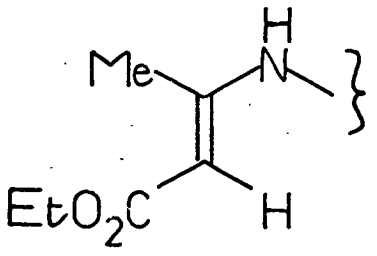
(310 b) (306 a) (318)

(307 b) + (308 b) (319)

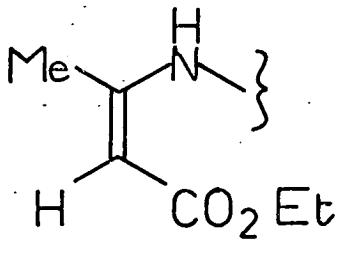
Scheme 39

may undergo a Dimroth rearrangement to give the isomer (315; R = H, Ac). Cyclization of the isomers (310 b or c) and (315; R = H or Ac) [preceded by solvolysis of the acetyl group in (310 c) and (315; R=Ac)] would then lead to the isomer mixture [(307 b) + (308 b)] (Scheme 37). Secondly, the triazolopyrimidine (307 b) may be formed initially and then undergo Dimroth rearrangement to give the isomer mixture [(307 b) + (308 b)] (Scheme 38). Thirdly, the vinylaminotriazole (310 b or c) may undergo a dissociation-re-association mechanism as outlined in Scheme 39. In this last mechanism, when (310 c) is used, a Dimroth rearrangement [(312) ⟶ (306 b)] must take place followed by solvolysis of the acetyl group [(306 b) ⟶ (306 a)] prior to re-association (see Scheme 36). As can be observed from Scheme 39, this last possibility is mechanistically impossible in the absence of a base (B).

Attempts to test the mechanisms described, have been made. Evidence for a Dimroth rearrangement prior to cyclization (Scheme 37) has been obtained from heating the pure vinylaminotriazole (310 b) under reflux in toluene for a prolonged period. The result was the isolation of a solid whose ^{1}H n.m.r. spectrum was consistent with a mixture of (310 b) and (315; R = H). However, the ^{1}H n.m.r. spectrum of the mixture may also be interpreted in terms of the formation of geometric isomers [e.g. (320) and (321)]. However, a significant feature of the mixture is that the integrated ratio of (310 b) relative to the other component is the same as the integrated ratio of (307 b) relative to (308 b) in the respective ^{1}H n.m.r. spectra.



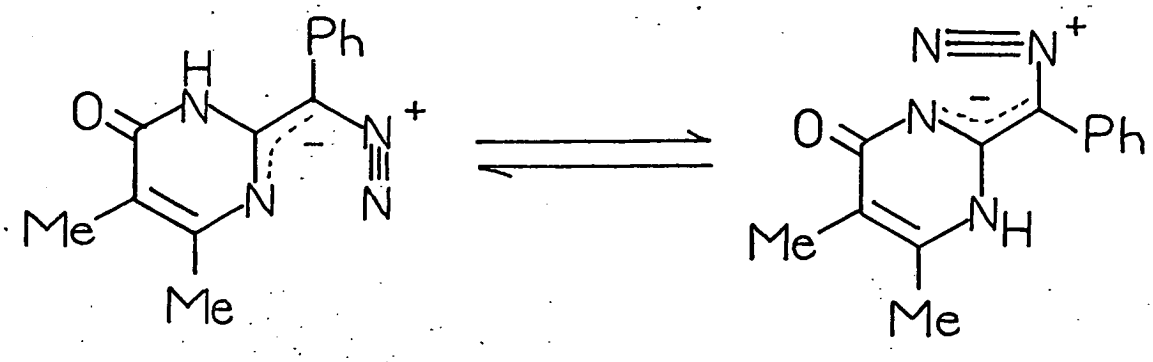
(320)



(321)

[The assignments of the structures (307 b) and (308 b) were made on the basis of arguments to be discussed later (see page 151).] This indicates that direct cyclization of [(310 b) + (315; R=H)] would result in the reported mixture [(307 b) + (308 b)] without further Dimroth rearrangement.

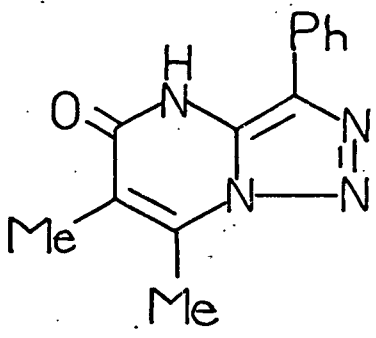
When the vinylaminotriazole (310 b) was heated under reflux in ethanolic piperidine or glacial acetic acid in the presence of acetylacetone, the result was the formation of the dimethyltriazolopyrimidine (311). Similarly, when (310 b) was heated under reflux in neat acetylacetone, (311) was isolated. These results are consistent with the mechanism outlined in Scheme 39. After the base catalysed elimination step [(310 b)⟶(306 a) + (318)] , instead of recombining with (318), (306 a) could be intercepted by acetylacetone to give (311). [The compound (311) is formed when the aminotriazole (306 a) is heated under reflux in acetylacetone.] In the described 'interception' reactions, the isomer mixture [(307 b) + (308 b)] is also isolated in the thermal and piperidine catalysed cases. However, in the reaction carried out in glacial acetic acid, an unidentified, two component mixture was obtained. Attempted separation of this mixture by fractional crystallisation or



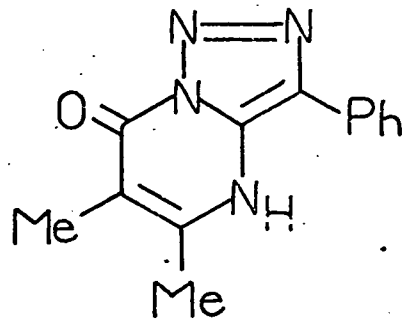
(327) (328)

(322) (323)

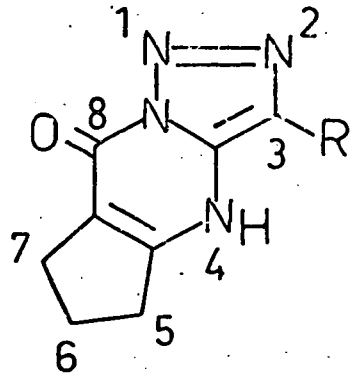
Scheme 40



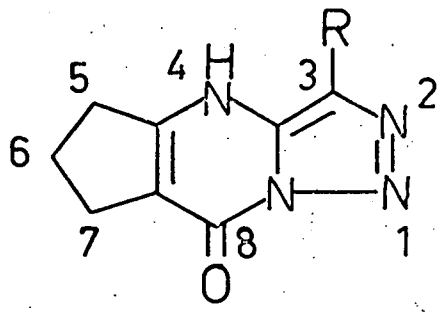
(322)



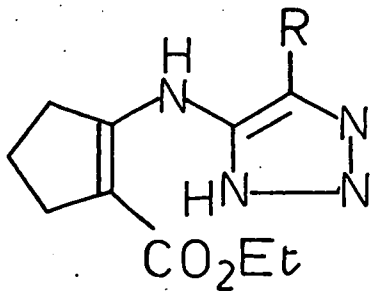
(323)



(324)



(325)



(326)

R

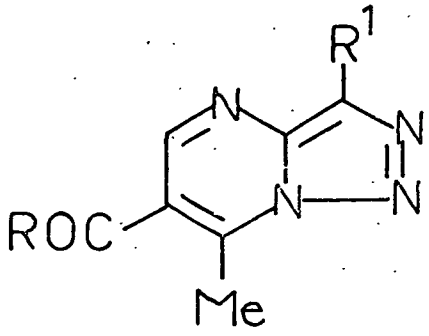
a; $-CONH_2$

b; Ph

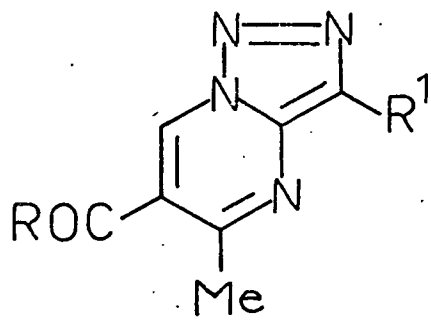
chromatography over silica proved unsuccessful. As has previously been stated, a mechanism of the type outlined in Scheme 39, requires the participation of a base (B). In the reactions described, this base (B) may be piperidine or the anion of acetylacetone. Thus it would appear unlikely that the dissociation - re-association mechanism (Scheme 39) operates when (310 b) is cyclized to [(307 b) + (308 b)] in the melt.

Support for a mechanism of the type outlined in Scheme 38 has been obtained in an investigation of analogous systems described later (see page 157).

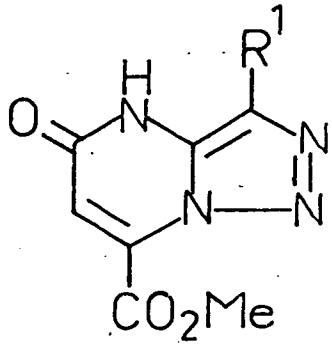
Ethyl 2-methylacetoacetate condensed with 5-amino-4-phenyl-1H-1,2,3-triazole (306 c) in the presence of piperidine to give the triazolopyrimidine (322). [The structure of (322) was assigned on the basis of arguments to be discussed later (see page 151).] However, when the described reaction was prolonged, a solid, whose properties were consistent with the isomer mixture [(322) + (323)] was isolated. This isomer mixture was also formed when the triazolopyrimidine (322) was heated under reflux in ethanolic piperidine for a prolonged period. When the isomer mixture [(322) + (323)] was heated under reflux in dimethylformamide, the single isomer (322) was regenerated. These results find analogy[13] in the formation of the triazolopyrimidines (307 a) and (308 a), and may best be interpreted (Scheme 40) in terms of the initial formation of (322) followed by the base catalysed isomerization [(322)$\rightleftharpoons$(327)$\rightleftharpoons$(328)$\rightleftharpoons$(323)]. The conversion of the isomer mixture [(322) + (323)] into the single isomer (322) under strictly thermal conditions suggests



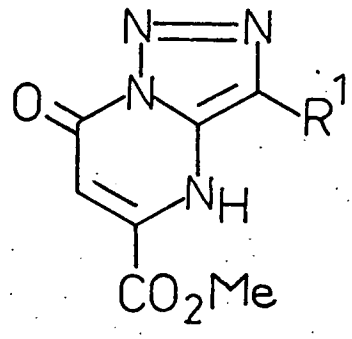
(329)



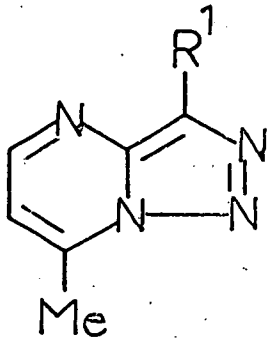
(330)



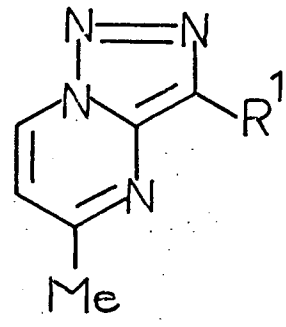
(331)



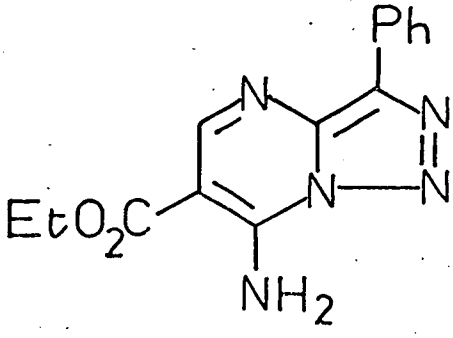
(332)



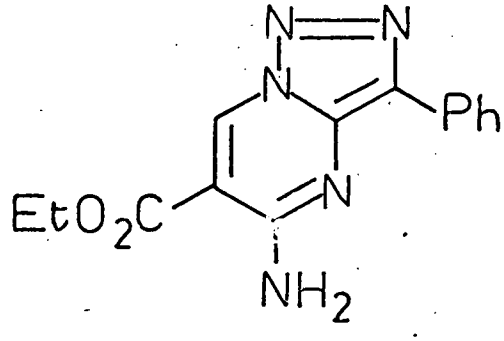
(333)



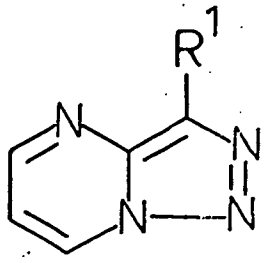
(334)



(335)



(336)



(337)

R^1

a; $.CONH_2$

b; Ph

the latter to be the thermally stable isomer.

When the aminotriazoles (306 a and c) were condensed, in ethanolic piperidine, with ethyl cyclopentanone-2-carboxylate, solids, whose properties are consistent with the structures [(324 a) and/or (325 a)] and [(324 b) and/or (325 b)] were formed. The product [(324 a) and/or (325 a)] did not give correct analytical data. The ^{1}H n.m.r. spectra of the products did not, in either case, show features, suitable for the further elucidation of their exact nature. In both reactions, condensates of the type (326 a and b) were also isolated. The assignment of the structures (326 a and b) followed from their isolation by acidification. The acidity of the by-products is consistent with the presence of the 1H-1,2,3-triazole nucleus. The condensate (326 a) was readily converted into the product [(324 a) and/or (325 a)] on crystallisation.

Ethoxymethyleneacetylacetone, acetoacetaldehyde dimethylacetal and malonaldehyde bis-(dimethylacetal) condensed smoothly with the aminotriazole (306 a) in dimethylformamide-hydrochloric acid to give the isomer mixtures [(329 a) + (330 a); R = Me], [(333 a) + (334 a)] and the triazolopyrimidine (337 a). The constitution of the isomer mixtures [(329 a) + (330 a); R = Me] and [(333 a) + (334 a)] was supported by their ^{1}H n.m.r. spectra, which showed that the isomer with the methyl group adjacent to the bridgehead nitrogen atom [(329 a; R = Me) and (333 a)] was, in each case, the major component. The structures of the isomers, in the mixtures described above, were assigned on the basis[88,100,101] of the enhanced deshielding afforded by a bridgehead nitrogen atom on a proton or methyl group attached

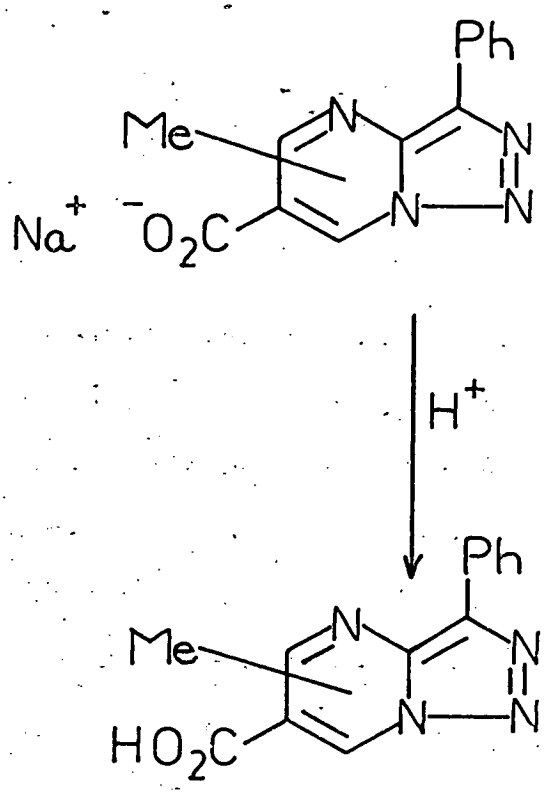
to an adjacent carbon atom. Thus, in the ^{1}H n.m.r. spectrum of the mixture [(333 a) + (334 a)], it is observed that Me-7 (333 a) absorbs at lower field than Me-5(334 a) and similarly H-5(333 a) absorbs at higher field than H-7 (334 a). Supporting evidence for such an assignment is provided by the splitting associated with Me(7)-H(6) in (333 a), as opposed to the undetectable splitting of Me(5)-H(6) in the structure (334 a). Splitting of this type has been interpreted in terms of bond fixation.[88,100,101]

An attempt to form the triazolopyrimidine [(329 a) or (330 a); R = OEt] by condensing the triazole (306 a) with ethyl ethoxymethylene-acetoacetate under the acidic conditions described, resulted in the isolation of a multicomponent mixture from which no pure material could be obtained. Similarly, ethoxymethyleneacetylacetone and ethyl ethoxymethyleneacetoacetate, failed to give any identifiable material when heated under reflux with the aminotriazole (306 a) in ethanolic piperidine or glacial acetic acid. An attempt to form the triazolopyrimidine [(331 a) or (332 a)] by heating the aminotriazole (306 a) and dimethyl acetylenedicarboxylate under reflux in glacial acetic acid, also resulted in the formation of an inseparable multicomponent mixture.

The isomer mixture [(333 b) + (334 b)] and the triazolopyrimidine (337 b) were formed when the aminotriazole (306 c) was stirred, with the appropriate protected β-dicarbonyl compounds [acetoacetaldehyde dimethylacetal and malonaldehyde bis-(dimethylacetal)], in ethanolic hydrochloric acid. Heating the triazole (306 c) together with ethoxymethyleneacetylacetone or ethyl ethoxymethyleneacetoacetate,

under reflux in ethanolic piperidine, resulted in the isolation of the isomer mixtures [(329 b) + (330 b); R = Me or OEt]. The predominant isomer in each of the mixtures [(329 b) + (330 b); R = Me,OEt] and [(333 b) + (334 b)] is the one with the methyl group adjacent to the bridgehead nitrogen atom (329 b; R = Me,OEt) and (333 b). These results are consistent with those obtained from the triazolecarboxamide (306 a), and the assignment of the structures of the components of the mixtures was achieved in a similar manner to that already described. When the aminotriazole (306 c) was heated under reflux together with ethyl ethoxymethylenecyanoacetate or dimethyl acetylenedicarboxylate in ethanolic piperidine, the result was the isolation of the triazolopyrimidines (335) or [(331 b) or (332 b)]. The assignment of the structure (335), to the product obtained from ethyl ethoxymethylenecyanoacetate, rather than the alternative structure (336), was made by comparison of its ^{1}H n.m.r. spectrum with that of the isomer mixture [(329 b) + (330 b); R = OEt]. It is reasonable to expect that the ^{1}H n.m.r. spectrum of (329 b; R = OEt) will be similar to that of (335). The product (335) was obtained in low yield, starting material also being recovered on work up of the reaction mixture. An attempt to condense the aminotriazole (306 c) with ethyl cyanoacetate resulted in the recovery of unchanged triazole (306 c).

The isomer mixture [(329 b) + (330 b); R = OEt] was hydrolysed, under basic conditions, to give an acid whose ^{1}H n.m.r. spectrum is consistent with either of the structures (338) or (339). The exact structure of the product could not be assigned on the basis of

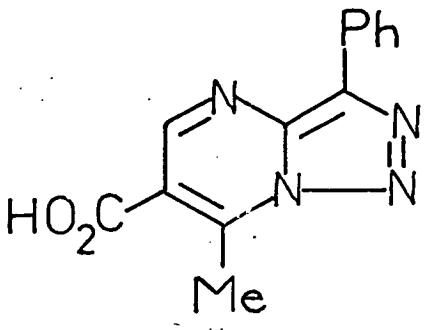


(338) and (339)

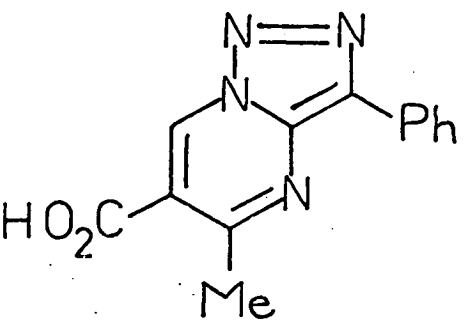
$-CO_2$

(333 b) + (334 b)

Scheme 41.

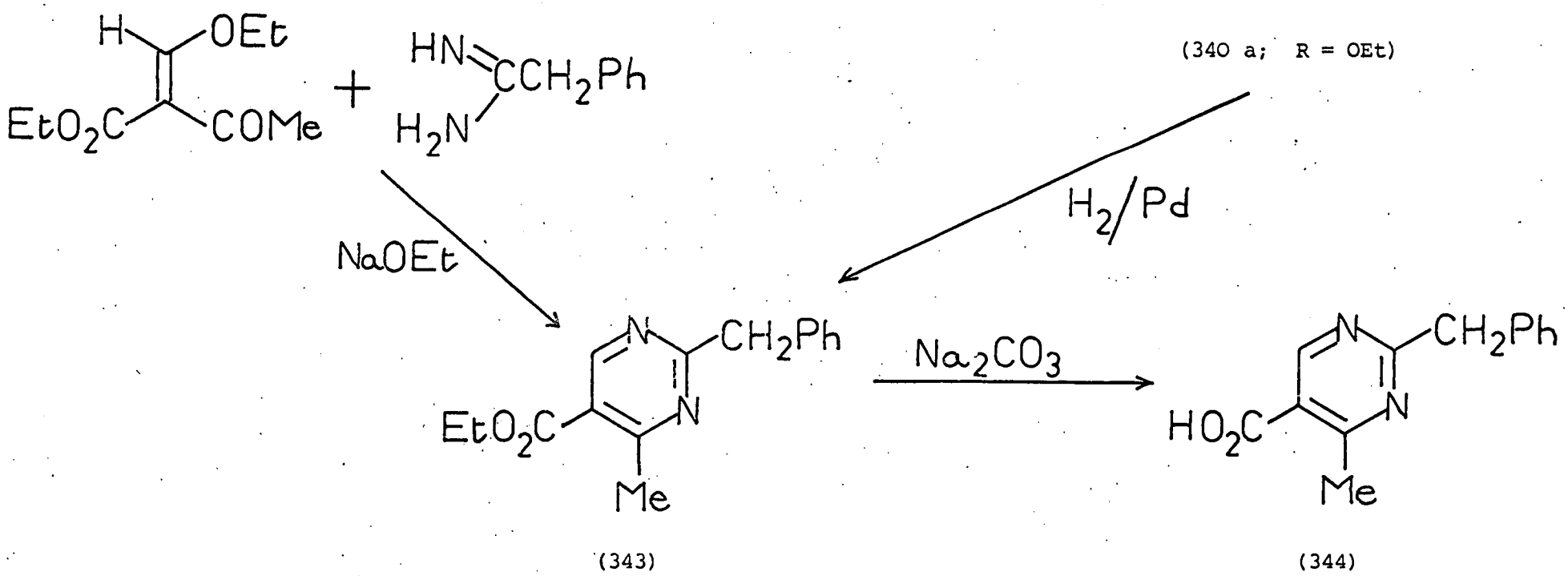


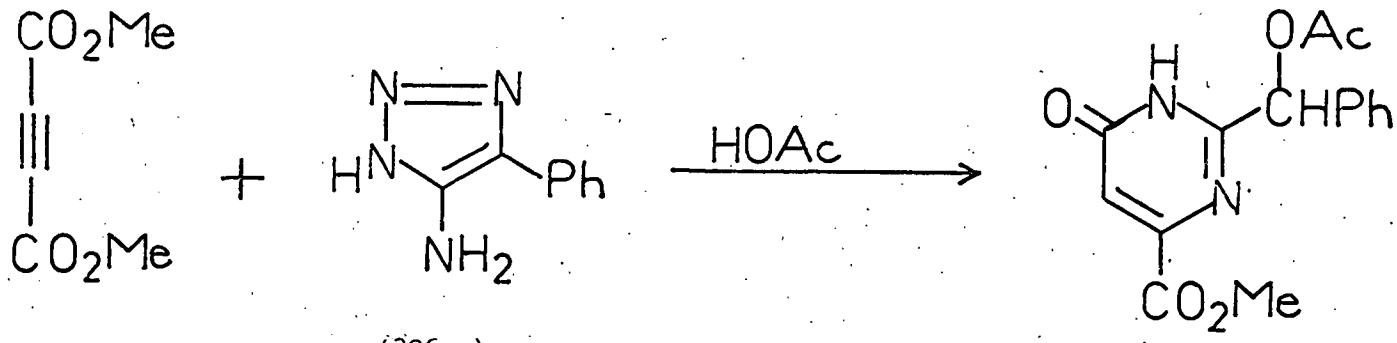
(338)



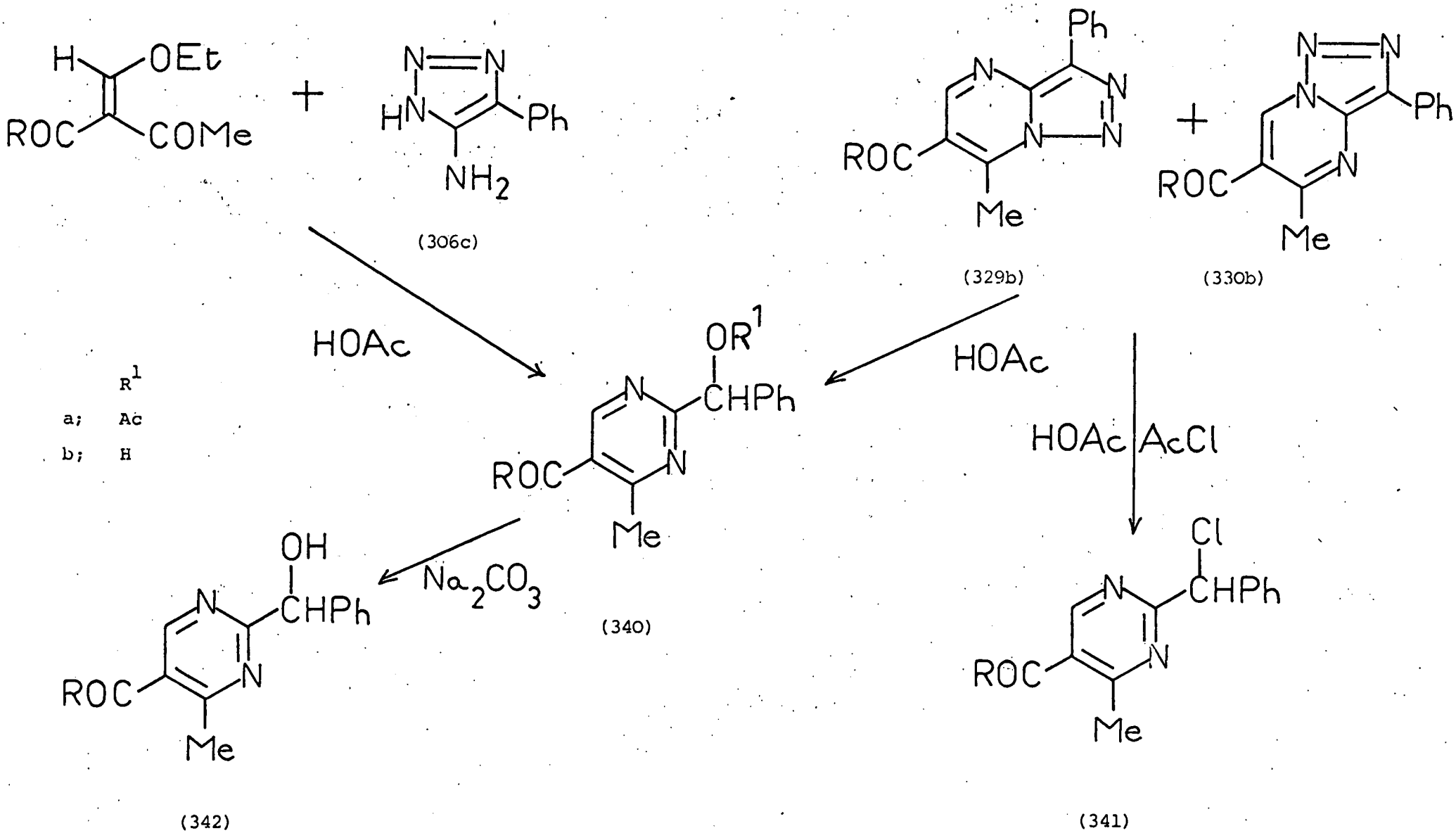
(339)

this spectrum. On acidification of the basic mother liquor from this reaction, the isomer mixture [(333 b) + (334 b)] was unexpectedly isolated. Consistent with the assigned structures [(333 b) and (334 b)] for the components, an attempt to redissolve the isomer mixture in dilute aqueous sodium hydroxide solution was unsuccessful. The most plausible interpretation of the result of this reaction is that hydrolysis of the substrate [(329 b) + (330 b); R = OEt], under alkaline conditions, gives rise to the sodium salts of the acids (338) and (339). However, liberation of the free acids (338) and (339) by acidification gives a stable acid and an acid which is unstable to decarboxylation (Scheme 41). The ^{1}H n.m.r. spectrum of the stable acid could not differentiate the structures (338) and (339). The isomer mixture [(333 b) + (334 b)] isolated in this manner had the same composition as that obtained by synthesis. The formation of the isomer mixture [(333 b) + (334 b)] rather than a single isomer [(333 b) or (334 b)] in the decarboxylation can be explained in terms of the formation of (333 b) or (334 b) and its subsequent Dimroth rearrangement [(333 b)$\rightleftharpoons$(334 b)] as discussed later.


H
OEt
EtO2C
COMe
HN
CCH2Ph
H2N
(340 a; R = OEt)
H2/Pd
NaOEt
N
CH2Ph
EtO2C
N
Me
Na2CO3
HO2C
(343)
(344)


CO2Me
CO2Me
N
N
HN
Ph
NH2
HOAc
OAc
H
O
N
CHPh
N
CO2Me
(306 c)
(345)

The Synthesis of Some 2-Substituted Pyrimidines



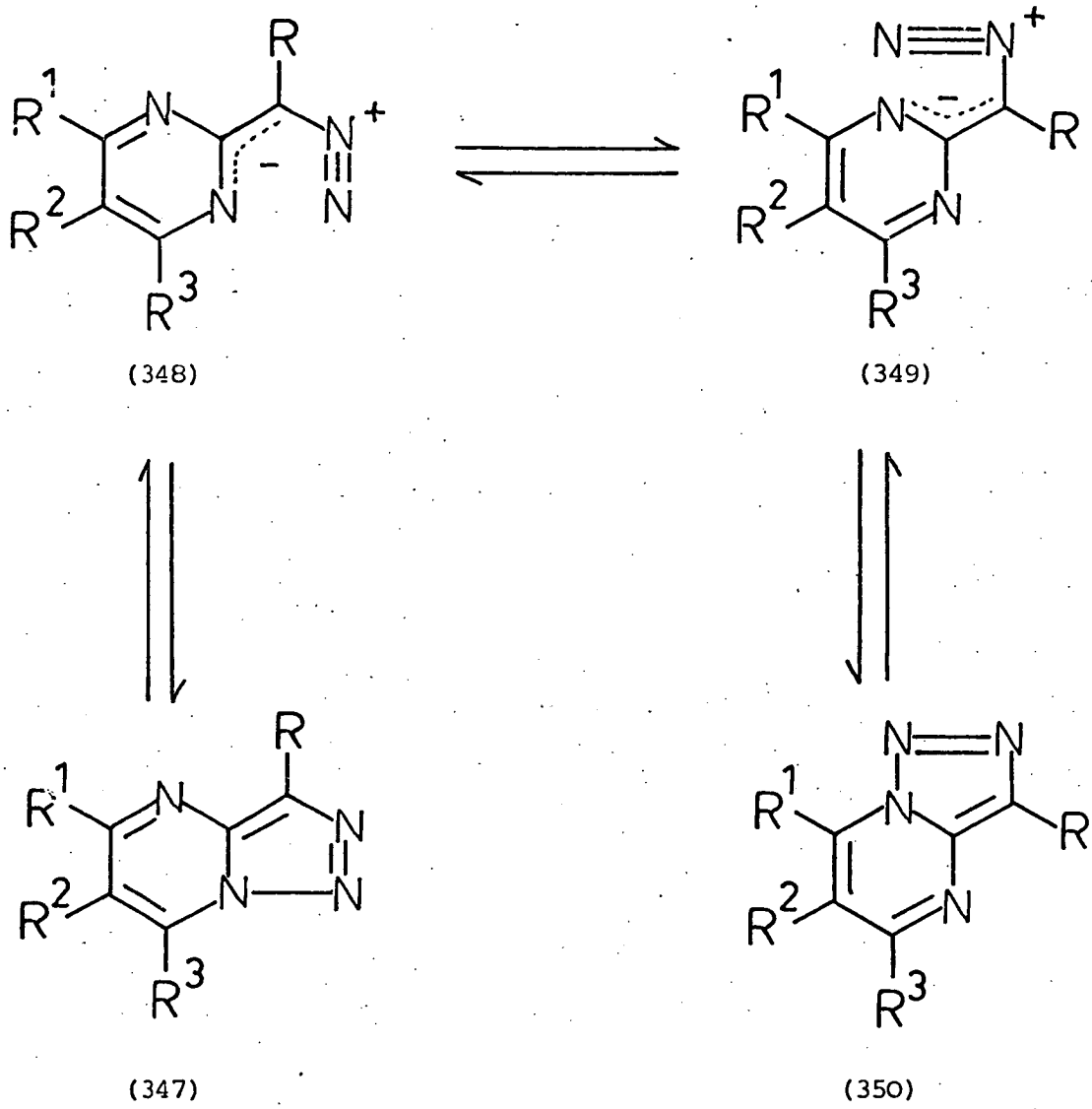
An attempt to relate the isomer mixtures [(329 b) + (330 b); R = Me and OEt] by their mutual conversion into the acid [(338) or (339)] was unsuccessful owing to the failure of [(329 b) + (330 b); R = Me] to undergo the haloform reaction [(329 b)+(330 b); R = Me ⟶ (338) or (339)].

The 2-substituted pyrimidines (340 a; R = Me and OEt) were obtained in good yield by heating the isomer mixtures [(329 b) + (330 b); R = Me and OEt], or the aminotriazole (306 c) and the appropriate ethoxymethylene compound, under reflux in glacial acetic acid (see Chapter 1.3). The assigned structures (340 a; R = Me and OEt) of the pyrimidines followed from their i.r. and ^{1}H n.m.r. spectra. The acetoxypyrimidine (340 a; R = OEt) was contaminated with the carbinol (340 b; R = OEt), separation of which, was achieved by chromatography over alumina. The pyrimidine derivatives [(340 a; R = Me and OEt) and (340 b; R = OEt)] were isolated as oils. Attempts to characterise these oils directly were discontinued due to the failure of (342; R = Me) [which was obtained by the alkaline hydrolysis of (340 a; R = Me)] to form 2,4-dinitrophenylhydrazone, semicarbazone or oxime derivatives. When the mixture (340 a and b; R = OEt) was subjected to alkaline hydrolysis, the solid acid (342; R = OH) was isolated. The chlorobenzyl compounds (341; R = Me and OEt), which were also isolated as oils, were obtained by carrying out the acetic acid catalysed scission of [(329 b) + (330 b); R = Me or OEt] in the presence of acetyl chloride. The formation of (341; R = Me and OEt), which were identified by their i.r. and ^{1}H n.m.r. spectra, finds analogy in the literature.[11b,13]

Additional evidence for the presence of a pyrimidine nucleus in the compounds obtained from the heterolytic, acid-catalysed scission of the triazolopyrimidine mixtures [(329 b) + (330 b); R = Me and OEt], was obtained by the synthesis of (343). Hydrogenolysis of the acetoxypyrimidine (340 a; R = OEt) gave the benzyl derivative (343), which was also unambiguously synthesized from phenylacetamidine[99] and ethyl ethoxymethyleneacetoacetate. Alkaline hydrolysis of (343) gave the solid acid (344), whose structure is assigned on the basis of its i.r., ^{1}H n.m.r. and mass spectral and analytical data. The confirmation of the structure (343) helps to establish the presence of a pyrimidine nucleus in the triazolopyrimidines [(329 b) and (330 b); R = Me or OEt].

When the aminotriazole (306 c) and dimethyl acetylenedicarboxylate were heated under reflux in glacial acetic acid, the solid pyrimidine (345) was obtained.

The question arises as to the exact nature of the formation of the isomer mixtures [(329 a) + (330 a); R = Me or OEt], [(329 b) + (330 b); R = Me or OEt], [(333 a) + (334 a)], and [(333 b) + (334 b)]. Two possibilities exist, namely the mixtures are equilibrium mixtures or, the mixtures are fixed and the components are not interconvertible. The latter possibility arises due to the bifunctionality of the aminotriazoles (306 a and c) and the substrates required for the synthesis of the triazolopyrimidines described. Thus, different orientation of addition may account for the formation of isomer mixtures. It is noticeable that each isomer mixture runs as a single spot on t.l.c. examination. When the ^{1}H n.m.r. spectrum of the isomer mixture [(333 b) + (334 b)] was



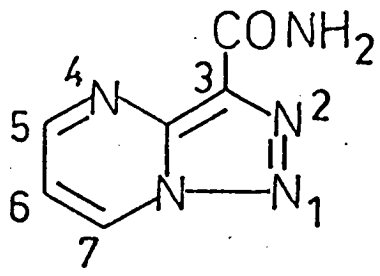
(348) (349)

(347) (350)

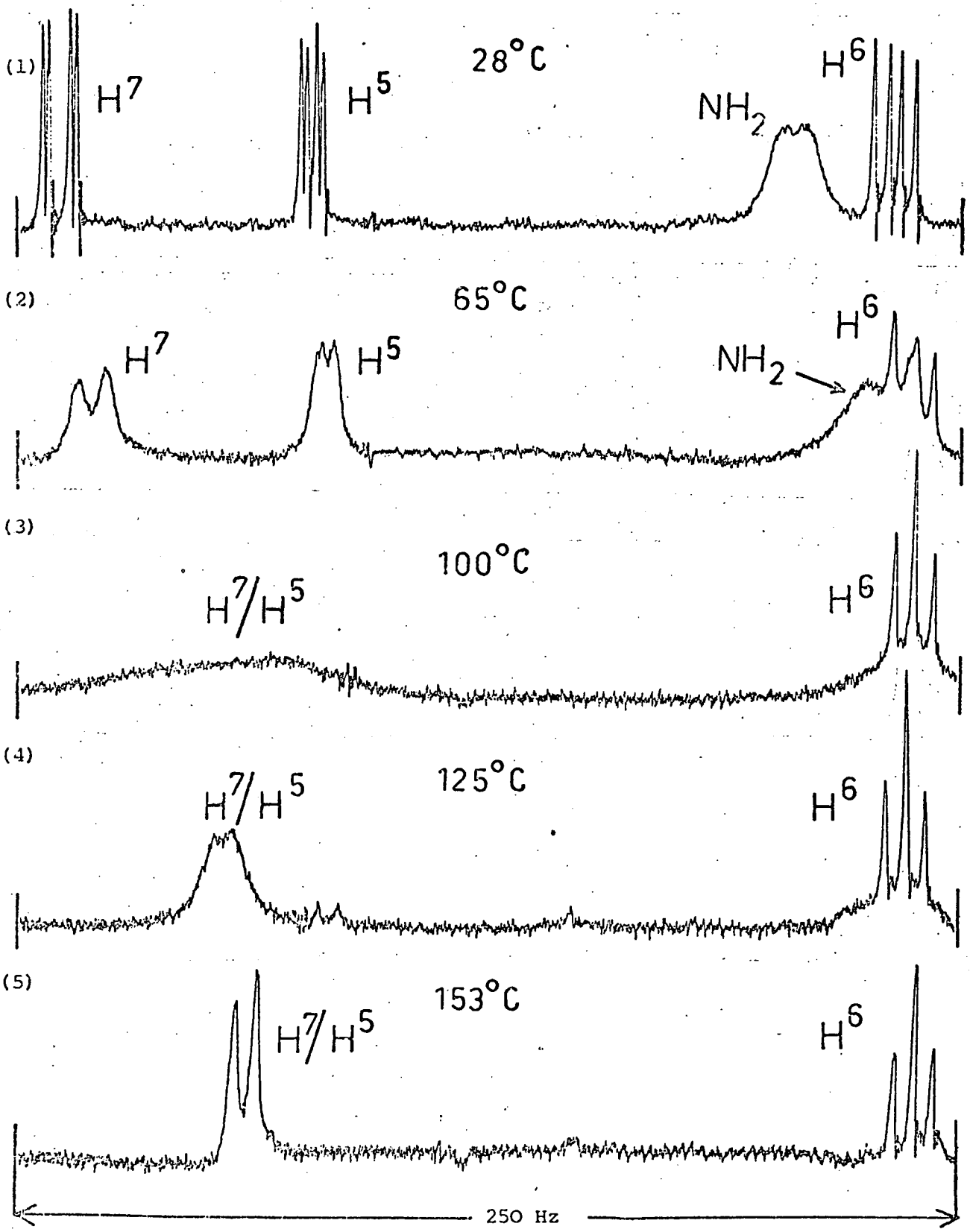
Scheme 42

Diagrams 1-5 - The Variable Temperature ^1H N.M.R.

Absorption of 1,2,3-Triazolo[1,5-a]pyrimidine-3-carboxamide (337a)

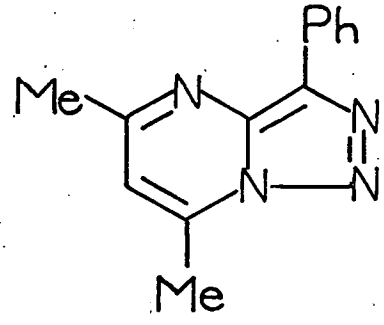


(337 a)



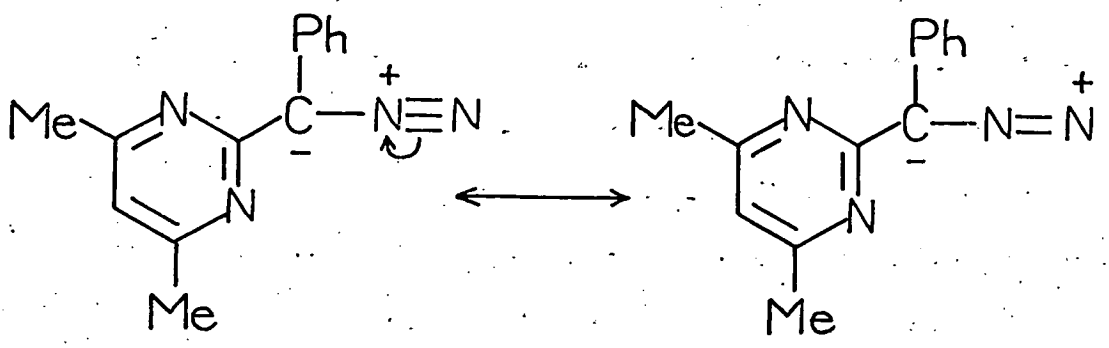
run in three different solvents, the composition of the mixture remained unaltered. It might be expected that the composition of an equilibrium mixture would change under these conditions.

However, convincing evidence for the concept of an equilibrium mixture (Scheme 42) was obtained when the ^{1}H n.m.r. spectra of the isomer mixtures [(329 a) + (330 a); R = Me], [(329 b) + (330 b); R = Me], [(333 a) + (334 a)] and [(333 b) + (334 b)], and the triazolopyrimidines (311), (337 a and b), and (346) were measured

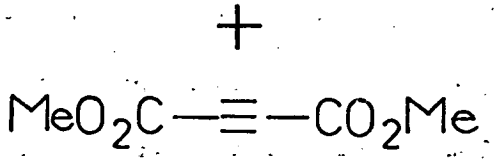


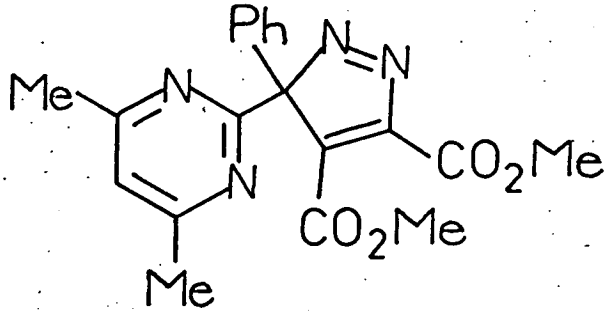
(346)

in dimethylsulphoxide at various temperatures. For example, when the ^{1}H n.m.r. spectrum of the isomer mixture [(333 a) + (334 a)] was run at suitably elevated temperatures, the Me-5 and Me-7 and H-7 and H-5 signals collapsed. Further elevation of the temperature resulted in the appearance of a single singlet attributable to coalesced Me-5 and Me-7, and a single singlet attributable to coalesced H-5 and H-7. The ^{1}H n.m.r. spectra, in [$^2H_6$] dimethylsulphoxide, of the other triazolopyrimidines described, showed similar dependence on temperature. When a similar study was carried out on the triazolopyrimidine (337 a) [i.e. (347; $R^1 = R^2 = R^3 = H$)], an interesting change occurred in the signals attributable to the pyrimidine protons (Diagrams 1-5).



(351) (352)





(353)

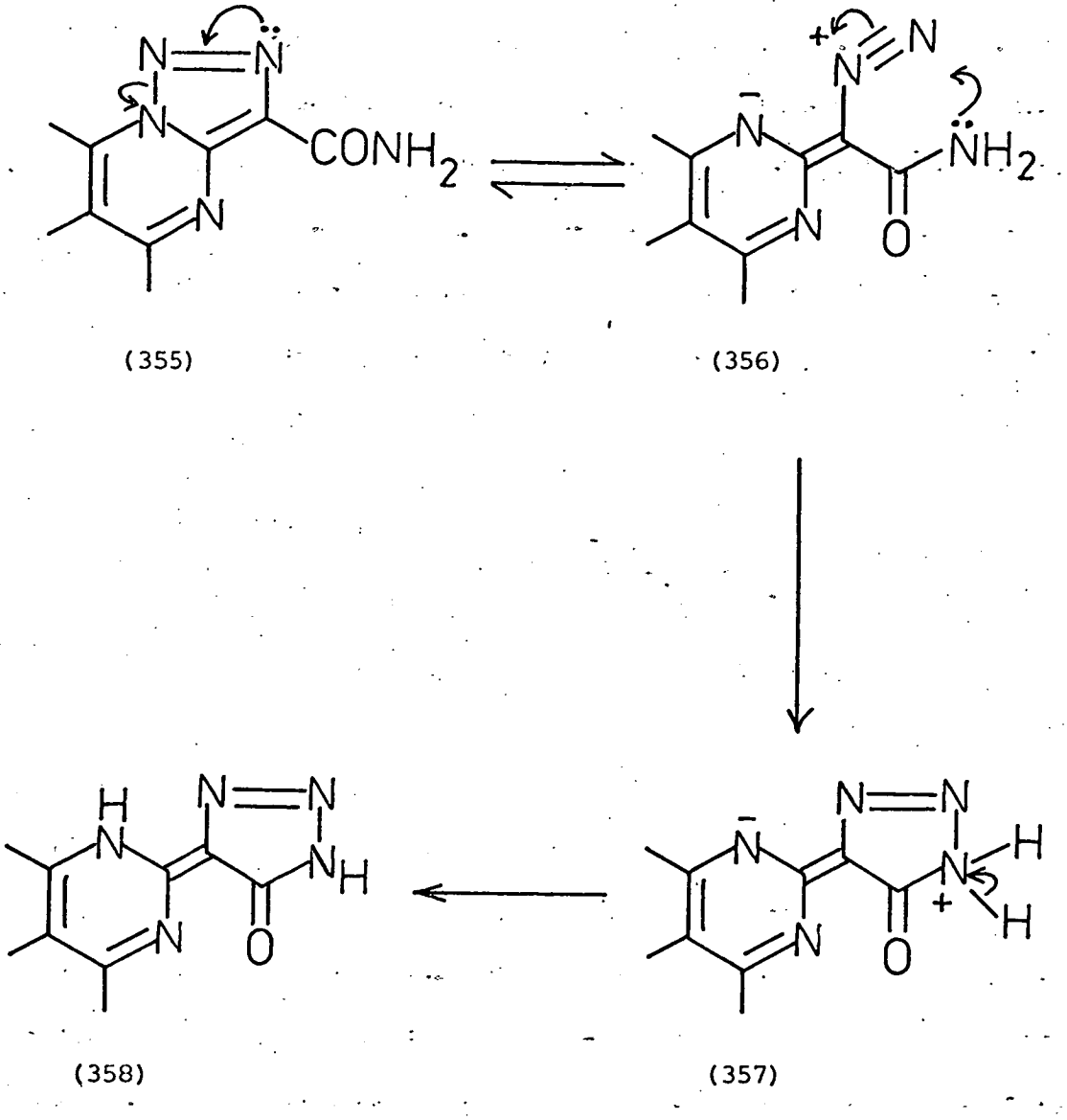
Scheme 43

The signals initially had the form of double doublets due to the splitting caused by H(5) - H(6), H(5) - H(7) and H(6) - H(7). However, when the temperature was raised, the signals collapsed and then at higher temperatures a doublet and a triplet appeared. Analogous results were obtained for the mixtures [(329 a) + (330 a); R = Me], [(329 b) + (330 b); R = Me], and [(333 b) + (334 b)] and for the compounds (311), (337 b) and (346).

These variable temperature effects may be interpreted in two ways. Either the structures (347) and (350) are undergoing such rapid interconversion that an averaged spectrum of (347) and (350) is being observed, or alternatively, at elevated temperature the open chain form [(348) $\rightleftharpoons$ (349)] is preferred. Each interpretation however, involves the existence of diazoalkylideneamine-triazole tautomerism. This is the first reported example of such an equilibrium, further evidence for which was obtained from the i.r. spectrum of a sample of [(329 a) + (330 a); R = Me] which had been kept at elevated temperature. The appearance of an absorption at 2100 cm^{-1} was consistent with the presence of a diazonium group (.$\overset{+}{N}$≡N), as contained in structures of the type (348) and (349).

An attempt to trap the diazo intermediate [cf. (348) $\rightleftharpoons$ (349)] (Scheme 43) by heating (346) in sulpholane in the presence of dimethyl acetylenedicarboxylate gave unchanged starting material, instead of the adduct (353).

It was noticeable that the triazolopyrimidine-3-carboxamides underwent the described ^{1}H n.m.r. spectral changes at lower temperatures than their 3-phenyl counterparts. This evidence supports the theory that an electron-withdrawing substituent



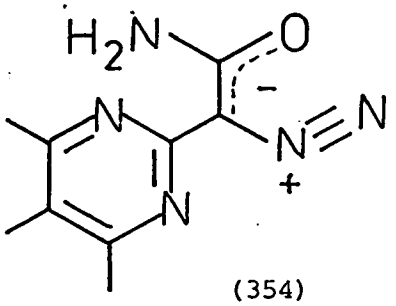
(355) (356)

(358) (357)

Scheme 44

helps destabilize structures of the type (347) and (350) relative to (348) and (349).

An interesting feature, relating to the inability of the triazolopyrimidine-3-carboxamides to lose nitrogen on attempted triazole scission, is observed in their mass spectra. Each carboxamide, as well as showing a well defined parent ion, shows an ion at $(M^+ - 83)$. This may be interpreted in terms of the formation of a primary fragment ion derived, by H-atom transfer and loss of the side chain, from open chain structures of the type (354). However, this result may be interpreted in another way, and causes



(354)

a doubt to be raised in the assignment of the triazolopyrimidine nucleus in such carboxamides (Scheme 44). Diazoalkylideneamine-triazole equilibrium of the type [(355) ⇌ (356)] followed by the cyclization [(356) ⟶ (357) ⟶ (358)] would result in the formation of a triazolone (358), which could lose 83 mass units in the form of the triazolone side chain. However, the possibility of the existence of such structures may be discounted on the basis of the inability of (311) to form a sodium salt or undergo ready acetylation. Such properties would be expected from the triazolone [e.g. (358)].

4.3. Experimental (For general experimental procedures, see Appendix)

5-Amino-1,2,3-triazoles (306 a and c)

5-Amino-1H-1,2,3-triazole-4-carboxamide (306 a) was prepared by the method of Hoover and Day,[67] m.p. 223° (from water)(lit.,[67] 225°).

5-Amino-4-phenyl-1H-1,2,3-triazole (306 c) was obtained by the method of Tennant and Sutherland,[11b] m.p. 124° (lit.,[67] 125°).

5-Acetamido-1H-1,2,3-triazole-4-carboxamide (306 b)

The aminotriazolecarboxamide (306 a)(2.6g; 0.02 mol) was heated under reflux in glacial acetic acid (20 ml) for 4.5 h. Evaporation of the solvent under reduced pressure followed by trituration of the residue with ether gave the acetic acid solvate of the monoacetyl compound (306 b)(3.6g), m.p. 269-272° (from glacial acetic acid), $\nu_{max.}$ 3350,3200br, and 2700br (OH,NH), 1710, 1690, and 1670(CO)cm^{-1}, τ [$(CD_3)_2SO$] 0-0.05 br(1H,s,OH), 2.16(1H,s,NH), 2.47(1H,s,NH), 7.84(3H,s,Ac), and 8.10(3H,s,Ac), which on crystallisation from water afforded the acetamidotriazolecarboxamide (306 b) (2.0g), m.p. 270-73°(lit.,[102] 268°), $\nu_{max.}$ 3400,3250, and 3100(NH), and 1680(CO)cm^{-1}, τ [$(CD_3)_2SO$] 2.18br(1H,s,NH), 2.49 br(1H,s,NH), and 7.84(3H,s,Ac).

The Reactions of the 5-Amino-1,2,3-triazoles (306 a-c) with Ethyl Acylacetates.

5-(2-Ethoxycarbonyl-1-methylvinylamino)-1H-1,2,3-triazole-4-carboxamide (310 b)

(a) A solution of the aminotriazole (306 a) (1.27g; 0.01 mol), ethyl acetoacetate (1.48g; 0.011 mol), and glacial acetic acid

(1.0 ml) in dimethylformamide (7.0 ml) was stirred at room temperature for 16h. The resultant solution was diluted with water (10 ml) and the precipitated solid was combined with a second crop obtained by evaporating the mother liquor, triturating with water and washing with ether. Crystallisation from ethanol afforded the monohydrate of the vinylaminotriazole (310 b) (1.4g), m.p. 175°, $\nu_{max.}$ 3450,3375, and 3150(NH), 1660br(CO), and 1610(C=C)cm^{-1}, τ [$(CD_3)_2SO$] 2.24br(1H,s,NH), 2.56br(1H,s,NH), 5.22(1H,s,olefinic CH), 5.93(2H,q,J7Hz,CH_2), 7.68 (3H,s,Me), and 8.82(3H,t,J7Hz,Me), m/e 239(M^+)($C_9H_{13}N_5O_3$ requires M,239).

Found: C,42.0; H,5.8; N,27.7%.

$C_9H_{13}N_5O_3.H_2O$ requires: C,42.0; H,5.8; N,27.3%.

When the vinylaminotriazole (310 b) was treated briefly with dilute aqueous sodium hydroxide, it gave a sparingly soluble salt which afforded unchanged (310 b) on acidification (identified by i.r. spectrum).

(b) When the aminotriazole (306 a)(1.27g; 0.01 mol) and ethyl acetoacetate (1.48g; 0.011 mol) were heated under reflux in benzene (250 ml) or toluene (500 ml) containing glacial acetic acid (6 ml) for 15-24h, unchanged triazole (306 a)(1.06-1.11g) was obtained on cooling. Evaporation of the mother liquor from the reaction in benzene followed by trituration of the residue with water gave the isomer mixture [(307 b) + (308 b)] (0.06g), m.p. 275° which was identical (m.p. and i.r. spectrum) with a sample obtained later.

1-Acetyl-5-(2-ethoxycarbonyl-1-methylvinylamino)-1,2,3-triazole-4-carboxamide (310 c)

(a) The vinylaminotriazole (310 b) (0.72g; 0.003 mol) was heated under reflux in acetic anhydride (7 ml) for 1 min and the solution was cooled to give the monoacetyl derivative (310 c) (0.70g) (83%), m.p. 196° (from ethyl acetate), $\nu_{max.}$ 3400,3250, and 3200(NH), and 1770,1690, and 1670(CO) cm^{-1}, τ [$(CD_3)_2SO$] 1.78br(1H,s,NH), 2.16br (1H,s,NH), 5.07(1H,s,olefinic CH), 5.90(2H,q,J7Hz,CH_2), 6.70(3H,s,Me), 7.29(3H,s,Me), and 8.80(3H,t,J7Hz,Me).

Found: C,47.3; H,5.3; N,25.2%.

$C_{11}H_{15}N_5O_4$ requires: C,47.0; H,5.3; N,24.9%.

(b) The acetyl derivative (310 c) (0.14g) slowly dissolved when it was stirred at room temperature with a mixture of aqueous N-sulphuric acid (3.0 ml) and ethanol (5.0 ml). After 1h the ethanol was evaporated off under reduced pressure at room temperature. The aqueous mother liquor was adjusted to pH 7 by the addition of solid sodium hydrogen carbonate to give the aminotriazole (306 a) (0.03g), m.p. 223° (from water), which was identical (m.p. and i.r. spectrum) with an authentic sample.

(c) The acetyl derivative (310 c) (0.28g; 0.001 mol) was heated under reflux in aqueous 75% w/v ethanol (10 ml) for 10 min and the solution was then concentrated under reduced pressure and diluted with a little water, to yield the acetamidotriazole (306 b) (0.07g), m.p. 264-9° (decomp.) (from water), identical (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the aqueous filtrate afforded the triazolecarboxamide (306 a) (0.06g), m.p. 214-9° (decomp) which was identical (m.p. and i.r. spectrum) with an authentic sample.

The Thermal Isomerization of the Vinylaminotriazole (310 b) in Refluxing Toluene

The vinylaminotriazole (310 b) (0.48g; 0.002 mol) was heated under reflux in toluene (200 ml) for 2-18h and the mixture was evaporated under reduced pressure to give a solid (0.41g) whose ^{1}H n.m.r. spectrum, τ [$(CD_3)_2SO$] 2.24br(s,NH), 2.56br(s,NH), 3.65[s,olefinic CH of (315; R = H)] 4.20br(s,NH), 5.20[s,olefinic CH of(310 b)], 5.91[dq, overlapping CH_2 of (310 b) and (315; R = H)], 7.59[s,olefinic Me of (315; R = H)], 7.66[s,olefinic Me of (310 b)], and 8.80[dt, overlapping Me of (310 b) and (315; R = H)], was consistent with a mixture of (310 b) (80%) and (315; R = H) (20%). Attempted separation of the mixture by fractional crystallisation was unsuccessful.

The Attempted Reaction of the Acetamidotriazole (306 b) with Ethyl Acetoacetate

The triazole (306 b) (0.84g; 0.006 mol) was stirred with ethyl acetoacetate (0.72g; 0.006 mol), and glacial acetic acid (0.5 ml) in dimethylformamide (7.5 ml) at room temperature for 17h. The solution was evaporated under reduced pressure and treated with water to give the unchanged acetamidotriazole (306 b) (77%).

The Attempted Thermal Condensation of the Triazole (306 a) with Ethyl Acetoacetate

The triazole (306 a) (0.64g; 0.005 mol) and ethyl acetoacetate (0.72g; 0.006 mol) were heated under reflux in anhydrous toluene (300 ml) for 3h. The unchanged triazole (306 a) was recovered (quant.) from the cooled reaction mixture.

4,7-Dihydro-5-methyl-7-oxo-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (307 b) and 4,5-Dihydro-7-methyl-5-oxo-1,2,3-triazolo-[1,5-a]pyrimidine-3-carboxamide (308 b).

(a) The isomer mixture [(307 b) + (308 b)] was formed[13] (73%) when a mixture of the aminotriazolecarboxamide (306 a) (6.4g; 0.05 mol) and ethyl acetoacetate (7.0g; 6.8 ml; 0.054 mol) was heated under reflux with piperidine (2.5 ml) in ethanol (600 ml) for 24h, followed by the evaporation of the mixture and treatment with aqueous dilute sulphuric acid.

(b) The triazole (306 a) (0.26g; 0.002 mol) and ethyl acetoacetate (0.26g; 0.002 mol) were heated under reflux in glacial acetic acid (5 ml) for 4h. Evaporation of the solvent under reduced pressure followed by trituration of the residue with water and crystallisation of the resultant solid from glacial acetic acid-ethanol gave the isomer mixture [(307 b) + (308 b)] (0.19g) (49%). Concentration of the aqueous mother liquor gave the acetamidotriazole (306 b) (0.05g), m.p. 265-9° (decomp.), which was identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

(c) The triazole (306 a) (0.64g; 0.005 mol) was heated under reflux in ethyl acetoacetate (15 ml) for 4h. Evaporation of the excess of ethyl acetoacetate under reduced pressure followed by trituration of the resultant oil with methanol-ether gave a solid, which when crystallised from glacial acetic acid-ethanol, afforded the isomer mixture [(307 b) + (308 b)] (0.10g) (11%).

(d) The vinylaminotriazole (310 b or c) was stirred at room temperature for 5 min in aqueous N-sodium hydroxide (1.0 ml), and the solution obtained was acidified with dilute aqueous sulphuric acid to give the isomer mixture [(307 b) + (308 b)] (52-62%).

(e) The vinylaminotriazole (310 b) (0.24g; 0.001 mol) was heated under reflux in ethanol (10 ml) containing piperidine (0.25 ml) for 24h, or in glacial acetic acid (5 ml) for 4h, and the resultant solution was evaporated and treated with aqueous dilute sulphuric acid or water to afford a solid, which when crystallised from glacial acetic acid-ethanol, gave the isomer mixture [(307 b) + (308 b)] (47-88%).

(f) The ethylideneaminotriazole (310 b) (0.10g) was melted at 180° on a Kofler block, and the solid, which crystallised in the melt, was purified by crystallisation from glacial acetic acid-ethanol, to give the isomer mixture [(307 b) + (308 b)] (37%).

The isomer mixture had the composition (307 b) (72%), (308 b) (28%) as estimated from the integrated ratio of the H-6 signal in the ^{1}H n.m.r. spectrum, τ [$(CD_3)_2SO$] 1.94br(s,NH), 2.40br(s,NH), 3.75(q,J0.4-0.5Hz,H-6), 4.16(q,J0.4-0.5Hz,H-6), 7.36(d,J0.4-0.5Hz, Me-7), and 7.58 (poorly resolved doublet, Me-5); m.p. 274-5° (from glacial acetic-acid-ethanol), $\nu_{max.}$ 3350,3250br, and 3200br(NH), 1670(CO), and 1640(NH def.)cm^{-1}, $\lambda_{max.}$ 210,243,250sh,276 infl.,294 infl., and 325nm(log ε 4.22,4.30,4.28,3.94,3.62, and 3.39), m/e 193 (M^+) and 110(M^+-83) (M,193)

Found:	C,43.4;	H,3.6;	N,36.4%.
$C_7H_7N_5O_2$ requires:	C,43.5;	H,3.7;	N,36.3%.

The solution obtained by heating the acetyl compound (310 c) (0.28g; 0.002 mol) under reflux in glacial acetic acid (5.0 ml) for 3h on cooling deposited the acetamidotriazole (306 b)(80%) which was identical (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the mother liquor afforded the isomer mixture [(307 b) + (308 b)] (0.05g), m.p. 274-5°.

Attempted separation of the isomer mixture [(307 b) + (308 b)] (a) by fractional crystallisation, (b) by chromatography over silica gel, or (c) by attempted preferential salt formation, by heating the mixture (0.0044 mol) with piperidine (0.0033 mol) in ethanol (150 ml) for 10 min and filtering off the solid deposited on cooling, was unsuccessful.

5,7-Dimethyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (311)

The triazole (306 a)(0.64g; 0.005 mol) was heated under reflux in acetylacetone (15.0 ml) for 2.5h. The solid deposited on cooling was combined with a second crop obtained by evaporating the filtrate and triturating the residue with ether to give the dimethyltriazolopyrimidine (311)(0.91g)(95%), m.p. 265°(from glacial acetic acid-ethanol), which was identical (m.p. and i.r. spectrum) with an authentic sample.[11b]

The compound (311) had m/e 191 (M^+) and 108 (M^+-83)(M,191) and was insoluble in aqueous dilute sodium hydroxide.

The Cyclisation of 5-(2-Ethoxycarbonyl-1-methylvinylamino)-1H-1,2,3-triazole-4-carboxamide (310 b) in the Presence of Acetylacetone

(a) The vinylaminotriazole (310 b)(0.60g; 0.0025 mol) was heated under reflux in acetylacetone (8.0 ml) for 4h. The solid

deposited on cooling was collected, washed with ether and combined with a second crop obtained by evaporating the mother liquor and triturating with ether-methanol. The solid was suspended in water (3.0 ml), and piperidine (0.25 ml) was added. The suspension was shaken and the insoluble solid was collected, washed with water and dried in vacuo to afford the dimethyltriazolopyrimidine (311) (0.23g) (48%), m.p. 262-4°, which was identical (m.p. and i.r. spectrum) with an authentic sample.[11b] The filtrate was acidified with aqueous dilute sulphuric acid and the resultant solid was collected washed with water and dried in vacuo to give the isomer mixture [(307 b) + (308 b)] (0.08 g) (17%) which was identical (m.p. 275° and i.r. spectrum) with a sample obtained previously.

(b) The vinylaminotriazole (310 b) (0.48g; 0.002 mol) and acetylacetone (0.80g; 0.82 ml; 0.008 mol) were heated under reflux with piperidine (0.50 ml) in ethanol (20 ml) for 24h. Evaporation of the reaction mixture followed by trituration of the residue with water gave the dimethyltriazolopyrimidine (311) (0.11g) (29%), m.p. 259-63°, which was identical (m.p. and i.r. spectrum) with an authentic sample.[11b] Acidification of the mother liquor with aqueous dilute sulphuric acid afforded the isomer mixture [(307 b) + (308 b)] (0.17g) (44%), m.p. 260-5°, which was identical (m.p. and i.r. spectrum) with a sample obtained previously.

(c) The vinylaminotriazole (310 b) (3.0g; 0.0125 mol) and acetylacetone (5.0g; 5.2 ml; 0.050 mol) were heated under reflux in glacial acetic acid (50 ml) for 4h. Evaporation of the reaction mixture followed by treatment of the residue with water and ether gave

the dimethyltriazolopyrimidine (311) (0.73g), m.p. 256-62°, which was identical (m.p. and i.r. spectrum) with an authentic sample.[11b] Evaporation of the mother liquor followed by trituration with ether-ethanol gave an unidentified solid (1.04g), m.p. 159-67° (from ethanol), $\nu_{max.}$ 3400, 3200, and 3100w(NH), and 1750, and 1690(CO) cm^{-1}, whose t.l.c. and ^1H n.m.r. spectrum, τ [$(CD_3)_2SO$] 2.34br(s,NH), 2.59br(s,NH), 2.79(s), 4.14(s), 7.60(s), and 7.88(s), indicated a two component mixture. Attempted separation of the mixture by chromatography over silica gel was unsuccessful.

Attempted Reaction of 5,7-Dimethyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (311) with Acetic Anhydride

The dimethyltriazolopyrimidine (311) (0.38g; 0.002 mol) was heated under reflux in acetic anhydride (6.0 ml) for 5 min. The solid, which was deposited on cooling, was collected, washed with ether and combined with a second crop obtained by evaporating the mother liquor and triturating the residue with ether, to afford unchanged starting material (311) (90%) (m.p. and i.r. spectrum identical with an authentic sample).

6,7-Dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidin-5(4H)-one (322) and 5,6-Dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidin-7(4H)-one (323)

(i) The aminotriazole (306 c) (0.80g; 0.005 mol) and ethyl 2-methyl-acetoacetate (0.72g; 0.71ml; 0.005 mol) were heated under reflux with piperidine (0.85g; 1.00 ml; 0.010 mol) in ethanol (80 ml) for 24h or 100h. The reaction mixture was evaporated and the residue was triturated with aqueous dilute sulphuric acid to

afford a solid which was combined with a second crop obtained by extracting the mother liquor with chloroform. The aqueous mother liquor was adjusted to pH8 by the addition of aqueous dilute ammonia solution and extracted with chloroform (A).

(a) After 24h, the dimethyltriazolopyrimidone (322) was obtained (0.06g) m.p. 235° (from ethanol-dimethylformamide), $\nu_{max.}$ 3100br(NH), and 1660(CO)cm^{-1}, $\lambda_{max.}$ 234,241,281sh,295,301sh, and 356nm(log ε 3.95, 4.02,3.83,3.93,3.88 and 3.82), τ [$(CD_3)_2SO$] 1.99-2.68(5H,m,ArH), 7.29 (3H,s,Me-7), and 7.92(3H,s,Me-6), m/e 240(M^+)(M,240).

Found: C,64.7; H,5.2; N,23.5%.

$C_{13}H_{12}N_4O$ requires: C,64.9; H,5.0; N,23.4%.

Evaporation of the extract (A) afforded the unchanged triazole (306 c)(0.50g) m.p. 115-8°, which was identical (m.p. and i.r. spectrum) with an authentic sample.

(b) After 100h, the isomer mixture [(322) + (323)] was obtained (0.45g) m.p. 211-229°(decomp.), $\nu_{max.}$ 3300br(NH), and 1680, and 1660 (CO)cm^{-1}. The isomer mixture was approximately 1:1 as estimated from the integrated ratio of Me-7(322) to Me-5(323) in the ^1H n.m.r. spectrum, τ [$(CD_3)_2SO$] 1.99-2.68(m,ArH), 7.29 [s,Me-7(322)], 7.55[s,Me-5(323)], 7.92[s,Me-6(322)], and [7.96 s,Me-6(323)]. Evaporation of the extract (A) afforded the unchanged triazole (306 c)(0.25g) m.p. 115-21° which was identical (m.p. and i.r. spectrum) with an authentic sample.

(ii) The 6,7-dimethyltriazolopyrimidone(322)(0.24g; 0.001 mol) was heated under reflux with piperidine (0.17g; 0.20 ml; 0.002 mol) in ethanol (10 ml) for 100h. Evaporation of the reaction mixture and treatment of the resultant oil with aqueous dilute sulphuric acid gave the isomer mixture [(322) + (323)] (0.24g) m.p. 208-227°(decomp.), which was identical (m.p., and i.r., and ^{1}H n.m.r. spectra) with a sample obtained previously.

(iii) The isomer mixture [(322) + (323)] (0.36g; 0.0015 mol) was heated under reflux in dimethylformamide (5.0 ml) for 2h. Evaporation of the reaction mixture under reduced pressure gave the 6,7-dimethyltriazolopyrimidone(322)(0.36g) m.p. 228-34°, which was identical (m.p., i.r., and ^{1}H n.m.r. spectra) with a sample obtained previously.

The Reaction of the 5-Amino-1H-1,2,3-triazoles(306 a and c) with Ethyl Cyclopentanone-2-carboxylate

The triazoles (306 a and c)(0.005 mol) and ethyl cyclopentanone-2-carboxylate (0.78g; 0.005 mol) were heated under reflux with piperidine (0.20 ml) in ethanol (25-80 ml) for 18-24h.

(a) The insoluble solid from the triazole (306 a) was filtered off and acidified with aqueous dilute sulphuric acid to give 3-carbamoyl-7,8-dihydro-6H-cyclopenta[e]-1,2,3-triazolo[1,5-a]-pyrimidin-5(4H)-one(324 a) and/or its isomer(325 a)(0.39g)(36%) m.p. 264°(from glacial acetic acid-ethanol), $\nu_{max.}$ 3400br, and 3200br(NH), and 1680br(CO) cm^{-1}, m/e 219(M^+)(M,219).

Found:	C,47.3;	H,4.4;	N,30.3%.
$C_9H_9N_5O_2$ requires:	C,49.3;	H,4.1;	N,31.9%.

Evaporation of the ethanolic mother liquor and treatment of the resultant oil with aqueous dilute sulphuric acid gave the vinylaminotriazole(326 a)(0.59g)(45%) m.p. 205-12°, $\nu_{max.}$ 3450,3350, and 3200br(NH), and 1660(CO)cm^{-1},τ [$(CD_3)_2SO$] 2.22br(1H,s,NH),2.51br(1H,s,NH),5.85(2H,q,J7Hz,CH_2),6.82-6.97(2H,m,CH_2),7.42-7.59(2H,m,CH_2),8.09-8.24(2H,m,CH_2), and 8.75(2H,t,J7Hz,Me), m/e 219(M^+-C_2H_5OH) (M,265), which when crystallised from ethanol-benzene gave the cyclized product(s)(324a) and/or(325 a).

(b) The reaction mixture from the triazole (306 c) was evaporated and the residue was treated with water and extracted with chloroform. The oil obtained from the extract, was triturated with aqueous dilute sulphuric acid to give a solid (1.14g) which when leached with hot ethanol gave the insoluble 7,8-dihydro-3-phenyl-6H-cyclopenta[e]-1,2,3-triazolo[1,5-a]pyrimidin-5-(4H)-one(324 b) and/or its isomer (325 b)(0.45g)(36%) m.p. 231°(decomp.)(from aqueous dimethylformamide), $\nu_{max.}$ 3200-3000br(NH), and 1660(CO)cm^{-1}, m/e 252(M^+)(M,252).

Found: C,66.7; H,4.8; N,22.3%.

$C_{14}H_{12}N_4O$ requires: C,66.6; H,4.8; N,22.2%.

The ethanol mother liquor was evaporated to afford the vinylaminotriazole(326 b)(0.60g)(40%) m.p. 129°(from benzene), $\nu_{max.}$ 3200br(NH), and 1650br(CO)cm^{-1},τ [$(CD_3)_2SO$]0.37(1H,s,NH),2.10-2.76(5H,m,ArH), 5.79(2H,q,J7Hz,CH_2), 7.03-7.19(2H,m,CH_2), 7.35-7.50(2H,m,CH_2), 8.01-8.31(2H,m,CH_2), and 8.74(3H,t,J7Hz,Me), m/e 298(M^+)(M,298).

Found: C,64.1; H,6.0; N,19.0%.

$C_{16}H_{18}N_4O_2$ requires: C,64.9; H,6.0; N,18.5%.

The Synthesis and Reactivity of Some 1,2,3-Triazolo[1,5-a]pyrimidines

The Synthesis of Some 1,2,3-Triazolo[1,5-a]pyrimidine-3-carboxamides

(a) The aminotriazolecarboxamide (306 a)(0.48g; 0.00375 mol) and ethoxymethyleneacetylacetone, ethyl ethoxymethyleneacetoacetate, malonaldehyde bis-(dimethylacetal), or acetoacetaldehyde dimethylacetal (0.00375 mol) were stirred in dimethylformamide (5.0 ml) containing concentrated hydrochloric acid (2.5 ml) at 35° for 30 min. The resultant solid was collected, washed well with water, and combined with a second crop obtained by diluting the mother liquor with a large volume of water, neutralizing with solid sodium hydrogen carbonate, buffering with glacial acetic acid and extracting with chloroform.

(i) Ethoxymethyleneacetylacetone afforded a mixture of 6-acetyl-7-methyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (329 a; R = Me) and 6-acetyl-5-methyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (330 a; R = Me)(0.58g)(71%), m.p. 155°(from ethanol), $\nu_{max.}$ 3350,3250w, and 3100br(NH), and 1680(CO)cm^{-1}. The isomer mixture which ran as a single spot on t.l.c. examination, had the composition (329 a; R = Me)(75%)/(330 a; R = Me)(25%) as estimated from the integrated ratio of Me-7(329 a; R = Me) to Me-5(330 a; R = Me) signals in the ^1H n.m.r. spectrum, τ [$(CD_3)_2SO$] 0.72 [s,H-5(329 a; R = Me) and H-7 (330 a; R = Me)], 2.28br(s,NH),6.86 [s,Me-7(329 a; R = Me)],7.24 [s, Ac(329 a and 330 a; R = Me)], and 7.27 [s,Me-5(330 a; R = Me)], m/e 219 (M^+), 136(M^+-83)(M,219).

Found: C,49.0; H,4.3; N,31.8%.

$C_9H_9N_5O_2$ requires: C,49.3; H,4.1; N,31.9%.

When the isomer mixture (329 a; R = Me) and (330 a; R = Me) was dried in the oven at 80° for 20h it had $\nu_{max.}$ 3300, 3150(NH), 2100 ($\overset{+}{N}\equiv N$), and 1680 and 1660(CO) cm^{-1}. The ^1H n.m.r. spectrum in [$^2H_6$]-dimethylsulphoxide was identical with that obtained previously.

(ii) Ethyl ethoxymethyleneacetoacetate afforded a gummy solid (0.40g), whose t.l.c. showed it to be a multicomponent mixture, which could not be purified by crystallisation from ethanol.

(iii) Malonaldehyde bis-(dimethylacetal) gave 1,2,3-triazolo[1,5-a]-pyrimidine-3-carboxamide (337 a) (0.38g) (62%), m.p. 216° (decomp.) (from ethanol-dimethylformamide); $\nu_{max.}$ 3400, 3300w, 3150 and 3050(NH), and 1690(CO) cm^{-1}, $\lambda_{max.}$ 221, 236sh, 274, 280 infl., and 315 infl. nm (log ε 4.27, 3.98, 3.70, 3.68 and 3.45), τ [$(CD_3)_2SO$] 0.38 [1H, dd, J(H-7/H-6) 7Hz, J(H-7/H-5) 2Hz, H-7], 1.03 [1H, dd, J(h-5/H-6) 4Hz, J(H-5/H-7) 2Hz, H-5], 2.26br (2H, s, NH), and 2.55 [1H, dd, J(H-6/H-7) 7Hz, J(H-6/H-5) 4Hz H-6], m/e 163(M^+), 80(M^+-83) (M, 163).

Found:	C, 44.2;	H, 3.2;	N, 43.2%.
$C_6H_5N_5O$ requires:	C, 44.2;	H, 3.1;	N, 42.9%.

(iv) Acetoacetaldehyde dimethylacetal gave a mixture of 7-methyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (333 a) and 5-methyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (334 a) (0.57g) (86%), m.p. 212° (decomp.) (from benzene-dimethylformamide $\nu_{max.}$ 3400, 3250br, and 3050(NH), and 1690w, and 1660br(CO), which ran as a single spot on t.l.c. examination, and had the composition (333 a) (70%)/(334 a) (30%) as estimated from the integrated ratio of Me-7 (333 a) to Me-5 (334 a) in the ^1H n.m.r. spectrum, τ [$(CD_3)_2SO$] 0.53 [d, J(H-7/H-6) 7Hz (334 a), H-7], 1.12 [d, J(H-5/H-6) 4Hz (333 a), H-5], 2.32br (s, NH),

2.64 [dd, J(H-6/H-5) 4Hz, J(H-6/Me-7) 1Hz (333a), H-6], 2.66 [d, J(H-6/H-7) 7Hz (334 a), H-6], 7.07 [d, J(Me-7/H-6) 1Hz (333a), Me-7], and 7.30 [s, Me-5 (334 a)]. The assignments of the signals in the multiplet at τ2.60-2.70 were made by expanding the spectrum to sweep width 100Hz and irradiating on the doublet at τ1.07. The isomer mixture [(333 a) + (334 a)] had m/e 177(M^+), 94(M^+-83) (M,177).

Found: C,47.6; H,4.2; N,40.1%.

$C_7H_7N_5O$ requires: C,47.5; H,4.0; N,39.5%.

(b) The aminotriazolecarboxamide (306 a) (0.38g; 0.003 mol) and ethoxymethyleneacetylacetone or ethyl ethoxymethyleneacetoacetate were heated under reflux with piperidine (0.10 ml) in ethanol (35 ml) for 1h. The reaction mixtures became very dark and were evaporated and treated with chloroform to afford gummy solids which were combined with second crops obtained from the chloroform extracts after washing with water (total 0.44-0.58g). T.l.c. examination of the products showed them to be multicomponent mixtures.

(c) The aminotriazolecarboxamide (306 a) (0.64g; 0.005 mol) and ethoxymethyleneacetylacetone, ethyl ethoxymethyleneacetoacetate, or dimethyl acetylenedicarboxylate (0.005 mol) were heated under reflux in glacial acetic acid (10ml) for 4h. Evaporation of the reaction mixtures afforded dark red oils which were insoluble in chloroform and which, when triturated with ethanol, gave tan coloured solids (0.66-0.74g). T.l.c. examination of the solids showed them to be multicomponent mixtures which were not purified by crystallisation from ethanol.

The solid obtained from ethoxymethyleneacetylacetone had m.p. 133-45°(decomp.). Crystallisation three times from ethanol, raised the m.p. to 148-72°(decomp.), but t.l.c. examination after crystallisation showed that the solid was still a multicomponent mixture.

The Synthesis of Some 3-Phenyl-1,2,3-triazolo[1,5-a]pyrimidines.

(a) The triazole (306 c)(0.80g; 0.005 mol) and ethoxymethylene-acetylacetone, ethyl ethoxymethyleneacetoacetate or ethyl ethoxymethylene-cyanoacetate, or dimethyl acetylenedicarboxylate (0.005 mol) were heated under reflux with piperidine (0.20 ml) in ethanol (20 ml) for 24h [1h in the case of the first two named ethoxymethylene compounds]. The reaction mixture was allowed to cool and any solid deposited was collected, washed with water and dried in vacuo at room temperature.

(i) Ethoxymethyleneacetylacetone afforded a mixture of 6-acetyl-7-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (329 b; R = Me) and 6-acetyl-5-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (330 b; R = Me)(1.04g)(83%), m.p. 191°(from ethanol), $\nu_{max.}$ 1680(CO) cm^{-1}, which ran as a single spot on t.l.c. examination, and had the composition (329 b; R=Me)(90%)/(330 b; R=Me)(10%) as estimated from the integrated ratio of Me-7(329 b;R = Me) to Me-5 (330 b; R = Me) in the ^1H n.m.r. spectrum, $\tau(CDCl_3)$ 0.68[s,H-7(330b; R = Me)], 1.10[s,H-5(329 b; R = Me)], 1.56-1.67(m,ArH), 2.40-2.65(m,ArH), 6.79[s,Me-7(329 b; R = Me)], 7.14[s,Me-5(330 b; R = Me)], 7.29 [s,Ac(329 b,R = Me)], and 7.34[s,Ac(330 b; R = Me)], m/e 252(M^+)(M,252).

Found: C,66.9; H,4.9; N,22.1%.

$C_{14}H_{12}N_4O$ requires: C,66.7; H,4.8; N,22.2%.

(ii) Ethyl ethoxymethyleneacetoacetate gave a mixture of ethyl 7-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-6-carboxylate (329 b; R = OEt) and ethyl 5-methyl-3-phenyl-1,2,3-triazolo[1,5-a]-pyrimidine-6-carboxylate(330 b; R = OEt) (0.99g)(71%), m.p. 118° (from ethanol), $\nu_{max.}$ 1720(CO)cm^{-1}, which ran as a single spot on t.l.c. examination, and had the composition (329 b;R = OEt)(93%)/ (330 b; R = OEt)(7%) as estimated from the integrated ratio of Me-7 (329 b; R = OEt) to Me-5(330 b; R = OEt) in the ^1H n.m.r. spectrum, $\tau(CDCl_3)$ 0.64[s,H-7(330 b; R = OEt)] , 1.01[s,H-5(329 b; R = OEt)] , 1.58-1.70 (m,ArH),2.43-2.67(m,ArH),5.55(q,J7Hz,CH_2),6.73[s,Me-7 (329 b; R = OEt)] , 7.10[s,Me-5(330 b; R = OEt)] , and 8.56(t,J7Hz, Me), m/e 282(M^+)(M,282).

Found: C,63.8; H,5.0; N,19.4%.

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

(iii) Ethyl ethoxymethylenecyanoacetate gave ethyl 7-amino-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-6-carboxylate(335) which was combined with a second crop obtained by evaporating the mother liquor treating the residue with aqueous dilute sodium hydroxide solution, extracting with chloroform and triturating with ether (total, 0.53g), m.p. 193° (from ethanol-dimethylformamide), $\nu_{max.}$ 3350,3200br(NH), and 1680(CO) cm^{-1}, $\lambda_{max.}$ 209,253,280,288 and 325 nm(log ε 4.39,4.21,3.87,3.98 and 4.33),$\tau(CDCl_3)$ 1.10(1H,s,H-5),1.54-1.65(2H,m,ArH),1.41-1.66(3H,m,ArH), 5.56(2H,q,J7Hz,CH_2), and 8.57(3H,t,J7Hz,Me),m/e 283(M^+)(M,283).

Found: C,59.4; H,4.6; N,24.7%.

$C_{14}H_{13}N_5O_2$ requires: C,59.4; H,4.6; N,24.7%.

Acidification of the aqueous mother liquor followed by extraction with chloroform gave an oil which t.l.c. examination showed to be a multicomponent mixture. Further adjustment of the mother liquor to pH8 with dilute aqueous ammonia solution, and extraction with chloroform, gave unchanged triazole(306 c)(0.11g), m.p. 113-9°(identified by m.p. and i.r. spectrum).

(iv) Dimethyl acetylenedicarboxylate gave a solution, which when evaporated and treated with dilute aqueous sulphuric acid and ether, yielded a solid, identified as methyl 4,5-dihydro-5-oxo-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-7-carboxylate(331 b) or methyl-4,7-dihydro-7-oxo-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-5-carboxylate (332 b)(0.96g)(71%), m.p. 150°(from ethanol), $\nu_{max.}$ 3100-2700br(NH), and 1740, and 1700(CO)cm^{-1}, $\lambda_{max.}$ 212,238 infl.,258,320 infl., and 360nm(log ε 4.16,4.03,4.15,3.42 and 3.86),τ($CDCl_3$) 2.28-2.71(5H,m,ArH), 3.49(1H,s,H-6), and 5.99(3H,s,Me),m/e 270(M^+)(M,270).

Found:	C,58.0;	H,4.0;	N,20.5%.
$C_{13}H_{10}N_4O_3$ requires:	C,57.8;	H,3.7;	N,20.7%.

Evaporation of the ether gave an oil (0.50g) which was shown by t.l.c. to be a multicomponent mixture.

When the triazole(306 c)(0.40g; 0.0025 mol) and ethyl cyanoacetate(0.29g; 0.28 ml; 0.0026 mol) were heated under reflux with piperidine (0.10 ml) in ethanol (25 ml) for 48h, and the resultant solution was evaporated and the residue was treated with water and washed with a little ether, unchanged triazole (306 c) was obtained and was combined with a second crop obtained by adjusting the mother liquor to pH8, extracting with chloroform and triturating the resultant oil with ether (total, 0.34g)(85%), m.p. 118°.

(b) The aminotriazole(306 c)(1.20g; 0.0075 mol) and malonaldehyde bis-(dimethylacetal) or acetoacetaldehyde dimethylacetal (0.0075 mol) were stirred in ethanol(10 ml) containing concentrated hydrochloric acid (5 ml) for 30 min at 35°. The resultant solid was collected, washed with water, and combined with a second crop obtained by diluting the mother liquor with water, extracting with chloroform, and triturating the residue with ethanol-ether.

(i) Malonaldehyde bis-(dimethylacetal) gave 3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidine(337 b)(1.34g)(91%), m.p. 188°(from ethanol-dimethylformamide), $\lambda_{max.}$ 213,233,257,279,299sh and 352nm(log ε 4.14,4.22,4.18,3.78, 3.56 and 3.56), τ($CDCl_3$)1.12[1H,dd,J(H-7/H-6)7Hz,J(H-7/H-5)2Hz,H-7], 1.36[1H,dd,J(H-5/H-6)4Hz,J(H-5/H-7)2Hz,H-5], 1.52-1.63(2H,m,ArH), 2.40-2.65(3H,m,ArH), and 3.03[1H,dd,J(H-6/H-7)7Hz,J(H-6/H-5)4Hz, H-6], m/e 196(M^+)(M,196).

Found: C,67.2; H,4.3; N,29.0%.

$C_{11}H_8N_4$ requires: C,67.4; H,4.1; N,28.5%.

(ii) Acetoacetaldehyde dimethylacetal gave a mixture of 7-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine(333 b) and 5-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine(334 b)(1.32g)(84%), m.p. 188°(from ethanol-dimethylformamide). The isomer mixture, which ran as a single spot on t.l.c. examination, had the composition (333 b)(85%)/(334 b)(15%) as estimated from the integrated ratio of Me-7(333 b) to Me-5(334 b) in the ^1H n.m.r. spectrum, τ ($CDCl_3$)1.29[d,J(H-7/H-6) 7Hz(334 b),H-7], 1.49[d,J(H-5/H-6)4Hz(333 b),H-5], 1.51-1.62(m,ArH), 2.40-2.68(m,ArH), 3.23[d,J(H-6/H-7)7Hz(334 b),H-6], 3.24[dd,J(H-6/H-5) 4Hz,J(H-6/Me-7)1Hz(333 b),H-6], 7.10[d,J(Me-7/H-6)1Hz(333 b),Me-7],

and 7.37[s,Me-5(334 b)]. The assignments of the signals in the multiplet at τ 3.18-3.27 were obtained by expanding the spectrum to sweep width 100Hz and irradiating on the doublet at τ 7.10. The isomer mixture [(333 b) + (334 b)] had m/e 210(M^+)(M,210).

Found: C,68.7; H,5.0; N,27.0%.

$C_{12}H_{10}N_4$ requires: C,68.5; H,4.8; N,26.7%.

7-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-6-carboxylic Acid (338) or 5-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine-6-carboxylic Acid(339)

The ethyl triazolopyrimidinecarboxylate isomer mixture [(329 b) + (330 b); R = OEt] (1.41g; 0.005 mol) was heated under reflux in ethanol(20 ml) containing aqueous 10% w/v sodium hydroxide solution (10 ml) for 20 min. The reaction mixture was evaporated and the residue was treated with water to give a solid which, when acidified with dilute aqueous sulphuric acid, gave the acid (338) or (339)(0.48g)(38%), m.p. 212° (from ethanol-dimethylformamide), $\nu_{max.}$ 3500-2500br(OH), and 1710(CO)cm^{-1}, $\lambda_{max.}$ 209,251,281sh and 335nm(log ε 4.03,3.93,3.72 and 4.21), τ [$(CD_3)_2SO$] 1.57[1H,s,H-5(338)or H-7(339)], 2.10-2.60(5H,m,ArH), and 7.40[3H,s,Me-7(338) or Me-5(339)], m/e 254(M^+)(M,254).

Found: C,61.4; H,4.2; N,22.1%.

$C_{13}H_{10}N_4O_2$ requires: C,61.4; H,4.0; N,22.1%.

Acidification of the aqueous mother liquor with aqueous dilute sulphuric acid gave the decarboxylated isomer mixture [(333 b) + (334 b)] (0.31g)(30%), m.p. 137-41°, which was identical, (m.p., i.r. and ^1H n.m.r. spectra), with a sample obtained previously, and had the composition (333 b)(81%)/(334 b)(19%) as estimated from the integrated ratio of Me-7(333 b) to Me-5(334 b) in the ^1H n.m.r. spectrum in [$^2H_6$]-dimethylsulphoxide. The isomer mixture [(333 b) + (334 b)] was insoluble in dilute aqueous sodium hydroxide solution.

The Attempted Reaction of the Acetyltriazolopyrimidine Isomer Mixture [(329b) + (330b); R = Me] with Hypochlorous Acid.

Chlorine gas was passed into a solution of sodium hydroxide (7.5g) in water (60 ml) at <0° (ice-salt bath) until the solution was neutral to litmus, and a solution of sodium hydroxide (1.3g) in water (5 ml) was then added. The mixture was stirred vigorously, warmed to 55°, and the isomer mixture [(329 b) + (330 b); R = Me] (5.04g; 0.02 mol) was added. No temperature rise was observed and the mixture was warmed to 70° and kept at this temperature for 45 min. The mixture was allowed to cool and solid sodium bisulphite was added to destroy any excess sodium hypochlorite. The reaction mixture was extracted with chloroform giving an oily residue which on trituration with ether gave the unchanged isomer mixture [(329 b) + (330 b); R = Me] (4.01g)(80%) m.p. 188°, which was identical (m.p. and i.r. spectrum) with a sample prepared previously.

The Synthesis of Some 2-Substituted Pyrimidines.

2-(α-Acetoxybenzyl)pyrimidines(340 a; R = Me or OEt)

(a) 2-(α-Acetoxybenzyl)-5-acetyl-4-methylpyrimidine(340 a; R = Me) was formed (84-93%) by heating the aminotriazole(306 c)(0.80g; 0.005 mol) and ethoxymethyleneacetylacetone (0.78g; 0.005 mol) or the isomer mixture [(329 b) + (330 b); R = Me] (0.50g; 0.002 mol) under reflux in glacial acetic acid (10 ml) for 4h. The reaction mixture was evaporated and the residue was extracted into chloroform and washed with a saturated aqueous solution of sodium hydrogen carbonate. The resultant oil did not crystallise and had i.r. and ^{1}H n.m.r. spectra consistent with the 2-substituted pyrimidine(340a; R = Me) $\nu_{max.}$ 1740 and 1690(CO)cm^{-1}, τ($CDCl_3$)1.07(1H,s,H-6),2.41-2.76(5H,m,ArH),3.30(1H,s,benzylic H), 7.29(3H,s,Me-4), 7.46(3H,s,Ac), and 7.79(3H,s,OAc).

(b) When the aminotriazole(306 c)(0.005 mol) and ethyl ethoxymethyleneacetoacetate (0.005 mol) or the isomer mixture [(329 b) + (330 b); R = OEt] (0.002 mol) were similarly treated with glacial acetic acid, a mixture of ethyl 2-(α-acetoxybenzyl)-4-methylpyrimidine-5-carboxylate (340 a; R = OEt) and ethyl 2-(α-hydroxybenzyl)-4-methylpyrimidine-5-carboxylate (340 b; R = OEt)(85-92%) was obtained. The mixture (1.17g) was separated by chromatography over alumina. Elution with benzene gave an oil whose i.r. and ^{1}H n.m.r. spectra were consistent with the acetoxy compound (340 a; R = OEt), $\nu_{max.}$ 1730br(CO)cm^{-1}, τ ($CDCl_3$)0.90(1H,s,H-6),2.40-2.74(5H,m,ArH),3.27(1H, s,benzylic H),5.65(2H,q,J7Hz,CH_2),7.11(3H,s,Me-4),7.80(3H,s,OAc), and 8.66(3H,t,J7Hz,Me). Further elution with benzene gave inseparable mixtures of (340 a; R = OEt) and (340 b; R = OEt)(0.21g)

followed by a pure sample of the hydroxy compound (340 b; R = OEt) which was an oil and had $\nu_{max.}$ 3450br(OH), and 1720(CO)cm^{-1}, τ($CDCl_3$) 0.91(1H,s,H-6),2.46-2.78(5H,m,ArH), 4.13(1H,s,benzylic H),5.04br(1H, s,OH),5.64(2H,q,J7Hz,CH_2), 7.10(3H,s,Me-4), and 8.64(3H,t,7Hz,Me).

2-(α-Hydroxybenzyl)pyrimidines (342; R = Me,OH)

The acetoxy compound (340 a; R = Me)(0.50g) and the 2-substituted pyrimidine mixture [(340 a) + (340 b); R = OEt] (0.50g) were heated under reflux with aqueous N-sodium carbonate solution (5 ml) in ethanol (10 ml) for 0.5-1 h. The reaction mixtures were evaporated, treated with water, and extracted with chloroform.

(a) The acetoxy compound (340 a; R = Me) gave an oil whose i.r. and ^1H n.m.r. spectra were consistent with 5-acetyl-2-(α-hydroxybenzyl)-4-methylpyrimidine(342; R = Me)(0.40g), $\nu_{max.}$ 3400br(OH), and 1690(CO)cm^{-1}, τ($CDCl_3$)1.06(1H,s,H-6),2.46-2.77(5H,m,ArH),4.14[1H,d,J(benzylic H-OH) 6Hz, benzylic H], 5.16[1H,d,J(OH-benzylic H)6Hz,OH],7.25(3H,s,Me-4), and 7.44(3H,s,Ac). Attempts to form 2,4-dinitrophenylhydrazone, oxime or semicarbazone derivatives of (342; R = Me) were unsuccessful.

(b) The 2-substituted pyrimidine mixture [(340 a) + (340 b); R = OEt] gave an oil which crystallised from ethanol-light petroleum to give 2-(α-hydroxybenzyl)-4-methylpyrimidine-5-carboxlic acid (342; R = OH (0.31g), m.p. 135°, $\nu_{max.}$ 3450-2500br(OH), and 1710(CO)cm^{-1}, τ ($CDCl_3$) 0.80(1H,s,H-6), 1.72br(1H,s,OH), 2.46-2.78(5H,m,ArH),4.08(1H,s,benzylic H), and 7.15(3H,s,Me-4).

Found:	C,63.8;	H,5.0;	N,11.5%.
$C_{13}H_{12}N_2O_3$ requires:	C,63.9;	H,5.0;	N,11.5%.

2-(α-Chlorobenzyl)pyrimidines (341; R = Me or OEt)

The triazolopyrimidine isomer mixtures [(329 b) + (330 b); R = Me], and [(329 b) + (330 b); R = OEt] (1.0g) were heated under reflux with acetyl chloride (10 ml) and glacial acetic acid (5.0 ml) for 1.5h. The reaction mixtures were evaporated, washed with saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform to give oils, which did not crystallise. The i.r. and ^{1}H n.m.r. spectra of the oils were consistent with the 2-(α-chlorobenzyl)pyrimidines(341; R = Me or OEt).

(a) 5-Acetyl-2-(α-chlorobenzyl)-4-methylpyrimidine(341; R = Me) had $\nu_{max.}$ 1690(CO) cm^{-1}, τ($CDCl_3$) 1.01(1H,s,H-6), 2.29-2.75(5H,m,ArH), 3.88 (1H,s,benzylic H), 7.25(3H,s,Me-4), and 7.42(3H,s,Ac).

(b) Ethyl 2-(α-Chlorobenzyl)-4 methylpyrimidine-5-carboxylate (341; R = OEt) had $\nu_{max.}$ 1720(CO) cm^{-1}, τ ($CDCl_3$) 0.87(1H,s,H-6), 2.32-2.78 (5H,m,ArH), 3.85(1H,s,benzylic H), 5.66(2H,q,J7Hz,CH_2), 7.10(3H,s,Me-4), and 8.66(3H,q,J7Hz,Me).

Ethyl 2-Benzyl-4-methylpyrimidine-5-carboxylate (343)

(a) The acetoxy compound (340 a; R = OEt) (0.63g; 0.002 mol) was hydrogenolysed in ethanol (50 ml) over 10% palladium-charcoal. Evaporation of the filtered reaction mixture gave an oil which was washed with saturated aqueous sodium hydrogen carbonate and extracted into chloroform to yield an oil whose i.r. and ^{1}H n.m.r. spectra were consistent with the benzylpyrimidine (343) (0.48g), $\nu_{max.}$ 1720(CO) cm^{-1}, τ($CDCl_3$) 0.97(1H,s,H-6), 2.65-2.82(5H,m,ArH), 5.64(2H,q,J7Hz,CH_2), 5.74(2H,s,benzylic CH_2), 7.23(3H,s,Me-4) and 8.64(3H,t,J7Hz,Me).

(b) Ethyl ethoxymethyleneacetoacetate (0.19g; 0.001 mol) and phenylacetamidine[98] (0.14g; 0.001 mol) in ethanol (5.0 ml) were heated under reflux with a solution of sodium (0.11g; 0.005 mol) in ethanol (25 ml) for 1h. The reaction mixture was evaporated, treated with water, and extracted with chloroform to give an oily solid, which when triturated with ether gave phenylacetamide[99] (0.12g), m.p. 151°(lit.,[99] 155°), $\nu_{max.}$ 3350, and 3150(NH), and 1640 (CO)cm^{-1}. Evaporation of the ether gave the benzylpyrimidine (343) (0.03g) which was identical (i.r. and ^1H n.m.r. spectra) with a sample obtained previously.

2-Benzyl-4-methylpyrimidine-5-carboxylic Acid (344)

The benzylpyrimidine (343) (0.46g; 0.0018 mol) was heated under reflux with aqueous N-sodium carbonate solution (5 ml) in ethanol (10 ml) for 1h. The reaction mixture was evaporated and the residue was dissolved in water and washed with chloroform. Acidification of the aqueous mother liquor with dilute aqueous sulphuric acid solution gave the acid (344) (0.29g) (71%), m.p. 175°(from aqueous ethanol), $\nu_{max.}$ 2600-2350br, and 1890br(OH), and 1710(CO)cm^{-1}, τ($CDCl_3$)0.81(1H,s,H-6), 2.69-2.84(5H,m,ArH),5.69(2H,s,benzylic CH_2), and 7.16(3H,s,Me-4), m/e 228(M^+)(M,228).

Found: C,68.7; H,5.4; N,12.2%.

$C_{13}H_{12}N_2O_2$ requires: C,68.4; H,5.3; N,12.3%.

Methyl 2-(α-Acetoxybenzyl)-3,4-dihydro-4-oxo-pyrimidine-6-carboxylate (345)

The aminotriazole (306 c) (0.80g; 0.005 mol) and dimethyl acetylenedicarboxylate (0.71g; 0.61 ml; 0.005 mol) were heated under reflux in glacial acetic acid (10 ml) for 4h. Evaporation of the reaction

mixture gave an oil which solidified on contact with ether to give the pyrimidone (345)(1.02g)(68%), m.p. 190°(from ethanol), $\nu_{max.}$ 3000br(NH), and 1750, and 1680br(CO)cm^{-1}, τ ($CDCl_3$)2.37-2.70(5H,m,ArH), 2.93(1H,s,H-5),3.40(1H,s,benzylic H), 6.08(3H,s,Me), and 7.75(3H,s, OAc), m/e 302(M^+)(M,302).

Found:	C,59.7;	H,4.7;	N,9.0%.
$C_{15}H_{14}N_2O_5$ requires:	C,59.6;	H,4.6;	N,9.3%.

Table 4

^{1}H N.m.r. study of the monomethyl isomer mixture [(333 b) + (334 b)]

Solvent	^{1}H N.m.r. signals[a] (τ)							Composition (%)	
	H-5(333 b)	H-7(334 b)	H-6(333 b)	H-6(334 b)	Me-7(333 b)	Me-5(334 b)	ArH	(333 b)	(334 b)
$CDCl_3$	1.49[b]	1.29[c]	3.19 ⟷	3.29[d]	7.10[e]	7.37	1.51-1.62[f] 2.40-2.68	85	15
$(CD_3)_2CO$	1.35[b]	0.92[c]	2.84 ⟷	2.92[d]	7.09[e]	7.31	1.50-1.61[f] 2.42-2.68	81	19
$(CD_3)_2SO$	1.27[b]	0.65[c]	2.72 ⟷	2.79[d]	7.11[e]	7.33	1.58-1.71[f] 2.38-2.64	82	18

[a] Signals were sharp singlets unless otherwise designated. [b] Doublet (J4Hz).

[c] Doublet (J7Hz). [d] Multiplet which on expansion to sweep width 100Hz becomes a doublet [J7Hz(334 b)] and a double doublet [J4Hz, J1Hz(333 b)]. [e] Becomes a doublet on expansion to sweep width 100Hz. [f] Multiplet.

^{1}H N.M.R. Studies on Some 1,2,3-Triazolo[1,5-a]pyrimidines.

The Room Temperature Study of the Isomer Mixture 7-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine(333 b)/5-Methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (334 b)

^{1}H n.m.r. spectra of the isomer mixture [(333 b) + (334 b)] were measured in deuteriochloroform, [$^2H_6$] acetone and [$^2H_6$]-dimethylsulphoxide at 28°. The results obtained are collected in Table 4. The percentage composition of the isomer mixture [(333 b) + (334 b)] was estimated in each case from the integrated ratio of the Me-7(333 b) to Me-5(334 b) signals.

The Variable Temperature Study of Some 1,2,3-Triazolo[1,5-a]pyrimidine-3-carboxamides

The ^{1}H n.m.r. spectra in [$^2H_6$] dimethylsulphoxide of:-

(a) 5,7-dimethyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (311),

(b) the 6-acetyltriazolo[1,5-a]pyrimidine isomer mixture [(329 a) + (330 a); R = Me],

(c) 1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (337 a),

(d) the methyltriazolo[1,5-a]pyrimidine isomer mixture [(333 a) + (334 a)],

were measured at 15° and 28° and thereafter at 5° intervals, using sweep width 250Hz. Extracts of the results obtained are collected in Tables 5-8. In each case the [$^2H_6$] dimethylsulphoxide solution was allowed to cool after reaching a temperature of 150° and the spectrum remeasured at 28° giving a spectrum identical with the original (measured at 28°). (See over).

Table 5

The variable temperature ^{1}H n.m.r. spectrum of 5,7-dimethyl-1,2,3-triazolo[1,5-a]pyrimidine-3-carboxamide (311), over a range which includes the Me-5 and Me-7 signals.

Temperature (°C)	Signals[a]		
	Me-5	Coalesced Me-5/Me-7	Me-7
15	270		291[b]
28	270		291[b]
57	268[c]		290br
88		277[c]	
118		274[c]	
143		271	

[a] All signals, measured in Hz from silicone oil as external standard at the temperature stated, were sharp singlets unless otherwise stated.

[b] Doublet (J1Hz).

[c] Broad singlet.

Table 6

Variable temperature ^1H n.m.r. signals of the acetyltriazolo[1,5-a]-pyrimidine isomer mixture [(329 a) + (330 a); R = Me]

Temperature (°C)	Signals[a]		
	Me-5(330 a)	Coalesced Me-5/Me-7	Me-7(329 a)
23	277		317
28	277		317
48	277br		317br
59		313br	
89		295br	
104°		292br	

[a] All signals, measured in Hz from silicone oil as external standard at the temperature stated, were sharp singlets unless otherwise designated.

Table 7

The variable temperature ^{1}H n.m.r. spectrum of 1,2,3-triazolo[1,5-a]-pyrimidine-3-carboxamide (337 a) over a range which includes the H-5, H-6, and H-7 signals.

Temperature(°C)	Signals[a]			
	H-6	H-5	Coalesced H-5/H-7	H-7
15	747[b]	900[c]		965[d]
28	747[b]	900[c]		965[d]
65	742[e]	896[f]		956[g]
100	736[e]		908[h]	
125	731[e]		909[i]	
153	726[e]		900[j]	

[a] All signals were measured in Hz from silicone oil as external standard at the temperature stated.

[b] Double doublet (J7Hz,J4Hz).

[c] Double doublet (J4Hz,J2Hz).

[d] Double doublet (J7Hz,J2Hz).

[e] Triplet(J5Hz).

[f] Broad doublet (J4Hz).

[g] Broad doublet (J7Hz). [h] Broad singlet.

[i] Broad doublet (J5Hz). [j] Doublet (J5Hz).

Table 8

The variable temperature ^{1}H n.m.r. spectrum of the methyltriazolo-[1,5-a]pyrimidine isomer mixture [(333 a) + (334 a)] over the range including the Me-7 (333 a) and Me-5 (334 a) signals

Temperature (°C)	Signals[a]		
	Me-5	Coalesced Me-5/Me-7	Me-7
15	272		296[b]
28	272		296[b]
62	271[c]		295[c]
88		289[c]	
114		282[c]	
134		280	

[a] All signals, measured in Hz from silicone oil as external standard at the temperature stated, were sharp singlets unless otherwise designated.

[b] Doublet (JlHz).

[c] Broad singlet.

The Variable Temperature Study of Some 3-Phenyl-1,2,3-triazolo-[1,5-a]pyrimidines

The ^{1}H n.m.r. spectra in [$^{2}H_{6}$]dimethylsulphoxide of:-

(a) 5,7-dimethyl-3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (346) (Table 9),

(b) the 6-acetyltriazolo[1,5-a]pyrimidine isomer mixture [(329 b) + (330 b); R = Me] (Table 10),

(c) 3-phenyl-1,2,3-triazolo[1,5-a]pyrimidine (337 b) (Table 11),

(d) the methyltriazolo[1,5-a]pyrimidine isomer mixture [(333 b) + (334 b)] (Table 12),

were measured at room temperature (28°) and thereafter at approximately 25° intervals. Signals obtained at 28° together with those obtained at the approximate coalescence temperature are listed in Tables 9-12. In each case the [$^{2}H_{6}$]dimethylsulphoxide solution was allowed to cool after reaching a temperature of 200° and the spectrum was remeasured at 28° giving a spectrum identical with the original (measured at 28°). (See over).

Tables (12)

Variable temperature ^{1}H n.m.r. signals of some 3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidines

	Temperature (^{o}C)	Signal[a]		
		Me-5	Coalesced Me-5/Me-7	Me-7
(9)	28	260		281[b]
	175		269br	
(10)	28	272		311
	125		282br	
		H-5	Coalesced H-5/H-7	H-7
(11)	28	883[c]		950[d]
	175		900br	
(12)	28	871[e]		933[f]
	175		890br	

[a] All signals, measured in Hz from silicone oil as external standard at the temperature stated, were sharp singlets unless otherwise designated.

[b] Doublet (J1Hz).

[c] Double doublet (J4Hz,J2Hz).

[d] Double doublet (J7Hz,J2Hz).

[e] Doublet (J7Hz).

[f] Doublet (J4Hz).

The Attempted Reaction of 5,7 Dimethyl-3-phenyl-1,2,3-triazolo-[1,5-a]pyrimidine (346) with Dimethyl Acetylenedicarboxylate

The triazolopyrimidine (346) (1.12g; 0.005 mol) and dimethyl acetylenedicarboxylate (0.85g; 0.73 ml; 0.006 mol) were heated at 180° in sulpholane (5.0 ml) for 0.5 h. The solution became very dark. Dilution with a large volume of water followed by extraction with chloroform gave an oil which when treated with water and ether gave a solid. Crystallisation from ethanol afforded the unchanged triazolopyrimidine (346) (0.35g). Evaporation of the ether gave an oil (2.03g) which on t.l.c. examination proved to be a multicomponent mixture.

APPENDIX

General Experimental Procedures

Crude solids obtained from reaction mixtures by filtration were dried *in vacuo* at room temperature unless otherwise stated.

Infrared spectra were measured for nujol suspensions or thin films using a Pye-Unicam S.P.200 Spectrophotometer; bands were either strong or very strong, unless otherwise specified (w) weak or (br) broad.

Ultraviolet spectra were measured for ethanol solutions using a Pye-Unicam S.P.600 Spectrophotometer; bands were clear, unless otherwise specified (sh) shoulder or (infl.) point of inflection.

Nuclear magnetic resonance (^{1}H n.m.r.) spectra were measured at 100MHz using a Varian HA100 instrument.

Mass spectra were measured at 800 Kv on an A.E.I. MS902 instrument.

Microanalyses were carried out by Alfred Bernhardt, West Germany, The National Physical Laboratory, and by Mr. Brian Clark and 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 in chloroform over silica, which was Kieselgel G.F.$_{254}$ nach Stahl (Typ 60), unless otherwise specified.

Column chromatography was carried out over 5% deactivated alumina or Fison's Silica Gel (100-200 mesh).

Solvents were of technical grade and light petroleum had b.p. 60-80°C.

Chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure.

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The Chemistry of Polyazaheterocyclic Compounds. Part VI.[1] Condensation Reactions of 5-Amino-1*H*-1,2,3-triazoles with Ethyl Acetoacetate and a New Type of Dimroth Rearrangement

By **Derek R. Sutherland, George Tennant,*** and **Robin J. S. Vevers,** Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

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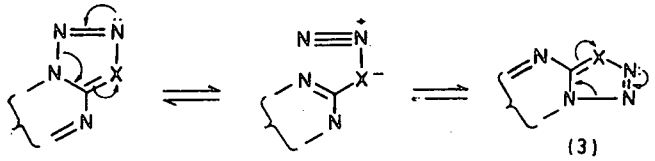
The Chemistry of Polyazaheterocyclic Compounds. Part VI.[1] Condensation Reactions of 5-Amino-1*H*-1,2,3-triazoles with Ethyl Acetoacetate and a New Type of Dimroth Rearrangement

By Derek R. Sutherland, George Tennant,* and Robin J. S. Vevers, Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

Condensation of 5-amino-4-phenyl-1*H*-1,2,3-triazole (4a) with ethyl acetoacetate in the presence of piperidine affords mainly 5-methyl-3-phenyl-*v*-triazolo[3,4-*a*]pyrimidin-7(4*H*)-one (9a), which is also the major product of the piperidine-catalysed cyclisation of the triazole derivatives (5a) and (7a). The isomer (10a) was only a minor product of these reactions. In contrast, heating a mixture of the amino-1,2,3-triazolecarboxamide (4c) and ethyl acetoacetate, or the vinylaminotriazole (5c) with piperidine in ethanol affords an inseparable mixture of the isomeric *v*-triazolo[3,4-*a*]pyrimidinecarboxamides (9b) and (10b). The thermal conversion of the *v*-triazolopyrimidine (9a) into the isomer (10a) and its re-formation from the latter by heating with piperidine in ethanol constitutes a new type of reversible Dimroth rearrangement. The course of the reactions are discussed.

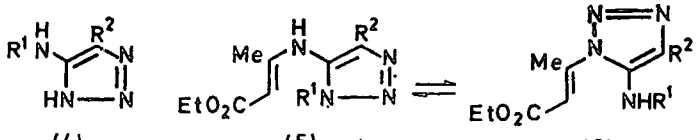
AZIDE–TETRAZOLE tautomerism [(1) ⇌ (2); X = N] and the attendant Dimroth-type rearrangements [(1) ⇌ (2) ⇌ (3); X = N] of fused tetrazoles are now well documented.[2] The analogous diazoalkylideneamine–triazole equilibrium has long been known for hydroxy-1,2,3-triazoles[3] and has been demonstrated recently for simple amino-1,2,3-triazoles[4] [*cf.* (1) ⇌ (2); X = CR]. Ring–Chain tautomerism of this type is almost certainly involved in the Dimroth rearrangements[5] of amino-



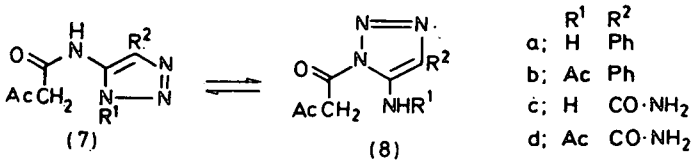
(1) (2) (3)

1,2,3-triazoles [*cf.* (1) ⇌ (2) ⇌ (3); X = CR] and in certain related processes.[6] So far, attempts[7] to detect equilibria of the type [(1) ⇌ (2); X = CR] in fused 1,2,3-triazoles have been unsuccessful. We now report further studies[1] of the synthesis and reactivity of the *v*-triazolo[3,4-*a*]pyrimidine ring system which were undertaken with the aim of demonstrating the hitherto unknown Dimroth-type rearrangement [(1) ⇌ (2) ⇌ (3); X = CR] in a fused 1,2,3-triazole.

Ethyl acetoacetate condensed readily with 5-amino-4-phenyl-1*H*-1,2,3-triazole (4a) in the presence of piperidine to give a product (X) which after drying at 140° and crystallisation, melted sharply and gave analytical data consistent with the molecular formula $C_{12}H_{10}N_4O$. The properties and transformations of this product are consistent with either of the possible *v*-triazolo[3,4-*a*]pyrimidine formulae (9a) or (10a). It showed broad i.r. absorption at 3100—2700 (>NH) and 1660 (>C=O) cm^{-1} attributable to a cyclic amide

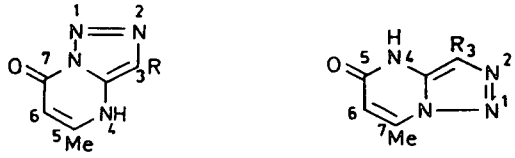


(4) (5) (6)

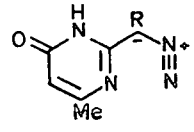


(7) (8)

a; R¹ = H, R² = Ph
b; R¹ = Ac, R² = Ph
c; R¹ = H, R² = CO·NH₂
d; R¹ = Ac, R² = CO·NH₂



(9) (10)



(11)

a; R = Ph
b; R = CO·NH₂

structure. The lack of diazo-absorption near 2000 cm^{-1} excludes the diazo-structure (11a). Its ^1H n.m.r. spectrum in [$^2H_6$]dimethyl sulphoxide contained a

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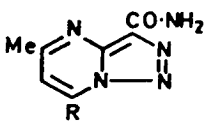
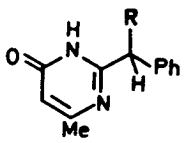
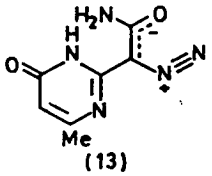


(12) R
a; Me
b; Ph



(14) R
a; H
b; OAc
c; $O_2C \cdot CF_3$
d; OH
e; Cl



(13)

poorly resolved quartet at τ 3·64 (1H) and a doublet at τ 7·31 (3H) in the ranges expected for H-6 and the exhibited an abundant fragment ion at $(M^+ - N_2)$ as well as a strong parent ion. Scission [1] in hot acetic acid or in acetic acid containing acetyl chloride gave the acetoxybenzylpyrimidine (14b) and the chlorobenzylpyrimidine (14e), respectively. Hydrogenolysis of both of these products yielded the known [9] 2-benzyl-6-methylpyrimidin-4(3*H*)-one (14a). Scission of the product (X) in trifluoroacetic acid occurred more slowly than for 5,7-dimethyl-3-phenyl-*v*-triazolo[3,4-*a*]pyrimidine.[1] Initially, the ^{1}H n.m.r. spectrum in trifluoroacetic acid (Table 1) shows a poorly resolved quartet at τ 3·07 (1H) and a doublet at τ 7·07 (3H) consistent with the presence of the ring-closed form (9a) or (10a). With time (Table 2) these signals diminish and are replaced by singlets at τ 2·79 (1H), 3·15 (1H), and 7·37 (3H) in the ranges expected [by analogy with the ^{1}H n.m.r. absorption of the acetoxybenzylpyrimidine (14b) (Table 2)] for H-5 and the benzylic and methyl protons of the trifluoroacetoxybenzylpyrimidine (14c). Ultimately (Table 2)

TABLE 1

^{1}H N.m.r. signals (τ) of *v*-triazolo[3,4-*a*]pyrimidines [a]

Compound	Solvent [b]	H-6	Me-5	Me-7	ArH	Others
(9a)	A	4·22	7·59			
(10a)	A	3·64 [c]		7·31 [d]	1·55—1·70 (m) [e]; 2·05—2·35 (m) [f]	
	B [g]	3·07 [c]		7·07 [d]	2·28 (m)	
(9b) [h]	A	4·16 [c,i]	7·58 [j]			1·94br [k]; 2·40br [k]
	B [l]	3·40 [c,m]	7·30 [j]			2·40br [k]
(10b) [h]	A	3·75 [c,i]		7·36 [n]		1·94br [k]; 2·40br [k]
	B	3·30 [j]		7·08 [j]		2·40br [k]
(12a) [o]	A	2·75	7·35	7·14		

[a] Signals were sharp singlets unless otherwise designated. [b] A, $(CD_3)_2SO$; B, $CF_3 \cdot CO_2H$. [c] Becomes a poorly resolved quartet on expansion to 100 Hz. [d] Becomes a doublet (*J* 1·1 Hz) on expansion to 100 Hz. [e] 2H. [f] 3H. [g] Spectrum in trifluoroacetic acid run immediately. [h] Part spectrum of the mixture of (9b) and (10b). [i] *J* 0·4—0·5 Hz. [j] Not resolved on expansion to 100 Hz. [k] NH. [l] Spectrum unchanged after 8 days at room temperature. [m] *J* 1·0 Hz. [n] Becomes a doublet (*J* 0·4—0·5 Hz) on expansion to 100 Hz. [o] Signals are 0·37 p.p.m. upfield from reported values (*cf.* ref. 1) owing to an error in the position of the lock signal in spectra recorded previously (*cf.* ref. 1).

TABLE 2

^{1}H N.m.r. signals (τ) of 2-substituted pyrimidines [a]

Compound	Solvent [b]	H-5	Me-6	Benzylic H	ArH	Others
(14a)	A	3·80	7·70	6·05	2·48—2·80 (m)	
	B	3·31	7·45	5·50	2·42—2·70 (m)	
(14b)	A	3·83	7·73 (d) [c]	3·53	2·30—2·50 (m) [d]; 2·50—2·72 (m)	7·76 [e]
	B	3·24	7·42 (d) [c]	2·86	2·42 (m)	7·59 [e]
(14c) [g,h]	B	3·15	7·37	2·79	2·23	
(14d)	B	2·75	6·36	2·26	1·46 (m)	
(14e)	A	3·77	7·68	4·13	2·30—2·47 (m) [d]; 2·53—2·70 (m) [f]	
	B	3·22	7·35	3·61	2·40br (m)	

[a] Signals were sharp singlets unless otherwise designated. [b] A, $CDCl_3$; B, $CF_3 \cdot CO_2H$. [c] *J* 0·8 Hz. [d] 2H. [e] OAc. [f] 3H. [g] Spectrum of compound (9a) run immediately, or of compound (10a) run after 2·0 h, in trifluoroacetic acid at room temperature. [h] After 48 h in trifluoroacetic acid, the spectrum becomes indentical with that of the alcohol (14d).

protons of the methyl group in (9a) or (10a) by analogy with *s*-triazolo[1,5-*a*]pyrimidines of closely related structure.[8] The presence of a fused 1,2,3-triazole nucleus is supported by the mass spectrum, which the spectrum becomes identical with that of the alcohol (14d) derived by alkaline hydrolysis of the acetoxy-compound (14b). Gradual contamination of the trifluoroacetic acid solution by atmospheric moisture accounts for the observed hydrolysis [(14c) ⟶ (14d)].

With the object of establishing the precise structure of the product (X) the unambiguous synthesis of structures

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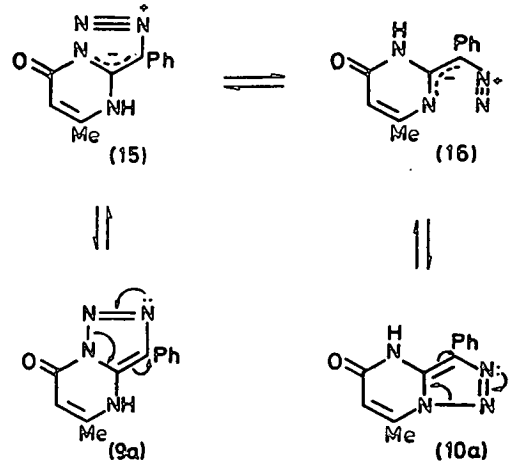
[9] A. Pinner, *Ber.*, 1889, **22**, 1612.

(9a) and (10a) by cyclisation of the condensates (5a) and (7a) was attempted. It has been shown [10] that condensation of an amino-1,2,4-triazole with the most electrophilic centre in a β-dicarbonyl compound under basic conditions involves initial attack at a ring N-atom, whereas mildly acidic media promote reaction at the primary amino-group. However, the general validity of these observations has been questioned.[11] In the present case, condensation of the amino-1,2,3-triazole (4a) with ethyl acetoacetate at room temperature under both basic and mildly acidic conditions yielded the same product, whose spectral properties are consistent with either of the vinylaminotriazole formulae (5a) or (6a). The former structure is established by the absence of a diazotisable centre and the formation of a monoacetyl derivative (5b) which shows i.r. carbonyl and ^{1}H n.m.r. absorption characteristic [5] of a 1,2,3-triazole ring *N*-acetyl group. Formation of the compound (5a) under basic conditions implies attack at the primary amino-group in preference to reaction at a ring N-atom and contrasts with the reported [10] behaviour of amino-1,2,4-triazoles. However, this apparent inconsistency in the reactivity of amino-1,2,3-triazoles is explained if initial attack at a ring N-atom to give (6a) is followed by base-catalysed Dimroth rearrangement [12] to the more stable isomer (5a).[5] The condensation of ethyl acetoacetate with the aminotriazole (4a) in refluxing toluene occurred between the ester group and the primary amino-group to afford the acetoacetylaminotriazole (7a). The side-chain position for the acetoacetyl group in this product is consistent with the absence of a diazotisable centre and the formation of a ring *N*-acetyl derivative (7b). The possibility of structural ambiguity due to the operation of Dimroth rearrangement [5] [*i.e.* (7a) ⇌ (8a) ⇌ (8b) or (7a) ⇌ (7b) ⇌ (8b)] concurrent with acetylation is excluded by the regeneration of the acetoacetylaminotriazole (7a) from the acetyl derivative (7b) by mild hydrolysis. Preferential condensation at the primary amino-group rather than at a ring N-atom is further demonstrated by the failure of the acetylaminotriazole (4b) [1] to condense with ethyl acetoacetate in refluxing toluene.

Both condensates (5a) and (7a) underwent piperidine-catalysed cyclisation to afford the same product, which, after purification, proved to be identical with the compound (X). This unexpected result is most readily explained in terms of Dimroth rearrangement prior to [(5a) ⇌ (6a) or (7a) ⇌ (8a)] or subsequent to [(9a) ⇌ (15) ⇌ (16) ⇌ (10a); *cf.* Scheme 1] cyclisation. Dissociation of either substrate (5a) or (7a) into the amino-1,2,3-triazole (4a) and ethyl acetoacetate (or an equivalent fragment) and subsequent recondensation at the alternative carbonyl centre in the latter is also a possible course (see later) which finds analogy in the condensation reactions of ethyl acetoacetate with aniline.[13] Rearrangement prior to cyclisation, though possible (see later), cannot be a major pathway since the formation of (X) by such a process would require the complete transformation under equilibrium conditions of one or other of the compounds (5a) or (7a) into the isomers (6a) or (8a), which are disfavoured on the grounds of lower stability (presence of an electron-withdrawing group on a ring N-atom [5]) and

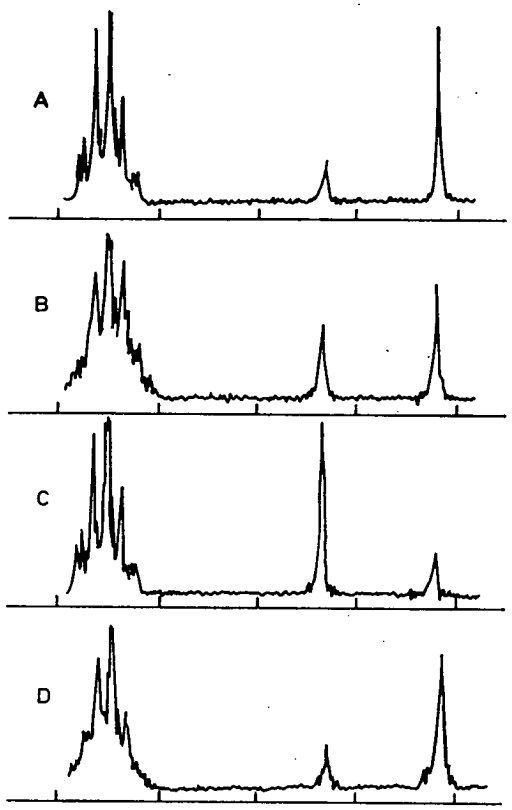


SCHEME 1

lower acidity (absence of triazole NH). However, the operation of rearrangement subsequent to cyclisation was revealed by a careful examination of the crude *v*-triazolopyrimidine product before purification. The ^{1}H n.m.r. spectrum in [$^2H_6$]dimethyl sulphoxide (Figure, A) of a sample *dried at room temperature* contained a poorly resolved quartet at τ 4·22 (1H) and a doublet at τ 7·59 (3H) at higher field than the proton resonances of H-6 and the methyl group in the pure compound (X), and attributable to a different species (Y). Compound (X) was also present to the extent of *ca.* 20% (as estimated from the integrated ratio of the H-6 signal in both species; *cf.* Figure, A), but increased in proportion (Figure, B) and ultimately became the predominant component (Figure, C) when the sample was heated at 140°. Attempted crystallisation of the impure sample of (Y) from ethanol also tended to promote the transformation (Y) → (X). On the other hand, heating for a short time with piperidine in ethanol reconverted the pure compound (X) mainly into compound (Y) (Figure, D), demonstrating the reversibility of the process (Y) ⇌ (X). The isomeric relationship of (Y) to (X) is supported by analytical and mass spectral data, and also by the reaction of (Y) with hot acetic acid or cold trifluoroacetic acid (*cf.* Tables 2 and 3) to afford the acetoxybenzyl- and trifluoroacetoxybenzyl-pyrimidines (14b and c), respectively. The interconversion of the compounds (X) and (Y) is most readily interpreted in terms of a new type of reversible Dimroth

[10] L. A. Williams, *J. Chem. Soc.*, 1961, 3046.
[11] E. C. Taylor and R. W. Hendess, *J. Amer. Chem. Soc.*, 1965, 87, 1980.
[12] E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, 1957, 22, 654.
[13] C. R. Hauser and G. A. Reynolds, *J. Amer. Chem. Soc.*, 1948, 70, 2402.

rearrangement [(9a) ⇌ (15) ⇌ (16) ⇌ (10a)] associated with a prototropic shift (*cf.* Scheme 1). The 7-oxo-structure (9a) is assigned to the base-stable isomer



^{1}H N.m.r. spectra of mixtures of (9a) and (10a) derived (a) by piperidine-catalysed condensation of ethyl acetoacetate with the aminotriazole (4a) followed by drying the product A, at room temperature; B, at 140° for 10 min; or C, at 140° for 60 min, or (b) by heating pure (10a) with ethanolic piperidine, followed by drying the product, D, at room temperature

[compound (Y)] in anticipation [10] of its greater acidity relative to the 5-oxo-isomer (10a). The assignment of the latter structure to the thermally stable isomer

TABLE 3

Triazole scission of the *v*-triazolo[3,4-*a*]pyrimidines (9a) and (10a) in trifluoroacetic acid at room temperature [a]

Substrate composition (%) [b]		Product composition (%) [c]		
(9a)	(10a)	(9a)	(10a)	(14c)
80	20	0	14—17	83—86
52	48	0	46	54
0	100	0	77	23

[a] Detected by the ^{1}H n.m.r. absorption at 100 MHz of a trifluoroacetic acid solution aged at room temperature for *ca.* 5 min. [b] Estimated from the integrated ratio of the Me-5 and Me-7 proton resonances of mixtures of (9a) and (10a), respectively. [c] Estimated from the integrated ratio of the Me-7 and Me-6 proton resonances of (10a) and (14c), respectively.

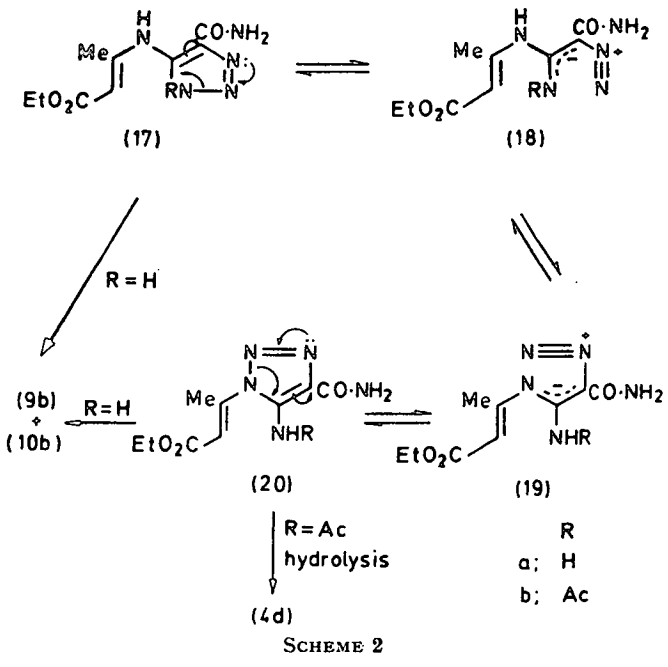
[compound (X)] is in accord with the expected [8] lower field position for the proton resonances of H-6 and the C-7 methyl group compared with those in the 7-oxo-structure (9a). The ^{1}H n.m.r. spectrum of impure (9a) in trifluoroacetic acid (Tables 2 and 3) shows immediate ring-opening to the trifluoroacetoxypyrimidine (14c), whereas scission of the contaminant (10a) occurs much more slowly. The greater rate of scission in the case of (9a) can be attributed to the greater destabilisation inherent in the direct attachment of a carbonyl group to a triazole ring N-atom and further supports the structures assigned to (9a) and (10a).

Piperidine in ethanol also catalysed the condensation of ethyl acetoacetate with the amino-1,2,3-triazolecarboxamide (4c). The product gave analytical and mass spectral data consistent with the formula $C_7H_7N_5O_2$ and showed i.r. absorption at 3350—3200 (>NH) and 1670 (>C=O) cm^{-1} in accord with either of the expected *v*-triazolo[3,4-*a*]pyrimidinecarboxamide structures (9b) and (10b). However, the ^{1}H n.m.r. spectrum in [$^2H_6$]-dimethyl sulphoxide showed poorly resolved quartets at τ 3·75 and 4·16 (each 1H) and a singlet and a doublet at τ 7·36 and 7·58 (each 3H) consistent with the presence of *both* isomers (9b) and (10b). Attempts to separate the mixture were unsuccessful. The isomer mixture was also formed when the amide (4c) was heated with ethyl acetoacetate in glacial acetic acid alone or in the presence of dimethylformamide. The acetylaminotriazolecarboxamide (4d) was a by-product of the former reaction. The lack of triazole scission under these conditions is in accord with the stabilising effect of the carboxamide group,[1] which also accounts for the stability of the isomer mixture to prolonged treatment with acetic and trifluoroacetic acids. The relative stability of the structures (9b) and (10b) to nitrogen loss is also demonstrated by the mass spectrum of the isomer mixture, which contains a strong molecular ion but lacks a fragment ion corresponding to ($M^+ - N_2$). Instead, the primary fragmentation process corresponds to the formation of an ion ($M^+ - 83$). The mass spectra of the *v*-triazolopyrimidine carboxamides (12a and b) [1] show similar primary fragment ions which may be formed by H-atom transfer and loss of the side-chain in radical cations derived from ring-opened structures of the type (13).

The inertness of the structures (9b) and (10b) to triazole scission implies a reluctance to undergo the ring opening [*cf.* Scheme 1; (9a; CO·NH$_2$ for Ph) ⇌ (15; CO·NH$_2$ for Ph)], which is a prerequisite of Dimroth rearrangement [(9b) ⇌ (10b)]. It was anticipated therefore, that the specific cyclisation of the condensates (5c) and (7c) to the structures (9b) and (10b) would be uncomplicated by their subsequent interconversion and so should provide a means for their unambiguous synthesis. Attempts to condense the amide (4c) with ethyl acetoacetate alone or in refluxing toluene either failed or gave the isomer mixture, thereby precluding the study of the acetoacetylaminotriazolecarboxamide (7c). In contrast, condensation of the amide (4c) with ethyl acetoacetate occurred smoothly in dimethylformamide at room temperature to give the vinylaminotriazole (5c), which was isolated as the hydrate. The structure of this product follows from its spectral properties and

from its conversion by acetylation into a ring *N*-acetyl derivative (5d). The attempted reconversion of this derivative by mild hydrolysis into the parent vinylaminotriazole (5c) resulted in complete degradation to the amide (4c). The structure (5c) is further supported by the failure of the acetylaminotriazole (4d) to condense with ethyl acetoacetate in the presence of acetic acid, demonstrating preferential attack on the primary amino-group under these conditions.[10]

Heating the vinylaminotriazole (5c) with piperidine in ethanol afforded not the single isomer (9b) but, contrary to expectations, the isomer mixture [(9b) + (10b)]. The isomer mixture was also the product when the compounds (5c and d) were heated under reflux with glacial acetic acid or when they were left in contact with cold aqueous alkali for a short time. Since Dimroth rearrangement before and after cyclisation is unlikely (see before), the formation of the isomer



SCHEME 2

mixture from the compound (5c) is most readily explained by a course involving dissociation–recombination (see before). Support for a dissociation–recombination mechanism is provided by reaction of the compound (5c) with acetylacetone alone, or in the presence of piperidine or glacial acetic acid, to give 5,7-dimethyl-*v*-triazolo[3,4-*a*]pyrimidine-3-carboxamide (12a),[1] which was also formed when the aminotriazolecarboxamide (4c) was heated in neat acetylacetone. The synthesis of (12a) from the amide (4c) and acetylacetone in piperidine–ethanol or acetic acid has already been described.[1] On the other hand, the observed formation of the isomer mixture from (5c) in the melt is difficult to reconcile with such a mechanism and indicates that rearrangement may become possible at elevated temperatures. Support for the operation of Dimroth rearrangement prior to cyclisation (*cf.* Scheme 2; R = H) under thermal conditions is provided by the conversion of the *pure* compound (5c) in refluxing toluene into a mixture of the starting compound and a component whose ^{1}H n.m.r. absorption is consistent with the isomeric structure (6c). Significantly, the observed ratio of (5c) to (6c) corresponds within experimental error to the proportions of (9b) and (10b) in the isomer mixture. The operation of a similar rearrangement process [(17b) ⇌ (18b) ⇌ (19b) ⇌ (20b)] before hydrolysis [(20b) ⇌ (4d)] provides a rationale for the conversion of the acetyl derivative (5d) in warm aqueous ethanol into a mixture of the acetamidotriazole (4d) and the parent amide (4c). However, in this case the acetyl group may play a crucial role [5] in promoting rearrangement.

EXPERIMENTAL

I.r. and u.v. spectra were recorded for Nujol suspensions and ethanolic solutions, respectively, with Unicam SP 200 and SP 800 instruments. N.m.r. spectra were measured at 100 MHz for solutions in deuteriochloroform, [$^2H_6$]dimethyl sulphoxide, or trifluoroacetic acid, at 28°, with tetramethylsilane as internal standard, with a Varian HA 100 instrument. Mass spectra were recorded at 70 eV and 150° (probe temperature) with an A.E.I. MS 902 spectrometer.

Light petroleum had b.p. 60—80°.

*5-Amino- and 5-Acetamido-*1H-1,2,3-*triazoles* (4).—5-Amino-4-phenyl-1*H*-1,2,3-triazole (4a) and 5-amino-1*H*-1,2,3-triazole-4-carboxamide (4c) were prepared as described previously.[1]

Heating the aminotriazolecarboxamide (4c) in glacial acetic acid gave the acetic acid solvate ☆ of the monoacetyl compound (4d), m.p. 269—272° (from glacial acetic acid), $\nu_{max.}$ 3350, 3200br, and 2700br (OH, NH), 1710, and 1690 (CO), and 1670 cm^{-1}, τ [$(CD_3)_2SO$] −0·05br (1H, s, OH), 2·16br (1H, s, NH), 2·47 (1H, s, NH), 7·84 (3H, s, Ac), and 8·10 (3H, s, Ac), which was converted by crystallisation from water into the acetamidotriazolecarboxamide (4d), m.p. 270—273° (lit.,[14] 268°), $\nu_{max.}$ 3400, 3250, and 3100 (NH), and 1680 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2·18br (1H, s, NH), 2·49br (1H, s, NH), and 7·84 (3H, s, Ac).

*5-(2-Ethoxycarbonyl-1-methylvinylamino)-4-phenyl-*1H-1,2,3-*triazole* (5a).—(*a*) A solution of the aminotriazole (4a) (4·8 g, 0·03 mol) and ethyl acetoacetate (4·3 g, 4·2 ml, 0·033 mol) in anhydrous benzene (250 ml) was heated under reflux with glacial acetic acid (0·5 ml) for 18 h. Evaporation of the mixture gave an oil which afforded the solid product (5a) (5·6 g) in contact with benzene–light petroleum.

(*b*) The *vinylaminotriazole* (5a) was also formed (0·4 g) by heating a mixture of the aminotriazole (4a) (0·4 g, 0·0025 mol) and ethyl acetoacetate (0·7 g, 0·7 ml, 0·0054 mol) under reflux (24 h) with a solution of sodium (0·23 g) in absolute ethanol (10·0 ml). The mixture was evaporated, treated with water and dilute aqueous sulphuric acid, and neutralised with aqueous ammonia. The product had m.p. 123° (from benzene–light petroleum), $\nu_{max.}$ 3200 (NH), 1640 (CO), and 1620br (C=C) cm^{-1}, τ ($CDCl_3$) 2·13—2·28 (2H, m, ArH), 2·45—2·75 (3H, m, ArH), 5·17 (1H, d, *J* 0·8 Hz, olefinic CH), 5·80 (2H, q, *J* 7 Hz, CH_2), 8·01 (3H, d, *J* 0·8 Hz, Me), and 8·71 (3H, t, *J* 7 Hz, Me) (Found: C, 61·7; H, 5·8; N, 20·5%; M^+, 272. $C_{14}H_{16}N_4O_2$ requires

☆ This product was formulated previously (*cf.* ref. 1) as a diacetyl derivative.

[14] L. L. Bennett and H. T. Baker, *J. Org. Chem.*, 1957, **22**, 707.

C, 61·8; H, 5·9; N, 20·6%; *M*, 272), and was converted by heating under reflux (15 min) with acetic anhydride into the *acetyl derivative* (5b) (96%), m.p. 115° (from benzene–light petroleum), $\nu_{max.}$ 3150 (NH), 1735 and 1665 (CO), and 1640 (C=C) cm^{-1}, τ ($CDCl_3$) 2·05—2·15 (2H, m, ArH), 2·35—2·50 (3H, m, ArH), 5·05 (1H, s, olefinic CH), 5·85 (2H, q, *J* 7 Hz, CH_2), 7·23 (3H, s, Ac), 7·60 (3H, s, Me), and 8·75 (3H, t, *J* 7 Hz, Me) (Found: C, 61·0; H, 5·7; N, 18·0. $C_{16}H_{18}N_4O_3$ requires C, 61·1; H, 5·7; N, 17·8%).

5-(2-Ethoxycarbonyl-1-methylvinylamino)-1H-1,2,3-triazole-4-carboxamide (5c).—A mixture of the amide (4c) (1·3 g, 0·01 mol) and ethyl acetoacetate (1·5 g, 1·5 ml, 0·011 mol) in dimethylformamide (7·0 ml) containing glacial acetic acid (1·0 ml) was stirred at room temperature for 16 h. The mixture was diluted with water (10·0 ml) and the precipitated solid was combined with a second crop obtained by evaporating the mother liquor and treatment with water, washed with ether, and crystallised to afford the *hydrate* of the vinylaminotriazole amide (5c) (1·4 g), m.p. 175° (from ethanol), $\nu_{max.}$ 3450, 3375, and 3150 (NH), 1660br (CO), and 1610 (C=C) cm^{-1}, τ [$(CD_3)_2SO$] 2·24br (1H, s, NH), 2·56br (1H, s, NH), 5·22 (1H, s, olefinic CH), 5·93 (2H, q, *J* 7 Hz, CH_2), 7·68 (3H, s, Me), and 8·82 (3H, t, *J* 7 Hz, Me) (M^+, 239. $C_9H_{13}N_5O_3$ requires *M*, 239) (Found: C, 42·0; H, 5·7; N, 27·7. $C_9H_{13}N_5O_3,H_2O$ requires C, 42·0; H, 5·8; N, 27·2%), which formed a sparingly soluble salt in dilute aqueous sodium hydroxide and was recovered unchanged on acidification. The hydrate of (5c) was converted in hot acetic anhydride into the *acetyl derivative* (5d) (83%), m.p. 196° (from ethyl acetate), $\nu_{max.}$ 3400, 3250, and 3200 (NH), and 1770, 1690, and 1670 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 1·78br (1H, s, NH), 2·16br (1H, s, NH), 5·07 (1H, s, olefinic CH), 5·90 (2H, q, *J* 7 Hz, CH_2), 6·70 (3H, s, Me), 7·29 (3H, s, Ac), and 8·80 (3H, t, *J* 7 Hz, Me) (Found: C, 47·3; H, 5·3; N, 25·2. $C_{11}H_{15}N_5O_4$ requires C, 47·0; H, 5·3; N, 24·9%).

Heating the compound (5c) (0·48 g, 0·002 mol) under reflux in toluene (300 ml) for 2 or 18 h, followed by evaporation of the solution gave a solid (0·41 g) whose ^{1}H n.m.r. spectrum, τ [$(CD_3)_2SO$] 2·24br (s, NH), 2·56br (s, NH), 3·65 [s, olefinic CH of (6c)] 4·20br (s, NH), 5·20 [s, olefinic CH of (5c)], 5·91 [dq, overlapping CH_2 of (5c) and (6c)], 7·59 [s, olefinic Me of (6c)], 7·66 [s, olefinic Me of (5c)], and 8·80 [dt, overlapping Me of (5c) and (6c)], was consistent with a mixture of (5c) (80%) and (6c) (20%). Attempts to separate the mixture by fractional crystallisation or chromatography were unsuccessful.

The acetyl derivative (5d) (0·14 g) slowly dissolved when it was stirred at room temperature with a mixture of aqueous N-sulphuric acid (3·0 ml) and ethanol (5·0 ml). After 1 h the ethanol was evaporated off under reduced pressure at room temperature, and the solution filtered. The aqueous mother liquor was adjusted to pH 7 to afford the amide (4c) (0·03 g), m.p. 223° (from water), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[1]

The compound (5d) (0·28 g) was heated under reflux in aqueous 75% w/v ethanol (10·0 ml) for 10 min. Concentration and dilution with water gave the acetamidotriazole (4d) (0·1 g), m.p. and mixed m.p. 270—273° (decomp.), identical (i.r. and ^{1}H n.m.r. spectra) with a sample prepared before. The colourless solid isolated by evaporating the aqueous filtrate was crystallised to yield the triazolecarboxamide (4c) (0·06 g), identified by comparison (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.[1]

The amide (4d) (0·84 g, 0·0055 mol) was stirred with ethyl acetoacetate (0·72 g, 0·7 ml, 0·0055 mol) and glacial acetic acid (0·5 ml) in dimethylformamide (7·5 ml) at room temperature for 17 h. The mixture was evaporated and treated with water to give unchanged amide (4d) (77%).

5-Acetoacetamido-4-phenyl-1H-1,2,3-triazole (7a).—A mixture of the aminotriazole (4a) (3·2 g, 0·02 mol) and ethyl acetoacetate (2·6 g, 2·5 ml, 0·02 mol) in anhydrous toluene (500 ml) was heated under reflux for 7 h. The ethanol formed was allowed to distill through a short Vigreux column. The solution was concentrated to 250 ml and cooled, and the solid was collected, combined with a second crop obtained by evaporating the mother liquors, and crystallised to yield the *acetoacetamidotriazole* (7a) (3·1 g), m.p. 161° (from benzene–ethanol), $\nu_{max.}$ 3150 and 3050 (NH), and 1695 (CO) cm^{-1}, τ ($CDCl_3$) 2·51—2·85 (5H, m, ArH), 6·25 (2H, s, CH_2), and 7·65 (3H, s, Me) (Found: C, 58·9; N, 4·9; N, 23·1%; M^+, 244. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 4·9; N, 23·0%; *M*, 244), which was converted in hot acetic anhydride into the *acetyl derivative* (7b) (90%), m.p. 182° (from benzene–light petroleum), $\nu_{max.}$ 3150 (NH), 1750, 1720, and 1680 (CO) cm^{-1}, τ ($CDCl_3$) 2·15—2·35 (2H, m, ArH), 2·42—2·62 (3H, m, ArH), 6·28 (2H, s, CH_2), 7·20 (3H, s, Ac), and 7·68 (3H, s, Ac) (Found: C, 59·0; H, 5·1; N, 20·3. $C_{14}H_{14}N_4O_3$ requires C, 58·7; H, 4·9; N, 19·6%). Hydrolysis of the compound (7b) by heating under reflux (0·5 h) with aqueous 10% w/v sodium hydroxide, and careful neutralisation with aqueous dilute sulphuric acid, gave the parent triazole (7a) (50%).

The triazole derivatives (4b) and (4c), heated under reflux with ethyl acetoacetate in anhydrous toluene as described before, were recovered unchanged (93—97%).

5-Methyl-3-phenyl-v-triazolo[3,4-a]pyrimidin-7(4H)-one (9a) *and 7-Methyl-3-phenyl-v-triazolo[3,4-a]pyrimidin-5(4H)-one* (10a).—(*a*) The amino-1,2,3-triazole (4a) (3·2 g, 0·02 mol) and ethyl acetoacetate (2·9 g, 2·8 ml, 0·022 mol) were heated under reflux with piperidine (0·5 ml) in ethanol (70·0 ml) for 27 h. Alternatively (*b*) the triazole derivative (5a) or (7a) (0·001 mol) was heated under reflux with piperidine (0·25 ml) in ethanol (10·0 ml) for 24 h. The gum obtained by evaporating the mixture was dissolved in warm water and acidified with dilute aqueous sulphuric acid. After drying *in vacuo* at room temperature, the ^{1}H n.m.r. spectrum [$(CD_3)_2SO$] (Figure, A) of the solid obtained (80—90%) showed it to be a mixture of the *v*-triazolopyrimidines (9a) (80%) and (10a) (20%), m.p. 232—234°, $\nu_{max.}$ 3100sh and 2700sh (NH), and 1660br (CO) cm^{-1} (Found: C, 63·8; H, 4·5; N, 24·7%; M^+, 226. $C_{12}H_{10}N_4O$ requires C, 63·7; H, 4·4; N, 24·8%; *M*, 226). Heating this solid at 140° for 2·0 h followed by crystallisation from ethanol gave the pure *v-triazolo[3,4-a]pyrimidine* (10a) (quant.), m.p. 240° (from ethanol), $\nu_{max.}$ 3150sh and 2700sh (NH), and 1665br (CO) cm^{-1}, $\lambda_{max.}$ 210, 243, 250sh, 276infl, 294infl, and 325 nm (log ε 4·22, 4·30, 4·28, 3·94, 3·62, and 3·39), *m/e* 226 (48%, M^+) and 198 (68, $M^+ - N_2$) (^{1}H n.m.r. data are shown in Table 1 and the Figure) (Found: C, 63·6; H, 4·5; N, 24·9. $C_{12}H_{10}N_4O$ requires C, 63·7; H, 4·4; N, 24·8%), which was reconverted into the isomer mixture of (9a) (80%) and (10a) (20%) (quant.) by heating with piperidine in ethanol and work-up as described before.

2-(α-Acetoxybenzyl)-6-methylpyrimidin-4(3H)-one (14b).—(*a*) A mixture of the aminotriazole (4a) (0·4 g) and ethyl acetoacetate (0·39 g, 0·38 ml) was heated under reflux in glacial acetic acid (5·0 ml) for 14 h. Alternatively (*b*) the *v*-triazolo[3,4-*a*]pyrimidine (10a) or the isomer mixture containing predominantly (9a) (see before) (0·0025 mol)

was heated under reflux in glacial acetic acid (25·0 ml) for 4 h. Evaporation gave a gum which was triturated with ether–light petroleum to yield the solid *acetoxybenzylpyrimidine* (14b) (60—90%), m.p. 187° (from benzene–light petroleum), $\nu_{max.}$ 3100sh and 2700sh (NH), and 1745 and 1660 (CO) cm^{-1} (^1H n.m.r. data in Table 2) (Found: C, 65·0; H, 5·8; N, 10·9. $C_{14}H_{14}N_2O_3$ requires C, 65·1; H, 5·4; N, 10·9%).

When reaction (*a*) was carried out for 3·5 h, the product was the acetamidotriazole (4b) (82%), m.p. 204° (from benzene–ethanol), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[1]

2-(α-*Hydroxybenzyl*)-6-*methylpyrimidin*-4(3H)-*one* (14d).—The acetoxybenzylpyrimidine (14b) (0·8 g) was heated under reflux with aqueous 10% w/v sodium hydroxide (5·0 ml) in ethanol (20·0 ml) for 30 min. Evaporation of the mixture gave a gum which was dissolved in water, acidified (aqueous dilute sulphuric acid), and adjusted to pH 7 with solid sodium hydrogen carbonate. The solid *alcohol* (14d) was collected and crystallised (0·56 g), m.p. 199° (from benzene–light petroleum), $\nu_{max.}$ 3400, 3150, and 2750 (NH), and 1665 (CO) cm^{-1} (^1H n.m.r. data in Table 2) (Found: C, 66·4; H, 5·7; N, 13·3. $C_{12}H_{12}N_2O_2$ requires C, 66·7; H, 5·6; N, 13·0%).

2-(α-*Chlorobenzyl*)-6-*methylpyrimidin*-4(3H)-*one* (14e).—The *v*-triazolopyrimidine (10a) or the isomer mixture in which (9a) predominates (0·004 mol) was heated under reflux with a mixture of acetyl chloride (30·0 ml) and glacial acetic acid (10·0 ml) for 1·75 h. Evaporation gave an oil which afforded the solid *chlorobenzylpyrimidine* (14e) in contact with benzene–light petroleum (61%), m.p. 194° (from ethanol), $\nu_{max.}$ 3200sh and 2750sh (NH) and 1680 (CO) cm^{-1} (^1H n.m.r. data in Table 2) (Found: C, 61·6; H, 4·9; N, 12·2. $C_{12}H_{11}ClN_2O$ requires C, 61·3; H, 4·7; N, 11·9%).

2-*Benzyl*-6-*methylpyrimidin*-4(3H)-*one* (14a).—The pyrimidine derivative (14b) or (14e) (0·001 mol), hydrogenolysed in ethanol over 10% palladium–charcoal, gave 2-benzyl-6-methylpyrimidin-4(3*H*)-one (14a) (62—82%), m.p. 175° (from water), $\nu_{max.}$ 3050sh and 2700sh (NH) and 1680 (CO) cm^{-1}, identical (mixed m.p. and i.r. spectrum) with an authentic sample.[9]

4,7-*Dihydro*-5-*methyl*-7-*oxo*-v-*triazolo*[3,4-a]*pyrimidine*-3-*carboxamide* (9b) *and* 4,5-*Dihydro*-7-*methyl*-5-*oxo*-v-*triazolo*-[3,4-a]*pyrimidine*-3-*carboxamide* (10b).—The isomer mixture (9b) and (10b) was formed (60—90%), (*a*) when the vinylaminotriazole (5c) (12·0 g, 0·05 mol) or a mixture of the aminotriazolecarboxamide (4c) (6·4 g, 0·05 mol) and ethyl acetoacetate (7·0 g, 6·8 ml, 0·054 mol) was heated under reflux with piperidine (2·5 ml) in ethanol (600 ml) for 24 h, or in glacial acetic acid (200 ml) for 4 h, and the mixture then evaporated and treated with aqueous dilute sulphuric acid or water, (*b*) when the vinylaminotriazole (5c) or (5d) (0·0005 mol) was stirred at room temperature for 5 min in aqueous N-sodium hydroxide (1·0 ml), and the solution obtained acidified (aqueous dilute sulphuric acid), (*c*) when the amide (4c) (0·32 g) and ethyl acetoacetate (0·4 g, 0·39 ml) were heated under reflux in dimethylformamide (4·0 ml) containing glacial acetic acid (0·25 ml) for 1·5 h, and the mixture was evaporated and treated with water, (*d*) when a mixture of the amide (4c) (0·64 g) and ethyl acetoacetate (15·0 ml) was heated under reflux for 4 h, concentrated, and diluted with ether, or (*e*) when the ethylideneaminotriazole (5c) (0·1 g) was melted at 180° on a Kofler block, and the solid which crystallised in the melt was purified. The isomer mixture had the composition (9b) (72%), (10b) (28%) as estimated from the integrated ratio of the H-6 signal in the ^1H n.m.r. spectrum (Table 1) of the mixture in [$^2H_6$]dimethyl sulphoxide; m.p. 274—275° (from glacial acetic acid–ethanol), $\nu_{max.}$ 3350, 3250br, and 3200br (NH), 1670 (CO), and 1640 (NH def.) cm^{-1}, $\lambda_{max.}$ 210, 243, 250sh, 276infl, 294infl, and 325 nm (log ε 4·22, 4·30, 4·28, 3·94, 3·62, and 3·39), *m/e* 193 (75%, M^+) and 110 (75, $M^+ - 83$) (Found: C, 43·4; H, 3·6; N, 36·4. Calc. for $C_7H_7N_5O_2$: C, 43·5; H, 3·7; N, 36·3%). The mixture was unchanged (m.p., and i.r. and ^1H n.m.r. spectra) after heating under reflux with glacial acetic acid or ethanolic piperidine for 8 days.

Evaporation of the aqueous filtrate from the acetic acid-catalysed reaction of the compound (5c) in (*a*) gave a solid which was crystallised to afford the triazole amide (4c) (21%).

The solution obtained by heating the acetyl compound (5d) (0·28 g) under reflux (3 h) in glacial acetic acid (5·0 ml), on cooling deposited the acetamidotriazole (4d) (80%), identical (m.p., mixed m.p., and i.r. spectrum) with an authentic sample. Evaporation of the acetic acid mother liquor and treatment with ether gave the isomer mixture of (9b) and (10b) (0·05 g).

5,7-*Dimethyl*-v-*triazolo*[3,4-a]*pyrimidine*-3-*carboxamide* (12a).—(*a*) The aminotriazolecarboxamide (4c) (0·64 g, 0·005 mol) was heated under reflux in acetylacetone (15·0 ml) for 2·5 h. The mixture was cooled and the precipitated solid was combined with a second crop obtained by evaporating the filtrate and treatment with ether to give the *v*-triazolo[3,4-*a*]pyrimidine (12a) (0·91 g).

(*b*) The vinylaminotriazole (5c) (3·0 g, 0·0125 mol) was heated under reflux with acetylacetone (5·0 g, 5·2 ml, 0·05 mol) in glacial acetic acid (50·0 ml) for 4 h. Evaporation of the mixture gave a solid which was treated with water and ether, washed (ethanol then ether), and dried to give the product (12a) (0·73 g).

(*c*) The vinylaminotriazole (5c) (0·6 g, 0·0025 mol) was heated under reflux in acetylacetone (8·0 ml) for 4 h, or with acetylacetone (1·02 g, 1·0 ml, 0·01 mol) in the presence of piperidine (0·6 ml) in ethanol (25·0 ml) for 24 h. The mixture was evaporated and treated with ether, and the resulting solid (0·28—0·35 g) was suspended in water (3·0 ml), treated with piperidine (0·25 ml), and filtered off to yield the *v*-triazolopyrimidine (12a) (0·11—0·23 g). Acidification of the aqueous filtrate with aqueous dilute sulphuric acid gave the isomer mixture of (9b) and (10b) (0·08—0·17 g), identified by comparison (m.p., and i.r. and ^1H n.m.r. spectra) with a sample prepared before.

The *v*-triazolopyrimidine (12a) had m.p. 265° (from ethanol–acetic acid), *m/e* 191 (55%, M^+) and 108 (100, $M^+ - 83$) (^1H n.m.r. data in Table 1), and was identified by comparison (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.[1]

Mass Spectral Data for v-*Triazolo*[3,4-a]*pyrimidines*.—The *v*-triazolopyrimidine (12a; Ph for $CO{\cdot}NH_2$) had *m/e* 224 (28%, M^+) and 196 (100, $M^+ - N_2$); compound (12b) had *m/e* 253 (100%, M^+) and 170 (100, $M^+ - 83$).

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