STUDIES IN ELECTROCYCLIC AROMATIC SUBSTITUTION BY THE DIAZO GROUP

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Dedication

To my wife Christian for her love, encouragement and patience and to my parents for all their help.

Acknowledgements

I would like to thank Dr. J.T. Sharp for his interest and encouragement, and for many stimulating discussions during the course of this work. The technical assistance of Messrs. T. Naisby, D. Thomas, J. Millar and J. Grunbaum and Mrs. J. McPherson has been invaluable and I am also indebted to Mrs. J. Gorrie for typing the manuscript.

Finally, I would like to thank Professor J.I.G. Cadogan for the use of laboratory facilities, and the Science Research Council for providing a grant.

Declaration

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

Post-Graduate Lectures

I declare that I have attended the following lectures etc., during the course of this research.

Organic Phosphorus Compounds in General Synthesis
by Prof. J.I.G. Cadogan and Dr. I. Gosney.

Organic Sulphur Compounds in General Synthesis
by Dr. D. Leaver

Chemistry at its most Colourful
by Staff of the Research Department,
I.C.I. Blackley.

The Encouragement and Exploitation of Inventiveness in the Oil Industry
by Mr. D.H. Desty and colleagues from B.P.

From Crawford to Kemball - 260 years a-growing
by Dr. W.P. Doyle

Edinburgh University Chemistry Department Seminars

Science Research Council Summer School

Abstract

This Thesis is concerned with the synthesis of 1,2-benzo- and 1,2-thienodiazepines by electrocyclic aromatic substitution reactions of the diazo group. The diazoalkenes were produced in aprotic solvent by the thermal decomposition of the sodium salts of the tosylhydrazones of α,β-unsaturated ketones.

The effect of substituents, in the aryl rings, on the product ratio obtained from the decomposition of 2-(diaryl-methylene)cyclopentanone tosylhydrazone sodium salts has been examined. The mechanism by which 1,2-benzodiazepines are formed in this reaction is discussed with reference to the effect of substituents and to the results of some deuterium labelling experiments.

The difference in the reactivity of the benzene and thiophene rings to substitution and the effect of steric constraints on the courses of these reactions is discussed.

Abstract

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INTRODUCTION

Diazoalkanes

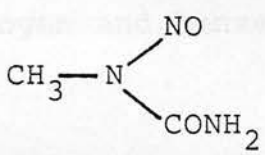
The first diazoalkane was prepared by Curtius[1] in 1883 by dissolving the ethyl ester of glycine, or its hydrochloride, in water and adding sodium nitrite, sulphuric acid and ether. On shaking, the diazo compound dissolved in the ether layer and was separated.

$$C_2H_5CO_2\text{-}CH_2\text{-}\overset{+}{N}H_3\overset{-}{Cl} \xrightarrow[H_2SO_4]{NaNO_2} C_2H_5OCO\text{-}CH{=}N_2$$

In the last forty years there has been renewed interest in diazoalkanes because they are one of the most important sources of carbenes. Diazoalkanes can also act as 1,3-dipoles and can be used to prepare heterocyclic systems such as pyrazolines, pyrazoles and diazepines. The chemistry of diazoalkanes has been reviewed.[2,3]

Synthesis

The classical methods of preparation of diazoalkanes involve treatment of a nitroso compound of the general formula $R.CH_2.N(NO).X$, with a suitable base to yield the diazoalkane $R.CH.N_2$. For example diazomethane is readily prepared by treating N-nitroso-N-methylurea (1) with base.[4]

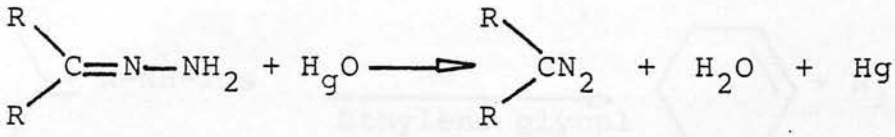


$$+ \; KOH \longrightarrow CH_2N_2 + KOCN + 2H_2O$$

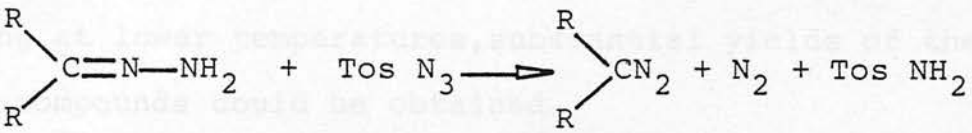
(1)

The original method of Curtius[1], namely the diazotisation of amines, requires a strongly electron-withdrawing substituent on the α-carbon atom of the amine and also an α-hydrogen.

Disubstituted diazo compounds can be prepared by the oxidation of ketone hydrazones with a variety of reagents including manganese dioxide,[5] lead tetra-acetate[6] and mercuric oxide.[7]



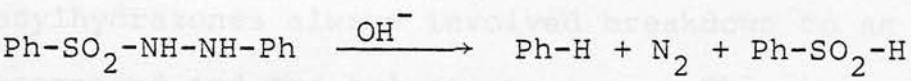
Hydrazones can be converted into diazoalkanes by treatment with toluene-p-sulphonyl azide.[8]



Diazoalkanes may also be prepared from tosylhydrazones by treatment with alkali. Since this is the method used in this research a more detailed account will be given.

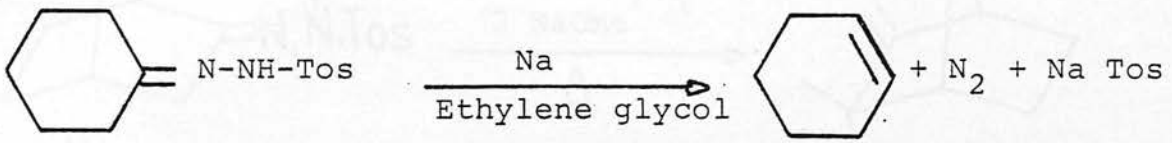
Base Induced Decompositions of Tosylhydrazones

In 1885, Escales[9] found that benzenesulphonylphenyl-hydrazide (2) was decomposed by warm alkali to give benzene, nitrogen and benzenesulphinic acid.



(2)

This led Bamford and Stevens[10] to investigate the possibility of olefin formation from the tosyhydrazones of readily enolisable ketones. This met with very limited success, but when they tried tosylhydrazones of non-readily enolisable ketones they obtained olefins in high yield. For example, cyclohexanone tosylhydrazone (3), when heated with a solution of sodium in ethylene glycol, produced cyclohexene quantitatively.



(3)

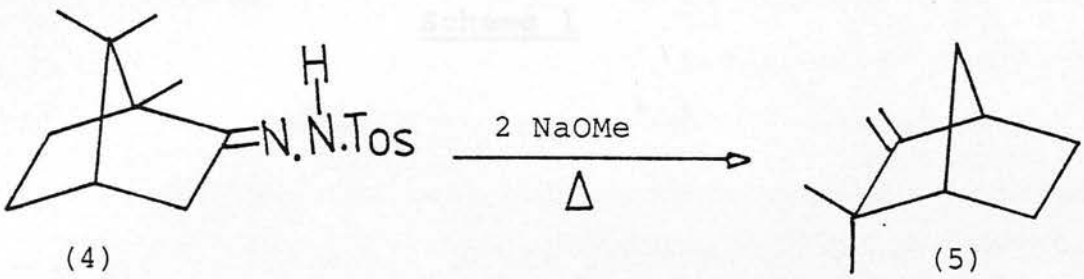
Tosylhydrazones of aromatic aldehydes and ketones gave diazo-compounds or products of their decomposition. By working at lower temperatures, substantial yields of the diazo-compounds could be obtained.

The mechanism of the decomposition has been intensively studied, and has been shown to depend on a large number of factors, including the ability of the solvent to donate and accept protons, the nature and concentration of the base, the presence of metal cations and the structural constraints on the substrate.

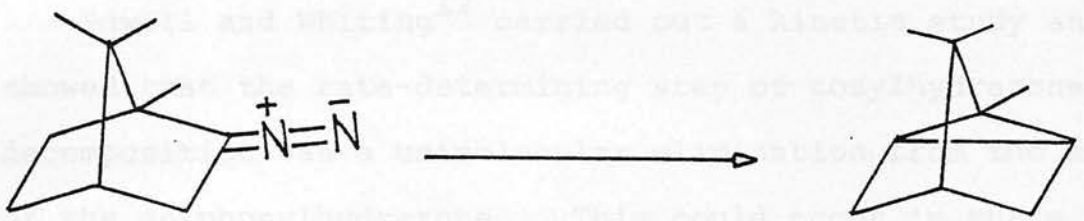
Effect of Solvent Polarity

In their original paper, Bamford and Stevens[10] ruled out the possibility that the mechanism of the decomposition of the tosylhydrazones always involved breakdown to an aliphatic diazo-compound and the sulphinate ion. This they concluded

from the fact that camphor tosylhydrazone (4) decomposed to give optically active camphene (5), which could not occur via diazocamphane (6) since Heubaum and Noyes[11] had previously shown that (6) decomposed to give tricyclene (7) and a subsequent isomerisation of this symmetrical hydrocarbon could not have led to the optically active camphene isolated.

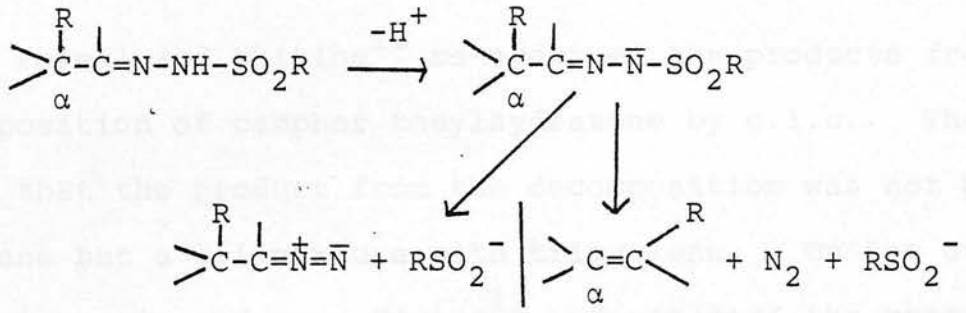


(4) (5)



(6) (7)

Bamford and Stevens suggested that the mechanism involved the removal of a proton with the formation of a negative charge on the adjacent nitrogen atom. This led to the release of the sulphinate anion and the rest of the molecule either remained intact as the diazo compound or underwent fission to give an olefin and nitrogen, with concomitant migration of one of the groups attached to C(α) (Scheme 1).



Scheme 1

Powell and Whiting[12] carried out a kinetic study and showed that the rate-determining step of tosylhydrazone decomposition was a unimolecular elimination from the anion of the sulphonylhydrazone. This could occur in three ways:

a) to give an aliphatic diazo compound,

b) to give a carbene, or

c) to give an olefin directly via a cyclic transition state in which the β-hydrogen is removed by the departing sulphinate residue.

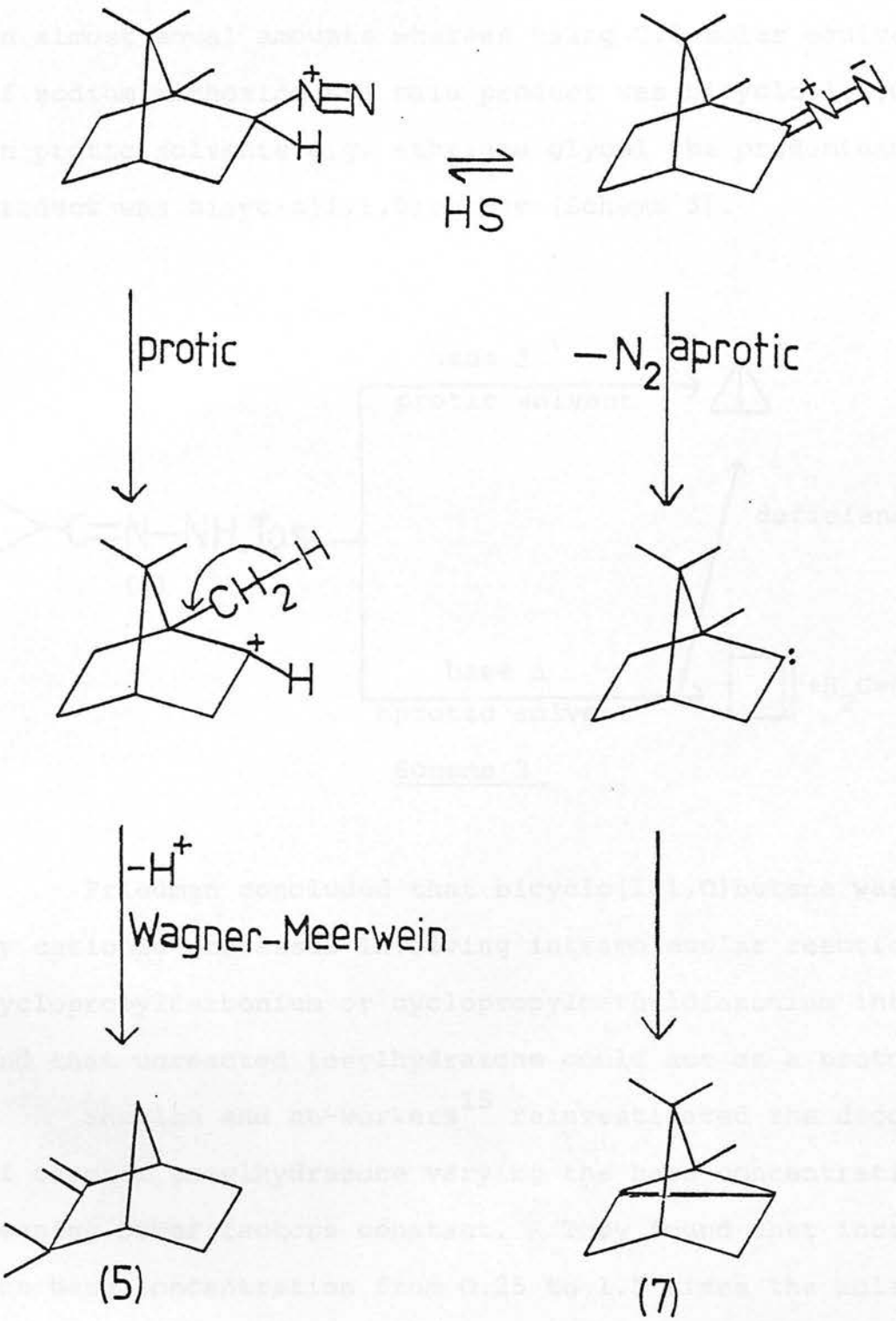
In order to ascertain which mechanism operated they studied the rates of decomposition of cyclohexanone and camphor tosylhydrazones. They found that these two tosylhydrazones decomposed at the same rate and with the same activation energy. This led them to conclude that (a) was the mechanism operating since in route (b) the camphor derivative should react faster due to anchimeric assistance of carbene formation and in (c) the camphor derivative would be expected to react more slowly since it could not lose two β-hydrogen atoms to form a cyclic transition state because of steric reasons.

Powell and Whiting[12] re-examined the products from the decomposition of camphor tosylhydrazone by g.l.c.. They found that the product from the decomposition was not pure camphene but a 4:1 mixture with tricyclene. On the other hand, Meerwein and van Emster[13] had reported the presence of a small amount of camphene in the decomposition of diazocamphane to tricyclene. In an attempt to explain these results, Powell and Whiting investigated the effect of changing the reaction solvent on the product ratio. They found that the ratio of camphene:tricyclene varied markedly with changes in the reaction solvent. When camphor tosylhydrazone was decomposed in ethylene glycol at 139° and 195° the amounts of tricyclene formed were 20% and 23% respectively. In 2-ethoxyethanol at 132° and in acetamide at 156° the amounts of tricyclene were 92% and 99% respectively.

This led them to the conclusion that diazocamphane was the intermediate in the decomposition. In aprotic solvents, the diazocamphane decomposes directly to give a carbene, which gives tricyclene via intramolecular C-H insertion (Scheme 2). In protic solvents, if proton donation is faster than the elimination of nitrogen, a diazonium ion is formed. The diazonium ion can lose nitrogen to give a carbonium ion which undergoes subsequent Wagner-Meerwein rearrangement to give camphene.

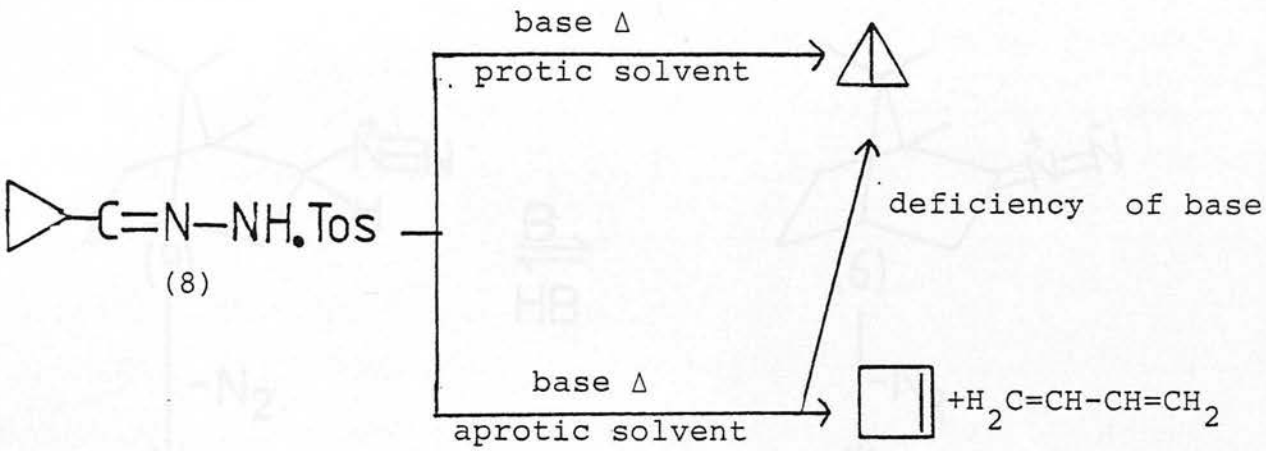
Effect of Base Concentration

Friedman and co-workers[14] studied the decomposition of cyclopropanecarboxaldehyde tosylhydrazone (8). They found that when the decomposition was carried out in diethyl



SCHEME 2

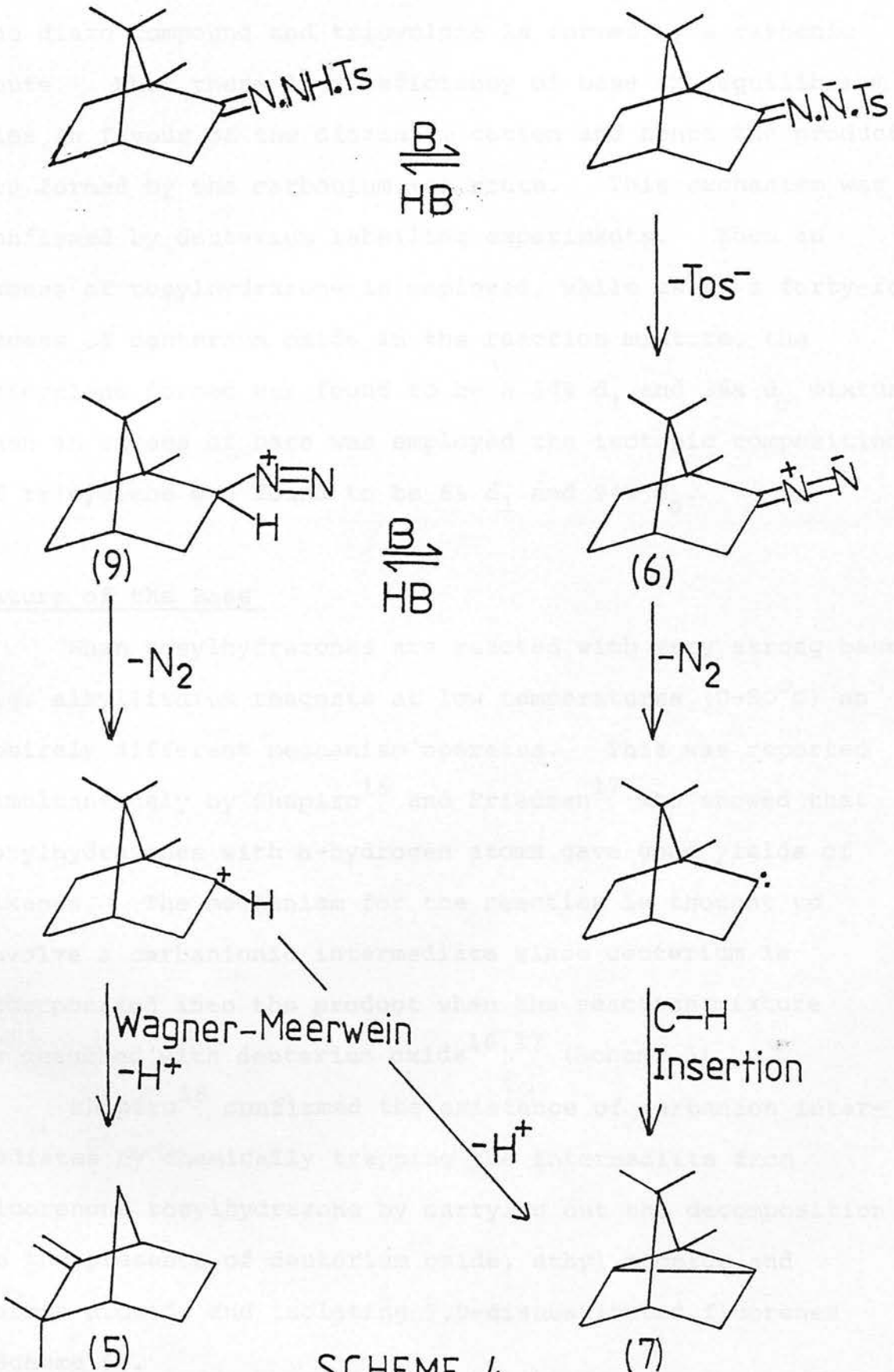
carbitol, using 1.8 molar equivalents of sodium methoxide as base, the products were cyclobutene and 1,3-butadiene in almost equal amounts whereas using 0.8 molar equivalents of sodium methoxide the main product was bicyclo[1,1,0]butane. In protic solvents e.g. ethylene glycol the predominant product was bicyclo[1,1,0]butane (Scheme 3).



Scheme 3

Friedman concluded that bicyclo[1,1,0]butane was formed by cationic processes involving intramolecular reaction of cyclopropylcarbonium or cyclopropylmethyldiazonium intermediates and that unreacted tosylhydrazone could act as a proton donor.

Shapiro and co-workers[15] reinvestigated the decomposition of camphor tosylhydrazone varying the base concentration while keeping other factors constant. They found that increasing the base concentration from 0.25 to 1.5 times the molar equivalent caused an increase in the proportion of tricyclene. They proposed that the mechanism involved an equilibrium between diazocamphane (6) and its diazonium cation (9) (Scheme 4).


N.NH.Ts
B
HB
N.N̄.Ts
-Tos⁻
(9)
(6)
-N₂
-N₂
H
Wagner-Meerwein
-H⁺
-H⁺
C—H
Insertion
(5)
(7)

SCHEME 4

When excess base is used the equilibrium lies in favour of the diazo compound and tricyclene is formed by a carbenic route. When there is a deficiency of base the equilibrium lies in favour of the diazonium cation and hence the products are formed by the carbonium ion route. This mechanism was confirmed by deuterium labelling experiments. When an excess of tosylhydrazone is employed, while using a forty-fold excess of deuterium oxide in the reaction mixture, the tricyclene formed was found to be a 64% d_1 and 36% d_o mixture. When an excess of base was employed the isotopic composition of tricyclene was found to be 6% d_1 and 94% d_o.

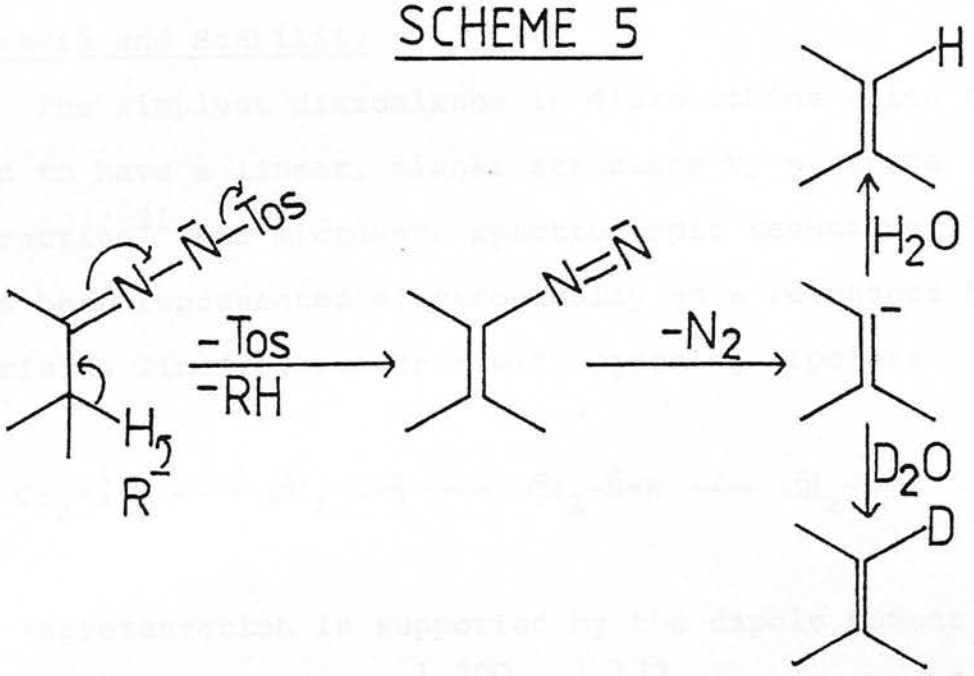
Nature of the Base

When tosylhydrazones are reacted with very strong bases e.g. alkyllithium reagents at low temperatures (0-90°C) an entirely different mechanism operates. This was reported simultaneously by Shapiro[16] and Friedman[17] who showed that tosylhydrazones with α-hydrogen atoms gave good yields of alkenes. The mechanism for the reaction is thought to involve a carbanionic intermediate since deuterium is incorporated into the product when the reaction mixture is quenched with deuterium oxide[16,17] (Scheme 5).

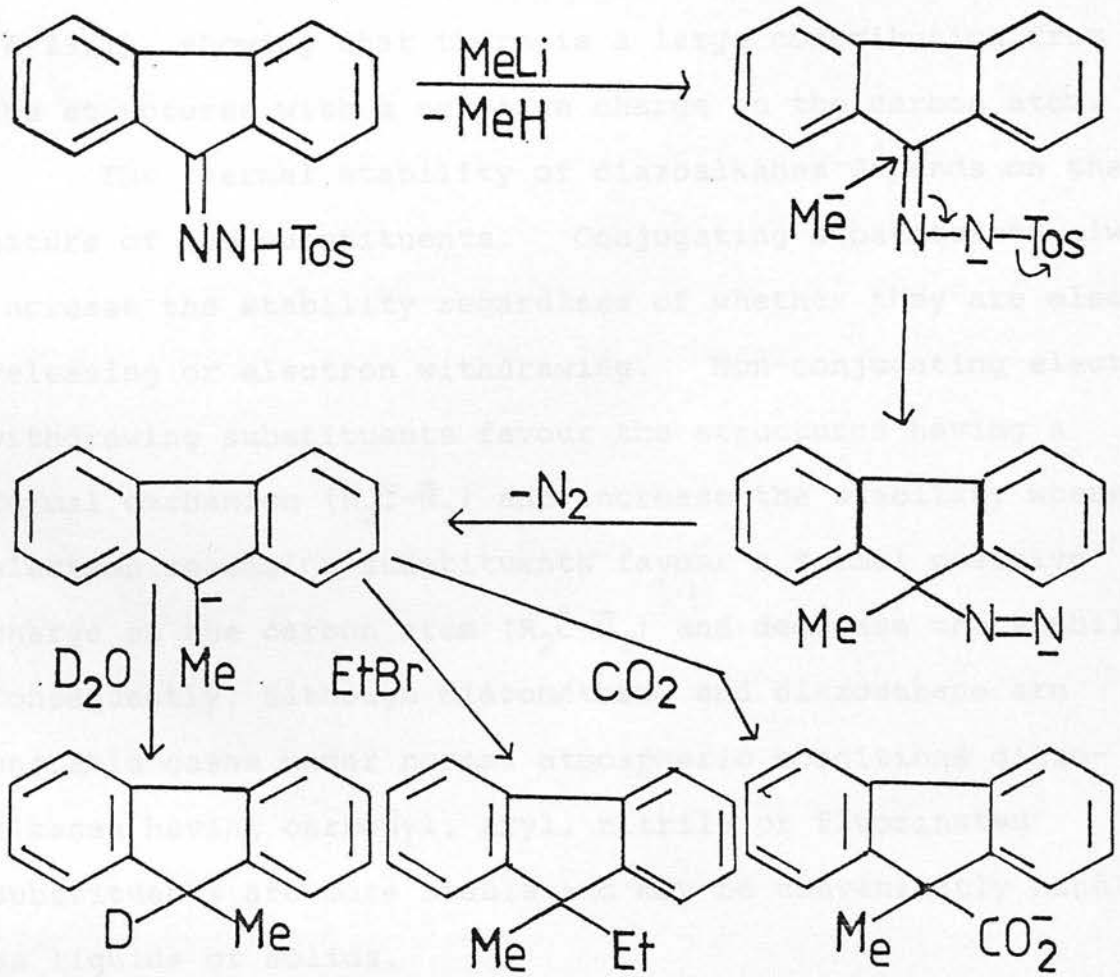
Shapiro[18] confirmed the existence of carbanion intermediates by chemically trapping the intermediate from fluorenone tosylhydrazone by carrying out the decomposition in the presence of deuterium oxide, ethyl bromide and carbon dioxide and isolating 9,9-disubstituted fluorenes (Scheme 6).

The Bamford-Stevens reaction has been reviewed recently.[19,20]

SCHEME 5



SCHEME 6



Structure and Stability

The simplest diazoalkane is diazomethane which has been shown to have a linear, planar structure by electron diffraction[21] and microwave spectroscopic techniques.[22] It is best represented electronically as a resonance hybrid, comprising linear structures with opposing dipoles:

$$CH_2=\overset{+}{N}=\overset{-}{N} \longleftrightarrow \overset{-}{C}H_2-N=\overset{+}{N} \longleftrightarrow \overset{-}{C}H_2-\overset{+}{N}=N \longleftrightarrow \overset{-}{C}H_2-N=\overset{+}{N}$$

This representation is supported by the dipole moment (1.4D) and the bond lengths (>C $\underline{1.300}$ N $\underline{1.139}$ N). Firl and co-workers[23] have used ^{13}C n.m.r. spectroscopy to show that the carbon in diazomethane has a high electron density (δ 23.1), showing that there is a large contribution from the structures with a negative charge on the carbon atom.

The thermal stability of diazoalkanes depends on the nature of the substituents. Conjugating substituents always increase the stability regardless of whether they are electron releasing or electron withdrawing. Non-conjugating electron withdrawing substituents favour the structures having a formal carbanion ($R_2\overset{-}{C}-\overset{+}{N}_2$) and increase the stability whereas electron releasing substituents favour a formal positive charge on the carbon atom ($R_2\overset{+}{C}-\overset{-}{N}_2$) and decrease the stability. Consequently, although diazomethane and diazoethane are unstable gases under normal atmospheric conditions diazoalkanes having carbonyl, aryl, nitrile or fluorinated substituents are more stable and may be conveniently handled as liquids or solids.

Reactions of Diazoalkanes

A) Diazoalkanes can sometimes be observed in reactions by their red colouration, and can be chemically trapped by their reaction with alkylphosphines[24] as shown in Scheme 7 to form phosphazines (10) which hydrolyse to give a hydrazone and phosphine oxide.

$$R_2C=\overset{+}{N}=\overline{N} \;+\; PR_3 \longrightarrow R_2C=N-N=PR_3\ (10)$$
$$\downarrow H_2O$$
$$R_2C=N-NH_2 \;+\; R_3P=O$$

Scheme 7

B) Carbene Formation

One of the most important reactions of diazoalkanes is the elimination of nitrogen to form carbenes. The photolysis or thermolysis of diazoalkanes in aprotic solvents provides the most common general route to carbenes.

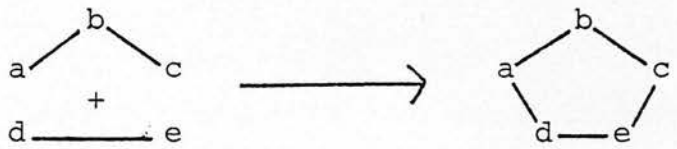
$$R_2C=N_2 \longrightarrow :CR_2 + N_2$$

Carbenes are neutral bivalent carbon intermediates which are very reactive and can undergo any or all of the following reactions: insertion, addition, rearrangement and reaction with their diazo precursor to give an azine. The reactions of carbenes have been extensively studied and reviewed.[25,26]

Another important feature of diazoalkanes, which is more relevant to this research, is their ability to react with retention of nitrogen, undergoing 1,3-dipolar cycloadditions. These can be divided into two types, either inter- or intramolecular.

C) Intermolecular 1,3-Dipolar Cycloadditions

Cycloadducts of diazoalkanes have been known since 1888[27] but it was not until the work of Huisgen[28] in the early 1960's that the classification "1,3-dipolar cycloaddition" became generally accepted. Huisgen defined a 1,3-dipole, a-b-c, such that atom a possesses an electron sextet i.e. an incomplete valence shell combined with a formal positive charge, and that atom c, the negatively charged centre has an unshared electron pair. Combination of such a 1,3-dipole with a multiple bond system d-e, the dipolarophile, is referred to as a 1,3-dipolar cycloaddition.



Compounds containing a sextet of electrons at a carbon, nitrogen or oxygen atom are not stable but stabilisation is possible if an unshared pair of electrons at atom b can relieve the electron deficiency at atom a by the formation of an additional bond. In the new mesomeric formula in which b now has a positive charge, all the atoms have completely filled valence shells.

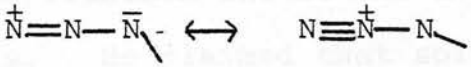
$$\overset{+}{a}=b-\overset{-}{c} \longleftrightarrow a\equiv\overset{+}{b}-\overset{-}{c} \qquad b=N$$

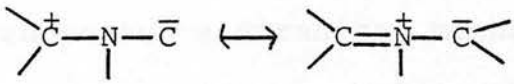
$$\overset{+}{a}-b-\overset{-}{c} \longleftrightarrow a=\overset{+}{b}-\overset{-}{c} \qquad b=N\text{-}R \text{ or } O$$

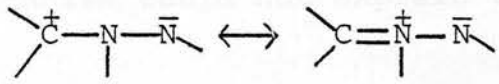
Sextet Octet

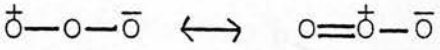
Diazoalkanes are just one example of the class of 1,3-dipoles which includes nitrile oxides, azides, azomethine ylides, azomethine imines and ozone.

nitrile oxides 

azides 

azomethine ylides 

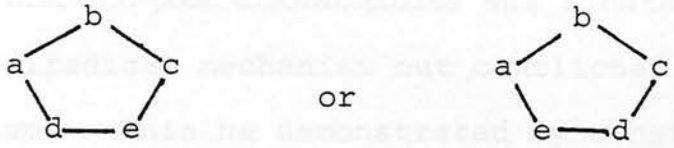
azomethine imines 

ozone 

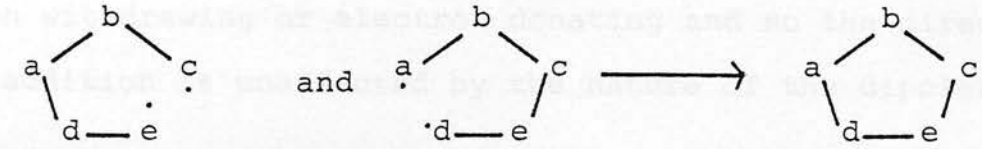
1,3-Dipolar cycloadditions exhibit common mechanistic features: the rate or stereochemistry is not greatly influenced by solvent polarity; they show low enthalpies of activation, and large negative entropies of activation; they produce five-membered cyclic compounds in which the stereochemistry of the reacting olefin is preserved; and the reaction rates are increased by conjugation of the dipolarophile but reduced by the steric effects of all types of substituent.

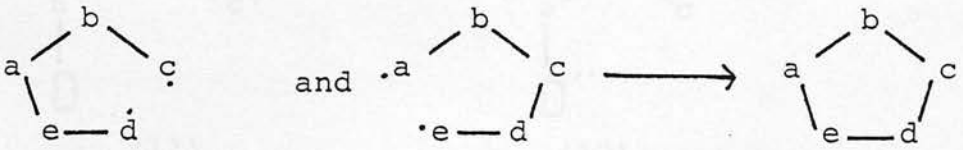
The mechanism of 1,3-dipolar cycloaddition has been the subject of some controversy. The two alternatives proposed are a concerted and a two-step mechanism. Huisgen[28] proposed a concerted [3+2] mechanism involving a cyclic transition state basing his argument on the cis-stereospecificity of the cycloaddition together with the activation parameters. The Woodward-Hoffman rules have shown that Huisgen's mechanism is allowed by orbital symmetry.

Firestone[29] proposed that the mechanism involved a two-step reaction with a discrete intermediate, a spin-paired diradical, being formed in the rate-determining step. He argued that ring closure was a more favourable pathway energetically than bond rotation and so the stereochemistry of the addition was cis. He claimed that solvent and conjugation effects supported a diradical mechanism and that a concerted mechanism could not explain the problem of orientation i.e.



He argued that the orientation could be predicted by considering "the best looking" of the four possible diradical intermediates taking into account steric, kinetic and σ-bond energy factors.

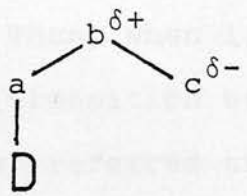




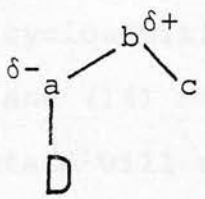
He admitted, however, that the factors governing radical formation and stability were so poorly understood that few secure predictions could be made.

Huisgen[30] defended the concerted mechanism on stereochemical, energetic and electronic grounds but admitted that orientation was still an unsolved problem.

In 1972, Firestone[31] reasserted the diradical mechanism. He argued that the predominant unidirectionality of orientation exhibited by most 1,3-dipoles towards both electron-rich and electron-poor dipolarophiles was a natural consequence of the diradical mechanism but conflicted with the concerted mechanism. This he demonstrated by considering the possible diradical intermediates (11) and (12) as Linnett structures[32] with partial formal charges, with the most stable diradical being that in which the most electronegative atom bears the most electronegative charge. This will then be the favoured diradical irrespective of whether the dipolarophile (D) is electron withdrawing or electron donating and so the direction of the addition is unaffected by the nature of the dipolarophile.



(11)



(12)

In 1973, however, Houk and his co-workers[33,34] applied perturbation theory to the problem of rationalising the regioselectivity in 1,3-dipolar cycloadditions.

Fukui[35] postulated that reactions take place in the direction of the maximum frontier orbital overlap i.e. between the HO (highest occupied) and LU (lowest unoccupied) orbitals. In concerted cycloadditions the favoured orientation will be that in which the centres whose frontier orbitals have the largest coefficients interact. Houk calculated the orbital energies and atomic orbital coefficients for all classes of 1,3-dipoles by CNDO/2. The calculated orbital energies were adjusted with the help of known ionisation potentials and transitions.

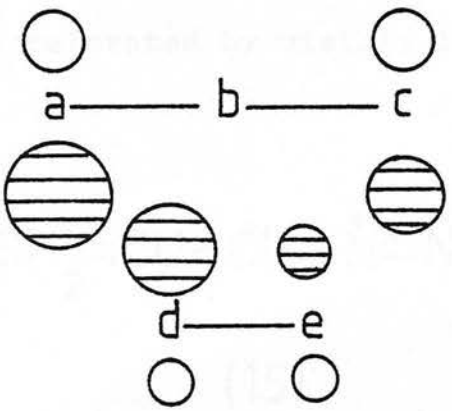
For diazomethane, the squares of the products of the CNDO/2 calculated frontier orbital coefficients, interacting with a dipolarophile at 175 pm separation, were as follows.

	HO			LU		
$N\equiv\overset{+}{N}-\overset{-}{C}H_2$	N	N	CH_2	N	N	CH_2
	0.85	0.04	1.57	0.56	1.12	0.66

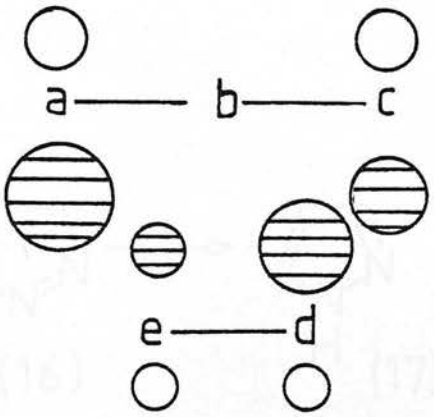
It can be seen from this calculation that the two termini have different orbital coefficients. The sizes of these coefficients can be represented pictorially as lobes. Thus, when 1,3-dipolar cycloaddition occurs, two possible transition states (13) and (14) may be visualised.

The preferred transition state will always be that in which the larger orbital coefficients interact. In this case (13).

(13)



(14)



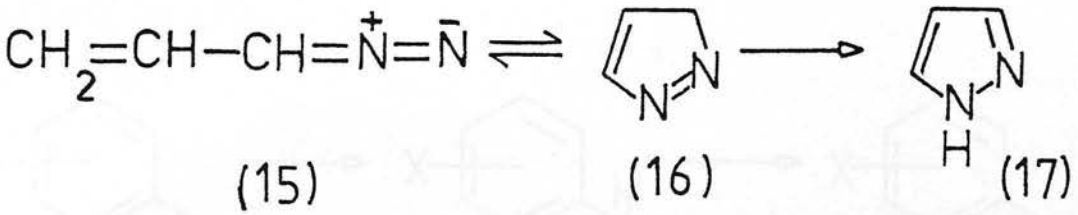
Since the relative energies of the HO and LU orbitals are determined by the substituents, and are the chief factors in determining the mode of regioselectivity and rates of reaction, Houk was able to achieve a complete rationalisation of the observed results in terms of substituent effects. Huisgen[36] has recently used this molecular orbital perturbation treatment as additional support for the concerted mechanism as well as refuting Firestone's earlier diradical arguments.

Firestone,[37] however, remains unconvinced and argues that perturbational molecular orbital theory bases its predictions on ground state interactions between reactants. He maintains that in this case calculations of ground-state orbitals are meaningless when the transition state lies more than 30-70 kJ/mole above the ground state in energy.

While the mechanistic debate continues the synthetic usefulness of the intermolecular cycloadditions of diazoalkanes remains unquestionable.

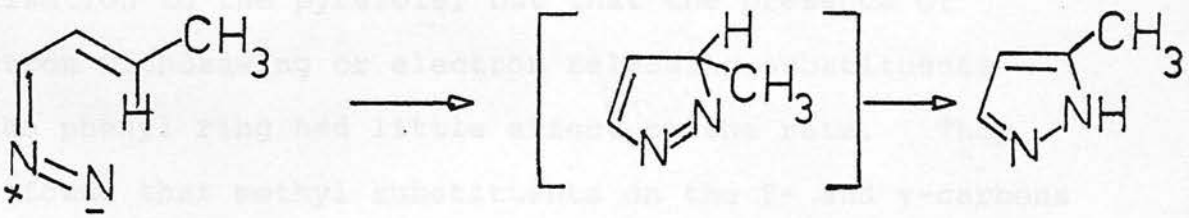
D) Intramolecular Cycloaddition Reactions

In 1935, Adamson and Kenner[38] and Hurd and Lui[39] showed that 3-diazopropene (15) underwent a slow intramolecular cycloaddition to give pyrazole (17) and that the reaction was accelerated by visible light.[38]



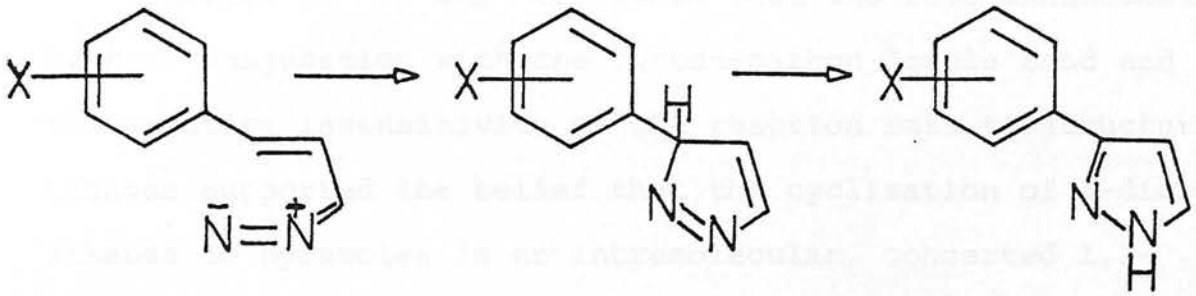
(15) (16) (17)

Ledwith and Parry[40] reinvestigated this reaction and postulated the intermediacy of the 3H-pyrazole (16) which acted as the absorbing species in the reaction since diazopropene was transparent at the wavelength used. Adamson and Kenner[38] also reported that the red colour of an ethereal solution of trans-1-diazo-2-butene (18) faded slowly at room temperature. Curtin and Gerber[41] later showed that the product was 3(5)-methylpyrazole (19).



(18) (19)

The mechanism of these reactions was studied by Brewbaker and Hart[42] who investigated a series of aryl and alkyl substituted diazoalkenes. They generated the diazoalkenes by treatment of ethyl alkenylnitrosocarbamates, in cyclohexene, with sodium methoxide, and obtained good yields of 1H-pyrazoles by allowing cyclisation to occur at 25°, (Scheme 8).



X = m-NO_2, p-Cl, p-CH_3

SCHEME 8

They found that the presence of an aryl substituent on the γ-carbon of the diazoalkene increased the rate of cyclisation to the pyrazole, but that the presence of electron withdrawing or electron releasing substituents in the phenyl ring had little effect on the rate. They also found that methyl substituents on the β- and γ-carbons of the diazoalkene slightly reduced the cyclisation rate whereas α-substitution had a marked accelerating effect. The relative rates of cyclisation of the three methyl substituted 3-diazopropenes as compared to 3-diazopropene itself are shown below.

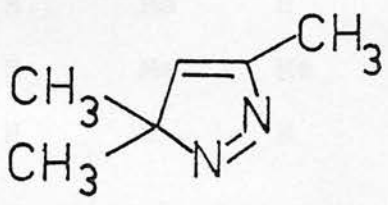
0.75 0.85 13.0

$C{=}C-C-N_2$

This accelerating effect is probably due to the electron release of the methyl group reducing the stability of the diazoalkene.

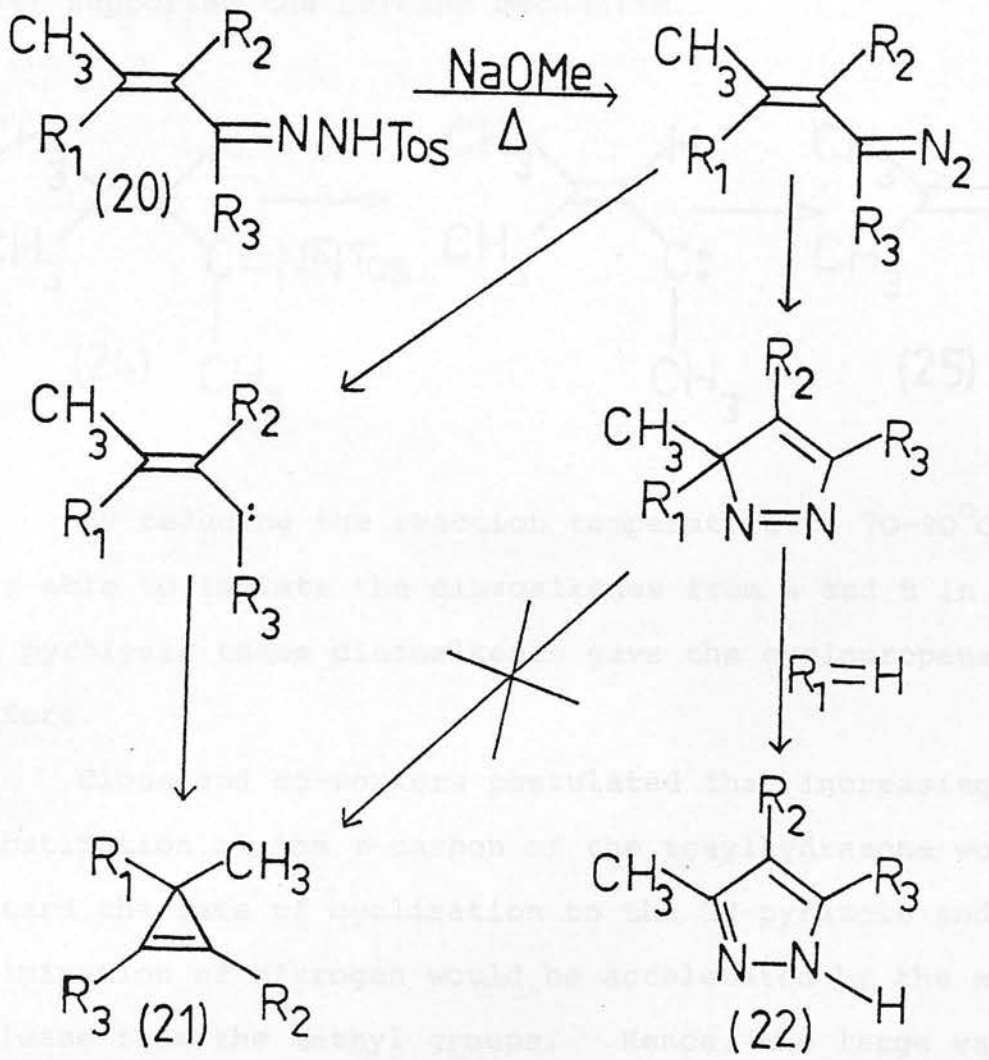
Brewbaker and Hart concluded that the rate enhancement by aryl conjugation with the carbon-carbon double bond and the relative insensitivity of the reaction rate to structural changes supported the belief that the cyclisation of 3-diazoalkenes to pyrazoles is an intramolecular, concerted 1,3-dipolar cycloaddition.

Closs and co-workers[43] reported the formation of pyrazoles from the thermal decomposition of the tosylhydrazone salts of α,β-unsaturated carbonyl compounds. They studied the decompositions of tosylhydrazones of type (20) (Scheme 9) in aprotic media at 160°-220° C using sodium methoxide as base to give alkyl-substituted cyclopropenes and in some cases pyrazoles. They rejected the possibility that the 3H-pyrazole could give rise to cyclopropene since 3,3,5-trimethylpyrazole (23) was stable under the reaction conditions.



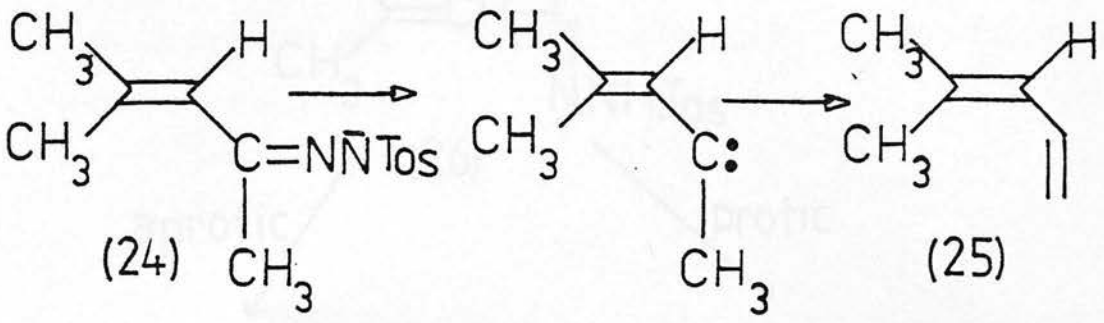
(23)

Scheme 9



Compound	R^1	R^2	R^3	Yield (21)%	Yield (22)%
A	Me	Me	H	72	
B	Me	H	Me	39	
C	Me	H	H	50	
D	H	Me	H	4	60
E	H	Me	Me	1.5	21
F	H	H	H	3	

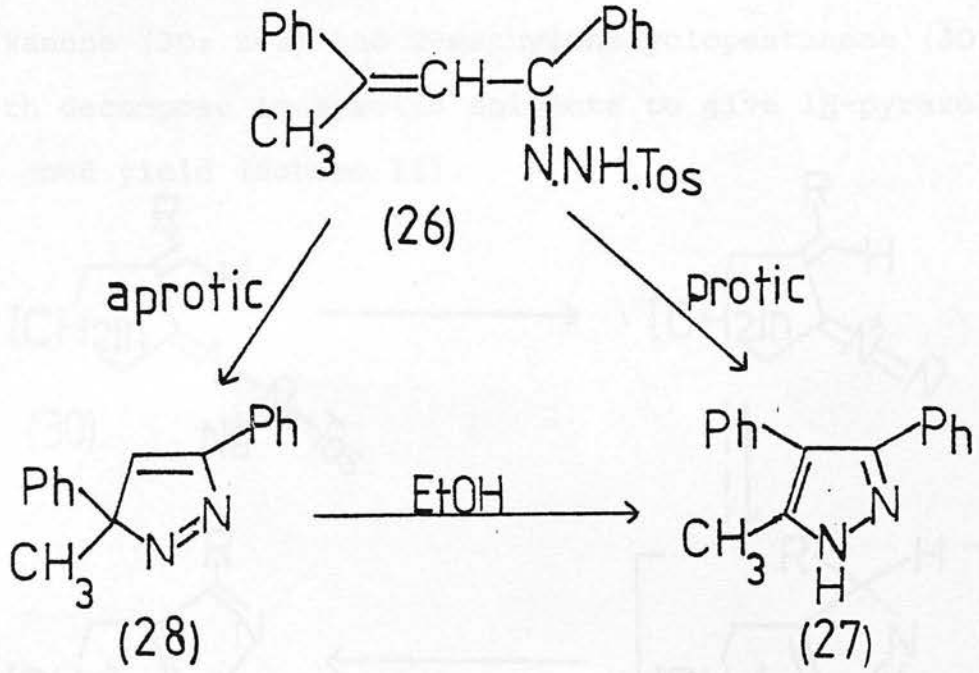
Also the formation of 4-methylpenta-1,3-diene (25) in the pyrolysis of 4-methylpent-3-ene-2-one tosylhydrazone (24) supported the carbene mechanism.



By reducing the reaction temperature to 70-90°C Closs was able to isolate the diazoalkenes from A and B in Scheme 9. On pyrolysis these diazoalkenes gave the cyclopropenes as before.

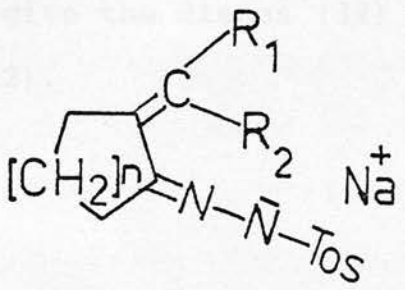
Closs and co-workers postulated that increasing methyl substitution at the β-carbon of the tosylhydrazone would retard the rate of cyclisation to the 3H-pyrazole and that elimination of nitrogen would be accelerated by the electron release from the methyl groups. Hence, the large variation in cyclopropene yields.

Sato and Watanabe[44] decomposed α-methylstyryl phenyl ketone tosylhydrazone (26) in both protic and aprotic solvents (Scheme 10). In a protic solvent (sodium methoxide in ethylene glycol), the decomposition gave 5-methyl-3,4-diphenylpyrazole (27), while in aprotic conditions (sodium hydride in n-hexane) 3-methyl-3,5-diphenylpyrazole (28) was obtained. The 3H-pyrazole (28) could be rearranged to the 1H-pyrazole by heating in ethanol.



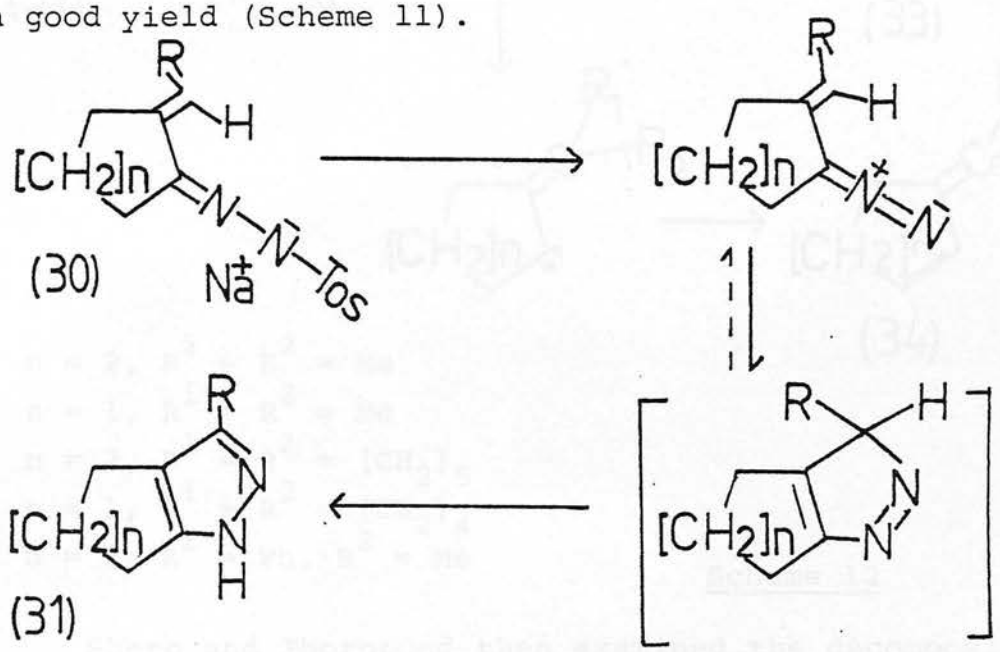
SCHEME 10

Sharp and Thorogood[45] investigated the decompositions of sodium salts of the tosylhydrazones of α-methylenecyclopentanones (29; n=1) and those of analogous α-methylenecyclohexanones (29; n=2) and acyclic unsaturated ketones. They have shown that the products of the thermal decomposition of the tosylhydrazones salts (29) depends on the nature of the substituents R^1 and R^2 and on the ring size.



(29)

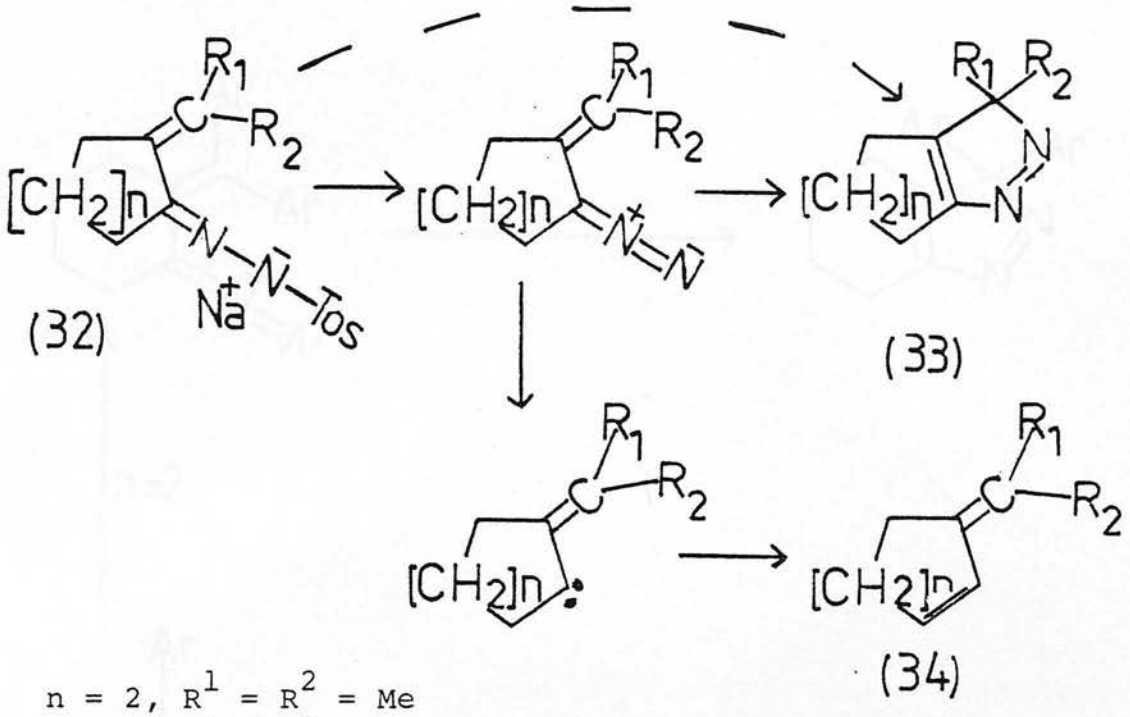
The decomposition of tosyhydrazone salts having only one substituent at the terminus of the double bond did not vary with ring size. The sodium salts of 2-methylenecyclohexanone (30; n=2) and 2-methylenecyclopentanone (30; n=1) both decompose in aprotic solvents to give 1H-pyrazoles (31) in good yield (Scheme 11).



	Yield
n = 1, R = Me	64%
n = 1, R = Ph	71%
n = 2, R = Ph	77%

Scheme 11

When the double bond has two alkyl substituents, however, the cyclohexanone derivatives (32; n=2) give 3H-pyrazoles (33) in high yield whereas the cyclopentanone derivatives (32; n=1) give the dienes (34) and no 3H-pyrazoles (Scheme 12).

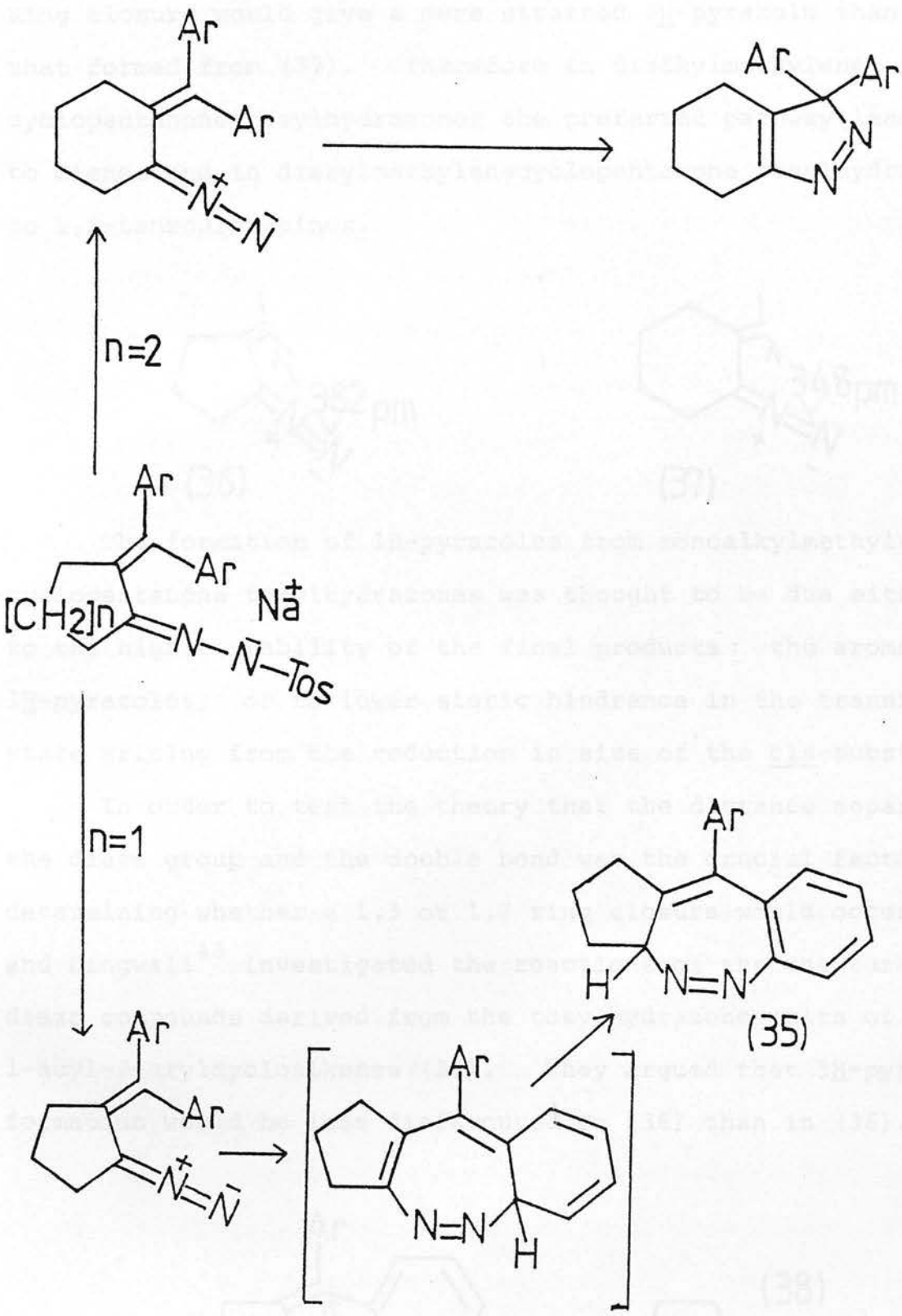


n = 2, $R^1 = R^2$ = Me
n = 1, $R^1 = R^2$ = Me
n = 2, $R^1 = R^2 = [CH_2]_5$
n = 1, $R^1 = R^2 = [CH_2]_4$
n = 2, R^1 = Ph, R^2 = Me

Scheme 12

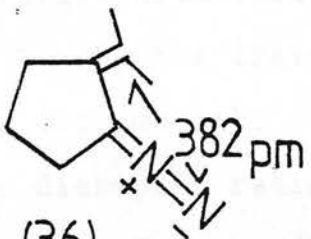
Sharp and Thorogood then examined the decomposition reactions of tosylhydrazone salts with two aryl groups on the methylene carbon and found that a different mode of cyclisation became possible (Scheme 13). When n=1, the diazo intermediate underwent 1,7 ring closure to give the 1,2-benzodiazepine (35). When n=2 the cyclisation proceeded via 1,5 ring closure to give exclusively pyrazoles.

A steric effect was postulated to explain these differences in behaviour between cyclopentanone and cyclohexanone tosylhydrazones. Models constructed from Drieding units show that the separation between the termini of the π system is about 35 pm greater in the five-membered ring system (36) than in the six-membered ring system (37). The former would therefore have to undergo a greater bending of the diazo group, from

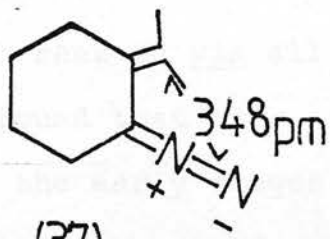


SCHEME 13

its preferred linear state, to achieve cyclisation. Ring closure would give a more strained 3H-pyrazole than that formed from (37). Therefore in dialkylmethylene-cyclopentanone tosylhydrazones the preferred pathway leads to dienes and in diarylmethylenecyclopentanone tosylhydrazones to 1,2-benzodiazepines.



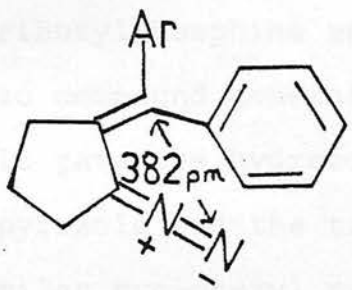
(36)



(37)

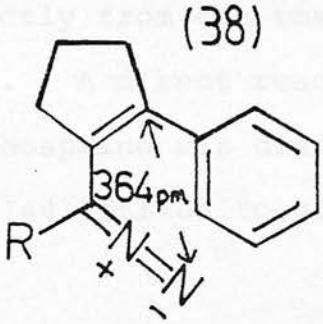
The formation of 1H-pyrazoles from monoalkylmethylene cyclopentanone tosylhydrazones was thought to be due either to the higher stability of the final products: the aromatic 1H-pyrazoles; or to lower steric hindrance in the transition state arising from the reduction in size of the cis-substituent.

In order to test the theory that the distance separating the diazo group and the double bond was the crucial factor in determining whether a 1,5 or 1,7 ring closure would occur Sharp and Dingwall[46] investigated the reactions of the unsaturated diazo compounds derived from the tosylhydrazone salts of 1-acyl-2-arylcycloalkenes (38). They argued that 3H-pyrazole formation would be less disfavoured in (38) than in (36).



(36)

(38)

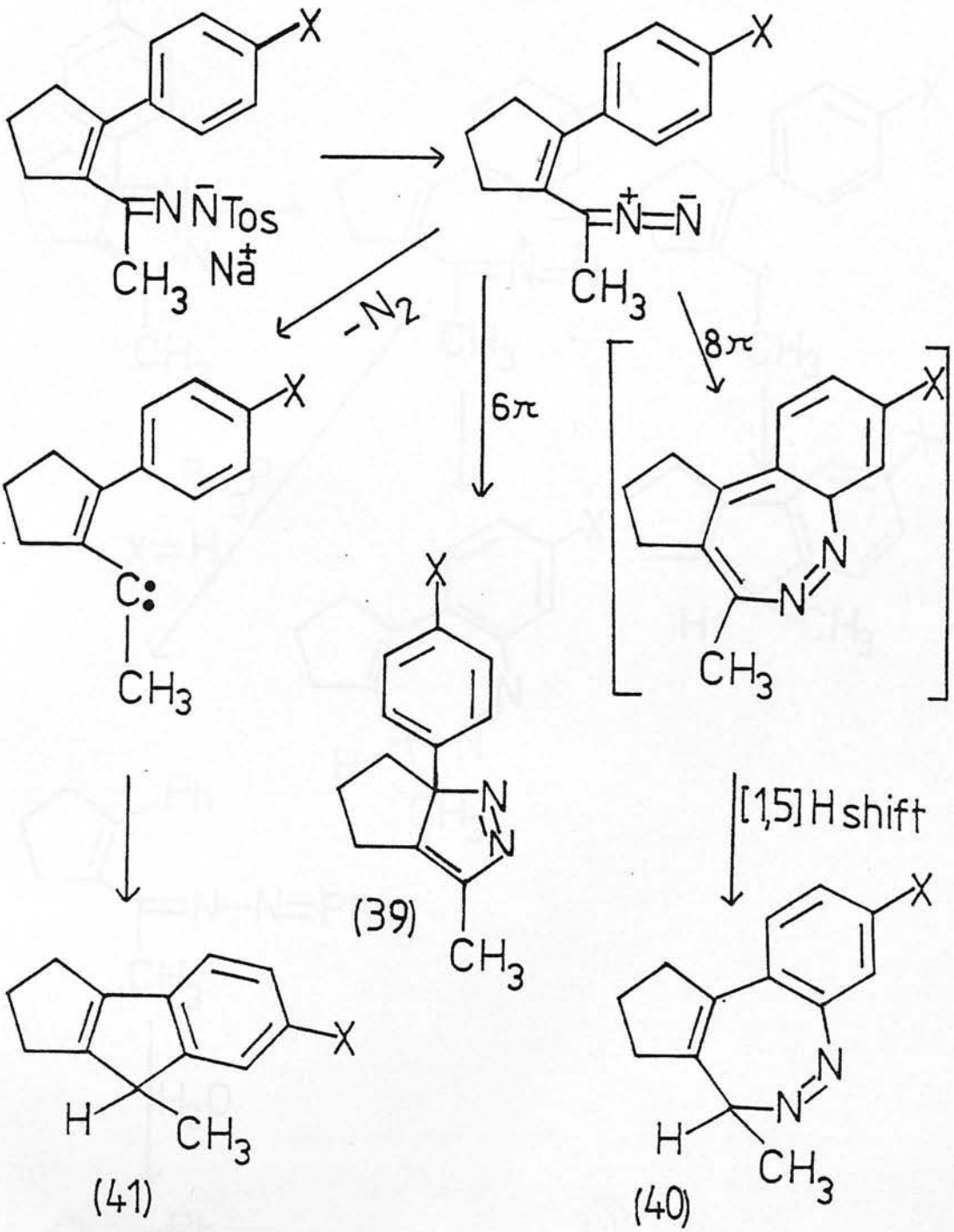


A complicating factor, however, was that in (36) the diazo group is kept in conjugation with the α,β double bond by the almost planar five-membered ring whereas in (38) there is free rotation about the 1,2 bond. Therefore it might be expected that both 1,5 and 1,7 ring closure will have higher entropies of activation thus making them less competitive with carbene formation.

When R = Me the diazocompound (38) reacted *via* all three modes (Scheme 14). Also it was found that the pyrazole to diazepine ratio was high in the early stages of the reaction but decreased as the reaction progressed suggesting that the pyrazole was being formed faster but subsequently converting to the diazepine. This was confirmed when thermolysis of the isolated pyrazole (39) at 80° produced both the diazepine (40) and the cyclopentaindene (41).

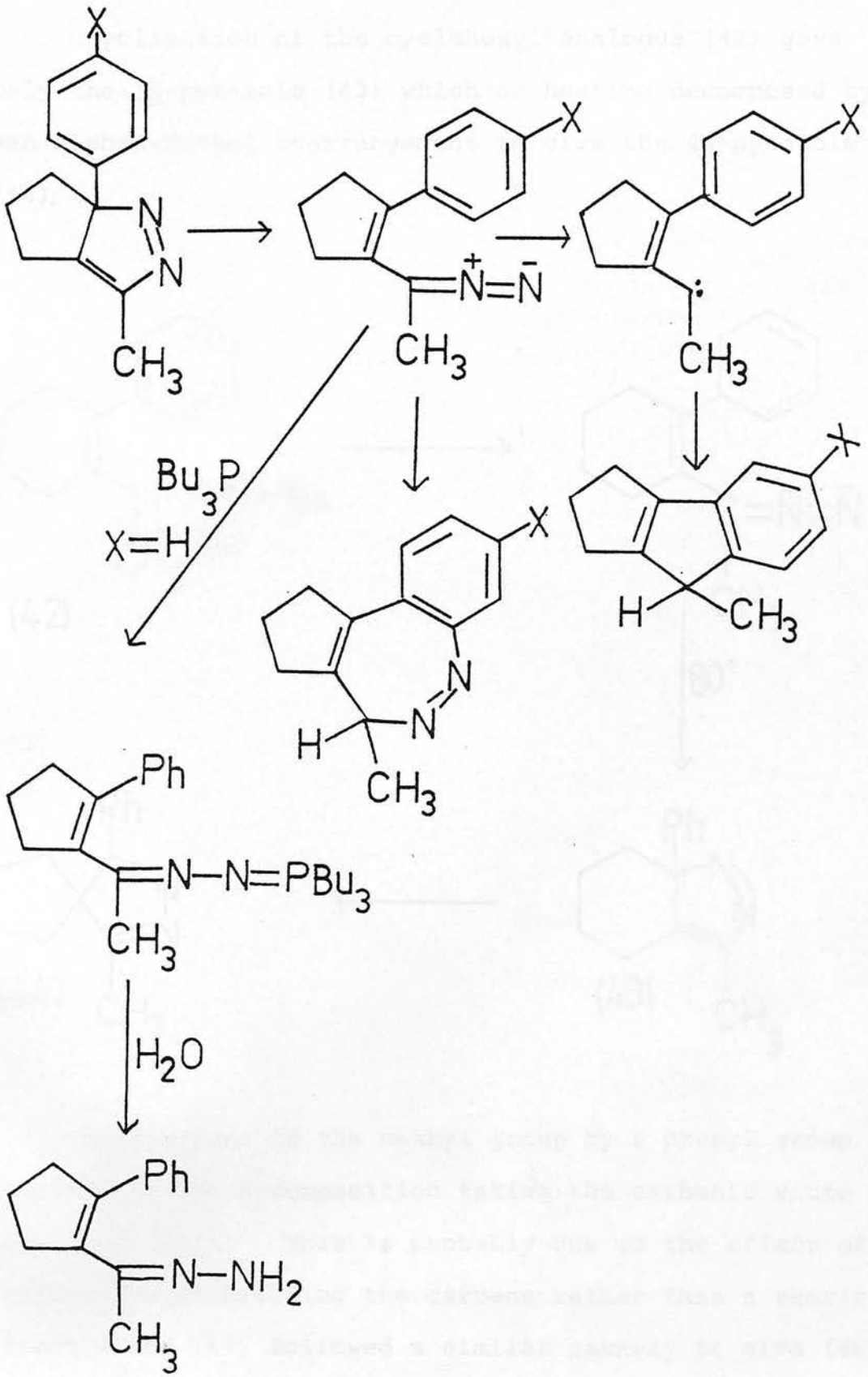
The conversion of (39) to (40) is a novel thermal reaction for 3*H*-pyrazoles which normally undergo the van Alphen-Huttel rearrangement in which one of the groups on the saturated carbon migrates to an adjacent atom to give either a 1*H*- or 4*H*-pyrazole. The rearrangement was shown, by a trapping experiment with tributylphosphine, to involve a reversal of the cyclisation step to give the diazo compound (Scheme 15).

Control reactions showed that the diazepine (40) did not react with tributylphosphine under the same conditions and that the diazo compound generated directly from the tosyl-hydrazone salt gave the hydrazone also. A direct reaction between the pyrazole and the tributylphosphine was discounted since the similar cyclohexyl pyrazole (44) failed to give a similar reaction (Scheme 15).



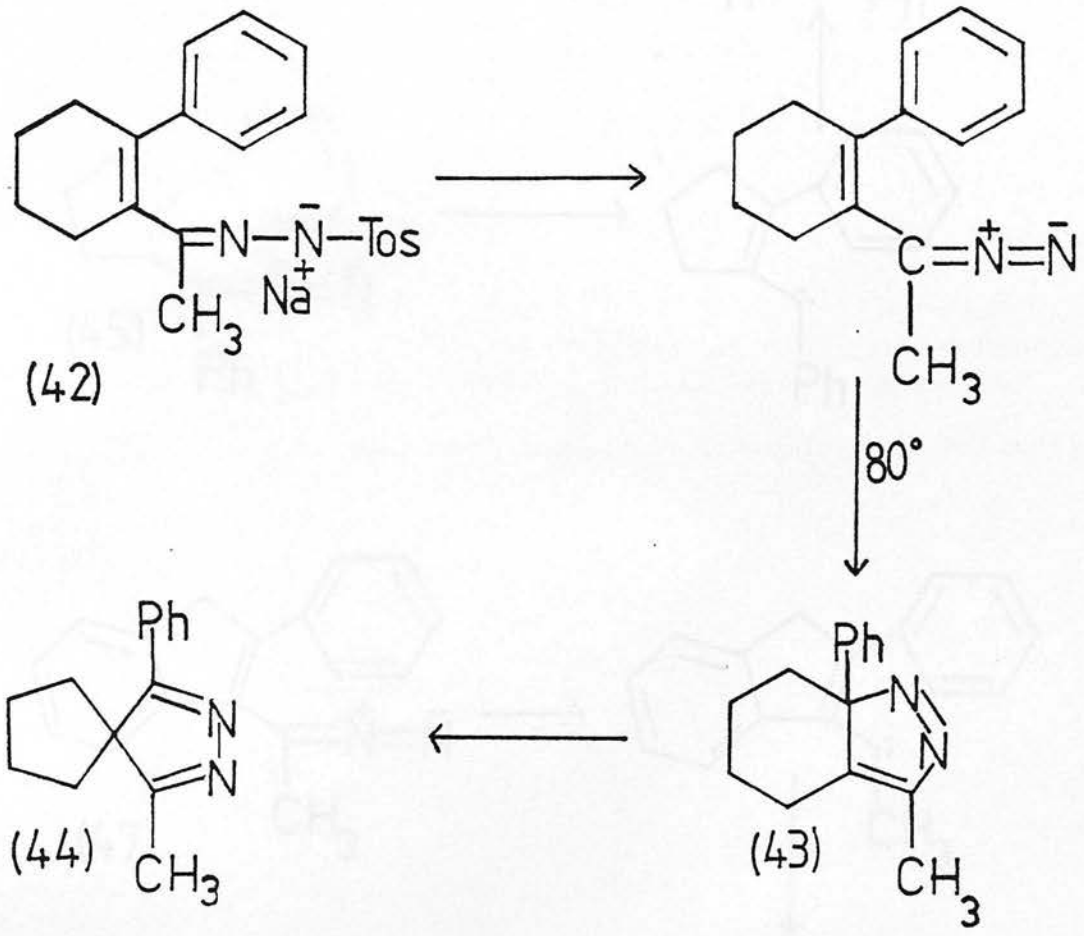
X=H	20%	46%	32%
X=Me	20	43	37
X=F	26	36	38

SCHEME 14

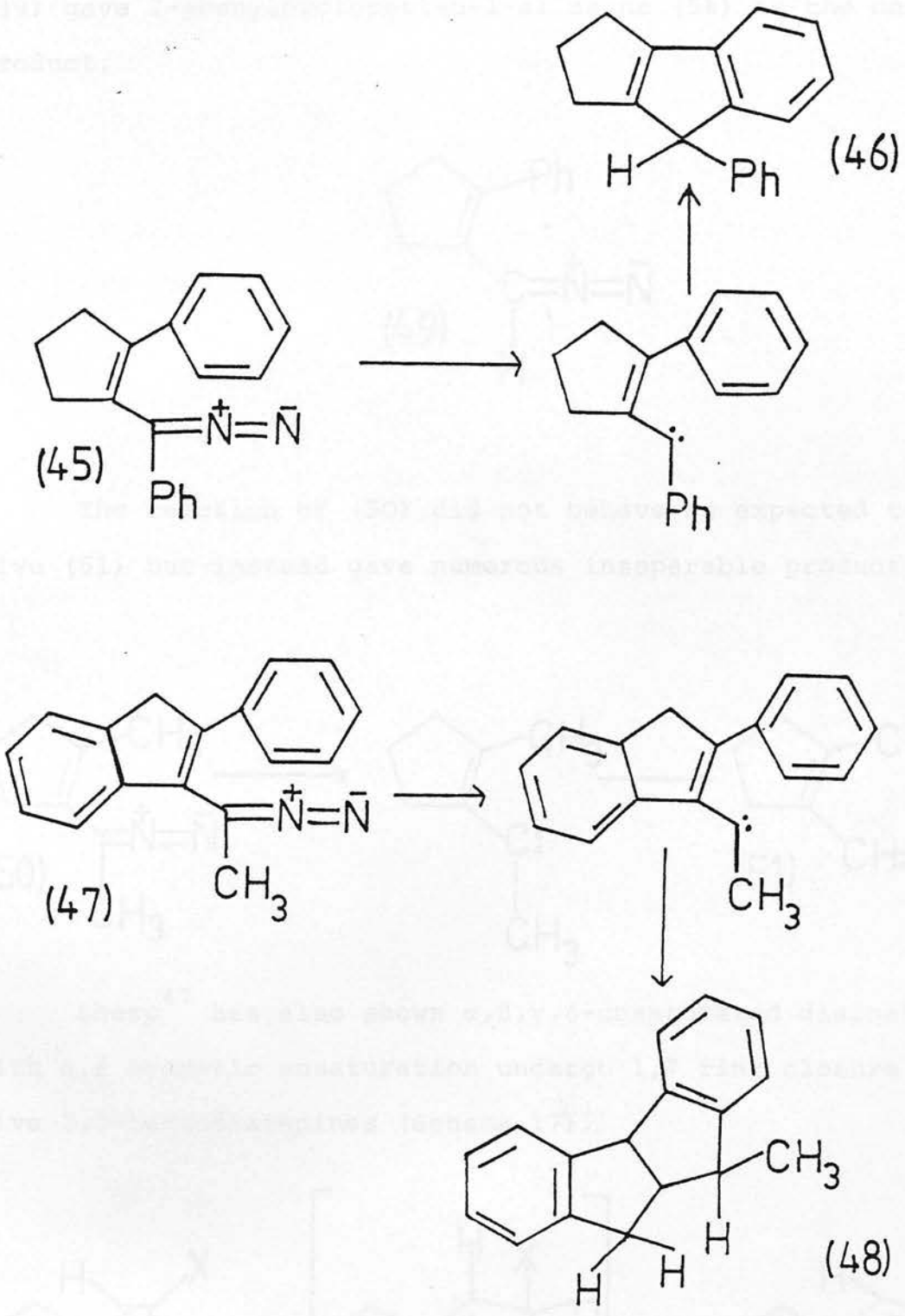

X
N
N
CH3
X
+
N=N
−
CH3
X
CH3
Bu3P
X=H
X
H
CH3
X
N
N
H
CH3
Ph
N–N=PBu3
CH3
H2O
Ph
N–NH2
CH3

SCHEME 15

Cyclisation of the cyclohexyl analogue (42) gave only the 3H-pyrazole (43) which on heating decomposed by the van Alphen-Huttel rearrangement to give the 4H-pyrazole (44).

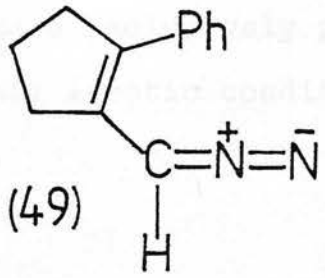


Replacement of the methyl group by a phenyl group (45) resulted in the decomposition taking the carbenic route to give (46) (95%). This is probably due to the effect of conjugation stabilising the carbene rather than a steric effect since (47) followed a similar pathway to give (48) (96%) (Scheme 16).



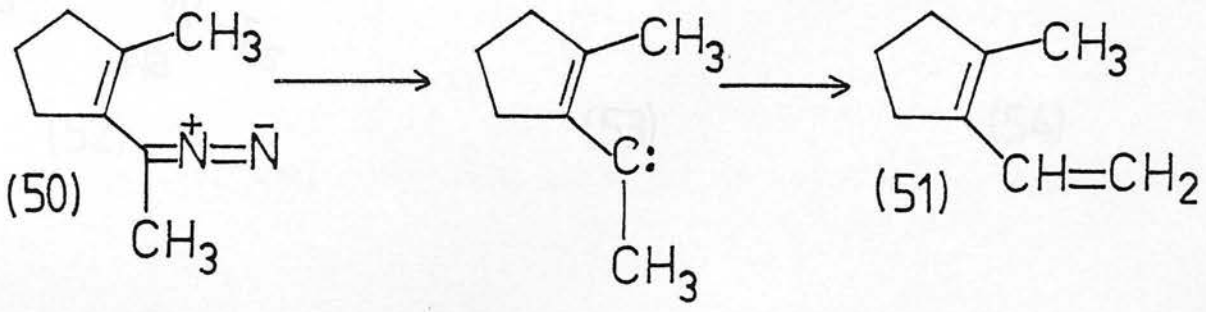
SCHEME 16

Replacement of the methyl group by a hydrogen did not promote electrocyclic reaction. The diazo compound (49) gave 2-phenylcyclopenten-1-al azine (5%) as the only product.



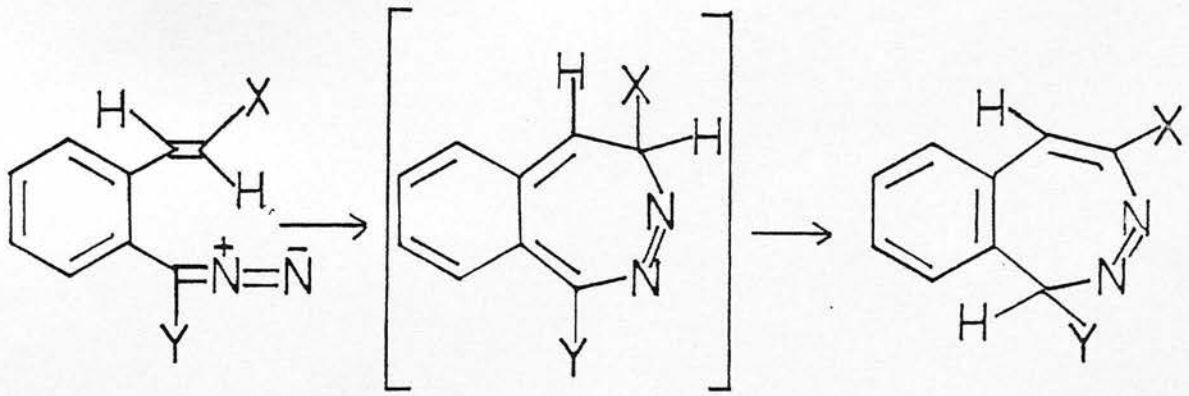
(49)

The reaction of (50) did not behave as expected to give (51) but instead gave numerous inseparable products.



(50) (51)

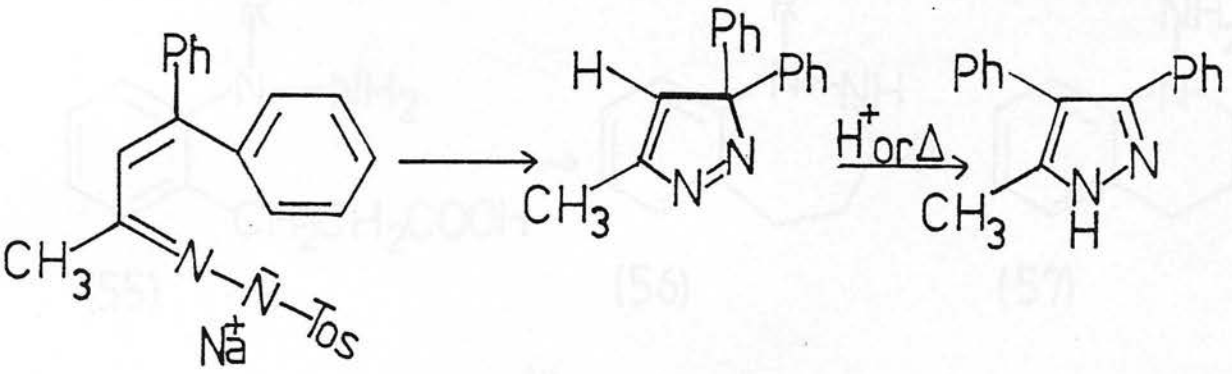
Sharp[47] has also shown α,β,γ,δ-unsaturated diazoalkenes with α,β aromatic unsaturation undergo 1,7 ring closure to give 2,3-benzodiazepines (Scheme 17).



SCHEME 17

A range of 1H-2,3-benzodiazepines was prepared from tosylhydrazone sodium salts of α-substituted styrenes and stilbenes. The inference that diazoalkane intermediates were present was drawn from the deep red colour observed in early stages of several cyclisations.

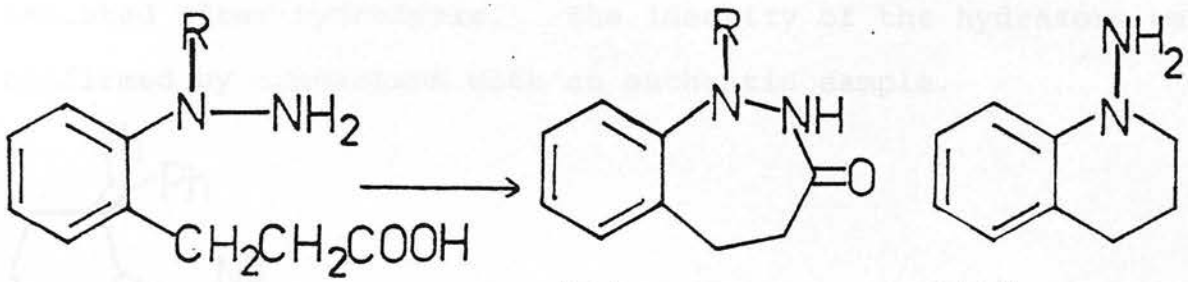
Acyclic systems[45] gave exclusively pyrazoles e.g. (52) when cyclised under rigidly aprotic conditions gave predominantly (53) (84%) and (54) (16%).



(52) (53) (54)

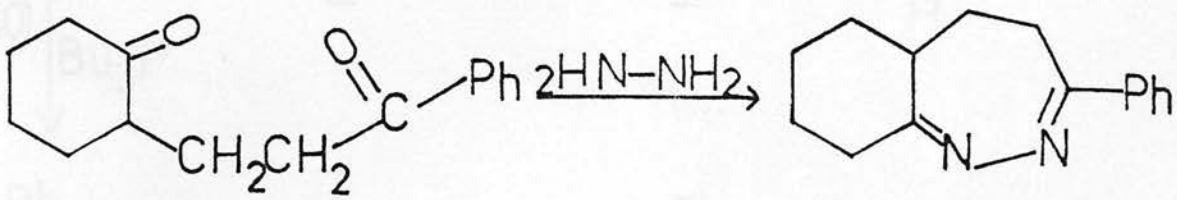
1,2-Benzodiazepines

Although 1,4-benzodiazepines have been extensively studied because of their useful biological activity as psychosedative and tranquilising agents the 1,2-benzodiazepines have received little attention. In 1883 Fischer and Kuzel[48] reported the cyclisation of o-hydrazinophenylpropionic acid (55; R = ethyl) to give 1-ethyl-1,2,4,5-tetrahydro-3H-1,2-benzodiazepin-3-one (56). An attempt to cyclise (55; R=H) yielded only the aminoquinolone (57).



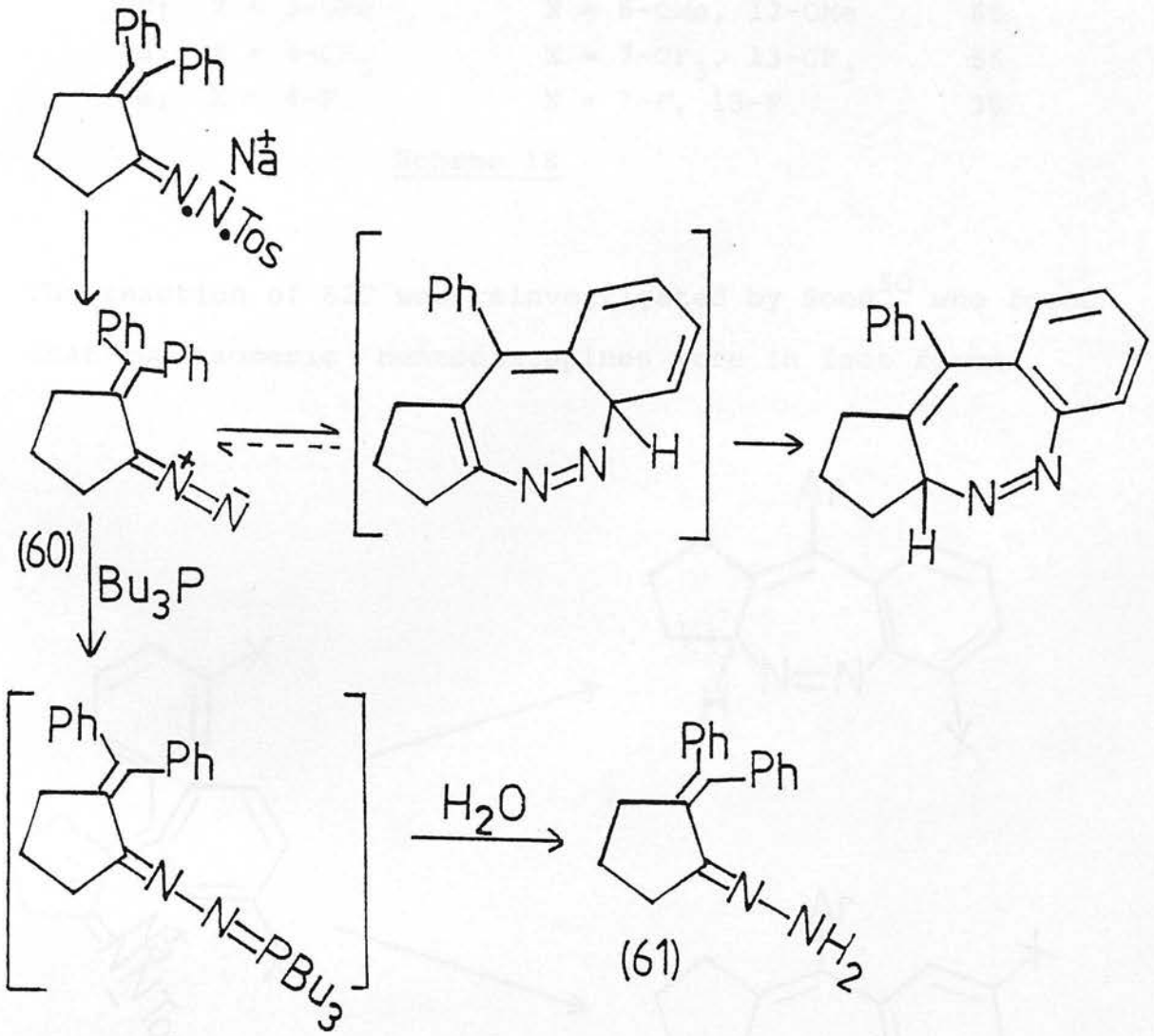
(55) (56) (57)

In 1952 Gill et al[49] reported that treatment of the diketone (58) with hydrazine gave the 4H-1,2-benzodiazepine (59).

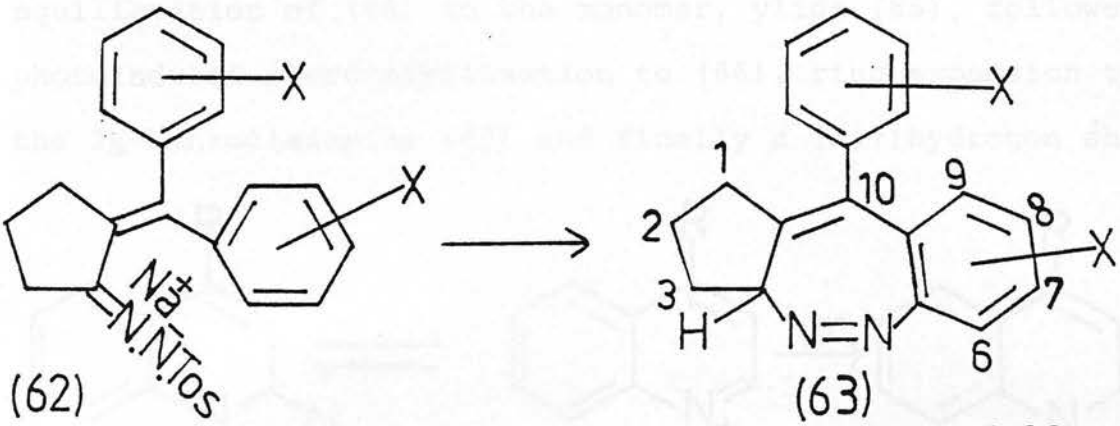


(58) (59)

These were the only references to 1,2-benzodiazepines in the literature until the work of Sharp and co-workers[45] which has already been mentioned in this introduction. Sharp and Thorogood[45] investigated the mechanism of diazepine formation. During these reactions a deep red colouration was present in the early stages which faded to yellow on completion indicating the presence of a diazo-intermediate (60). This was shown to be a diazepine precursor by a trapping experiment. In the presence of tributylphosphine no red colour was observed and the hydrazone (61) (85%) was isolated after hydrolysis. The identity of the hydrazone was confirmed by comparison with an authentic sample.



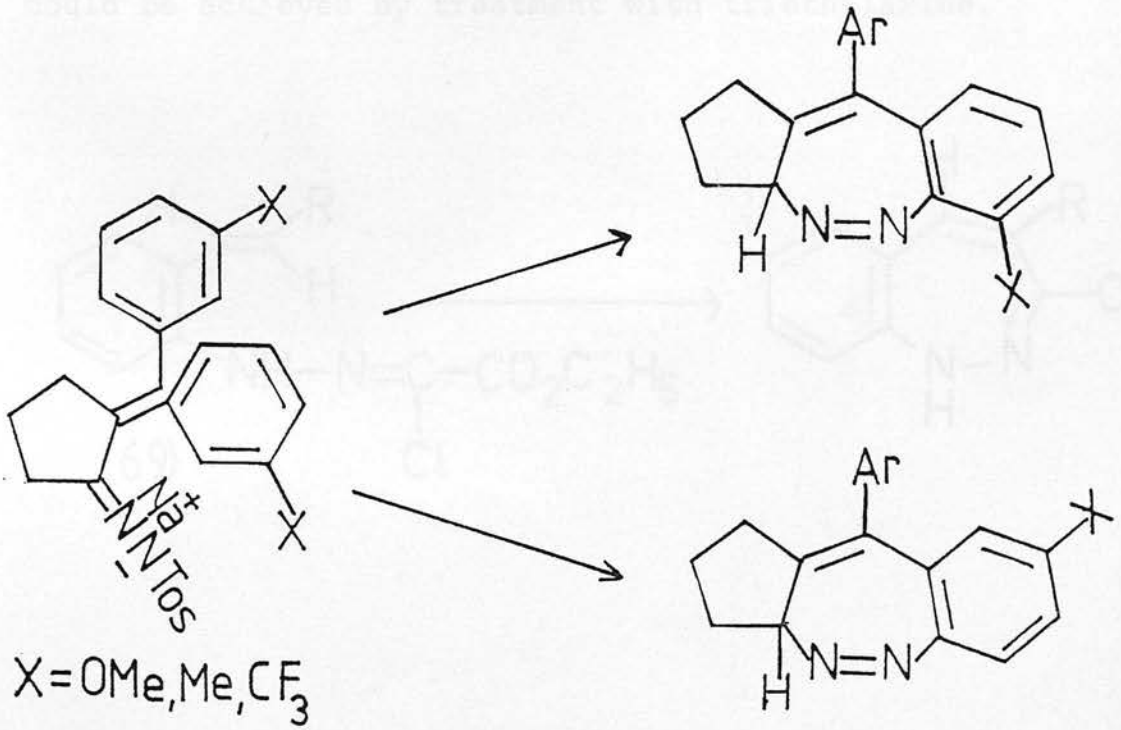
This reaction to give 1,2-benzodiazepines was shown to be general for a variety of aryl groups (Scheme 18).



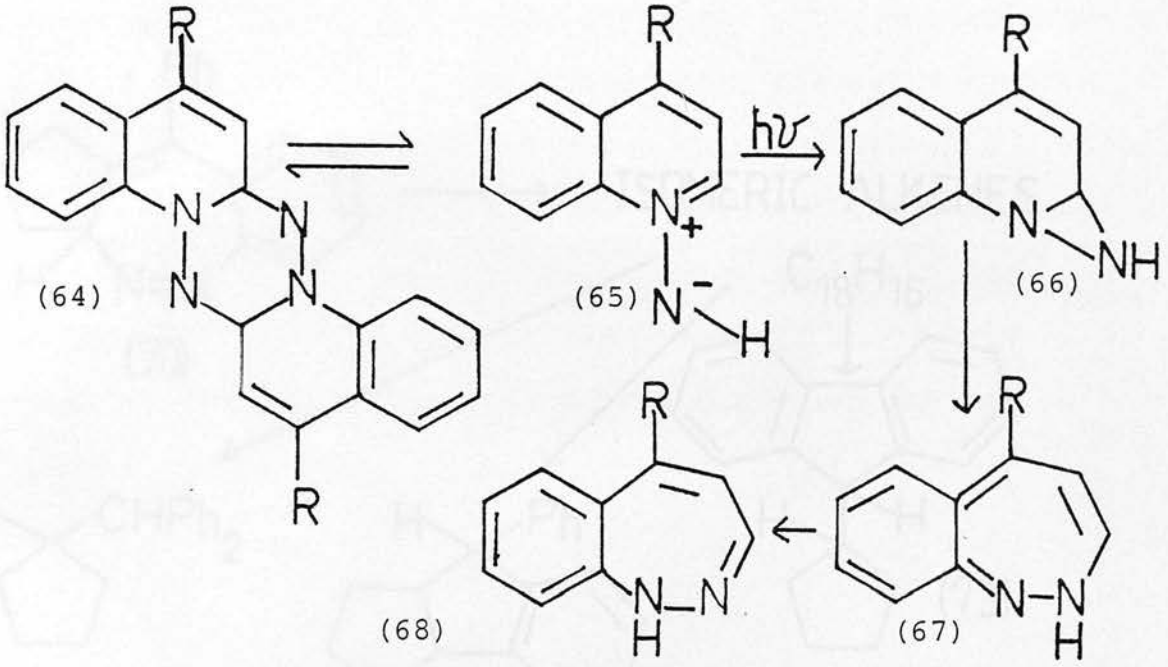
			Yield %
a;	X = H	X = H	80
b;	X = 4-Me	X = 7-Me, 13-Me	68
c;	X = 3-OMe	X = 6-OMe, 12-OMe	68
d;	X = 4-CF_3	X = 7-CF_3, 13-CF_3	56
e;	X = 4-F	X = 7-F, 13-F	38

Scheme 18

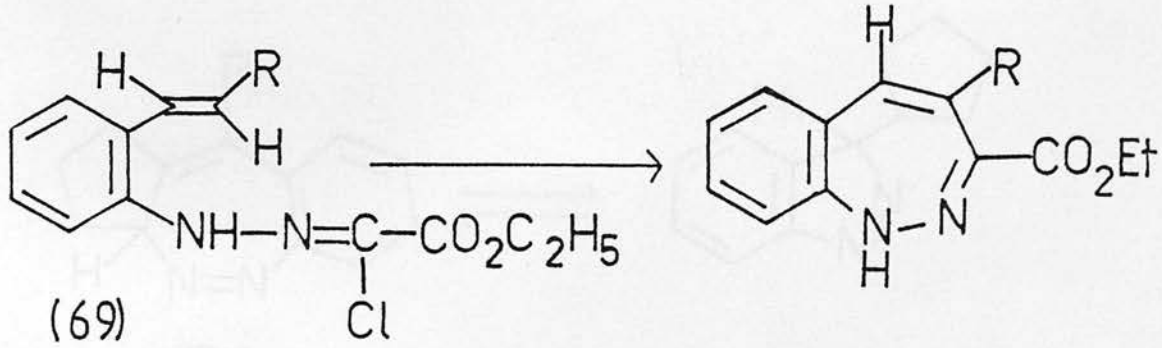
The reaction of 62C was reinvestigated by Sood[50] who found that two isomeric benzodiazepines were in fact formed.



Tsuchiya[51] has reported the formation of 1H-1,2-benzodiazepines (68) by the photolysis of N-iminoquinolinium ylide dimers (64). The mechanism postulated for this reaction is equilibration of (64) to the monomer, ylide (65), followed by photoinduced electrocyclisation to (66), ring expansion to the 2H-benzodiazepine (67) and finally a [1,7]hydrogen shift.

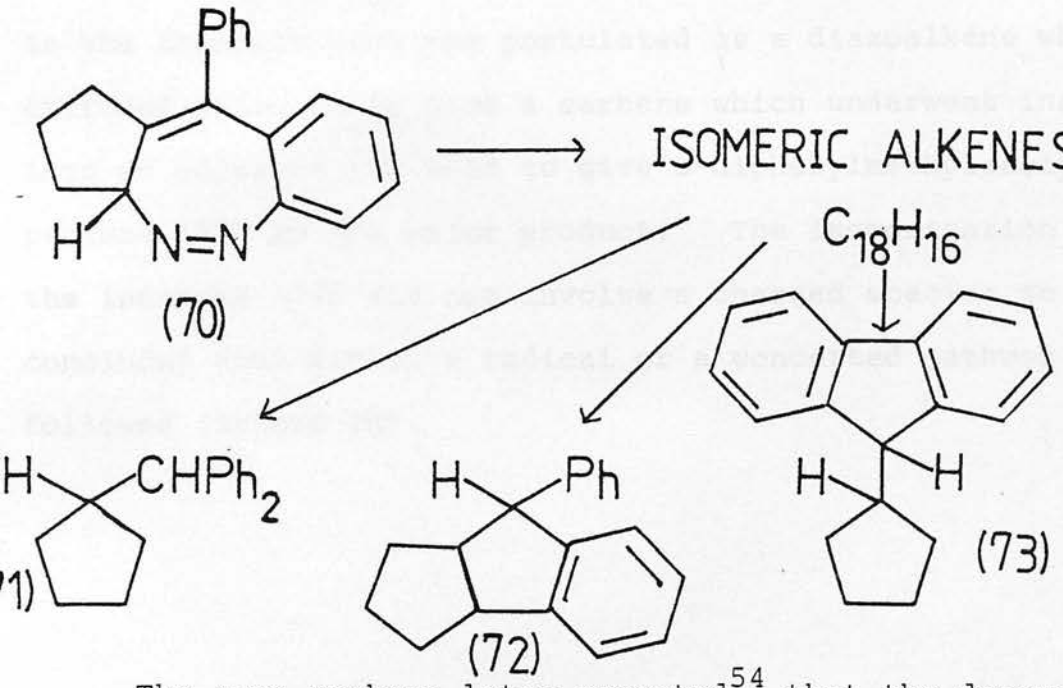


Garanti[52] showed that the cyclisation of phenylhydrazoyl chlorides (69) bearing α,β-unsaturation in the ortho position could be achieved by treatment with triethylamine.

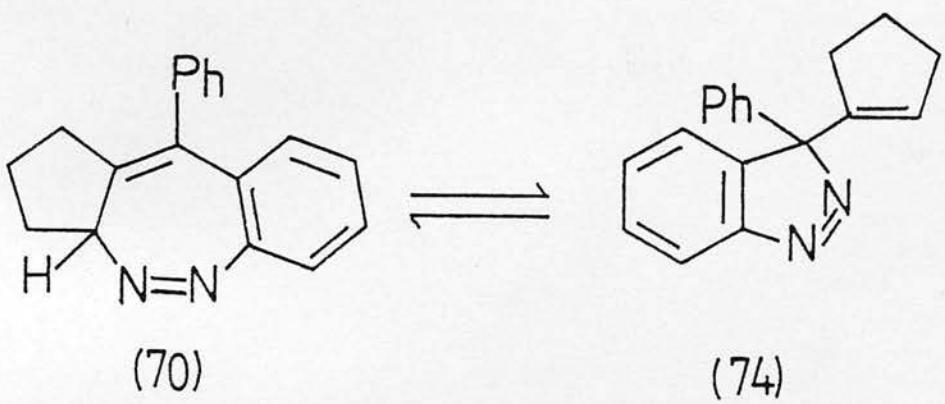


Thermolysis of 1,2-Benzodiazepines

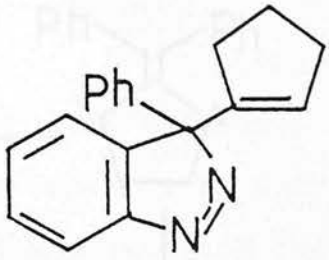
McEwan and Sharp[53] reported that the thermolysis of the 3H-1,2-benzodiazepine (70) in the gas phase at 400°C and at 110-220°C in various solvents produced a mixture of alkene isomers which on hydrogenation gave compounds (71) to (73) which were identified with authentic samples.



The same workers later reported[54] that the decomposition of (70) was accompanied by a faster equilibration with the isomeric 3H-indazole (74) via a 1,3-shift of the azo group.



The mechanism of these reactions was studied in detail by Stefaniuk.[55] He showed that the primary products of the decomposition of (70) were compounds (75) to (79) (Scheme 19). As a result of trapping experiments with tributylphosphine and deuterium labelling experiments he concluded that two separate pathways were involved in the thermal decomposition and isomerisation of 3H-1,2-benzodiazepines. The intermediate in the decomposition was postulated as a diazoalkene which extruded nitrogen to give a carbene which underwent insertion into an adjacent C-H bond to give 3-diphenylmethylenecyclopentene (77) as the major product. The isomerisation with the indazole (74) did not involve a charged species so he concluded that either a radical or a concerted pathway is followed (Scheme 20).



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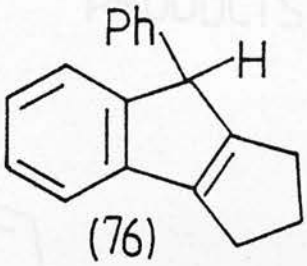

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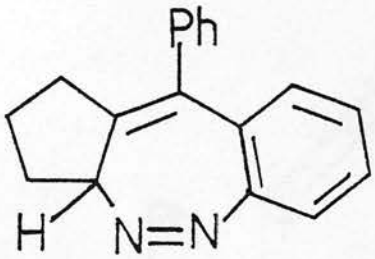

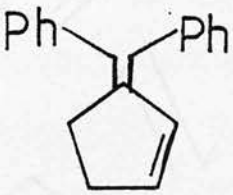

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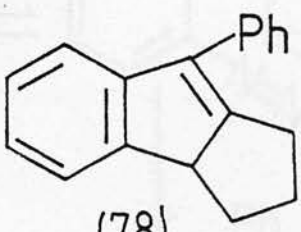

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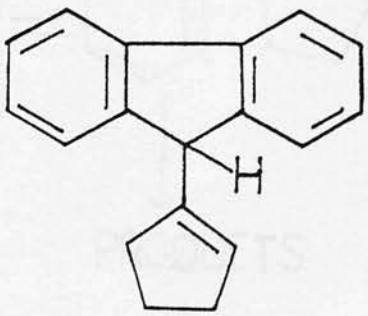
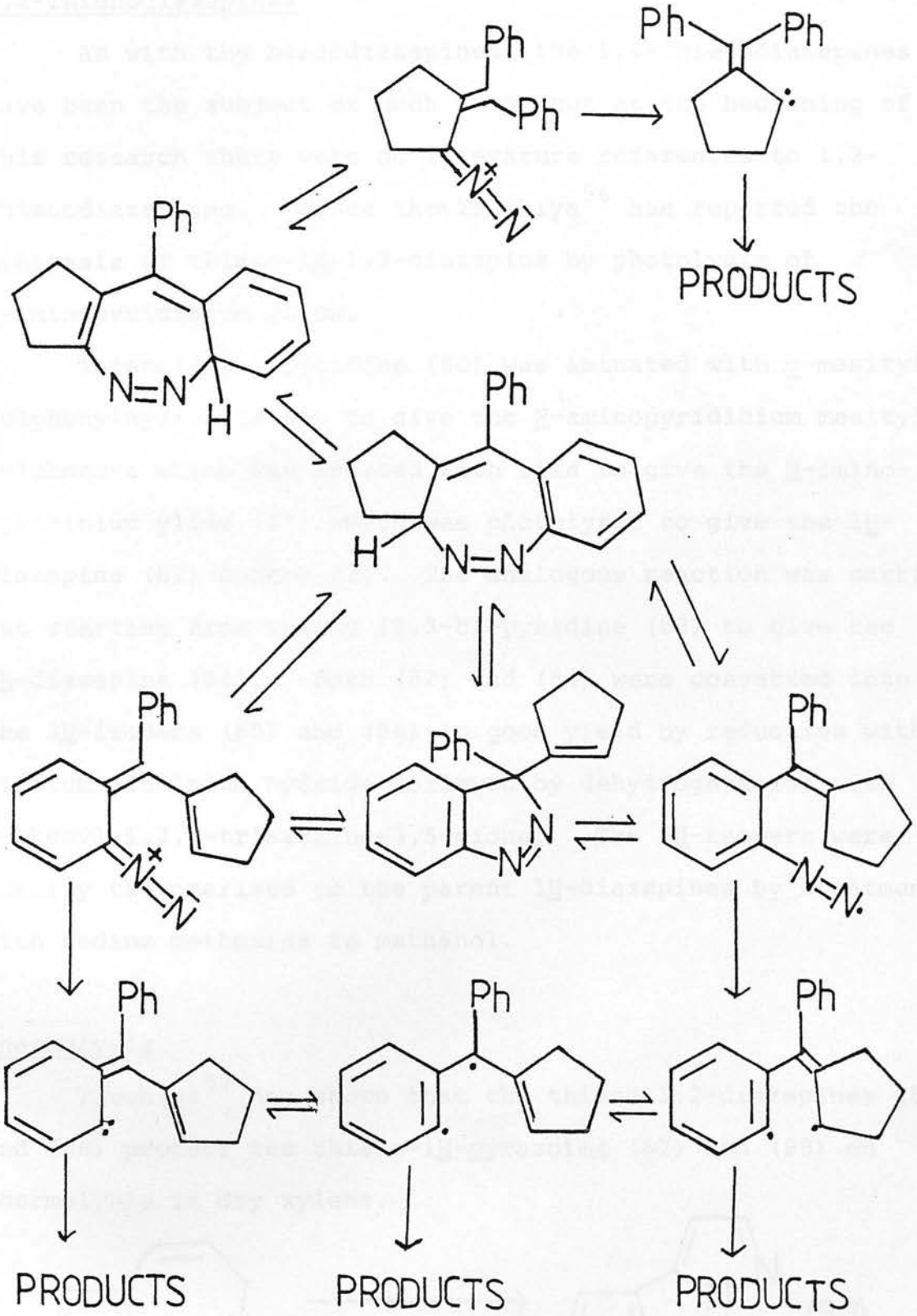


(79)

SCHEME 19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SCHEME 20

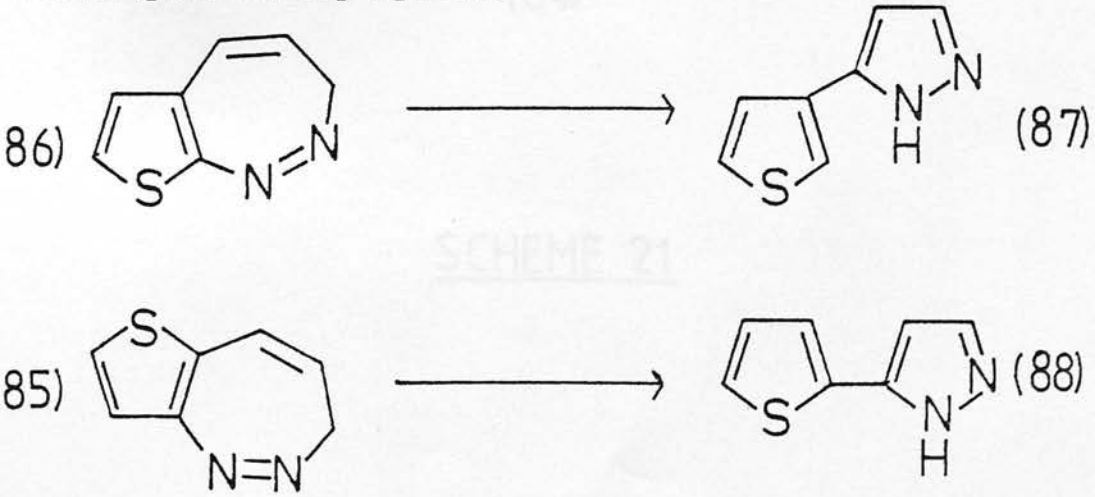
1,2-Thienodiazepines

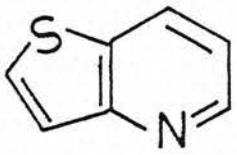
As with the benzodiazepines, the 1,4-thienodiazepines have been the subject of much study but at the beginning of this research there were no literature references to 1,2-thienodiazepines. Since then Tsuchiya[56] has reported the synthesis of thieno-1H-1,2-diazepine by photolysis of N-iminopyridinium ylide.

Thieno[3,2-b]pyridine (80) was aminated with o-mesitylene-sulphonylhydroxylamine to give the N-aminopyridinium mesitylene-sulphonate which was treated with base to give the N-imino-pyridinium ylide (81) which was photolysed to give the 1H-diazepine (82) (Scheme 21). The analogous reaction was carried out starting from thieno [2,3-b]-pyridine (83) to give the 1H-diazepine (84). Both (82) and (84) were converted into the 3H-isomers (85) and (86) in good yield by reduction with lithium aluminium hydride followed by dehydrogenation with 4-phenyl-1,2,4-triazoline-3,5-dione. The 3H-isomers were readily tautomerised to the parent 1H-diazepines by treatment with sodium methoxide in methanol.

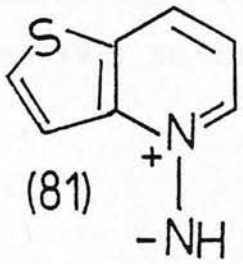
Thermolysis

Tsuchiya[57] has shown that the thieno-1,2-diazepines (85) and (86) produce the thieno-1H-pyrazoles (87) and (88) on thermolysis in dry xylene.





(80)



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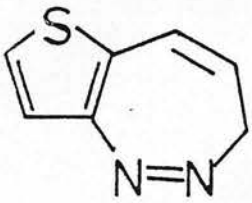

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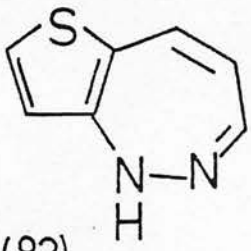

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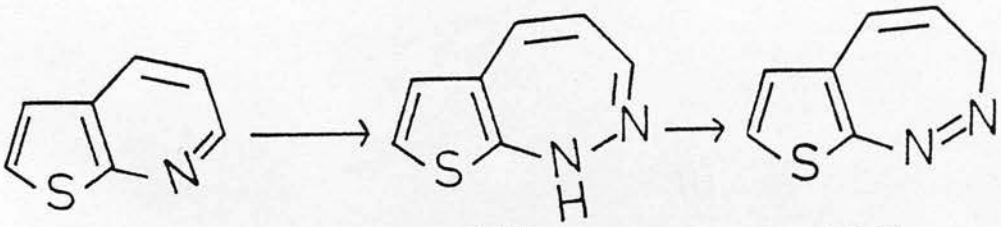
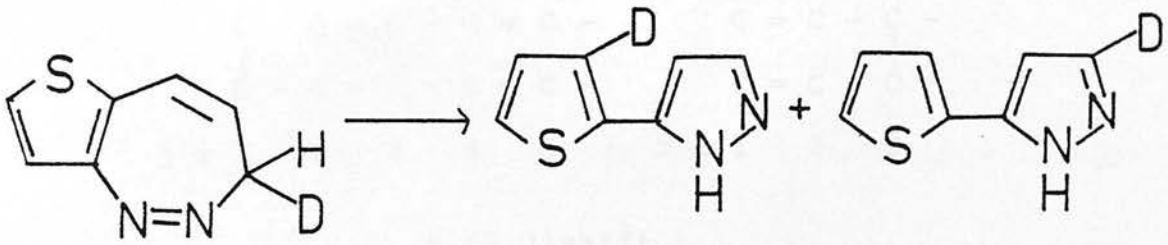


(83) (84) (86)

SCHEME 21

The mechanism suggested involved a thermally allowed [1,5]hydrogen shift, followed by C-N bond fission and ring closure to give the products. Support for this mechanism was obtained when thermolysis of the deuteriated diazepine (89) resulted in the formation of (90) and (91) in the ratio of 1:3.

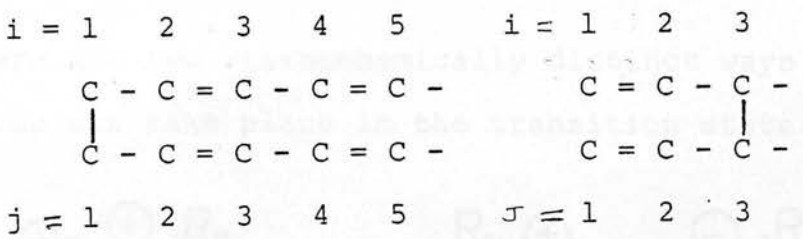


(89) (90) (91)

Thermal [i,j] Sigmatropic Rearrangements

Woodward and Hoffman[58] defined a sigmatropic change of order [i,j], as the migration of a σ bond, flanked by one or more π-electron systems, to a new position whose termini are (i-1) and (j-1) atoms removed from the original bonded loci in an uncatalysed intramolecular process.

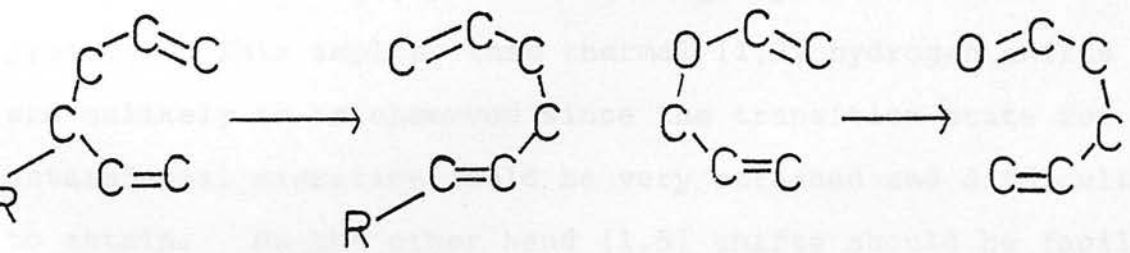
e.g.



a [3,3]shift

Thus the well-known Cope and Claisen rearrangements are sigmatropic changes of order [3,3].

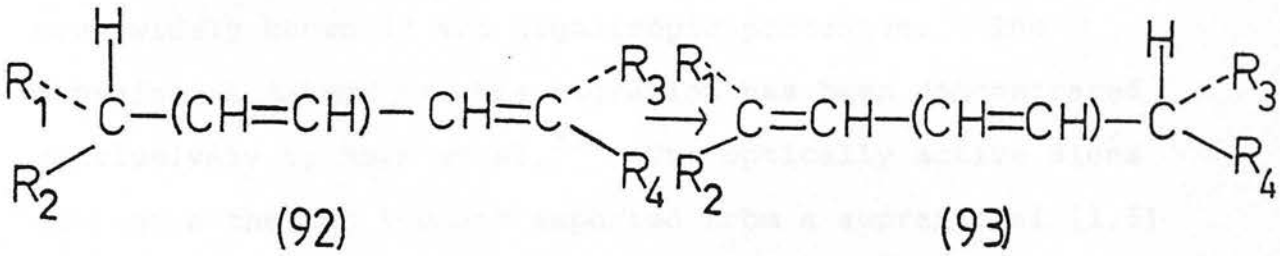
The Cope Rearrangement The Claisen Rearrangement



Certain sigmatorpic changes where i=1 are collectively named [1,j] sigmatropic reactions.

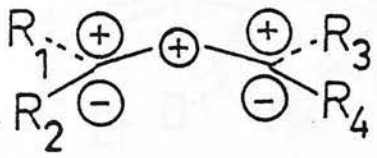
In the case of a [1,j] shift of a hydrogen atom between the ends of a polyene (92) → (93), then in the cyclic transition state the bonding hydrogen orbital must overlap simultaneously with orbitals on both the terminal carbon atoms. These carbon orbitals must also overlap with the other p-orbitals of the

polyene chain. The orbital on C-1 eventually becomes a p-orbital of the polyene while that on C-j becomes the sp^3 orbital of the new C-H bond.



(92) (93)

There are two stereochemically distinct ways in which the overlap can take place in the transition state:



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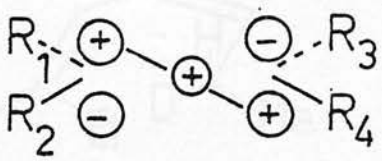
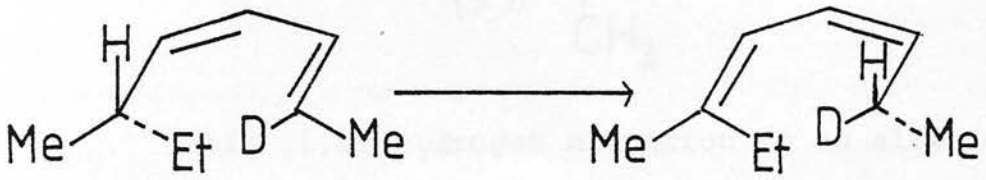


ANTARA

The selection rules predict that suprafacial [1,5] hydrogen shifts in neutral polyenes are thermally allowed, whereas [1,3] and [1,7] shifts must go by an antarafacial process. This implies that thermal [1,3] hydrogen shifts are unlikely to be observed since the transition state for antarafacial migration would be very strained and difficult to attain. On the other hand [1,5] shifts should be facile. The experimental observations fit in with this pattern: whereas concerted uncatalysed [1,3] hydrogen shifts have not been established in small or medium sized rings, [1,5] shifts in dienes are well known and there is evidence to support the view that they are concerted reactions.

[1,5] Sigmatropic Hydrogen Migration

[1,5] Sigmatropic hydrogen migration has been studied extensively in a wide variety of systems and is perhaps the most widely known of all sigmatropic processes. The suprafacial nature of this migration has been demonstrated conclusively by Roth et al.[59] The optically active diene (94) gave the two isomers expected from a suprafacial [1,5] shift, but gave neither of the isomers that would result from an antarafacial migration.



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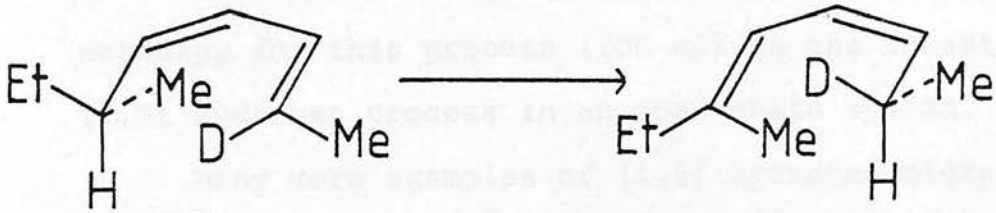
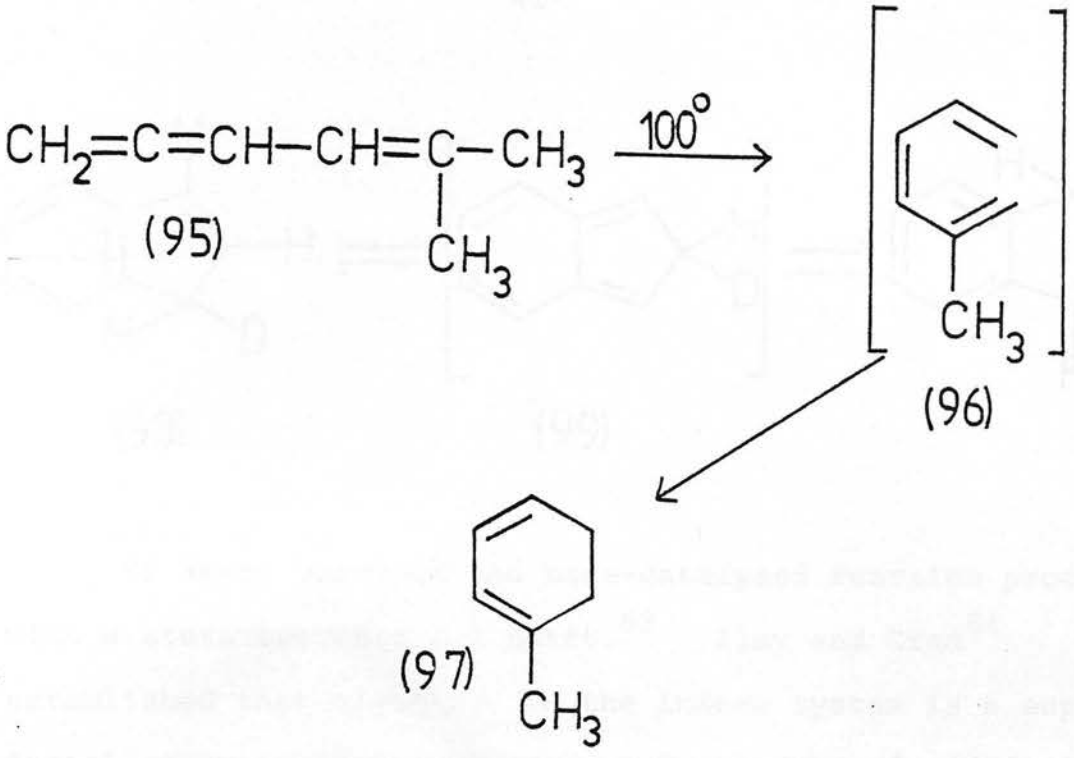


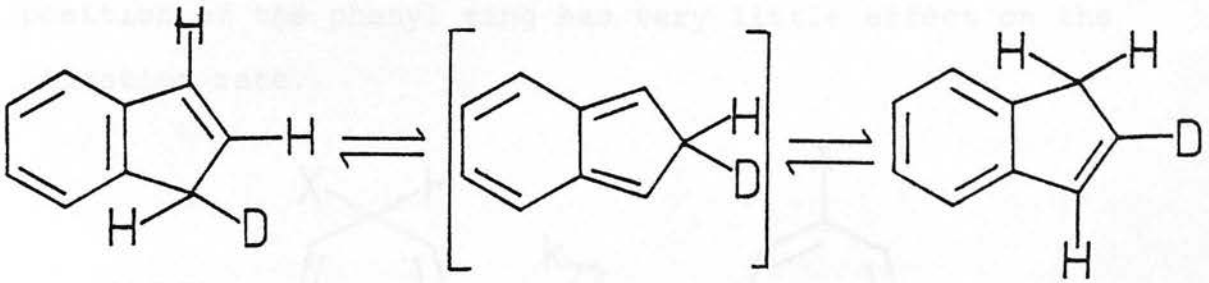
(94)

A particularly facile [1,5] hydrogen migration has been studied by Skattebol.[60] In the gas phase, 5-methyl-1,2,4-hexatriene (95) rearranges quantitatively to cis-2-methyl-1,3,5-hexatriene (96) which undergoes ring closure to 1-methyl-1,3-cyclohexadiene (97) under the reaction conditions.



This [1,5] hydrogen migration to an allenic carbon proceeds at a reasonable rate ($k(113^{\circ}C) = 2.73 \times 10^{-4}$ sec^{-1}) at temperatures 100° lower than for comparable conjugated 1,3-dienes such as 2-methyl-1,3-pentadiene.[61] The activation enthalpy for this process (100 kJ) is the lowest of any known [1,5] hydrogen process in an open chain system.

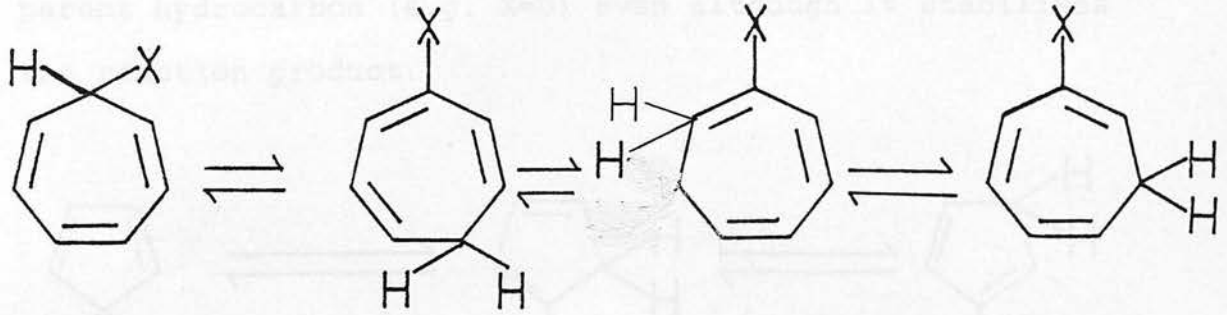
Many more examples of [1,5] hydrogen migrations in cyclic molecules have been studied. Roth[62] established that thermal hydrogen migration in indene was a concerted [1,5] process by substituting deuterium for hydrogen in appropriate positions and following the migration process by n.m.r. techniques. When 1-deuterio-indene (98) was heated at $200^{\circ}C$ the deuterium label was scrambled over all the non-benzenoid carbons, despite the necessity of proceeding through the unstable iso-indene (99).



(98) (99)

In sharp contrast the base-catalysed reaction proceeds with a stereospecific 1,3 shift.[63] Almy and Cram[64] established that migration in the indene system is a supra-facial, stereospecific process, and also showed a definite isotope effect that favoured hydrogen migration over deuterium migration.

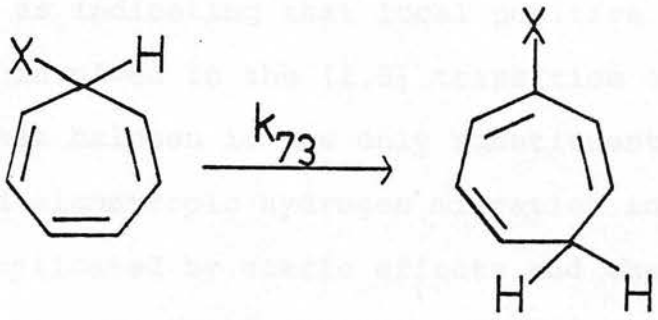
[1,5] migration in the 1,3,5-cyclohexatriene system has been extensively studied. Kloosterziel and his co-workers[65-68] have demonstrated that hydrogen migration occurs in the following sequence.



X=H, D, Me, Ph, p-$Me_2NC_6H_4$, OMe, SMe, CN.

These workers have also shown that migration rates from C-7 in (100) are dependent on the nature of X as are the final equilibrium compositions. Substitution of a

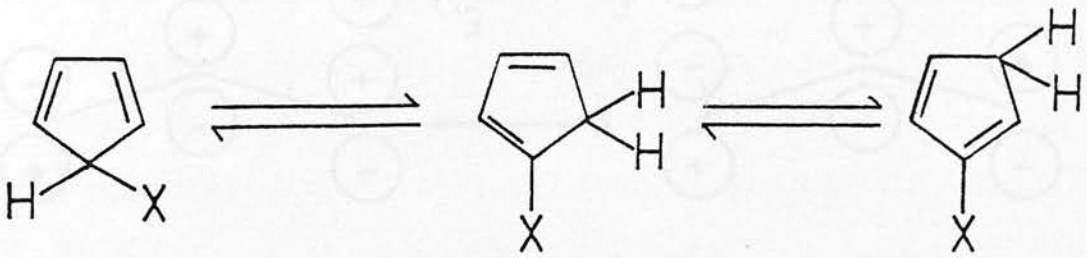
strongly activating (electron-donating) group on the para position of the phenyl ring has very little effect on the migration rate.

(100) 

k_{73}: $NMe_2 > OMe, Ph, \underline{p}\text{-}Me_2NPh > CN > SMe > Me > H$

Nozoe and Takashi[69] confirmed that phenyl and methoxyl were equal in rate-enhancing capability and that both were faster than hydrogen.

Breslow and co-workers[70] have studied the effect of halogen substitution on [1,5] hydrogen migration in cyclopentadiene (101). They found that halogen substitution slows the rate of hydrocarbon migration compared to the parent hydrocarbon (e.g. X=D) even although it stabilises the reaction product.



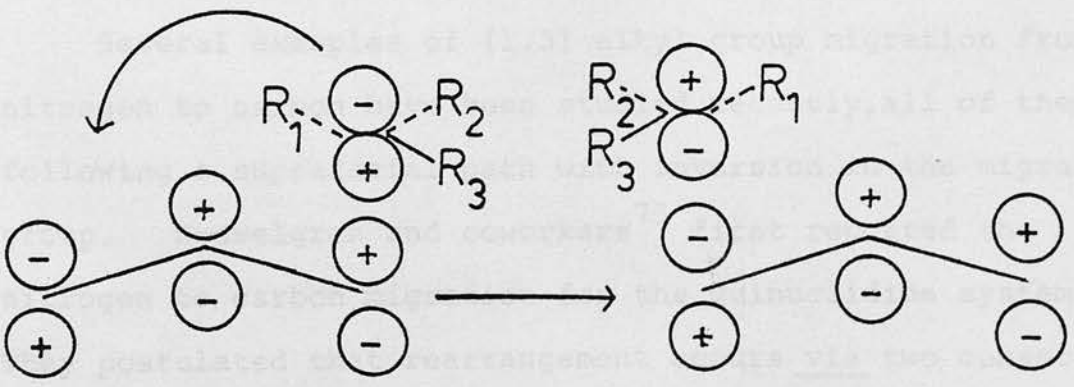
(101)

A considerable rate differential also exists between the halogen-SUBSTITUTED CYCLOPENTADIENES : (H > Cl > Br > I). Breslow has rationalised this behaviour as indicating that local positive charges on carbon must be involved in the [1,5] transition state. The fact remains that halogen is the only substituent which is known to retard sigmatropic hydrogen migration in a simple situation uncomplicated by steric effects and the mechanism of this retardation is still obscure and open to interpretation.

[1,j]Carbon Migrations

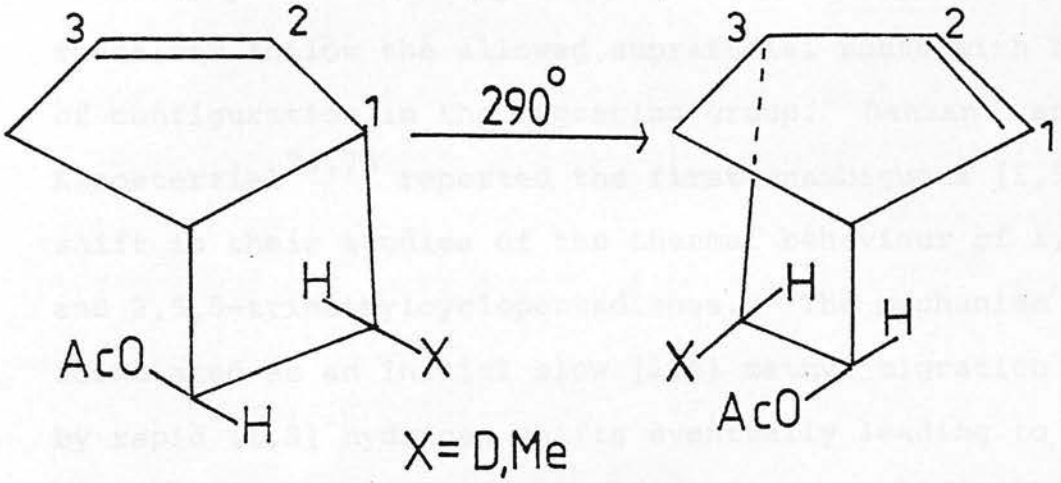
1) Alkyl Groups

When an alkyl group undergoes a [1,j] migration the same rules apply as for [1,j] hydrogen migrations. In addition, however, the opposite lobe of the alkyl bonding orbital can be used in the formation of a new σ-bond at the j-th carbon atom.

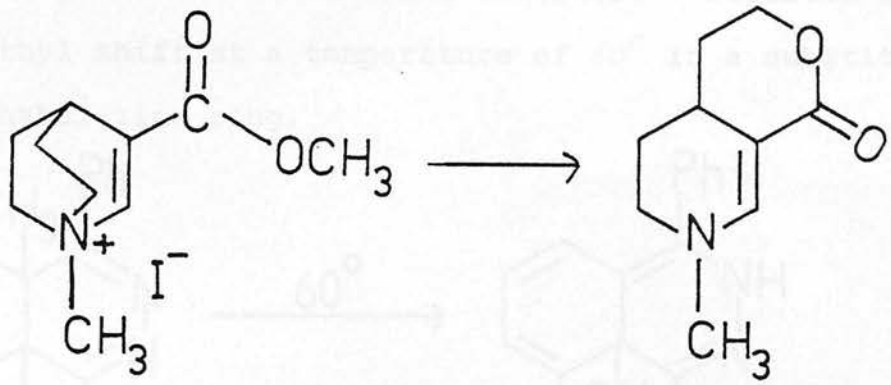


Two modes of [1,3] migration of sp^3-hybridised carbon are therefore allowed according to orbital symmetry considerations, suprafacial migration with inversion of configuration of the migrating carbon or antarafacial migration with retention. As in the case of hydrogen migration antarafacial migration is geometrically very strained and a clear-cut example of [1,3] antarafacial migration has yet to be described.

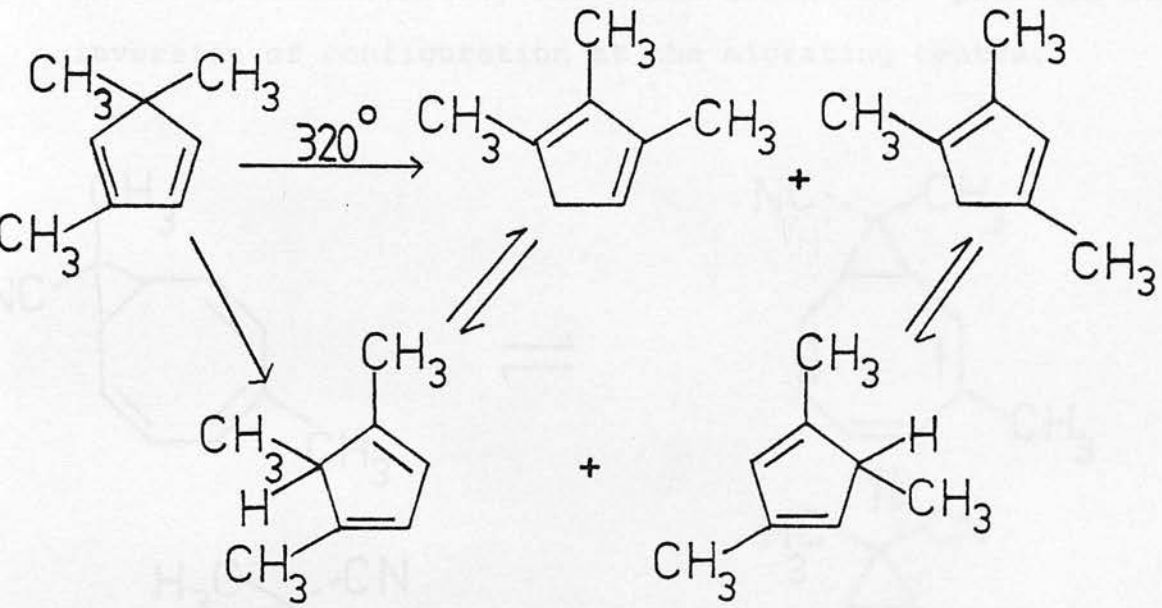
Berson and Nelson[71,72] have shown that inversion does occur for the suprafacial pathway in an elegant example in the bicyclo [3.2.0] hept-2-ene system.



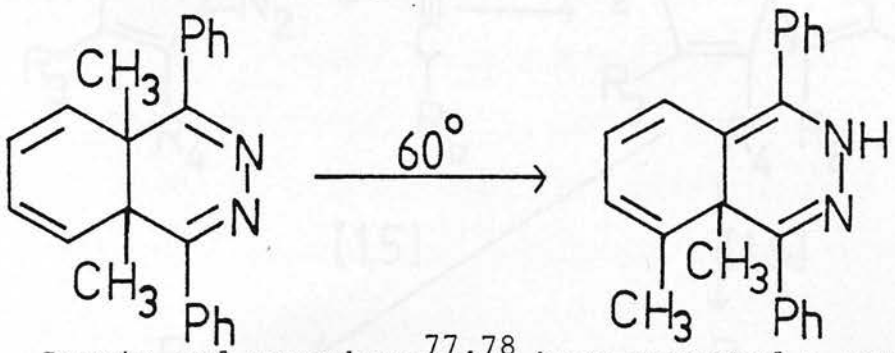
Several examples of [1,3] alkyl group migration from nitrogen to carbon have been studied recently,all of them following a suprafacial path with inversion in the migrating group. Hasselgren and coworkers[73] first reported the nitrogen to carbon migration for the quinuclidine system. They postulated that rearrangement occurs via two consecutive [1,3] shifts, each resulting in inversion. The first shift is from nitrogen to carbon while the second is from carbon to oxygen.



[1,5] alkyl group migration is now well documented in several cyclic dienic systems. All of the well-studied reactions follow the allowed suprafacial route with retention of configuration in the migrating group. Dehaan and Kloosterziel[74,75] reported the first unambiguous [1,5] alkyl shift in their studies of the thermal behaviour of 1,5,5- and 2,5,5-trimethylcyclopentadienes. The mechanism may be formulated as an initial slow [1,5] methyl migration followed by rapid [1,5] hydrogen shifts eventually leading to a preponderance of the more stable trimethylcyclopentadienes.

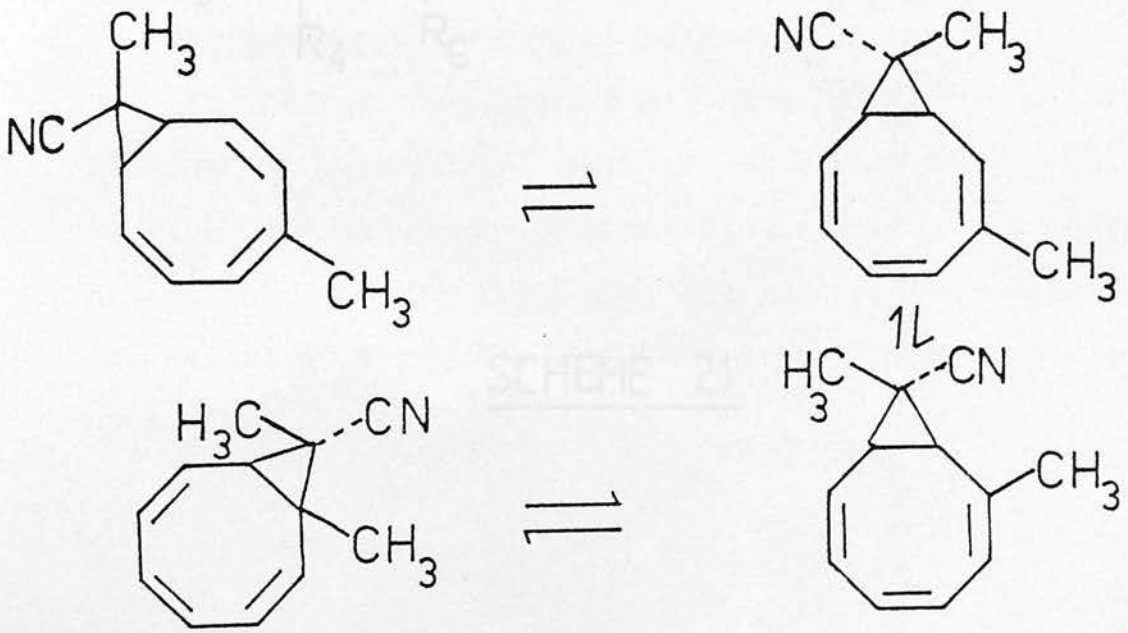


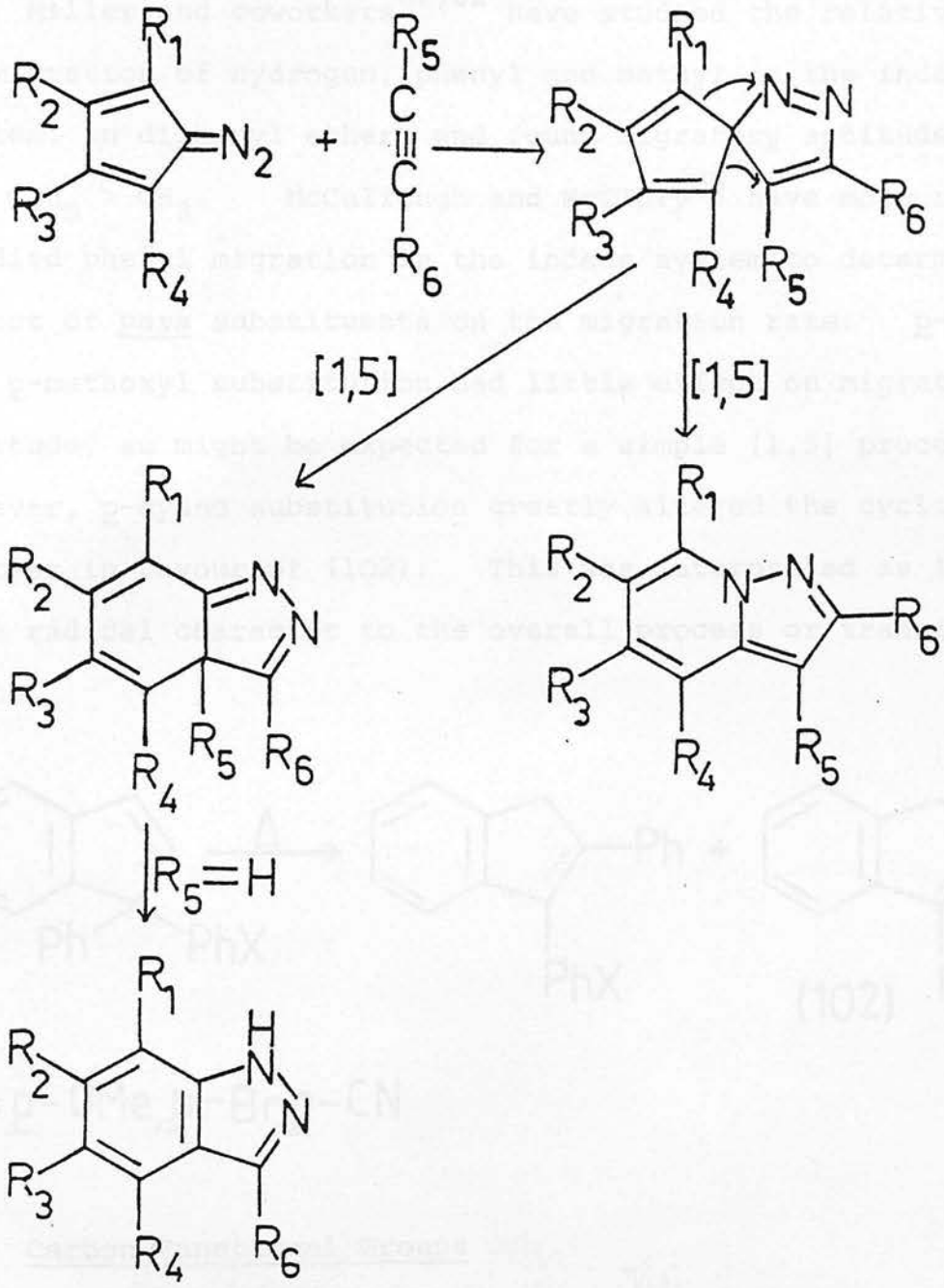
[1,5] alkyl migration has been found in several heterocyclic dienes. Maier and coworkers[76] reported a [1,5] methyl shift at a temperature of 60° in a substituted dihydrophthalazine ring.



Sergio and coworkers[77,78] have reported a particularly facile [1,5] alkyl shift from intermediary spiropyrazoles formed in the cycloaddition of disubstituted acetylenes to diazocyclopentadienes (Scheme 21). These [1,5] shifts are described as spontaneous and are in obvious contrast to the hydrocarbon analogues described by Kloosterziel[79] which rearrange at 280-380°.

Only one definite example of [1,7] carbon migration has been studied. Klarner[80] was able to establish that each step in the circumambulatory mechanism shown below proceeds with inversion of configuration at the migrating centre.

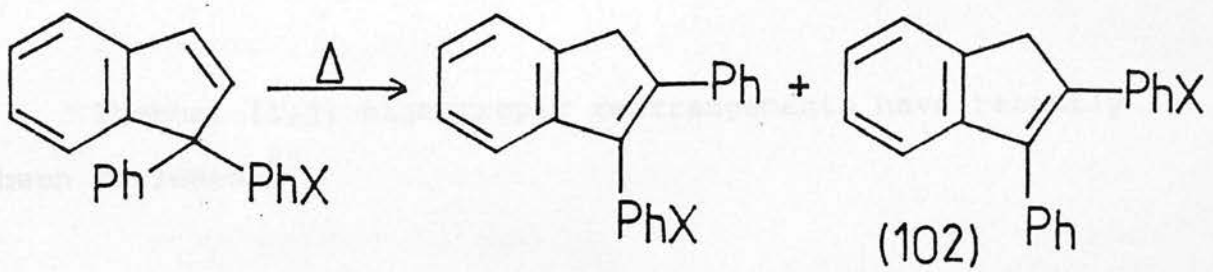




SCHEME 21

2) Aromatic Groups

Miller and coworkers[81,82] have studied the relative rates of migration of hydrogen, phenyl and methyl in the indene system, in diphenyl ether, and found migratory aptitudes where $H > C_6H_5 > CH_3$. McCullough and McClory[83] have more recently studied phenyl migration in the indene system to determine the effect of para substituents on the migration rate. p-Bromo and p-methoxyl substitution had little effect on migratory aptitude, as might be expected for a simple [1,5] process; however, p-cyano substitution greatly altered the cyclisation process in favour of (102). This was interpreted as indicating some radical character to the overall process or transition state.

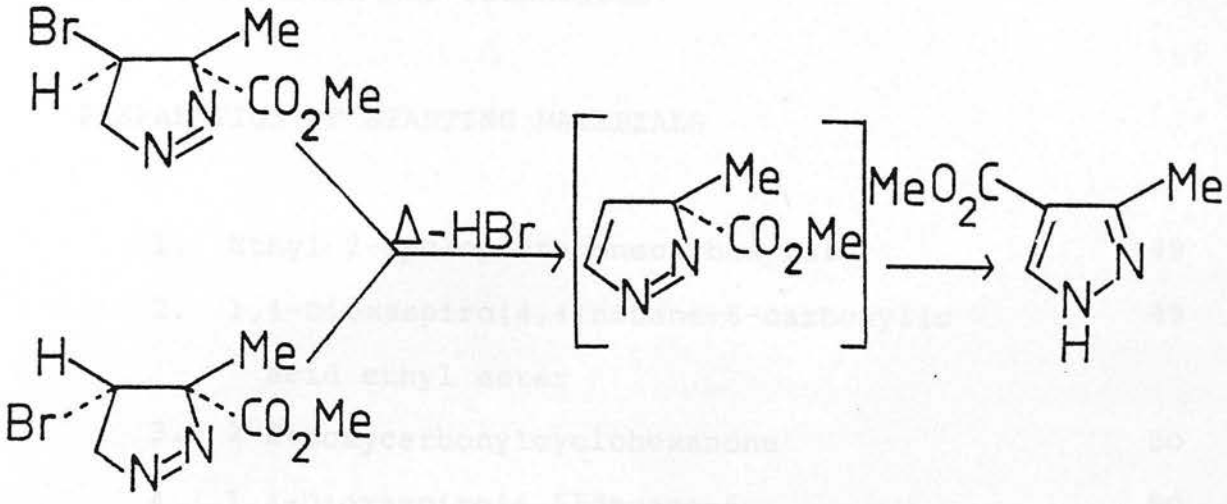


X= p-OMe, p-Br, p-CN

3) Carbon Functional Groups

In the past few years there have been a number of reports of apparent sigmatropic migration of carbon functional groups in five- and six-membered diene ring systems. With few exceptions, the migrating atom has been sp^2-hybridised, and the majority of reports have been concerned with carboalkoxy migration.

The first example of a [1,5] carboalkoxy shift was observed by McGreer and Wigfield[84] during the thermal dehydrobromination of 4-bromo-3-methyl-3-carbomethoxy-1-pyrazoline.



Thermal [1,j] sigmatropic rearrangements have recently been reviewed.[85]

Experimental

Page No.

ISOMERISATION REACTIONS OF DIAZEPINES AND PYRAZOLES

SPECTRAL APPENDICES

Symbols and Abbreviations

The symbols used in this Thesis are those in common use. In addition, the following symbols are used:

H.P.L.C.	high performance liquid chromatography
D.M.E.	1,2-dimethoxyethane
D.M.F.	N,N-dimethylformamide

Instrumentation and Techniques

Nuclear Magnetic Resonance Spectroscopy

Nuclear Magnetic Resonance Spectroscopy

^{1}H N.m.r. spectra were obtained on Varian EM-360 (60 M Hz) and HA 100 (100 M Hz) spectrometers, the latter operated by Mr. J.R.A. Millar. ^{13}C N.m.r. spectra were obtained on a Varian CFT 20 spectrometer operated by Mr. J.R.A. Millar.

Mass Spectrometry

Mass spectra were obtained on an AEI MS 902 spectrometer, operated by Mr. D.J.A. Thomas.

Infrared Spectroscopy

Liquid samples were examined as thin films and solid samples as nujol mulls, both on polished sodium chloride plates, using a Perkin-Elmer 157 G grating spectrometer.

Elemental Analysis

Microanalyses were carried out by Mr. J. Grunbaum using a Perkin-Elmer model 240 analyser.

Gas Liquid Chromatography

A Pye Series 104 Chromatograph containing columns with an internal diameter of $^{1}/_{4}$" of length 5' was used for analytical investigations. This chromatograph used a flame ionisation detector and nitrogen carrier gas. The following stationary phases, supported on 80-100 mesh celite were employed: silicone elastomer (SE 30), carbowax and silicone oil (OV 1 and OV 17).

High Performance Liquid Chromatography

The high performance liquid chromatography analysis utilised a 15 x 0.5 cm metal column packed with Spherisorb 5 μm silica or alumina, used with Jobling/Milton-Roy constant flow reciprocating pumps and u.v. detectors: Cecil CE212 (variable wavelength) or Jobling /LDC (fixed wavelength). A Spectra-Physics Minigrator integrator was used to measure peak areas.

Medium Pressure Preparative Liquid Chromatography

Glass columns (100 x 1.5 cm and 100 x 2.5 cm) packed with silica gel (Merck Kieselgel 60,230-400 mesh) were used and were cleaned between separations by back flushing with dry ethyl acetate. Samples were either injected or pre-absorbed onto a small scrubber column (25 x 1.5 cm), packed as above, which protected the separation column from contamination. The diaphragm-type pump (100 p.s.i. maximum) was supplied by Metering Pumps Ltd. and the U.V. detector (280 nm) supplied by Jobling(LDC).

Thin Layer Chromatography

Chromatograms were obtained on 0.33 mm layers of alumina (Merck, Aluminium oxide G) or silica gel (Merck, Kieselgel G). Components in the developed chromatogram were detected by their fluorescence in ultraviolet light, or by their reaction with iodine.

Melting Points

The melting points of all new compounds were obtained on a Kofler hot-stage apparatus.

Drying

Anhydrous magnesium sulphate was used to dry all organic solutions, unless otherwise stated.

Purification of Solvents

"Super-dry" ethanol was prepared as described by Vogel[86] (method 1).

1,2-Dimethoxyethane, benzene and cyclohexane were freshly distilled from calcium hydride as required.

Petrol refers to the fraction b.p. 40-60° unless otherwise stated.

Preparation of Starting Materials

1. Ethyl 2-cyclopentanonecarboxylate

Diethyl adipate (250 g, 1.25 mol) was added to well-stirred mixture of sodium hydride (82 g, 80% dispersion, 2.68 mol) in sodium-dried toluene (800 ml) at 45°. The mixture was stirred vigorously at room temperature for 7 h and then left standing overnight at room temperature. The reaction mixture was acidified with concentrated hydrochloric acid and water (500 ml) was added. The organic layer was separated and the aqueous layer extracted with toluene. The toluene solutions were then combined, dried and concentrated under reduced pressure to give a colourless oil. Distillation of the oil gave ethyl 2-cyclopentanonecarboxylate (128.5 g, 66%) b.p. 116° at 18 mm Hg (lit.,[87] 108-110° at 12-13 mm Hg); i.r. (film) 1760 (C=O) and 1730 cm^{-1}(C=O).

2. 1,4-Dioxaspiro[4,4]nonane-5-carboxylic acid ethyl ester

This compound was prepared by the method of Thorogood.[87] Ethyl 2-cyclopentanonecarboxylate (142 g, 0.92 mol), ethylene glycol (111 g, 1.79 mol), 4-toluenesulphonic acid (0.85 g) and dry benzene (316 ml) were heated under reflux for 8 h and the water formed in the reaction removed using a Dean and Stark apparatus. After cooling the reaction mixture, benzene (85 ml) was added, and the benzene solution washed with sodium carbonate solution (2 x 100 ml, 15% w/v), and then with water (2 x 100 ml). The benzene solution was dried and concentrated under reduced pressure to give a colourless oil. Distillation gave 1,4-dioxaspiro[4,4] nonane-5-carboxylic acid ethyl ester (101.6 g, 55%), b.p. 76° at 0.5 mm Hg (lit.,[87] 98-100° at 0.7 mm Hg).

Examination by g.l.c. (2½% OV 17 125°) showed that the product was pure. I.r. (film) 1730 cm^{-1} (C=O).

3. 2-Ethoxycarbonylcyclohexanone

This compound was prepared in collaboration with Mr. T.W. Naisby, by the method of Snyder, Brooks and Shapiro,[88] in which diethyl oxalate and cyclohexanone were reacted together in the presence of base. The products were distilled on a Nester-Faust spinning band apparatus to give 2-ethoxycarbonylcyclohexanone (44%) b.p. 72° at 0.4 mm Hg (lit.,[87] 94-96° at 7 mm Hg).

4. 1,4-Dioxaspiro[4,5]decane-6-carboxylic acid ethyl ester

This compound was prepared in collaboration with Mr. T.W. Naisby by the method of Thorogood[87] in which 2-ethoxycarbonylcyclohexanone was condensed with ethylene glycol. Distillation gave 1,4-dioxaspiro[4,5]decane-6-carboxylic acid ethyl ester (61%) b.p. 131-132° at 9 mm Hg (lit.,[87] b.p. 126-127° at 8 mm Hg).

5. 4-t-Butylaniline

This was prepared by the method of Harger[89] in which a mixture of 4-t-butylnitrobenzene, iron powder, ethanol and water was reacted with concentrated hydrochloric acid. The crude product was extracted from the mixture and distilled to give 4-t-butylaniline (72%) b.p. 120° at 16 mm Hg (lit.,[89] 108-110° at 8 mm Hg).

6. 4-t-Butylacetanilide

Acetylation of 4-t-butylaniline was effected using the method of Harger[89] by the addition of acetic anhydride to a boiling solution of the amine in acetic acid. The product was crystallised from a 6:1 benzene:petrol solution to yield 4-t-butylacetanilide (76%) m.p. 172-173° (lit.,[89] 174°).

7. 2-Bromo-4-t-butylacetanilide

This was prepared by an adaptation of the method of Johnson and Sandborn[90] involving the direct bromination of 4-t-butylacetanilide in glacial acetic acid at 45°. Recrystallisation from benzene yielded 2-bromo-4-t-butylacetanilide (74%) m.p. 152-154° (lit.,[91] 156-158°).

8. 1-Bromo-3-t-butylbenzene

This was prepared by the method of Berliner and Chen.[92] 2-Bromo-4-t-butylacetanilide was boiled under reflux in ethanol and concentrated hydrochloric acid for 4 h. The reaction mixture was concentrated under reduced pressure, cooled and filtered to give 2-bromo-4-t-butylanilinehydrochloride (85%). The hydrochloride was diazotised and then reacted with hypophosphorous acid. Distillation produced 1-bromo-3-t-butylbenzene (75%) b.p. 102° at 11 mm Hg (lit.,[92] 71-72° at 4 mm Hg). ^{1}H N.m.r. spectrum: see Appendix.

9. 1-Bromo-3-ethoxybenzene

This was prepared by the method of Doran[93] involving the reaction of 3-bromophenol with diethylsulphate in aqueous sodium hydroxide solution. Separation of the organic layer and distillation produced 1-bromo-3-ethoxybenzene (70%) b.p. 106° at 12 mm Hg (lit.,[93] 228-231° at 760 mm Hg). ^{1}H N.m.r. spectrum: see Appendix.

10. 2-Bromo-4-ethylacetanilide

This was prepared by an adaptation of the method of Johnson and Sandborn[89] involving the direct bromination of 4-ethylacetanilide, which had been prepared *in situ* by boiling 4-ethylaniline in glacial acetic acid. The product was recrystallised from petrol:benzene 4:1 giving 2-bromo-4-ethylacetanilide (62%) m.p. 90° (lit.,[92] 93°).

11. 1-Bromo-3-ethylbenzene

This was prepared by the method of Berliner and Chen.[92] 2-Bromo-4-ethylacetanilide was boiled under reflux in ethanol and concentrated hydrochloric acid for 4 h. On cooling the reaction mixture was filtered to give 2-bromo-4-ethylaniline-hydrochloride (90%). The hydrochloride was diazotised and then reacted with hypophosphorous acid. Distillation produced 1-bromo-3-ethylbenzene (84%) b.p. 86° at 16 mm Hg (lit.,[92] 64° at 5 mm Hg). ^{1}H N.m.r. spectrum: see Appendix.

12. 1-Bromo-3,5-dimethylbenzene

This compound was prepared by Mr. C.B. Argo, as part of an Honours Project,[94] by the bromination of 1-amino-2,4-dimethylbenzene using the method of Fischer and Windaus[95]

followed by diazotisation and deamination using the method of Fieser.[95] Distillation of the crude product gave 1-bromo-3,5-dimethylbenzene (49%) b.p. 82-83° at 1 mm Hg. (lit.,[95] 98-99° at 20 mm Hg). ^{1}H N.m.r. spectrum: see Appendix.

13. 2-Amino-3-bromotoluene

This compound was prepared in collaboration with Mr. T.W. Naisby.

a) 2-Nitro-3-aminotoluene

This compound was prepared by the method of Tomisek et al[97] from 3-toluic acid. 3-Toluic acid was nitrated, with fuming nitric acid, to give 2-nitro-3-toluic acid (50%) m.p. 214-217° (lit.,[96] 213-220°) which was then suspended in concentrated sulphuric acid and reacted with sodium azide to give 2-nitro-3-aminotoluene (72%) m.p. 105-107° (lit.,[97] 108-111°).

b) 2-Nitro-3-bromotoluene

This compound was prepared by an adaptation of the method of Geerling and Wibaut[98] by the diazotisation of 2-nitro-3-aminotoluene with sodium nitrite in hydrobromic acid in the presence of copper oxide and copper powder. Distillation gave 2-nitro-3-bromotoluene (68%) b.p. 128-129° at 15 mm Hg (lit.,[98] 152-154° at 30 mm Hg).

c) 2-Amino-3-bromotoluene

This was prepared by an adaptation of the method of Burton, Hammond and Kenner,[99] by the reduction of 2-nitro-3-bromotoluene by stannous chloride. Distillation gave 2-amino-3-bromotoluene (56%) b.p. 68-70° at 0.9 mm Hg (lit.,[98] 124-160° at 36 mm).

14. Deuterohypophosphorous Acid

This was prepared by the method of Hammond and Grundemeier[100] involving the exchange of hypophosphorous acid with deuterium oxide. Hypophosphorous acid (60 ml of 50%) was concentrated to constant weight on a high vacuum rotary evaporator at 20°. Deuterium oxide (99.5%)(34 ml) was added and the solution left standing for 30 h, after which the deuterium oxide was removed on a high vacuum rotary evaporator. This process was repeated twice and then deuterium oxide (34 ml) was added to dilute the acid to 50 vol.%.

15. 2-$^2H_2$-Amino-3-bromotoluene

This was prepared by an adaptation of the method of Renaud, Kovachic and Leitch.[101] Deuterium oxide (25 ml) containing one pellet of potassium hydroxide was added to 2-amino-3-bromotoluene (20.5 g). The mixture was boiled under reflux under dry nitrogen with vigorous stirring for 2 h. The organic layer was separated and the process repeated. Separation gave 2-$^2H_2$-amino-3-bromotoluene (20 g).

16. 4-$^2H_2$-Amino-3-bromotoluene

This was prepared by Mr. I.D. Thomson as part of a Carnegie Project,[102] using the procedure described for 2-$^2H_2$-amino-3-bromotoluene.

17. 2-Deutero-3-bromotoluene

This was prepared by an adaptation of the method of Renaud, Kovachic and Leitch.[101] 2-$^2H_2$-Amino-3-bromotoluene (19.6 g 0.1 mol) was added to 50% deuterohypophorous acid in deuterium oxide and deuterium oxide (30 ml). The mixture

was warmed until it became homogeneous and then cooled rapidly to -5°C with vigorous stirring to produce a fine suspension of the amine salt. A solution of sodium nitrite (8.0 g) in deuterium oxide (10 ml) was added slowly with vigorous stirring so that the temperature was maintained at -5°. After the addition the solution was stirred at -5° for 30 min, then left standing at 0°C overnight.

The mixture was extracted with ether and the combined extracts were washed with water, sodium bicarbonate solution, and finally water and then, dried and evaporated under reduced pressure. Distillation gave 2-deutero-3-bromotoluene (10.1 g, 56%) b.p. 66-67° at 12 mm Hg.

The deuterium content was estimated by 100 mHz ^{1}H n.m.r. and found to be 97%.

18. 4-Deutero-3-bromotoluene

This was prepared by Mr. I.D. Thomson[102] by the deamination of 4-d_2-amino-3-bromotoluene in deuterohypophosphorous acid by the same procedure as described for 2-deutero-3-bromotoluene. The deuterium content was estimated by mass spectroscopy and found to be 92%.

19. 2,3,5-Tribromothiophene

This was prepared by the method of Troyanowsky[103] by direct bromination of thiophene. The crude product was distilled giving 2,3,5-tribromothiophene (65%) b.p. 119-120° at 12 mm Hg (lit.,[103] 135-138° at 17 mm Hg).

20. 3-Bromothiophene

This was prepared by the method of Gronowitz[104] involving the dehalogenation of 2,3,5-tribromothiophene by zinc dust in glacial acetic acid and water. The crude product was steam distilled from the reaction mixture and then distillation gave 3-bromothiophene (74%) b.p. 160° at 760 mm Hg (lit.,[104] 159-161° at 760 mm Hg).

21. 3-Thiophenecarboxaldehyde

This was prepared by the method of Gronowitz[105] involving the addition of 3-thienyllithium (prepared from 3-bromothiophene and n-butyllithium at -70°C) to N,N-dimethylformamide in ether. Distillation gave 3-thiophenecarboxaldehyde (45%) b.p. 70° at 12 mm Hg (lit.,[105] 86-87° at 20 mm Hg).

22. Di-(3-thienyl)carbinol

This was prepared by the method of Gronowitz[106] involving the reaction of 3-thienyllithium with 3-thiophenecarboxaldehyde at -70°. Recrystallisation from ligroin gave di-(3-thienyl)carbinol (77%) m.p. 68° (lit.,[106] 68-69°).

23. Di-3-thienyl ketone

This was prepared by the method of Gronowitz[106] involving the oxidation of di-(3-thienyl)carbinol in acetic acid by chromium trioxide. Recrystallisation from methanol gave di-3-thienyl ketone (58%) m.p. 75-76° (lit.,[106] 78-80°).

24. Di-2-thienyl ketone

This was prepared by the method of Acheson, MacPhee, Philpott and Barltrop[107] involving the reaction of 2-thienoic acid with thiophene in the presence of phosphoric anhydride. The crude product was distilled giving di-2-thienyl ketone (65%) m.p. 86° (from ligroin) (lit.,[107] 88-89°).

25. 2-Benzoylthiophene

This was prepared by the method of Hartough and Kosak[108] involving the reaction of benzoyl chloride with thiophene in the presence of fused zinc chloride. The crude product was distilled giving 2-benzoylthiophene (37%) m.p. 54-55° (ligroin) (lit.,[108] 56.5-57°).

26. Cyclohexanone-*N*,*N*-dimethylhydrazone

This was prepared by boiling cyclohexanone and 1,1-*N*,*N*-dimethylhydrazine in benzene under reflux. The water formed was removed by a Dean and Stark apparatus. After removal of the benzene, distillation gave cyclohexanone-*N*,*N*-dimethyl hydrazone (80%) b.p. 55° at 11 mm Hg (lit.,[109] 59-60° at 11.5 mm).

27. 4-Cyanobutyltriphenylphosphonium bromide

5-Bromovaleronitrile (1 g, 6 mmol) and triphenylphosphine (1.7 g, 7 mmol) were boiled under reflux in xylene (20 ml) for 26 h. On cooling the colourless precipitate was filtered off and recrystallised from amyl alcohol to give 4-cyanobutyl-triphenylphosphonium bromide (2.2 g, 86%) m.p. 229-231° (lit.,[110] 230-232°) (Found: C,64.9; H,5.4; N,3.3. Calcd. for $C_{23}H_{23}BrNP$ C, 65.1; H, 5.4; N, 3.3%); i.r. (nujol) 2250 cm^{-1} (C≡N).

Preparation of α,β-Unsaturated Ketones

The following ketones were prepared by adaptations of the method of Sharp and Thorogood.[45]

1. 2-[Bis-(3-t-butylphenyl)methylene]cyclopentanone

A Grignard reagent was prepared from 3-t-butylbromobenzene (21.3 g, 0.1 mol) in dry ether (75 ml) and magnesium (2.4 g, 0.1 mol) in ether (100 ml). The mixture was boiled under reflux for 90 min, then cooled to 0° and a solution of 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester (9 g, 0.045 mol) in ether (50 ml) added over 1 h with vigorous stirring. The mixture was stirred at room temperature for 1 h, then heated at reflux for 30 min. On cooling the complex was decomposed with aqueous ammonium chloride (100 ml, 25% w/v). The ether layer was separated and evaporated under reduced pressure to give a yellow oil.

The oil was dissolved in ethanol (60 ml) and heated to reflux, then water (20 ml) containing concentrated hydrochloric acid (5 drops) was added with vigorous stirring. The mixture was boiled under reflux with stirring for 15 min then allowed to cool.

The ethanol was removed under reduced pressure and the oil extracted with ether. The ether extracts were combined, washed with water, dried and evaporated under reduced pressure giving a yellow oil. Purification by medium pressure chromatography on silica (2.5 x 100 cm) using petrol containing an increasing proportion of ether gave 2-[bis-(3-t-butylphenyl)methylene]cyclopentanone (4.32 g, 27%) as a yellow oil which could not be crystallised (Found: C, 86.5; H, 8.9 $C_{26}H_{32}O$ requires C, 86.6; H, 8.95%); i.r. (Nujol) 1715 cm^{-1} (C=O). ^1H N.m.r. and mass spectra: see Appendix.

2. 2-[Bis-(3-chlorophenyl)methylene]cyclopentanone

a) (2 Oxocyclopentyl)(bis-3-chlorophenyl)methanol

A Grignard reagent was prepared by the addition of freshly distilled 3-bromochlorobenzene (50 g, 0.26 mol) in dry ether (75 ml) to magnesium (8 g, 0.33 mol) in ether (150 ml). The mixture was boiled under reflux for 15 min and then a solution of 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester (24 g, 0.12 mol) in ether (75 ml) was added slowly with vigorous stirring. The mixture was boiled and stirred for 3 h, cooled, and aqueous ammonium chloride (200 ml, 20% w/v) was added slowly to decompose the complex. The ether layer was separated and the aqueous layer extracted with ether (2 x 50 ml); the ethereal solutions were combined and concentrated to give a yellow oil.

The oil was heated to reflux in ethanol (150 ml), then water (50 ml) containing concentrated hydrochloric acid (2 ml) was added with vigorous stirring. The mixture was boiled and stirred for 15 min, cooled, and stirred at room temperature for 5 h. The ethanol was removed under reduced pressure and ether (200 ml) and water (100 ml) added. The ether layer was separated, dried, and evaporated giving a yellow oil which was recrystallised from ethanol to give (2-oxocyclopentyl)(bis-3-chlorophenyl)methanol (7.4 g, 18%) as white needles, m.p. 109-110^{o} (Found: C, 64.8; H, 4.9. $C_{18}H_{16}Cl_2O_2$ requires C, 64.5; H, 4.8%), ^{1}H n.m.r. ($CDCl_3$) δ 7.4-7.1 (8H,m), 3.9 (1H,s), 3.3 (1H,t), 2.4-1.7 (6H,m); i.r. (Nujol) 3440 (OH), and 1730 cm^{-1} (C=O).

b) 2-[Bis-(3-chlorophenyl)methylene]cyclopentanone

(2-Oxocyclopentyl)(bis-3-chlorophenyl)methanol (4.0 g, 0.012 mol) and 4-toluenesulphonic acid (0.4 g) were boiled in dry benzene (200 ml) for 1 h. The water formed was removed using a Dean and Stark apparatus. The reaction mixture was cooled, washed with sodium bicarbonate solution (10%, w/v), then water, and then dried and evaporated under reduced pressure giving a yellow oil which was recrystallised from ethanol to give 2-[bis-(3-chlorophenyl)methylene]cyclopentanone (2.65 g, 70%) as yellow cubes m.p. 80-81° (Found: C, 68.1; H, 4.4. $C_{18}H_{14}Cl_2O$ requires C, 68.15; H, 4.45%); i.r. (Nujol) 1710 cm^{-1} (C=O). ^1H N.m.r. and mass spectra: see Appendix.

3. 2-[Bis-(3-ethoxyphenyl)methylene]cyclopentanone

A Grignard reagent was prepared from 3-ethoxybromo benzene (10.0 g, 0.05 mol) in dry ether (25 ml) and magnesium (1.35 g, 0.056 mol) in ether (50 ml). The mixture was boiled under reflux for 0.5 h, then cooled to 0° and a solution of 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester (4.0 g, 0.02 mol) in ether (20 ml) added over 1 h with vigorous stirring. The mixture was stirred at 0° for 1.5 h, boiled under reflux for 0.5 h then cooled and the complex decomposed with aqueous ammonium chloride (60 ml, 25% w/v). The ether layer was separated and evaporated under reduced pressure to give a yellow oil.

The oil was dissolved in ethanol (30 ml) and heated to boiling point, then water (10 ml) and concentrated hydrochloric acid (1 drop) were added with vigorous stirring. The mixture was boiled under reflux for 15 min, with stirring, then allowed to cool. The ethanol was removed under reduced pressure and the product extracted with ether. The ether extracts were combined washed with aqueous sodium bicarbonate (10%, w/v) then water, dried and evaporated to give a yellow oil which was chromatographed on silica (2.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether gave 2-[bis-(3-ethoxyphenyl) methylene]cyclopentanone (1.4 g, 21%) as yellow cubes m.p. 82-84^{o} (from ethanol) (Found: C,78.6; H,7.2. $C_{22}H_{24}O_3$ requires C, 78.5; H, 7.2%) i.r. (Nujol) 1710 cm^{-1} (C=O) ^{1}H N.m.r. and mass spectra: see Appendix.

Further elution gave (2-oxocyclopentyl)(bis-3-ethoxyphenyl)methanol as white needles (0.58 g, 8%) m.p. 121-123^{o} (from ethanol).

(Found: C, 74.4; H,7.5. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.4%); i.r. (Nujol) 3400 (OH) and 1720 cm^{-1}(C=O).

4. 2-[Bis-(3-ethylphenyl)methylene]cyclopentanone

A Grignard reagent was prepared from 3-ethylbromobenzene (10.0 g, 0.054 mol) in dry ether (25 ml) and magnesium (1.5 g, 0.0625 mol) in ether (50 ml). The mixture was boiled for 0.5 h then cooled to 0^{o} and 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester (5.0 g, 0.025 mol) in ether (25 ml) added over 1 h with vigorous stirring. The mixture was stirred at 0^{o} for 1.5 h then boiled under reflux for 0.5 h. On cooling the complex was decomposed with aqueous

ammonium chloride (60 ml, 25% w/v). The ether layer was separated and evaporated under reduced pressure to give a yellow oil.

The oil was dissolved in ethanol (30 ml) and heated to reflux then water (10 ml) containing concentrated hydrochloric acid (1 drop) was added with vigorous stirring. The mixture was boiled under reflux for 15 min then allowed to cool.

The ethanol was removed under reduced pressure and the oil extracted with ether. The ether extracts were combined, washed with water, with aqueous sodium bicarbonate (10% w/v) and finally water, dried and evaporated to give a yellow oil which was chromatographed on silica (2.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether gave a yellow oil which was recrystallised from petrol at -50^{o} to give 2-[bis-(3-ethylphenyl)methylene]cyclopentanone (2.35 g, 31%) m.p. $48-50^{o}$ (Found: C, 86.6; H, 8.0. $C_{22}H_{24}O$ requires C, 86.8; H, 7.95%); i.r. (Nujol) 1720 cm^{-1} (C=O). ^{1}H N.m.r. and mass spectra: see Appendix.

5. 2-[Bis-(3-trifluoromethylphenyl)methylene]cyclopentanone

A Grignard reagent was prepared from 3-bromobenzotrifluoride (45 g, 0.2 mol) in dry ether (100 ml) and magnesium (6.25 g, 0.26 mol). 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester (17.5 g, 0.0875mol) in ether (100 ml) was added slowly with vigorous stirring at room temperature. The reaction mixture was boiled under reflux for 1 h. On cooling the complex was composed by aqueous ammonium chloride (200 ml, 20% w/v). The ether layer was separated and evaporated under reduced pressure to give a yellow oil.

The oil was boiled under reflux in a mixture of ethanol (150 ml), water (125 ml), and concentrated sulphuric acid (5 ml) for 5 h. The ethanol was evaporated off under reduced pressure and the residue extracted with ether. The ether extracts were combined, dried and evaporated giving a brown oil which was recrystallised from petrol:ethanol, 2:1 to give 2-[bis-(3-trifluoromethylphenyl)methylene] cyclopentanone (8.2 g, 24%) as yellow cubes m.p. 65-66° (lit.,[50] 65-66°); ^{1}H n.m.r. and i.r. data identical with those reported.

6. 2-[Bis-(3-methoxyphenyl)methylene]cyclopentanone

A Grignard reagent was prepared from m-bromoanisole (42.22 g 0.225 mol) in ether (75 ml) and magnesium (6.8 g, 0.28 mol) in ether (75 ml). The mixture was boiled under reflux for 15 min then cooled to room temperature and a solution of 1,4-dioxaspiro [4,4]nonane-6-carboxylic acid ethyl ester (21.2 g, 0.106 mol) in ether (80 ml) added over 0.5 h with vigorous stirring. The mixture was stirred for 1 h then boiled under reflux with stirring for 3 h.

After the usual work up the oil was boiled under reflux in ethanol (200 ml), water (150 ml) and concentrated sulphuric acid (5 ml) for 5 h. The ethanol was evaporated under reduced pressure and the oil extracted with ether. The ether extracts were combined, dried and evaporated to give a yellow oil. Recrystallisation from methanol gave 2-[bis-(3-methoxyphenyl)methylene]cyclopentanone (8.72 g, 27%) as yellow plates m.p. 104-105° (lit.,[87] 106°); ^{1}H n.m.r. and i.r. spectral data identical with those reported.

7. 2-(Di-m-tolylmethylene)cyclopentanone

A Grignard reagent was prepared from 3-bromotoluene (45.5 g, 0.27 mol) in dry ether (125 ml) and magnesium (8.25 g, 0.33 mol) in ether (35 ml). The mixture was boiled under reflux for 1 h then cooled to room temperature and a solution of 1,4-dioxaspiro[4,4]nonane-5-carboxylic acid ethyl ester (22.6 g, 0.113 mol) in ether (80 ml) added slowly with vigorous stirring. The mixture was then boiled under reflux for 0.5 h.

After the usual work up the oil was boiled under reflux in methanol (80 ml), water (50 ml) and concentrated hydrochloric acid (4 ml) for 7 h with vigorous stirring. The reaction mixture was cooled and filtered to give 2-(di-m-tolylmethylene)cyclopentanone (8.4 g, 24%) as yellow plates m.p. 124-125° from ethanol (lit.,[50] 121-122°); (Found: C, 86.8; H, 7.4. Calc. for $C_{20}H_{20}O$: C, 86.9; H, 7.3%); ^1H n.m.r. and i.r. spectral data identical with those reported.

8. 2-[Bis-(2-^{2}H-3-methylphenyl)methylene]cyclopentanone

A Grignard reagent was prepared from 2-deutero-3-bromotoluene (10 g, 0.058 mol) in ether (30 ml) and magnesium (1.5 g, 0.06 mol) in ether (50 ml). The mixture was boiled under reflux for 40 min, then cooled to 0° and 1,4-dioxaspiro[4,4]nonane-5-carboxylic acid ethyl ester (5 g, 0.025 mol) in ether (50 ml) added over 1 h with vigorous stirring. The mixture was stirred at room temperature for 0.5 h and then the complex was decomposed by aqueous ammonium chloride (50 ml, 30% w/v). The ether layer was separated and the ether

removed under reduced pressure. The yellow oil produced was heated to reflux in ethanol (30 ml) and then water (10 ml) containing concentrated hydrochloric acid (0.15 ml) added with vigorous stirring. The mixture was boiled under reflux for 15 min then the ethanol was removed under reduced pressure. The product was extracted with ether. The combined ether extracts were washed with water, dried and evaporated to give a yellow oil. The oil was recrystallised from ethanol to give 2-[bis-(2-^{2}H-3-methylphenyl)methylene] cyclopentanone (1.85 g, 27%) m.p. 126-127^{o}. The deuterium content was found to be 93% by mass spectroscopy.

See Appendix for spectra and calculation.

9. 2-[Bis-(2-^{2}H-5-methylphenyl)methylene]cyclopentanone

This compound was prepared by Mr. I.D. Thomson[102] as part of a Carnegie project using an identical procedure to that given in 8 but starting from 3-bromo-4-deutero-toluene. Recrystallisation from ethanol give 2-[bis-(2-^{2}H-5-methyl-phenyl)methylene]cyclopentanone (1.4 g, 18%) m.p. 122-123^{o}. The Deuterium content was calculated by leVms as 93%.
See Appendix for spectra and calculation.

10. 2-[Bis-(3,5-dimethylphenyl)methylene]cyclopentanone

This compound was prepared by Mr. C.B. Argo,[94] as part of an Honours project by the reaction of the Grignard reagent, prepared from 1-bromo-3,5-dimethylbenzene, with 1,4-dioxaspiro [4,4]nonane-6-carboxylic acid ethyl ester. Hydrolysis and dehydration gave a yellow oil which was purified by medium pressure chromatography on silica (2.5 x 100 cm) to give

2-[bis-(3,5-dimethylphenyl)methylene cyclopentanone (10%) as yellow plates m.p. 114-115° (from ethanol) (Found: C, 87.0; H,8.0. $C_{22}H_{24}O$ requires C, 86.8; H, 7.95%); i.r. (Nujol) 1695 cm^{-1} (C=O).

^1H N.m.r. spectrum: see Appendix.

11. 2-(Bis-(3,5-dimethylphenyl)methylene]cyclohexanone

a) (2-Oxocyclohexyl)(bis-3,5-dimethylphenyl)methanol

A Grignard reagent was prepared from magnesium (2.0 g, 0.08 mol) in dry ether (100 ml) and 1-bromo-3,5-dimethylbenzene (14.25 g, 0.076 mol) in ether (50 ml). The mixture was boiled under reflux for 1.5 h, then cooled to room temperature and 1,4-dioxaspiro[4,5]decane-6-carboxylic acid ethyl ester (7.0 g, 0.0327 mol) in ether (50 ml) added over 2h with vigorous stirring. The mixture was boiled under reflux for 0.5 h then cooled and the complex decomposed by aqueous ammonium chloride (150 ml, 20% w/v). The ether layer was separated and the ether removed under reduced pressure to give a yellow oil. The oil was dissolved in ethanol (60 ml) and heated to reflux then water (20 ml) containing concentrated hydrochloric acid (0.4 ml) was added with vigorous stirring. The mixture was stirred and boiled under reflux for 20 min then the ethanol was removed under reduced pressure. The oil produced was extracted with ether. The ether extracts were combined, washed with water, dried and evaporated under reduced pressure giving an oil which was purified by medium pressure chromatography on silica (2.5 x 100 cm). Elution with petrol containing an increasing amount of ether produced a white solid which was recrystallised from ethanol

to give (2-oxocyclohexyl)(bis-3,5-dimethylphenyl)methanol (3.33 g, 30%) as white needles m.p. 149-150° (Found: C, 81.95; H, 8.4. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.4%); i.r. (Nujol) 3480 (OH) and 1690 cm^{-1} (C=O); ^1H n.m.r. ($CDCl_3$) δ 7.0 (4H, d), 6.7 (2H, s), 4.4 (1H, s, OH), 3.5 (1H, t), 2.2 (12H, s), 2.3-1.7 (8H, m).

b) 2-[Bis-(3,5-dimethylphenyl)methylene]cyclohexanone

(2-Oxocyclohexyl)(bis-3,5-dimethylphenyl)methanol (2.83 g, 0.0093 mol) was boiled under reflux in dry benzene (40 ml) containing 4-toluenesulphonic acid (0.02 g) for 0.5 h. After cooling, the benzene solution was washed with water, sodium bicarbonate solution (10% w/v) and then water. The solution was dried and evaporated under reduced pressure to give an oil which was recrystallised from ethanol to give 2-[bis-(3,5-dimethylphenyl)methylene]cyclohexanone (2.59 g, 97%) as pale yellow needles m.p. 105-106° (Found: C, 68.5; H, 8.2. $C_{23}H_{26}O$ requires C, 86.75; H, 8.2%); i.r. (Nujol) 1680 cm^{-1}(C=O).

^1H N.m.r. and mass spectra: see Appendix.

12. 2-(Di-2-thienylmethylene)cyclopentanone

a) A Grignard reagent was prepared from 2-bromothiophene (50 g, 0.306 mol) in dry ether (70 ml) and magnesium (8 g, 0.33 mol) in ether (200 ml). The mixture was boiled under reflux for 1 h then cooled to 0° and 1,4-dioxaspiro [4,4]nonane-6-carboxylic acid ethyl ester (28.0 g, 0.14 mol) in ether (75 ml) added over 75 min with vigorous stirring.

The mixture was boiled under reflux for 3 h then cooled to 0° and aqueous ammonium chloride (300 ml, 25% w/v) added slowly with vigorous stirring. The ether layer was separated and the ether removed under reduced pressure to give a yellow oil from which a white solid crystallised out on the addition of ethanol (150 ml), water (50 ml) and concentrated hydrochloric acid (1 ml). The solid was collected by filtration, dried and recrystallised from ethanol to give 6-(1,4-dioxaspiro[4,4]nonyl)(di-2-thienyl)methanol (28.66 g, 64%) m.p. 81-82° (Found: C,59.75; H, 5.6. $C_{16}H_{18}O_3S_2$ requires C, 59.6; H, 5.6%); i.r. (Nujol) 3460 cm^{-1} (OH); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

b) 6-(1,4-Dioxaspiro[4,4]nonyl)di-2-thienylmethanol (10.0 g, 0.031 mol) was heated to reflux in ethanol (100 ml) with vigorous stirring. Water (30 ml) containing concentrated hydrochloric acid (0.5 ml) was added and boiling at reflux continued for 10 min. The ethanol was removed under reduced pressure and water (100 ml) added. The mixture was extracted with ether and the combined extracts were dried and evaporated to give a yellow oil which was separated on silica (2.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether gave 2-(di-2-thienylmethylene)cyclopentanone (2.64 g, 33%) as yellow plates m.p. 90-91° (from ethanol). (Found: C, 64.4; H, 4.7. $C_{14}H_{12}OS_2$ requires C, 64.6; H, 4.65%); i.r. (Nujol) 1700 cm^{-1} (C=O); ^1H n.m.r. and mass spectra: see Appendix.

Further elution gave a colourless oil which was identified as 2-hydroxyethyl 6,6-di-2-thienylhex-5-enoate (5.1 g, 51%) (Found: C, 59.65; H, 5.55. $C_{16}H_{18}O_3S_2$ requires C, 59.6; H, 5.6%); i.r. (Film) 3450 (OH) and 1730 cm^{-1} (C=O); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

13. 2-(Di-3-thienylmethylene)cyclopentanone

a) 3-Bromothiophene (10.0 g, 0.0615 mol) in dry ether (30 ml) was cooled to -70° and added with vigorous stirring to n-butyl lithium (40 ml, 1.6 molar solution in hexane) cooled to -70° under dry nitrogen. The mixture was stirred for 5 min and then 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester (5.0 g, 0.025 mol) in ether (25 ml) cooled to -70° was added over 10 min. The solution was stirred at -70° for 1 h and then water (75 ml) was added and the cooling bath removed. The ether layer was separated, dried and evaporated to give a colourless oil which was recrystallised from ethanol to give 6-(1,4-dioxaspiro[4,4]nonyl)di-3-thienyl methanol (2.9 g, 36%) as white needles m.p. 98° (Found: C, 59.5; H, 5.5. $C_{16}H_{18}O_3S_2$ requires C, 59.6; H, 5.6%); i.r. (Nujol) 3460 cm^{-1} (OH); ^1H n.m.r. and mass spectra: see Appendix.

b) 6-(1,4-Dioxaspiro[4,4]nonyl)di-3-thienyl methanol (5.0 g, 0.0156 mol) was heated to reflux with vigorous stirring in ethanol (125 ml) and then dilute hydrochloric acid (0.65 ml) was added. The solution was boiled under reflux for 15 min and then the ethanol removed under reduced pressure. The oil was dissolved in ether, washed with water, dried and evaporated giving a yellow oil which was separated by medium pressure chromatography on silica (2.5 x 100 cm). Elution with

petrol containing an increasing proportion of ether gave 2-(di-3-thienylmethylene)cyclopentanone (0.88 g, 22%) as yellow needles m.p. 78-80° (from ethanol); (Found: C, 64.5; H, 4.6. $C_{14}H_{12}OS_2$ requires C, 64.6; H, 4.65%); i.r. (nujol) 1695 cm^{-1} (C=O); ^1H n.m.r. and mass spectra. See Appendix.

Further elution gave 2-hydroxyethyl 6,6-di-3-thienylhex-5-enoate (2.28 g, 46%) as a colourless oil which could not be crystallised (Found: C, 59.8; H, 5.6%; $C_{16}H_{18}O_3S_2$ requires C, 59.6; H, 5.6%); i.r. (Film) 3430 (OH) and 1720 cm^{-1} (C=O); ^1H n.m.r. and mass spectra: see Appendix.

14. 4,4-Di-2-thienylbut-3-en-2-one

This was prepared by an adaptation of the method of Corey.[111] n-Butyllithium (17.5 ml, 1.6 M solution in hexane) was added to di-isopropylamine (2.02 g, 0.02 mol) at 0° with stirring under dry nitrogen. The mixture was stirred at 0° for 20 min and then acetone-N,N-dimethyl-hydrazone (2 g, 0.02 mol) in dry tetrahydrofuran (15 ml) was added dropwise by syringe. After stirring at 0° for 0.5 h the solution was cooled to -70° and di-2-thienyl ketone (3.6 g, 0.0185 mol) in tetrahydrofuran (20 ml), cooled to -70°, added dropwise. The solution was stirred for 1 h then allowed to warm up to 0° and then water (25 ml) added. The mixture was extracted with methylene chloride and the combined extracts washed with water, dried and evaporated to give an oil. The oil was dissolved in ethanol (40 ml) and hydrochloric acid (1 M, 40 ml) was added with stirring. The mixture was stirred overnight then extracted with methylene chloride. The combined extracts were washed with water, dried and evaporated to give a yellow oil which

was purified by medium pressure chromatography on silica (2.5 x 100 cm). Elution with petrol containing an increasing amount of ether gave 4,4-di-2-thienylbut-3-en-2-one as a yellow oil which could not be crystallised (2.45 g, 57%) (Found: C, 61.6; H, 4.4. $C_{12}H_{10}OS_2$ requires C, 61.5; H, 4.3%); i.r. (Film) 1650 cm^{-1} (C=O); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

15. 4,4-Di-3-thienylbut-3-en-2-one

This was prepared by an adaptation of the method of Corey.[111] n-Butyllithium (5.5 ml, 1.6 M solution in hexane) was added to di-isopropylamine (0.78 g, 0.0077 mol) at 0° with stirring under dry nitrogen. The mixture was stirred at 0° for 20 min and then acetone-N,N-dimethylhydrazone (0.77 g, 0.0077 mol) in dry tetrahydrofuran (12 ml) was added slowly. After stirring at 0° for 0.5 h the solution was cooled to -70° and di-3-thienyl ketone (1.5 g, 0.0077 mol) in tetrahydrofuran (12 ml), cooled to -70° added dropwise. The solution was stirred at -70° for 1 h then allowed to warm up to 0° and then water (25 ml) added. The mixture was extracted with methylene chloride and the combined extracts washed with water, dried and evaporated. The resultant oil was dissolved in ethanol (20 ml) and hydrochloric acid (1 M, 20 ml) was added with stirring. The mixture was stirred overnight then extracted with methylene chloride. The combined extracts were washed with water, dried and evaporated to give a yellow oil which was purified by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing amount of ether gave 4,4-di-3-thienylbut-3-en-2-one (1.22 g, 68%) as a yellow oil which could not be

crystallised (Found: C, 61.6; H, 4.2. $C_{12}H_{10}OS_2$ requires C, 61.5; H, 4.3%); i.r. (Film) 1650 cm^{-1} (C=O); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

16. 2-(Phenyl-2-thienylmethylene)cyclohexanone

a) 2-((Hydroxy)phenyl-2-thienylmethyl)cyclohexanone dimethylhydrazone

n-Butyllithium (8.0 ml, 1.27 M solution in hexane) was added slowly with stirring to di-isopropylamine (1.06 g, 0.01 mole) under dry nitrogen at 0°. Stirring was continued for 20 min at 0° and then cyclohexanone-N,N-dimethylhydrazone (1.40 g, 0.01 mole) in dry tetrahydrofuran (10 ml) was added slowly. The solution was stirred at 0° for 2 h then cooled to -70° and 2-benzoylthiophene (1.88 g, 0.01 mol) in tetrahydrofuran (10 ml), cooled to -70°, was added dropwise. The solution was stirred at -70° for 2 h and then allowed to warm up to room temperature overnight. Water (25 ml) was added and the mixture neutralised with dilute hydrochloric acid. The mixture was extracted with methylene chloride and the combined extracts washed with water, dried and evaporated to give an oil which was recrystallised from ethanol to give 2-((hydroxy)phenyl-2-thienylmethyl)cyclohexanone dimethylhydrazone (1.43 g, 41%) m.p. 101-102° (Found: C, 69.4; H, 7.4; N, 8.6. $C_{19}H_{24}N_2OS$ requires C, 69.5; H, 7.4; N, 8.5%).

b) (2-Oxocyclohexyl)phenyl-2-thienylmethanol

2-((Hydroxy)phenyl-2-thienylmethyl)cyclohexanone dimethylhydrazone (0.20 g, 0.0006 mol) was dissolved in ethanol (10 ml) and hydrochloric acid (2.5 ml, 1M) was added with stirring. The mixture was stirred at room temperature for 24 h and the white precipitate collected by filtration and

recrystallised from ethanol to give (2-oxocyclohexyl)phenyl-2-thienylmethanol (0.0869 g, 50%) m.p. 127-128° (Found: C, 71.5; H, 6.4. $C_{17}H_{18}O_2S$ requires C, 71.3; H, 6.3%).

c) 2-(Phenyl-2-thienylmethylene)cyclohexanone

(2-Oxocyclohexyl)phenyl-2-thienylmethanol (0.90 g, 0.0031 mol) was boiled under reflux in dry benzene (25 ml) with 4-toluenesulphonic acid (0.01 g) for 20 min. On cooling the solution was washed with aqueous sodium carbonate (10% w/v) and with water, dried and evaporated to give a yellow oil which was recrystallised from ethanol to give 2-(phenyl-2-thienylmethylene)cyclohexanone (0.71 g, 84%) m.p. 119-120° (Found: C, 76.0; H, 6.1. $C_{17}H_{16}OS$ requires C, 76.1; H, 6.0%); i.r. (Nujol) 1730 cm^{-1} (C=O); ^1H n.m.r. and mass spectra: see Appendix.

17. Attempted preparation of 2-(di-2-thienylmethylene) cyclohexanone

a) 6-(1,4-Dioxaspiro[4,5]decyl)di-2-thienylmethanol

A Grignard reagent was prepared from 2-bromothiophene (10.0 g, 0.06 mol) in ether (30 ml) and magnesium (1.5 g, 0.062 mol) in ether (50 ml). The mixture was boiled under reflux for 45 min then cooled to 0° and 1,4-dioxaspiro[4,5] decane-6-carboxylic acid ethyl ester (5.0 g, 0.025 mol) in ether (50 ml) added over 2 h with vigorous stirring. The mixture was stirred at room temperature for 30 min then aqueous ammonium chloride (100 ml, 15% w/v) added. The ether layer was separated, dried and evaporated to give an oil which was recrystallised from ethanol at -50° to give 6-(1,4-dioxaspiro[4,5]decyl)di-2-thienylmethanol (3.38 g,

43%) m.p. 96-97° (Found: C, 60.75; H, 6.0. $C_{17}H_{20}O_3S_2$ requires C, 60.7; H, 6.0%); i.r. (Nujol) 3380 cm^{-1}(OH); ^1H n.m.r. and mass spectra: see Appendix.

b) Hydrolysis of 6-(1,4-dioxaspiro[4,5]decyl)di-2-thienylmethanol

6-(1,4-Dioxaspiro[4,5]decyl)di-2-thienylmethanol (1 g, 0.003 mol) was heated to reflux in ethanol (25 ml) and then dilute hydrochloric acid (3 drops) added. The solution was boiled under reflux for 15 min then the ethanol removed under reduced pressure to give an oil which was purified by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing proportion of ether gave 2-hydroxyethyl 7,7-di-2-thienylhept-6-enoate (0.83 g, 83%) as a colourless oil (Found: C, 60.5; H, 5.85. $C_{17}H_{20}O_3S_2$ requires C, 60.7; H, 6.0%); i.r. (Nujol) 3450 (broad)(OH) and 1730 cm^{-1} (C=O); ^1H n.m.r. and mass spectra: see Appendix.

18. Attempted preparation of 2-(di-3-thienylmethylene) cyclohexanone

a) 6-(1,4-Dioxaspiro[4,5]decyl)di-3-thienylmethanol

n-Butyllithium (50 ml, 1.6 M solution in hexane) at -70° was added with vigorous stirring to 3-bromothiophene (12.5 g, 0.077 mol) in dry ether (50 ml) at -70° under dry nitrogen. After stirring for 5 min 1,4-dioxaspiro[4,5] decane-6-carboxylic acid ethyl ester (6.10 g, 0.0285 mol) in ether (50 ml) was added over 12 min. The solution was stirred at -70° for 100 min and then water (100 ml) added and the mixture allowed to warm up to room temperature.

The ether layer was separated, dried and evaporated to give an oil which was recrystallised from ethanol to give 6-(1,4-dioxaspiro[4,5]decyl)di-3-thienylmethanol (5.17 g, 54%) m.p. 102-103° (Found: C, 60.6; H, 6.0. $C_{17}H_{20}O_3S_2$ requires C, 60.7; H, 6.0%); i.r. (Nujol) 3420 cm^{-1} (OH); ^1H n.m.r. and mass spectra: see Appendix.

b) Hydrolysis of 6-(1,4-dioxaspiro[4,5]decyl)di-3-thienylmethanol

6-(1,4-Dioxaspiro[4,5]decyl)di-3-thienylmethanol (1 g, 0.003 mol) was heated to reflux in ethanol (25 ml) and then dilute hydrochloric acid (3 drops) was added. The solution was boiled under reflux for 15 min then the ethanol removed under reduced pressure to give an oil which was purified by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing amount of ether gave 2-hydroxyethyl 7,7-di-3-thienylhept-6-enoate (0.75 g, 75%) as a colourless oil which could not be crystallised (Found: C, 60.9; H, 5.9. $C_{17}H_{20}O_3S_2$ requires C, 60.7; H, 6.0%); i.r. (Nujol) 3400 (broad) (OH) and 1720 cm^{-1} (C=O); ^1H n.m.r. and mass spectra: see Appendix.

Preparation of p-Tolylsulphonylhydrazones

The following tosylhydrazones were prepared by admixture of warm (45°) ethanolic solutions of the unsaturated ketone and 4-tolylsulphonylhydrazine (1 mol equiv.) with addition of a few drops of concentrated hydrochloric acid. The product crystallised in good yield overnight. Some tosylhydrazones contained some solvated ethanol which could not be removed by vacuum drying; this was removed by dissolving the tosylhydrazones in chloroform followed by evaporation under reduced pressure.

2-[Bis-(3t-butylphenyl)methylene]cyclopentanone tosylhydrazone

Yield 72% m.p. 183° (decomp.)(from methanol). (Found: C, 74.8; H, 7.6; N, 5.4. $C_{33}H_{40}N_2SO_2$ requires C, 75.0; H, 7.6; N, 5.3%); i.r. (Nujol) 3200 cm^{-1} (NH); ^1H n.m.r. spectrum: see Appendix.

2-[Bis-(3-chlorophenyl)methylene]cyclopentanone tosylhydrazone

Yield 89% m.p. 181-182° (decomp.)(from ethanol)(Found: C, 61.95; H, 4.5; N, 5.7. $C_{15}H_{22}Cl_2N_2O_2S$ requires C, 61.85 H, 4.6; N, 5.8%); i.r. (Nujol) 3180 cm^{-1}(NH); ^1H n.m.r. and mass spectra: see Appendix.

2-[Bis-(3-ethoxyphenyl)methylene]cyclopentanone tosylhydrazone

Yield 62% m.p. 145-147° (decomp.)(from ethanol). (Found: C, 68.7; H, 6.3; N, 5.7. $C_{29}H_{32}N_2O_4S$ requires C, 69.0; H, 6.4; N, 5.55%); i.r. (Nujol) 3190 cm^{-1} (NH); ^1H n.m.r. and mass spectra: see Appendix.

2-[Bis-(3-ethylphenyl)methylene]cyclopentanone tosylhydrazone

Yield 87% m.p. 180-181° (decomp.) (from ethanol). (Found: C, 73.85; H, 6.9; N, 5.9. $C_{29}H_{32}N_2SO_2$ requires C, 73.7; H, 6.8; N, 5.9%); i.r. (Nujol) 3160 cm^{-1} (NH); ^1H n.m.r. and mass spectra: see Appendix.

2-[Bis-(3-trifluoromethylphenyl)methylene cyclopentanone tosylhydrazone

Yield 64% m.p. 179-180° (decomp.) (from ethanol:ethylacetate, 2:1) (lit.,[50] 190-191°); i.r. (Nujol)3200 cm^{-1} (NH).

2-[Bis-(3-methoxyphenyl)methylene]cyclopentanone tosylhydrazone

Yield 62% m.p. 147-148° (decomp.) (from ethanol) (lit.,[50] 148-149° (decomp.)); i.r. (Nujol) 3210 cm^{-1}(NH).

2-[Bis-(3-methylphenyl)methylene]cyclopentanone tosylhydrazone

Yield 79% m.p. 165-166° (decomp.)(from ethanol:ethylacetate 1:1)(lit.,[50] 175-176° (decomp.)); i.r. (Nujol) 3200 cm^{-1} (NH).

2-[Bis-(2-^{2}H-3-methylphenyl)methylene]cyclopentanone tosylhydrazon

Yield 93% m.p. 166-168° (decomp.) (from ethanol); i.r. (Nujol) 3200 cm^{-1}.

2-[Bis-(2-^{2}H-5-methylphenyl)methylene]cyclopentanone tosylhydrazon

This compound was prepared by Mr. I.D. Thomson,[102] yield 80% m.p. 163-164° (decomp.) (from ethanol); i.r. (Nujol) 3200 cm^{-1}.

2-[Bis-(3,5-dimethylphenyl)methylene]cyclopentanone tosylhydrazone

This compound was prepared by Mr. C.B. Argo.[94] Yield 63% m.p. 185-187° (decomp.) (Found: C, 73.5; H, 6.9; N, 5.7. $C_{29}H_{32}N_2O_2S$ requires C, 73.7; H, 6.8; N, 5.9%) i.r. (Nujol) 3160 cm^{-1} (NH).

2-[Bis-(3,5-dimethylphenyl)methylene]cyclohexanone tosylhydrazone

Yield 41% m.p. 174-175° (decomp.) (from ethanol) (Found: C, 73.9; H, 7.0; N, 5.7. $C_{30}H_{34}N_2O_2S$ requires C, 74.05; H, 7.0; N, 5.8%); i.r. (Nujol) 3170 cm^{-1} (NH).

2-(Di-2-thienylmethylene)cyclopentanone tosylhydrazone

Yield 87% m.p. 193-195° (decomp.) (from ethanol) (Found: C, 58.8; H, 4.6; N, 6.5. $C_{21}H_{20}N_2O_2S_3$ requires C, 58.85; H, 4.7; N, 6.5%) i.r. (Nujol) 3270 cm^{-1} (NH); mass spectrum: see Appendix.

2-(Di-3-thienylmethylene)cyclopentanone tosylhydrazone

Yield 82% m.p. 152-154° (decomp.). A satisfactory analysis could not be obtained on this compound due to occlusion of solvent.

4,4-Di-2-thienylbut-3-en-2-one tosylhydrazone

Yield 89% m.p. 142-143° (decomp.) (from methanol) (Found: C, 56.8; H, 4.4; N, 7.1. $C_{19}H_{18}N_2O_2S_3$ requires C, 56.7; H, 4.5; N, 7.0%) i.r. (Nujol) 3158 cm^{-1} (NH); mass spectrum: see Appendix.

4,4-Di-3-thienylbut-3-en-2-one tosylhydrazone

Yield 87% m.p. 157-159° (decomp.) (from methanol) (Found: C, 56.8; H, 4.5; N, 7.0. $C_{19}H_{18}N_2O_2S_3$ requires C, 56.7; H, 4.5; N, 7.0%). i.r. (Nujol) 3180 cm^{-1} (NH); mass spectrum: see Appendix.

2-(Phenyl-2-thienylmethylene)cyclohexanone tosylhydrazone

Yield (54%) m.p. 158-159° (decomp.) (from ethanol) (Found: C, 65.8; H, 5.6; N, 6.45. $C_{24}H_{24}N_2O_2S_2$ requires C, 66.0; H, 5.5; N, 6.4%) i.r. (Nujol) 3170 (NH); mass spectrum: see Appendix.

Preparation and Decomposition of the Sodium Salts of the Tosylhydrazones

The sodium salts were prepared by the addition of the solid tosylhydrazone (ca. 5% molar excess) to a solution of sodium ethoxide in super-dry ethanol. The solution was stirred in the dark for 1 h. In some cases the sodium salt precipitated out at this stage. The ethanol was evaporated using a rotary evaporator under anhydrous conditions and with the temperature below 45°. The sodium salt was then dried under high vacuum over phosphorus pentoxide for at least 12 h, in the dark.

Freshly distilled dry solvent was added and the reaction mixture boiled under reflux, with stirring, under dry nitrogen, in the dark. During the decompositions, small samples of the reaction mixture were withdrawn and shaken with dilute

acid, in order to hydrolyse any residual sodium salt, and extracted with ether. The ether layer was analysed for unreacted tosylhydrazone by t.l.c., The reaction was continued until no tosylhydrazone remained. The reaction mixture was then cooled and sodium toluene-4-sulphinate was filtered off. The filtrate was evaporated to give the products.

Measurement of Isomer Ratios

The following procedure was used to measure the relative amounts of the 6- and 8-substituted diazepines. The sodium salt was prepared in the usual way using the tosylhydrazone (ca. 1 g) and super-dry ethanol (75 ml). After stirring in the dark for 1 h, three aliquots (25 ml) were pipetted into three flasks and each aliquot dried in the usual way. Freshly distilled dry solvent (25 ml) was added to each: cyclohexane, D.M.E. and D.M.F. respectively. Each solution was heated in a silicone oil bath at 80° ($\pm$ 0.2°), with stirring, under dry nitrogen, in the dark for 18 h. After heating the flasks were stored at -20° in the dark and then all three reaction mixtures were analysed at the same time using H.P.L.C. on silica and alumina columns. Calibration mixtures of the authentic diazepines were used to ascertain the relative extinction coefficients of the two diazepines at 254 nm.

The peak area ratios of the diazepines in the reaction mixtures were determined by injecting three samples and measuring the peak areas using a Minigrator integrator. The peak area ratios were then converted to molar ratios using

the correction factor obtained from the calibration mixtures. The calculation is illustrated for the decomposition of 2-[bis (3-chlorophenyl)methylene]cyclopentanone tosylhydrazone.

1. 2-[Bis-(3-chlorophenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.1200 g, 5.2 mmol) in super-dry ethanol (100 ml) and 2-[bis-(3-chlorophenyl)methylene]cyclopentanone tosylhydrazone (2.6 g, 5.4 mmol). After the usual drying procedure freshly distilled dry benzene (100 ml) was added and the mixture boiled under reflux for 4.5 h. Initially the solution turned a deep red in colour and then slowly became yellow with a white precipitate. The sodium toluene-4-sulphinate (0.82 g) was filtered off and the filtrate evaporated to give a yellow oil which was chromatographed on alumina (5% deactivated, 1.6 x 25 cm). Elution with petrol containing an increasing proportion of ether gave 1,2,3,3a-tetrahydro-6-chloro-10-(3-chlorophenyl)benzo[c] cyclopenta[f][1,2]diazepine (0.94 g, 55%) as yellow needles m.p. 99-100° (from ethanol)(Found: C, 65.8; H, 4.25; N, 8.7. $C_{18}H_{14}N_2Cl_2$ requires C, 65.7; H, 4.3; N, 8.5%); i.r. (Nujol) 1595 (N=N) and 1565 cm^{-1} (C=C); ^{13}C n.m.r., ^{1}H n.m.r. and mass spectra: see Appendix. Further elution gave 1,2,3,3a-tetrahydro-8-chloro-10-(3-chlorophenyl)benzo [e]cyclopenta[f][1,2]diazepine (0.40 g, 23%) as yellow needles m.p. 151-152° (from ethanol) (Found: C, 65.8; H, 4.3; N, 8.7. $C_{18}H_{14}N_2Cl_2$ requires C, 65.7; H, 4.3; N, 8.5%); i.r. (Nujol) 1595 (N=N) and 1570 cm^{-1} (C=C); ^{13}C n.m.r., ^{1}H n.m.r. and mass spectra: see Appendix.

Measurement of Isomer Ratios

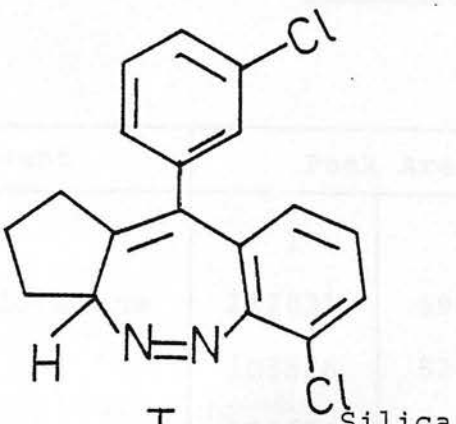
a) The salt was prepared from sodium (0.0475 g, 2.0 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1 g, 2.1 mmol). This solution of the sodium salt was divided into three parts and the decompositions carried out in cyclohexane, D.M.E., and D.M.F. as described in the general procedure. The decomposition products were analysed using H.P.L.C. on silica and alumina columns using 5% ether in 50% water saturated hexane and 5% ether in 25% water saturated hexane respectively. The results are shown in Tables 1(a) and 1(b).

b) A duplicate reaction was carried using sodium (0.0453 g, 1.97 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1 g, 2.1 mmol). The results are shown in Table 1(c).

2. 2-[Bis-(3-ethoxyphenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.0893 g, 3.88 mmol) in super-dry ethanol (70 ml) and the tosylhydrazone (2.00 g, 3.96 mmol). After the usual drying procedure freshly distilled dry benzene (70 ml) was added and the solution boiled under reflux for 8 h. Initially the solution turned deep red in colour and then became yellow with a white precipitate. On cooling the reaction mixture was filtered to give sodium toluene-4-sulphinate (0.68 g). The filtrate was evaporated and the residue was triturated with petrol/ether giving a yellow solid which was recrystallised from ethanol to give 1,2,3,3a-tetrahydro-6-ethoxy-10-(3-ethoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.70 g, 53%) m.p. 100-101^{o} as yellow needles (Found: C. 75.7; H, 7.0;

Table 1(a)



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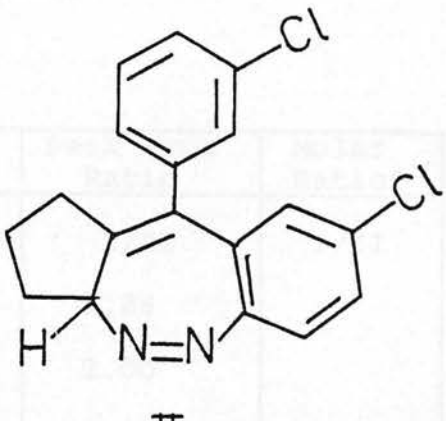


II

Silica

The calibration mixture contained I(4.3 mg) and II(6.3 mg) in chloroform. ∴ Molar Ratio (I/II) is 0.682.

Peak Area		
I	II	Peak Area Ratio I/II
45769	63390	0.722
48464	66334	0.730
46941	65651	0.715
		0.723 average

$$\therefore x = \frac{\text{Molar Ratio}}{\text{Peak Area Ratio}} = \frac{0.682}{0.723} = 0.943$$

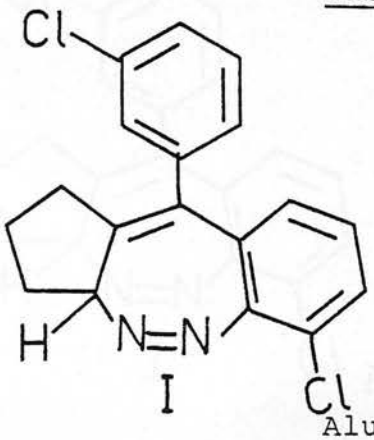
∴ x = correction factor (I/II) = 0.943

Table 1(a) (contd.)

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	112631	59691	1.88	
	105526	52728	2.00	
	108624	53247	2.04	
			1.97	1.86
D.M.E.	150396	48924	3.07	
	143390	50029	2.86	
	137452	47811	2.87	
			2.90	2.73
D.M.F.	129745	41452	3.13	
	115739	36396	3.18	
	112354	36536	3.07	
			3.13	2.95

*correction factor = 0.943

Table 1(b)



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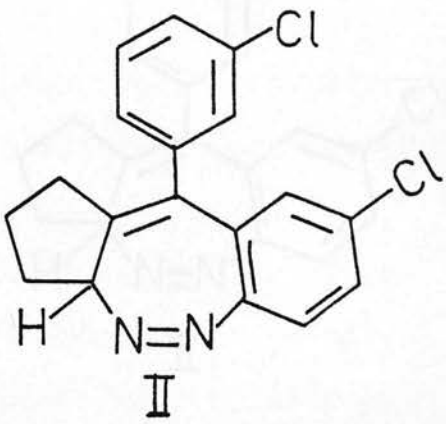


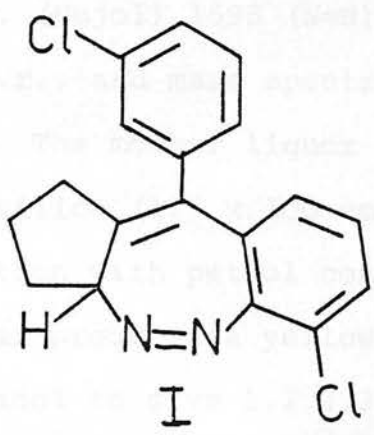
II

Alumina

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	146575	79564	1.84	
	130376	68508	1.90	
	125732	66879	1.88	
			1.87	1.87
D.M.E.	148727	54395	2.73	
	151022	51573	2.92	
	143971	51235	2.81	
			2.82	2.82
D.M.F.	156902	54419	2.88	
	151022	51573	2.92	
	150216	51621	2.91	
			2.90	2.90

*correction factor 1.00.

Table 1(c)



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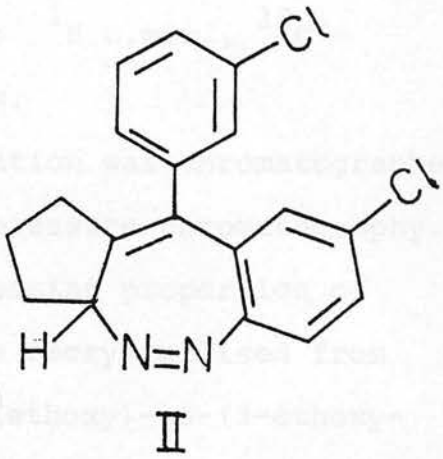


II

Alumina

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	170080	91597	1.86	
	177887	95043	1.87	
	169563	92154	1.84	
			1.86	1.96
D.M.E.	158302	63375	2.50	
	160893	59793	2.69	
	172165	66217	2.60	
			2.60	2.74
D.M.F.	199860	68834	2.90	
	196411	66171	2.97	
	193697	66334	2.92	
			2.93	3.09

*correction factor 1.06

N, 8.1. $C_{22}H_{24}N_2O_2$ requires C, 75.8; H, 6.9; N, 8.0%); i.r. (Nujol) 1595 (N=N) and 1550 (C=C); ^1H n.m.r., ^{13}C n.m.r., and mass spectra: see Appendix.

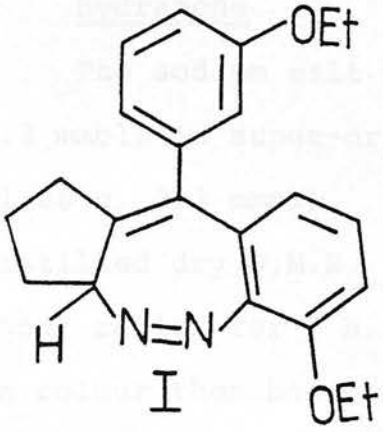
The mother liquor from the trituration was chromatographed on silica (1.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether produced a yellow solid which was recrystallised from ethanol to give 1,2,3,3a-tetrahydro-8-(ethoxy)-10-(3-ethoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.30 g, 22%) m.p. 145°. (Found: C, 75.6; H, 7.0; N, 7.85. $C_{22}H_{24}N_2O_2$ requires C, 75.8; H, 6.9; N, 8.0%); i.r. (Nujol) 1600 (N=N) and 1580 cm^{-1} (C=C); ^1H n.m.r. ^{13}C n.m.r. and mass spectra: see Appendix.

Further elution produced more 1,2,3,3a-tetrahydro-6-ethoxy-10-(3-ethoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.05 g, Total Yield 56%).

Measurement of Isomer Ratios

(a) The salt was prepared from sodium (0.0435 g, 1.89 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1 g, 1.98 mmol). This solution of the sodium salt was divided into three and the decompositions carried out in cyclohexane, D.M.E. and D.M.F. as described in the general procedure. The isomer ratios were measured by H.P.L.C. [alumina-1,4 dioxan (15%) in 25% water saturated hexane]. The results are given in Table 2.

Table 2



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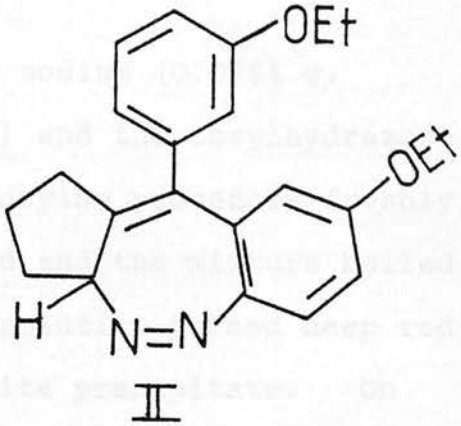


II

Alumina

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	109946	99250	1.11	
	103621	93605	1.11	
	100592	90623	1.11	
			1.11	1.35
D.M.E.	135305	109727	1.23	
	127162	104231	1.22	
	125396	101126	1.24	
			1.22	1.49
D.M.F.	11054	70411	1.58	
	120627	75866	1.59	
	100359	63208	1.59	
			1.59	1.94

*correction factor 1.22

3. 2-[Bis-(3-ethylphenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.0764 g, 3.3 mmol) in super-dry ethanol (100 ml) and the tosylhydrazone (1.66 g, 3.3 mmol). After the usual drying procedure freshly distilled dry D.M.E. (100 ml) was added and the mixture boiled under reflux for 7 h. Initially the solution turned deep red in colour then became yellow with a white precipitate. On cooling the reaction mixture was filtered to give sodium toluene-4-sulphinate (0.55 g). The filtrate was evaporated and chromatographed on silica (1.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether produced 1,2,3,3a-tetrahydro-6-ethyl-10-(3-ethylphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.58 g, 57%) as a yellow oil which could not be crystallised (Found: C, 83.3; H, 7.8; N, 8.75. $C_{22}H_{24}N_2$ requires C, 83.5; H, 7.6; N, 8.85%); i.r. ($CHCl_3$) 1600 (N=N) and 1580 cm^{-1} (C=C); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Further elution gave 1,2,3,3a-tetrahydro-8-ethyl-10-(3-ethylphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.17 g, 17%) as yellow needles from ethanol m.p. 105-106°. (Found: C, 83.7; H, 7.8; N, 9.1. $C_{22}H_{24}N_2$ requires C, 83.5; H, 7.6; N, 8.85%); i.r. (Nujol) 1600 (N=N) and 1580 cm^{-1} (C=C); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Measurement of Isomer Ratios

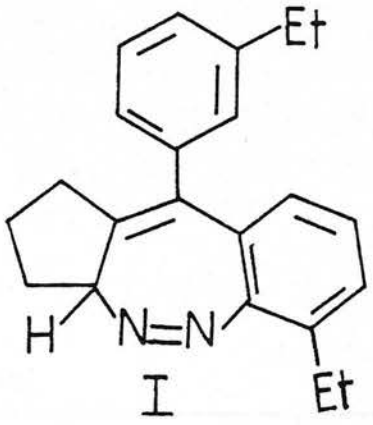
(a) The salt was prepared from sodium (0.0468 g, 2.03 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.05 g, 2.2 mmol). This solution of the sodium salt was divided into three and the decompositions carried out in cyclohexane, D.M.E. and D.M.F. as described in the general procedure. The isomer ratios were measured by H.P.L.C. [silica-1,4 dioxan (5%) in hexane (50% water saturated)] and the results are given in Table 3a.

(b) A duplicate reaction was carried out using sodium (0.0388 g, 1.68 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (0.83 g, 1.74 mmol). The results are shown in Table 3(b).

4. 2-[Bis-(3-trifluoromethylphenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.0598 g, 2.6 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.51 g, 2.7 mmol). After the normal drying procedure freshly distilled dry D.M.E. (75 ml) was added and the mixture boiled under reflux for 8 h. Initially the solution turned deep red then faded to give a yellow solution and a white precipitate. The sodium toluene-4-sulphinate (0.46 g) was filtered off and the yellow filtrate evaporated to give a yellow oil which was chromatographed on silica (1.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether produced 1,2,3,3a-tetrahydro-6-trifluoromethyl-10-(3-trifluoromethylphenyl) benzo[c]cyclopenta[f][1,2]diazepine (0.17 g, 16.5%) as yellow needles from ethanol m.p. 108-109° (lit.,[50] 108-109°)

Table 3(a)



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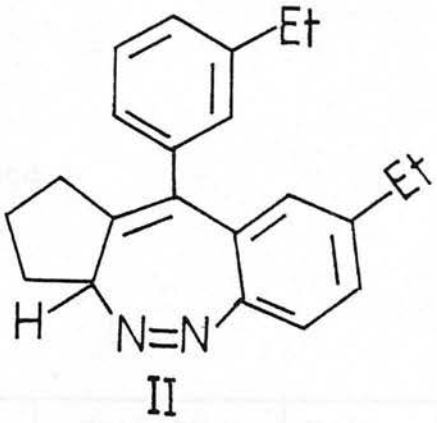


II

Alumina

(a)

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	214670	75889	2.83	
	197412	69466	2.84	
	193671	69168	2.80	
			2.82	3.47
D.M.E.	214911	83857	2.56	
	198662	78945	2.52	
	189214	74788	2.53	
			2.54	3.12
D.M.F.	205985	91425	2.25	
	176201	77281	2.28	
	148753	64675	2.30	
			2.28	2.80

*correction factor 1.23

Table 3(a) (contd.)

Silica

(b)

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	171619	62015	2.77	
	173858	64462	2.70	
	183098	66738	2.74	
			2.74	3.56
D.M.E.	179214	71973	2.49	
	181635	71792	2.53	
	185291	75017	2.47	
			2.50	3.25
D.M.F.	165249	74692	2.21	
	171945	76442	2.25	
	183702	81284	2.26	
			2.24	2.91

*correction factor 1.30

Table 3b

I & II as in Table 3a

Silica

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
Cyclohexane	151738	54050	2.81	
	179797	65339	2.75	
	171264	51506	2.78	
			2.78	3.61
D.M.E.	147680	62818	2.35	
	151919	65212	2.33	
	162917	67882	2.40	
			2.36	3.07
D.M.F.	142503	62032	2.30	
	157101	72268	2.17	
	167901	75631	2.22	
			2.23	2.90

*correction factor 1.30

(Found: C, 60.7; H, 3.4; N, 7.0. Calc. for $C_{20}F_6H_{14}N_2$: C, 60.6; H, 3.6; N, 7.1%); i.r. (Nujol) 1590 (N=N) and 1570 cm^{-1} (C=C). ^1H n.m.r. spectrum: see Appendix.

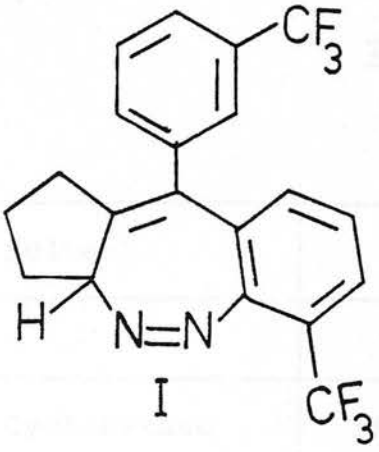
Further elution gave 1,2,3,3a-tetrahydro-8-trifluoromethyl-10-(3-trifluoromethylphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.47 g, 46%) as yellow needles from ethanol m.p. 137-138° (lit.,[50] 138-139°) (Found: C, 60.5; H, 3.5; N, 7.0. Calc. for $C_{20}F_6H_{14}N_2$: C, 60.6; H, 3.6; N, 7.1%); i.r. (Nujol) 1595 (N=N) and 1570 cm^{-1} (C=C). ^1H n.m.r. spectrum: see Appendix.

Measurement of Isomer Ratios

(a) The salt was prepared from sodium (0.0524 g, 2.3 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.3 g, 2.4 mmol). This solution was divided into three and the decompositions carried out in cyclohexane, D.M.E. and D.M.F. as described in general procedure. The isomer ratios were measured by H.P.L.C. [silica-1,4-dioxan (3%) in 50% water-saturated hexane][alumina-1,4-dioxan (3%) in 25% water-saturated hexane]. The results are shown in Table 4(a).

(b) A duplicate measurement was carried out using sodium (0.0518 g, 2.25 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.35 g, 2.4 mmol). The results are shown in Table 4(b).

Table 4(a)



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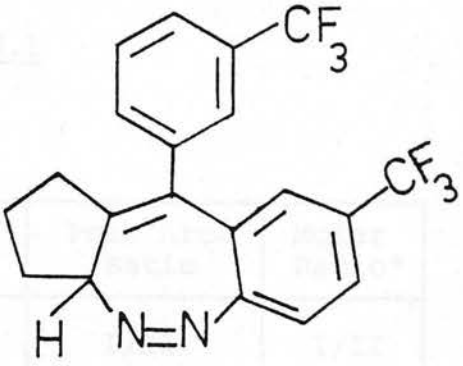


II

Silica

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
Cyclohexane	34115	72190	0.472	
	37109	78557	0.472	
	29619	62086	0.477	
			0.474	0.512
D.M.E.	36256	60673	0.597	
	29721	48929	0.607	
	30266	50695	0.597	
			0.600	0.648
D.M.F.	37434	41295	0.906	
	50099	55431	0.904	
	56316	61174	0.920	
			0.910	0.983

*correction factor 1.08

Table 4(a)(contd.)

Alumina

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
Cyclohexane	34385	63048	0.545	
	35467	64914	0.546	
	35758	64825	0.551	
			0.547	0.551
D.M.E.	31885	49800	0.640	
	36376	56367	0.645	
	33649	54590	0.616	
			0.634	0.639
D.M.F.	60073	64792	0.927	
	52289	54845	0.953	
	60170	61837	0.973	
			0.951	0.959

*correction factor 1.01

Table 4(b)

I & II as in Table 4a

Alumina

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	24632	54288	0.454	
	21175	46931	0.451	
	26063	57799	0.451	
			0.452	0.470
D.M.E.	55984	88270	0.634	
	45804	71709	0.639	
	48716	77506	0.628	
			0.634	0.659
D.M.F.	46618	48685	0.957	
	34550	35696	0.968	
	58504	60184	0.972	
			0.966	1.005

*correction factor 1.04

5. 2-[Bis-(3-methoxyphenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.0915 g, 4.0 mmol) in super-dry ethanol (50 ml) and the tosylhydrazone (2.0 g, 4.2 mmol). After the normal drying procedure freshly distilled dry benzene (70 ml) was added and the mixture boiled under reflux for 7 h. Initially the solution turned deep red then faded to give a yellow solution and a white precipitate. The sodium toluene-4-sulphinate (0.53 g) was filtered off and the yellow filtrate evaporated to give a yellow oil which was recrystallised from ethanol to give 1,2,3,3a-tetrahydro-6-methoxy-10-(3-methoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.53 g, 39%) as yellow plates m.p. 163-165° (lit.,[50] 164-166°); ^{1}H n.m.r. spectrum: see Appendix.

The mother liquor from the recrystallisation was chromatographed on deactivated alumina (1.6 x 15 cm) (Grade III). Elution with petrol containing an increasing proportion of ether produced 1,2,3,3a-tetrahydro-8-methoxy-10-(3-methoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.106 g, 8%) as a yellow oil which could not be crystallised. ^{1}H n.m.r. spectrum: see Appendix.

Further elution gave more 1,2,3,3a-tetrahydro-6-methoxy-10-(3-methoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.26 g, Total 62%).

Measurement of Isomer Ratios

(a) The salt was prepared from sodium (0.0485 g, 2.1 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.15 g, 2.4 mmol). The decompositions were carried out in cyclohexane, D.M.E. and D.M.F. as described in the general procedure.

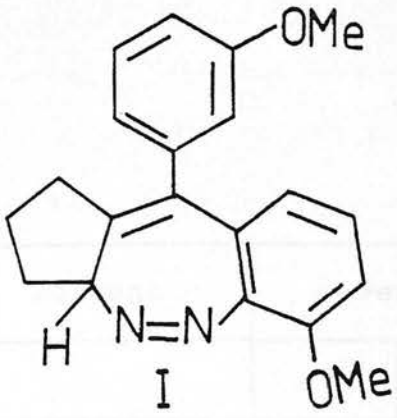
The isomer ratios were measured by H.P.L.C. [silica and alumina (25% 1,4-dioxan in hexane). The results are shown in Table 5(a).

6. 2-[Bis-(3-methylphenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.176 g, 7.6 mmol) in super-dry ethanol (120 ml) and the tosylhydrazone (3.55 g, 8 mmol). After the normal drying procedure freshly distilled dry cyclohexane (100 ml) was added and the mixture boiled under reflux for 5 h. Initially the solution turned deep red then faded to give a yellow solution and a white precipitate. The sodium toluene-4-sulphinate (1.28 g) was filtered off and the yellow filtrate evaporated to give a yellow oil which was recrystallised from ethanol to give 1,2,3,3a-tetrahydro-6-methyl-10-(3-methylphenyl)benzo[c] cyclopenta[f][1,2]diazepine (1.22 g, 56%) m.p. 118-120° (lit.,[50] 119-121°) (Found: C, 83.5; H, 7.1; N, 9.6. Calc. for $C_{20}H_{20}N_2$: C, 83.3; H, 7.0; N, 9.7%); ^1H n.m.r. spectrum: see Appendix.

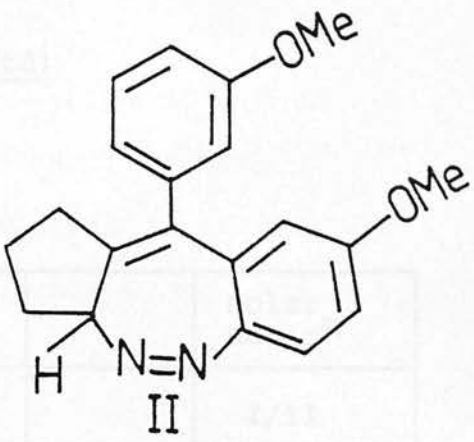
The mother liquor from the recrystallisation was chromatographed on deactivated alumina. Elution with petrol containing an increasing proportion of benzene produced more 1,2,3,3a-tetrahydro-6-methyl-10-(3-methylphenyl)benzo[c] cyclopenta[f][1,2]diazepine (0.24 g, Total 67%). Further elution produced 1,2,3,3a-tetrahydro-8-methyl-10-(3-methylphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.151 g, 7%) m.p. 111-112° (lit.,[50] 111-112°) (from ethanol) (Found: C, 83.5; H, 7.0; N, 9.8. Calc. for $C_{20}H_{20}N_2$: C, 83.3; H, 7.1; N, 9.6%); ^1H n.m.r. spectrum: see Appendix.

Table 5(a)



I

Alumina



II

Solvent	Peak Area		Peak Area Ratio		Molar Ratio*
	I	II	I/II		I/II
cyclohexane	8906	8647	1.03		1.25
	6503	6193	1.05		1.27
	7627	7783	0.98		1.19
					1.23
D.M.E.	1860	1540	1.21		1.46
	1892	1603	1.18		1.43
	1769	1487	1.19		1.44
					1.44
D.M.F.	2250	1188	1.89		2.29
	3650	1680	2.17		2.62
	2792	1403	1.99		2.41
					2.44

*correction factor 1.21

Table 5(a)(contd)

Silica

Solvent	Peak Area		Peak Area Ratio		Molar Ratio*
	I	II	I/II		I/II
Cyclohexane	8731	8714	1.00		1.19
	7926	8432	0.94		1.12
	8342	8512	0.98		1.17
					1.16
D.M.E.	10215	8883	1.15		1.37
	11391	9905	1.15		1.31
	13276	13017	1.00		1.19
					1.29
D.M.F.	15297	7765	1.97		2.35
	14683	7491	1.96		2.32
	15021	7664	1.96		2.32
					2.33

*correction factor 1.19

Measurement of Isomer Ratios

(a) The salt was prepared from sodium (0.0503, 2.2 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1 g, 2.3 mmol). This solution was divided into three and the decompositions carried out in cyclohexane, D.M.E. and D.M.F. as described in the general procedure. The isomer ratios were measured by H.P.L.C. [silica - 1,4-dioxan (3%) in 50% water-saturated hexane]. The results are shown in Table 6(a).

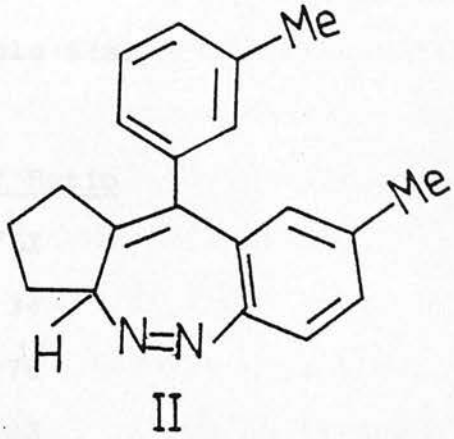
(b) A duplicate reaction was carried out using sodium (0.0495 g, 2.15 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.05 g, 2.3 mmol). The isomer ratios were measured by H.P.L.C. [silica, 1,4-dioxan (3%) in 50% water-saturated hexane]. The results are shown in Table 6(b).

7. 2-[Bis-(2-^{2}H-3-methylphenyl)methylene]cyclopentanone tosylhydrazone

The salt was prepared from sodium (0.0483 g, 2.1 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (87.5% d_2, 12.5% d_1) (1 g, 2.24 mmol). This solution of the sodium salt was divided into three and each portion dried in the usual way. To each was added freshly distilled dry D.M.E. (25 ml), cyclohexane (25 ml) and D.M.F.(25 ml) respectively. Each mixture was boiled under reflux, with stirring, in the dark, for 5 h under dry nitrogen. The relative amounts of each isomer were determined using H.P.L.C. on alumina [3% 1,4-dioxan in hexane (25% water saturated)] and the results are shown in Table 7.

Table 6(a)

I



II

Silica

Solvent	Peak Area		Peak Area Ratio	Molar Ratio*
	I	II	I/II	I/II
cyclohexane	18601	5167	3.60	
	15306	4159	3.68	
	19012	5125	3.71	
			3.66	4.28
D.M.E.	10156	3419	2.97	
	11553	3751	3.08	
	11201	3697	3.03	
			3.03	3.48
D.M.F.	13267	4789	2.77	
	14905	5035	2.96	
	14103	4948	2.85	
			2,86	3.35

*correction factor 1.17

Table 6(b)

I and II as for Table 6(a)

Solvent	Molar Ratio I/II
cyclohexane	4.34
D.M.E.	3.76
D.M.F.	3.83

The reaction mixtures were combined and the sodium toluene-4-sulphinate (0.40 g) filtered off. The filtrate was evaporated and separated by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing proportion of ether produced 1,2,3,3a-tetrahydro-6-methyl-10-(2-^{2}H-3-methylphenyl)benzo[c][3a-^{2}H]cyclopenta[f][1,2]diazepine (I) (0.26 g, 43%) m.p. 122-123° (from ethanol). This compound was identified by ^{1}H n.m.r. and mass spectroscopy. Mass spectroscopy showed 83.55% dideuteration and 16.4% monodeuteration. See Appendix for calculation.

Further elution produced 1,2,3,3a-tetrahydro-8-methyl-9-^{2}H-10-(2-^{2}H-3-methylphenyl)benzo[c]cyclopenta[f][1,2]diazepines (II)(0.20 g, 33%) m.p. 117° (from ethanol). This compound was identified by ^{1}H n.m.r. and mass spectroscopy. Mass spectroscopy showed 91.2% dideuteration and 8.8% monodeuteration. See Appendix for calculation.

Deuterium Balance

Tosylhydrazone contains 87.5% d_2 and 12.5% d_1

∴ Total deuterium content in 2.1 mmol starting material

$$= \left(\frac{2 \times 87.5 \times 2.1}{100}\right) + \left(\frac{12.5 \times 2.1}{100}\right)$$

$$= \underline{\underline{3.94 \text{ mmol}}}$$

∴ Theor. deuterium content in 76% yield of products

$$= \underline{\underline{2.99 \text{ mmol}}}$$

Estimated deuterium content of (I)

$$= \left(\frac{0.26}{290} \times 1000\right)\left(\frac{2 \times 83.55}{100} \times \frac{16.4}{100}\right)$$

$$= \underline{\underline{1.64 \text{ mmol}}}$$

Estimated deuterium content of (II)

$$= \left(\frac{0.20}{290} \times 1000\right)\left(\frac{2 \times 91.2}{100} \times \frac{8.8}{100}\right)$$

$$= \underline{\underline{1.32 \text{ mmol}}}$$

$\therefore$ loss of deuterium

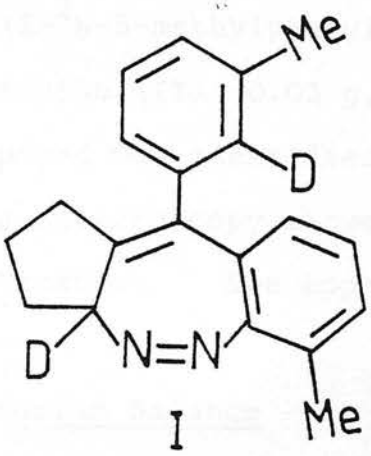
$$= \underline{\underline{1\%}}$$

8. 2-[Bis-(2-^{2}H-5-methylphenyl)methylene]cyclopentanone tosylhydrazone

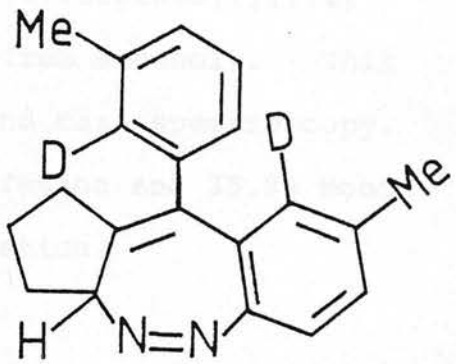
The decompositions and measurement of the isomer ratios were carried out by Mr. I.D. Thomson.[102] Sodium (0.0452 g, 1.96 mmol) was dissolved in super-dry ethanol (75 ml) with stirring. An aliquot of this solution (25 ml) was added to the tosylhydrazone (85% d_2, 15% d_1) (0.302 g, 0.67 mmol) and the mixture was stirred in the dark for 1 h and then dried in the usual way. Freshly distilled D.M.E. (25 ml) was added and the mixture boiled under reflux for 5 h in the normal way. A second aliquot (25 ml) was treated in the same way but with the third aliquot (25 ml) the solvent used for the decomposition was cyclohexane (25 ml). The relative amounts of each isomer were determined using H.P.L.C. on alumina [3% 1,4-Dioxan in hexane (25% water saturated)] and the results are shown in Table 8.

The reaction mixtures were combined and the sodium toluene-4-sulphinate (0.37 g) filtered off. The filtrate was evaporated and separated by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing proportion of ether produced 1,2,3,3a-tetrahydro-5-methyl-9-^{2}H-10-(2-^{2}H-5-methylphenyl)benzo[c]cyclopenta[f][1,2]diazepine (I) (0.34 g, 60%) m.p. 122-124^o (from ethanol). This compound was identified by ^{1}H n.m.r. and

Table 7



I



II

Alumina

Solvent	Peak Area Ratio	Molar Ratio*
	I/II	I/II
DME	0.845	
	0.841	
	0.846	
	0.844	0.987
cyclohexane	0.991	
	0.999	
	1.002	
	0.997	1.166

*correction factor = 1.17

mass spectroscopy. Mass spectroscopy showed 85.2% dideuteration and 14.8% monodeuteration. See Appendix for calculation.

Further elution produced 1,2,3,3a-tetrahydro-8-methyl-10-(2-^{2}H-5-methylphenyl)benzo[c][3a-^{2}H]cyclopenta[f][1,2]diazepine (II) (0.03 g, 5%) m.p. 90^{o} (from ethanol). This compound was identified by ^{1}H n.m.r. and mass spectroscopy. Mass spectroscopy showed 64.1% dideuteration and 35.9% monodeuteration. See Appendix for calculation.

Deuterium Balance

Tosylhydrazone contains 85% d_2 and 15% d_1

∴ Total deuterium content in 1.96 mmol starting material

$$= \left(\frac{2 \times 85 \times 1.96}{100}\right) + \left(\frac{15 \times 1.96}{100}\right)$$

$$= \underline{\underline{3.63 \text{ mmol}}}$$

∴ Theoretical deuterium content in 65% yield of products

$$= \underline{\underline{2.36 \text{ mmol}}}$$

Estimated deuterium content of (I)

$$= \left(\frac{0.34}{290} \times 1000\right)\left(\frac{2 \times 85.2}{100} + \frac{14.8}{100}\right)$$

$$= \underline{\underline{2.17 \text{ mmol}}}$$

Estimated deuterium content of (II)

$$= \left(\frac{0.03}{290} \times 1000\right)\left(\frac{2 \times 64.1}{100} + \frac{35.9}{100}\right)$$

$$= \underline{0.17 \text{ mmol}}$$

Estimated deuterium content of products

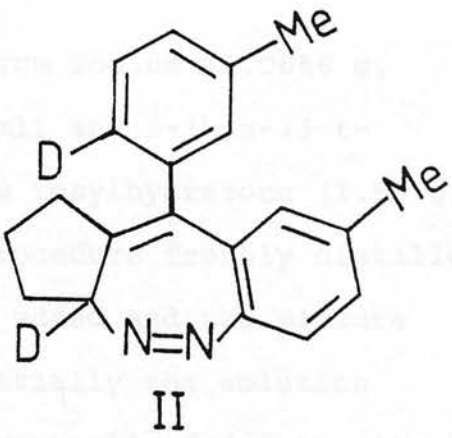
$$= \underline{\underline{2.34 \text{ mmol}}}$$

∴ loss of deuterium

$$= \underline{\underline{0.85\%}}$$

Table 8

I



II

Alumina

Solvent	Peak Area Ratio	Molar Ratio*
DME	I/II 11.91 11.48 11.65	I/II
	11.68	13.70
cyclohexane	14.59 14.76 14.97	
	14.75	17.25

*correction factor = 1.17

9. 2-[Bis-(3-t-butylphenyl)methylene]cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.0666 g, 2.9 mmol) in super-dry ethanol (75 ml) and 2-[bis-(3-t-butylphenyl)methylene[cyclopentanone tosylhydrazone (1.58 g, 3 mmol). After the usual drying procedure freshly distilled dry 1,2-dimethoxyethane (75 ml) was added and the mixture boiled under reflux for 5.5 h. Initially the solution turned a deep red in colour which eventually faded to give a yellow solution and a white precipitate. The sodium toluene-4-sulphinate (0.48 g) was filtered off and the yellow filtrate evaporated to give a yellow oil which was purified by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing amount of ether produced 1,2,3,3a-tetrahydro-8-t-butyl-10-(3-t-butylphenyl) benzo[c]cyclopenta[f][1,2]-diazepine (0.63 g, 64%) as a yellow oil (Found: C, 83.9; H, 8.7; N, 7.4. $C_{26}H_{32}N_2$ requires C, 83.8; H, 8.7; N, 7.5%); i.r. ($CHCl_3$) 1595 (N=N) and 1575 cm^{-1} (C=C). ^1H n.m.r. ^{13}C n.m.r. and mass spectra: see Appendix.

10. 2-[Bis-(3,5-dimethylphenyl)methylene]cyclopentanone tosylhydrazone

This decomposition was carried out by Mr. C.B. Argo. The sodium salt was prepared from sodium (0.0577 g, 2.5 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (1.185 g, 2.5 mmol). After the normal drying procedure freshly distilled dry D.M.E. (25 ml) was added and the solution heated to reflux, under dry nitrogen with magnetic stirring in the dark.

A deep red colour was observed which faded to give a yellow solution and white precipitate. Filtration of the sodium toluene-4-sulphinate and evaporation of the filtrate produced a yellow solid which was recrystallised from ethanol to give 1,2,3,3a-tetrahydro-6,8-dimethyl-10-(3,5-dimethylphenyl)benzo[c]cyclopenta[f][1,2]diazepine (0.527 g, 66.4%) as yellow plates m.p. 169-170° (Found: C, 83.3; H, 7.7; N, 8.85. $C_{22}H_{24}N_2$ requires C, 83.5; H, 7.6; N, 8.85%); i.r. (Nujol) 1600 (N=N) and 1590 cm^{-1} (C=C); ^1H n.m.r. spectrum: see Appendix.

11. 2-[Bis-(3,5-dimethylphenyl)methylene]cyclohexanone tosylhydrazone

The sodium salt was prepared from sodium (0.0455 g, 1.98 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.0 g, 2.05 mmol). After the usual drying procedure freshly distilled dry D.M.E. (50 ml) was added and the mixture heated to reflux, under dry nitrogen, with stirring, in the dark. No red colour was observed. The mixture was refluxed for 1 h then cooled and filtered to produce sodium toluene-4-sulphinate (0.21 g). The filtrate was evaporated and the resultant white solid chromatographed on silica using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether produced a white solid which was recrystallised from petrol/ethanol to give 4,5,6,7-tetrahydro-3,3-bis-(3,5-dimethylphenyl)-indazole (0.25 g, 44%) m.p. 130° (Found: C, 83.35; H, 7.9; N, 8.3. $C_{23}H_{26}N_2$ requires C, 83.6; H, 7.9; N, 8.5%); i.r. (Nujol) 1645 cm^{-1} (N=N); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Further elution gave 2-[bis-(3,5-dimethylphenyl) methylene]cyclohexanone tosylhydrazone (0.13 g, 13%) m.p. 174°.

12. 2-(Di-2-thienylmethylene)cyclopentanone tosylhydrazone

The sodium salt was prepared from sodium (0.0517 g, 2.2 mmol) in super-dry ethanol (75 ml) and the hydrazone (1 g, 2.3 mmol). After the usual drying procedure freshly distilled dry D.M.E. (75 ml) was added and the mixture heated at reflux for 1 h. No red colour was observed. Filtration produced sodium toluene-4-sulphinate (0.33 g). Evaporation of the filtrate gave a yellow solid which was recrystallised from ethanol to give 5a,6,7,8-tetrahydro-10-(2-thienyl)cyclopenta[f]thieno[3,2-c][1,2]diazepine m.p. 120-121° (0.52 g, 85%) as yellow needles. (Found: C, 61.5; H, 4.5; N, 10.2. $C_{14}H_{12}N_2S_2$ requires C, 61.8; H, 4.4; N, 10.3%); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

13. 2-(Di-3-thienylmethylene)cyclopentanone tosylhydrazone

The sodium salt was prepared form sodium (0.0491 g, 2.13 mmol) in super-dry ethanol (75 ml) and the hydrazone (1 g, 2.33 mmol). After the usual drying procedure freshly distilled dry D.M.E. (75 ml) was added and the mixture refluxed for 0.5 h. The reaction mixture was cooled and filtered to give sodium toluene-4-sulphinate (0.37 g). The filtrate was evaporated to give 5,6,7,7a-tetrahydro-4-(3-thienyl)cyclopenta [f]thieno[2,3-c][1,2]diazepine (0.52 g, 90%) m.p. 158-159° as yellow needles (from ethanol) (Found: C, 61.75; H, 4.4; N, 10.25. $C_{14}H_{12}N_2S_2$ requires C, 61.8; H, 4.4; N, 10.3%); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

14. 2-(Phenyl-2-thienylmethylene)cyclohexanone tosylhydrazone

The salt was prepared from sodium (0.0246 g, 1.07 mmol) in super-dry ethanol (40 ml) and the tosylhydrazone (0.4907 g, 1.12 mmol). After the usual drying procedure freshly distilled dry D.M.E. (40 ml) was added and the solution warmed slowly to boiling with stirring under dry nitrogen in the dark. When the boiling point was reached the solution became cloudy as a white precipitate was formed but no red colour was observed. After boiling under reflux for 1 h the reaction mixture was cooled and filtered giving sodium toluene-4-sulphinate (0.1600 g). The filtrate was evaporated and then chromatographed on silica (1.5 x 100 cm) using medium pressure chromatography. Elution with petrol containing an increasing proportion of ether produced 4,5,6,7-tetrahydro-3-phenyl-3-(2-thienyl)indazole (0.2561 g, 85%) as white needles m.p. 86-87° (from ethanol)(Found: C, 73.0; H, 5.8; N, 10.1. $C_{17}H_{16}N_2S$ requires C, 72.8; H, 5.75; N, 10.0%); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Further elution produced 6,7,8,9-tetrahydro-10-(2-thienyl)cyclohexa[f]thieno[3,2-c][1,2]diazepine (0.0287 g, 9.5%) m.p. 100-101° as yellow needles from ethanol (Found: C, 72.6; H, 5.95; N, 9.7. $C_{17}H_{16}N_2S$ requires C, 72.8; H, 5.75; N, 10.0%); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

15. 4,4-Di-2-thienylbut-3-en-2-one tosylhydrazone

The sodium salt was prepared from sodium (0.0437 g, 1.9 mmol) in super-dry ethanol (25 ml) and the tosylhydrazone (0.81 g, 2.02 mmol). After stirring in the dark for 1 h, the ethanol was removed under reduced pressure and the salt dried under high vacuum for 0.25 h. Freshly distilled dry D.M.E. (25 ml) was added and the flask swirled gently. The D.M.E. was removed under reduced pressure and the salt dried under high vacuum for 0.25 h. More D.M.E. (25 ml) was added and the process repeated. The salt was dried overnight under high vacuum over phosphorus pentoxide. Freshly distilled D.M.E. (25 ml) was added and the mixture warmed slowly to boiling under dry nitrogen with stirring in the dark. No red colour was observed. After boiling under reflux for 0.5 h t.l.c. showed that reaction was complete and that two products had been formed. On cooling sodium toluene-4-sulphinate (0.30 g) was collected by filtration. The filtrate was evaporated and separated by medium pressure chromatography in silica (1.5 x 100 cm). Elution with petrol containing an increasing amount of ether produced 3,3-di-2-thienyl-5-methylpyrazole (0.23 g, 49%) as colourless needles from petrol/benzene m.p. 73° (Found: C, 58.7; H, 4.1; N, 11.6. $C_{12}H_{10}N_2S_2$ requires C, 58.5; H, 4.1; N, 11.4%); i.r. ($CHCl_3$) 1635 cm^{-1} (N=N); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Further elution produced 3-methyl-5-(2-thienyl)thieno [3,2-c][1,2]diazepine (0.0906 g, 19%) as yellow needles from ethanol m.p. 97° (Found: C, 58.4; H, 4.1; N, 11.4. $C_{12}H_{10}N_2S_2$ requires C, 58.5; H, 4.1; N, 11.4%); i.r. ($CHCl_3$) 1575 cm^{-1} (N=N); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

16. 4,4-Di-3-thienylbut-3-en-2-one tosylhydrazone

The sodium salt was prepared from sodium (0.0615 g, 2.7 mmol) in super-dry ethanol (75 ml) and the tosylhydrazone (1.2 g, 3 mmol). After stirring in the dark for 1 h, the ethanol was removed under reduced pressure and the salt dried under high vacuum for 0.25 h. Freshly distilled dry D.M.E. (25 ml) was added and the flask swirled gently. The D.M.E. was removed under reduced pressure and the salt dried under high vacuum for 0.25 h. More D.M.E. (25 ml) was added and the process repeated. The salt was dried overnight under high vacuum over phosphorus pentoxide. Freshly distilled D.M.E. (75 ml) was added and the mixture warmed slowly to boiling under dry nitrogen, with stirring in the dark. No red colour was observed. After boiling under reflux for 0.5 h t.l.c. showed that reaction was complete and that two products had been formed. On cooling sodium toluene-4-sulphinate (0.35 g) was collected by filtration. The filtrate was evaporated and separated by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing amount of ether produced 3,3-di-3-thienyl-5-methyl pyrazole (0.28 g, 43%) as colourless needles from petrol/benzene m.p.85° (Found: C, 58.6; H, 4.15; N, 11.35. $C_{12}H_{10}N_2S_2$ requires C, 58.5; H, 4.1; N, 11.4%); i.r. (Nujol) 1630 cm^{-1} (N=N); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Further elution produced 3-methyl-5-(3-thienyl)thieno [2,3-c][1,2]diazepine (0.053 g, 8%), as a yellow oil which could not be crystallised, (Found: m/e 246.028888. $C_{12}H_{10}N_2S_2$ requires 246.028539); i.r. ($CHCl_3$) 1580 cm^{-1} (N=N); ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix.

Thermolysis of 1,2,3,3a-tetrahydro-6-chloro-10-(3-chlorophenyl)benzo[c]cyclopenta[f][1,2]diazepine

1,2,3,3a-Tetrahydro-6-chloro-10-(3-chlorophenyl)benzo[c]cyclopenta[f][1,2]diazepine (50 mg) was boiled under reflux in dry toluene (10 ml) in the dark and the reaction monitored by H.P.L.C. A second peak gradually appeared and was identified as 1,2,3,3a-tetrahydro-8-chloro-10-(3-chlorophenyl)benzo[c]cyclopenta[f][1,2]diazepine by comparison of its retention time with an authentic sample. After 6 h the peak area ratio of the 6-chloro diazepine to the 8-chloro diazepine was 8:1.

Thermolysis of 1,2,3,3a-tetrahydro-6-ethoxy-10-(3-ethoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine

1,2,3,3a-Tetrahydro-6-ethoxy-10-(3-ethoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (129 mg) was boiled under reflux in dry toluene (10 ml) in the dark under dry nitrogen for 5.5 h. The toluene was removed under reduced pressure and the oil recrystallised from ethanol giving 1,2,3,3a-tetrahydro-8-ethoxy-10-(3-ethoxyphenyl)benzo[c]cyclopenta[f][1,2]diazepine (15 mg, 12%) m.p. 144°. The identity of this compound was confirmed by ^{1}H n.m.r.

Thermolysis of 1,2,3,3a-tetrahydro-6-methyl-10-(3-methylphenyl)benzo[c]cyclopenta[f][1,2]diazepine

This compound was boiled under reflux in dry D.M.E., toluene and xylene in the dark under dry nitrogen and monitored by H.P.L.C. In the first case no reaction was observed. In toluene and xylene the benzodiazepine decomposed to give several products which although not identified were probably mixture of indazole and hydrocarbons on the basis of

H.P.L.C. retention times. No 1,2,3,3a-tetrahydro-8-methyl-10-(3-methylphenyl)benzo[c]cyclopenta[f][1,2]diazepine was observed in either reaction.

Thermolysis of 3-methyl-5-(2-thienyl)thieno[3,2-c[[1,2] diazepine

3-Methyl-5-(2-thienyl)thieno[3,2-c][1,2]diazepine (20 mg) was boiled under reflux in dry D.M.E. (5 ml) and the reaction monitored by H.P.L.C. After 30 min a second peak was observed. This was identified as 3,3-di-2-thienyl-5-methylpyrazole by a comparison of retention time with an authentic sample. After 2 h the peak area ratio of diazepine to pyrazole was 2.5:1.

Thermolysis of 3-methyl-5-(3-thienyl)thieno[2,3-c][1,2] diazepine

3-Methyl-5-(3-thienyl)thieno[2,3-c][1,2]diazepine (30 mg) was heated at 80° in d_6-benzene (0.5 ml) in an n.m.r. tube and the reaction monitored by ^1H n.m.r. The doublet characteristic of the diazepine gradually disappeared as the doublet characteristic of 3,3-di-3-thienyl-5-methylpyrazole appeared. After 3 h no diazepine could be detected in the reaction mixture. The identity of the pyrazole was confirmed by a comparison of its retention time with an authentic sample by H.P.L.C.

Thermolysis of 3,3-di-2-thienyl-5-methylpyrazole

3,3-Di-2-thienyl-5-methylpyrazole (163 mg) was boiled under reflux in dry D.M.E. (25 ml) for 2.5 h in the dark. The D.M.E. was removed under reduced pressure and the mixture

separated by medium pressure chromatography on silica (1.5 x 100 cm). Elution with petrol containing an increasing amount of ether produced 3,3-di-2-thienyl-5-methylpyrazole (70 mg, 43%) m.p. 73° and 3-methyl-5-(2-thienyl)thieno[3,2-c][1,2]diazepine (46 mg, 28%) m.p. 96-97°. The identity of both compounds was confirmed by ^{1}H n.m.r.

Thermolysis of 3,3-di-3-thienyl-5-methylpyrazole

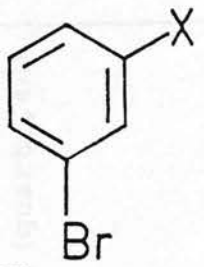
a) 3,3-Di-3-thienyl-5-methylpyrazole (25 mg) was boiled under reflux in dry D.M.E. (10 ml) in the dark for 12 h. The reaction was monitored by H.P.L.C. No diazepine formation was observed and starting material was recovered unchanged.

b) 3,3-Di-3-thienyl-5-methylpyrazole (25 mg) was boiled under reflux in dry toluene (10 ml) in the dark for 24 h. The reaction was monitored by H.P.L.C. No diazepine formation was observed but a gradual decomposition of the pyrazole took place. The products were not identified.

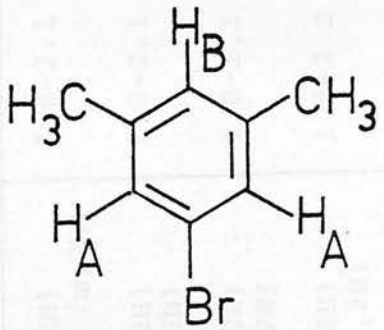
Appendix 1

Bromobenzenes

^{1}H n.m.r ($CDCl_3$) δ



X	Aromatic	CH_2	CH_3
$-C(CH_3)_3$	7.1-7.5 (m,4H)	-	1.3 (s,9H)
$-OCH_2CH_3$	6.7-7.2 (m,4H)	4.1 (q,2H)	1.5 (t,3H)
$-CH_2CH_3$	7.2-7.5 (m,4H)	2.7 (q,2H)	1.3 (t,3H)

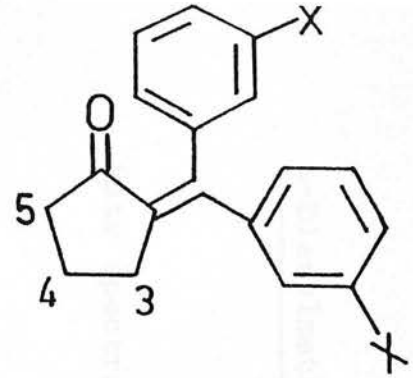


H_A	H_B	CH_3
7.15 (2H)	6.9 (1H)	2.2 (6H)

Appendix 2

α-Diarylmethylenecyclopentanones

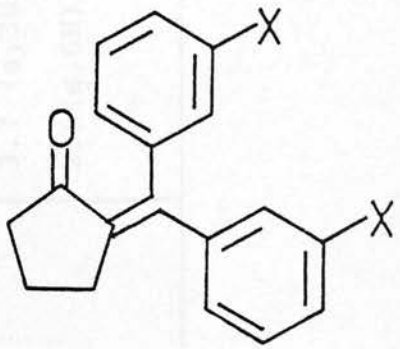
^{1}H N.m.r. spectral data ($CDCl_3$)



X	Ar	$CH_{2(3\ 5)}$	$CH_{2(4)}$	$CH_{2(X)}$	$CH_{3(X)}$
$-C(CH_3)_3$	6.7-7.4 (m,8H)	2.9 (t,2H) 2.2-2.5 (m,2H)	1.8-2.1 (m,2H)	-	1.3 (s,9H)
-Cl	6.9-7.4 (m,8H)	2.8 (t,2H) 2.4 (m,2H)	1.8-2.1 (m,2H)	-	-
$-OCH_2CH_3$	6.7-7.4 (m,8H)	2.8 (t,2H) 2.4 (m,2H)	1.8-2.1 (m,2H)	2.9 (quart.,4H)	1.3 (t,6H)
$-CH_2CH_3$	6.9-7.4 9M,8H)	2.8 (t,2H) 2.35 (m,2H)	1.8-2.O (m,2H)	2.6 (quart.,4H)	1.2 (t, 6H)
-OMe	6.6-7.4 (m,8H)	2.8 (t,2H) 2.2-2.6 (m,2H)	1.6-2.1 (m,2H)	-	2.7 (s,6H)
-Me	6.9-7.4 (m,8H)	2.8 (t,2H) 2.3-2.5 (m,2H)	1.8-2.1 (m,2H)	-	2.3 (s,6H)
$-CF_3$	7.2-7.7 (m,8H)	2.8 (t,2H) 2.2-2.6 (m,2H)	1.8-2.2 (m,2H)	-	-

Appendix 3

α-Diarylmethylenecyclopentanones



Mass spectral data (m/e, % relative abundance)

X = $-C(CH_3)_3$ 360(57), 359(43), 345(7), 304(25), 303(100), 289(7), 254(9), 247(6), 165(11), 150(7), 135(22), 106(50), 105(37), 91(71), 57(71).

X = -Cl 318(67), 317(77), 316(100), 315(97), 283(22), 281(60), 227(16), 225(39), 190(33).

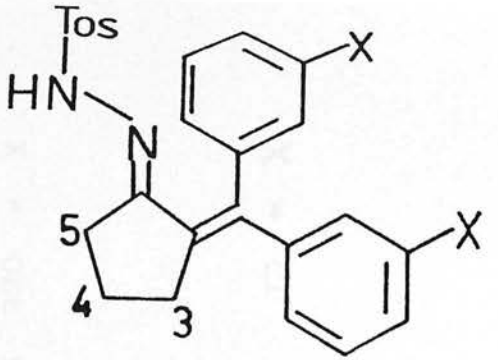
X = -OEt 336(100), 335(64), 308(4), 307(8), 291(36), 280(9), 251(4), 223(4), 215(4), 165(4).

Appendix 4

Tosylhydrazones of

α-diarylmethylenecyclopentanones

^1H N.m.r. spectral data ($CDCl_3$)



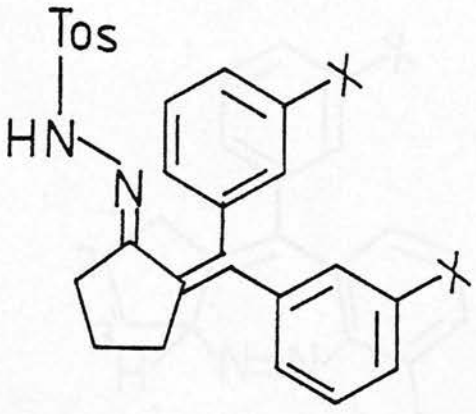
X	Ar + NH	CH_2(3+5)	CH_2(4)	CH_3(Tosyl)	CH_2(X)	CH_3(X)
$-C(CH_3)_3$	6.8-7.3(m,13H)	2.3-2.7(m,4H)	1.6-2.0(m,2H)	2.4(s,3H)		1.3(s,9H) 1.25(s,9H)
-Cl	6.8-7.3(m,13H)	2.3-2.6(m,4H)	1.6-1.9(m,2H)	2.4(s,3H)	-	-
$-OCH_2CH_3$	6.6-7.4(m,13H)	2.2-2.6(m,4H)	1.6-1.9(m,2H)	2.4(s,3H)	3.8-4.1(m,2H)	1.2-1.5(m,6H)
$-CH_2CH_3$	6.7-7.3(m,13H)	2.2-2.8(m,4H)	1.6-1.9(m,2H)	2.4(s,3H)	2.2-2.8(m,4H)	1.3(t,3H) 1.2(t,3H)
-OMe	6.6-7.5(m,13H)	2.2-2.7(m,4H)	1.6-2.0(m,2H)	2.4(s,3H)	-	3.75(s,3H) 3.7 (s,3H)
-Me	6.8-7.4(m,13H)	2.2-2.7(m,4H)	1.7-2.0(m,2H)	2.4(s,3H)	-	2.5(s,6H)
$-CF_3$	7.1-7.7(m,13H)	2.2-2.7(m,4H)	1.7-2.0(m,2H)	2.4(s,3H)	-	-

Appendix 5

Tosylhydrazones of

α-diarylmethylenecyclopentanones

Mass spectral data



X = Cl 485(4), 483(6), 331(20), 329(30), 302(65), 301(20), 300(100), 265(40), 156(35), 139(20), 92(40), 91(75).

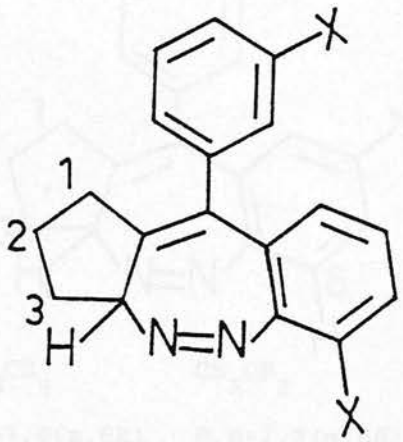
X = OEt 504(1), 503(2), 349(8), 321(34), 320(100), 292(5), 291(4), 202(17), 189(15), 156(15), 139(17), 92(27), 91(41).

X = Et 472(9), 471(15), 317(27), 288(100), 260(19), 259(21), 231(13), 230(10), 229(11), 215(15), 156(17), 139(15), 91(32).

Appendix 6

1,2-Benzodiazepines

^{1}H N.m.r. spectral data ($CDCl_3$)



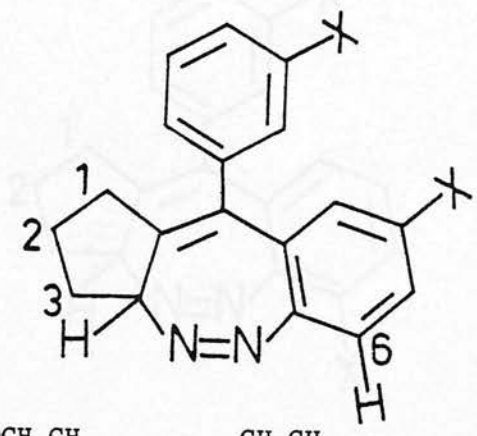
X =	Cl	OCH_2CH_3	CH_2CH_3
Ar	6.9-7.5(m,7H)	6.7-7.4(m,7H)	6.9-7.3(m,7H)
C-H_2(3_β)	3.1-3.3(m,1H)	3.2(m,1H)	3.2(m,1H)
CH_2(1,2,3α+3a)	2.1-2.8(m,6H)	2.0-2.8(m,6H)	2.0-2.7(m,6H)
CH_2(X)	-	4.2(q,2H)	2.0(q,2H)
		3.9(q,2H)	2.6(q,2H)
CH_3(X)	-	1.5(t,3H)	1.21(t,3H)
		1.35(t,3H)	1.98(t,3H)

X =	OMe	Me	CF_3
Ar	4.7-7.4(m,7H)	6.9-7.3(m,7H)	7.0-7.6(m,7H)
C-$H_{(3\beta)}$	3.1-3.3(m,1H)	3.1-3.3(m,1H)	3.1-3.4(m,1H)
CH_2(1,2,3 + 3a)	2.0-2.7(m,6H)	2.0-2.7(m,6H)	1.8-3.0(m,6H)
CH_3(X)	4.0 (s,3H)	2.5 (s,3H)	
	3.8 (s,3H)	2.3 (s,3H)	

Appendix 7

1,2-Benzodiazepines

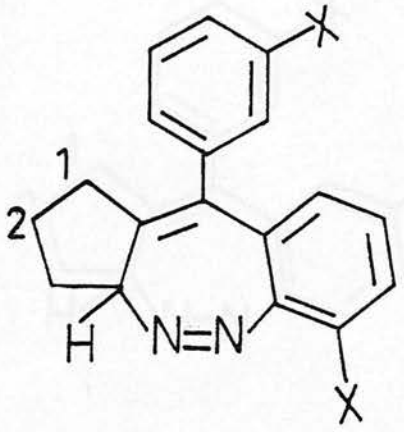
^{1}H N.m.r. spectral data ($CDCl_3$)



X =	t-Bu	Cl	OCH_2CH_3	CH_2CH_3
Ar	7.1-7.5(m,6H)	6.9-7.4(m,6H)	6.5-7.4(m,6H)	6.9-7.3(m,6H)
C-H(6)	7.8(d,1H)	7.7(d,1H)	7.7(d,1H)	7.65(d,1H)
$C\text{-}H_{(3\beta)}$	3.2-3.0(m,1H)	3.1-3.3(m,1H)	3.0-3.3(m,1H)	3.05-3.25(m,1H)
CH_2(1 2)		2.1-2.8(m,6H)	2.0-2.9(m,6H)	2.0-2.9(m,6H)
CH(3α,3a)				
CH_2(X)	-	-	4(q,2H)	2.6(m,4H)
			3.9(q,2H)	
CH_3(X)	1.3(s,9H)	-	1.4(t,3H)	1.2(t,3H)
	1.2(s,9H)		1.3(t,3H)	1.15(t,3H)

X =	OMe	Me	CF_3
Ar	6.5-7.5(m,6H)	6.9-7.3(m,6H)	7.0-7.8(m,6H)
$C\text{-}H_{(6)}$	7.8(d,J=8Hz,1H)	7.8(d,J=8Hz,1H)	8.0(d,J=Hz,1H)
$C\text{-}H_{(3\beta)}$	3.1-3.3(m,1H)	3.1-3.3(m,1H)	3.1-3.4(m,1H)
$CH_{2(1,2,3\alpha\ 3a)}$	2.0-2.9(m,6H)	2.1-2.9(m,6H)	1.9-2.9(m,6H)
$CH_{3(X)}$	3.8(s,3H)	2.25(s,3H)	-
	3.7(s,3H)	2.35(s,3H)	

Appendix 8

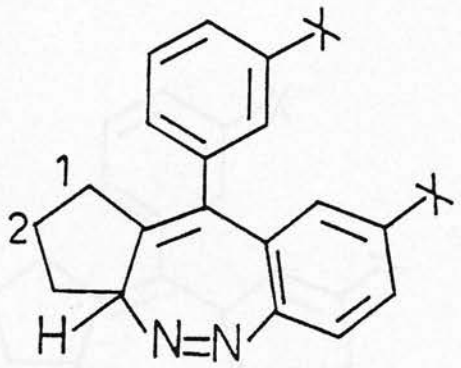


1,2-Benzodiazepines

^{13}C N.m.r. spectral data ($CDCl_3$)

X	Chemical Shifts from T.M.S. (p.p.m.)
-Cl	C_1-C_3: 26.6, 32.2, 32.6. C_{3a}: 76.1. Aromatic and olefinic carbons: 127.0, 127.2, 127.7, 128.0, 129.6, 129.8, 130.8, 131.4, 132.4, 134.2, 140.7, 145.3, 148.1.
-OEt	2 x CH_3: 14.8. C_1-C_3: 26.7, 32.4, 32.6. 2 x CH_2: 63.4, 64.8. C_{3a}: 75.8. Aromatic and olefinic carbons: 108.3, 113.6, 116.0, 120.9, 122.3, 127.4, 129.1, 130.6, 133.0, 141.0, 142.8, 143.8, 154.7, 158.8.
-Et	2 x CH_3: 15.2, 15.6. C_1-C_3: 25.1, 26.8, 28.8. 2 x CH_2: 32.5. C_{3a}: 75.4. Aromatic and olefinic carbons: 125.5, 126.8, 127.1, 127.4, 128.1, 129.6, 129.7, 133.5, 139.8, 141.3, 143.1, 144.1, 150.2.

Appendix 9

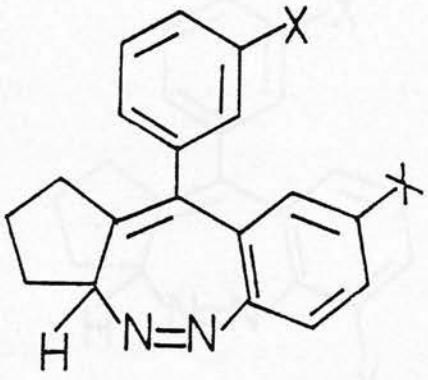


1,2-Benzodiazepines

^{13}C N.m.r. spectral data ($CDCl_3$)

X	Chemical shifts from T.M.S. (p.p.m.)
$-C(CH_3)_3$	2 x $-C(CH_3)_3$: 30.9, 31.2, 34.55, 34.6. C_1-C_3: 26.7, 32.5, 32.6. C_{3a}: 74.45. Aromatic and olefinic carbons: 123.2, 123.9, 125.5, 126.9, 127.4, 127.5, 127.55, 130.0, 133.4, 138.9, 142.4, 149.8, 150.1, 150.7.
-Cl	C_1-C_3: 26.7, 32.6, 32.6. C_{3a}: 75.0. Aromatic and olefinic carbons: 126.4, 128.0, 128.2, 129.45, 129.9, 130.7, 131.1, 132,8, 134.4, 140.4, 145.3, 150.3
-OEt	2 x CH_3: 14.6, 14.8. C_1-C_3: 26.7, 32.5, 32.8. 2 x CH_2: 63.5, 63.6. C_{3a}: 74.3. Aromatic and olefinic carbons: 112.2, 113.7, 114.3, 116.1, 122.4, 129.25, 130.2, 132.3, 132.5, 140.8, 142.9, 146.85, 157.1, 158.9.
-Et	2 x CH_3: 15.5, 15.6. C_1-C_3: 26.8, 32.5, 32.75. 2 x CH_2: 28.8. C_{3a}: 74.5. Aromatic and olefinic carbons: 125.8, 126.9, 127.4, 127.8, 128.0, 128.1, 129.7, 130.6, 133.0, 139.5, 142.9, 143.3, 144.2, 150.5.

Appendix 10

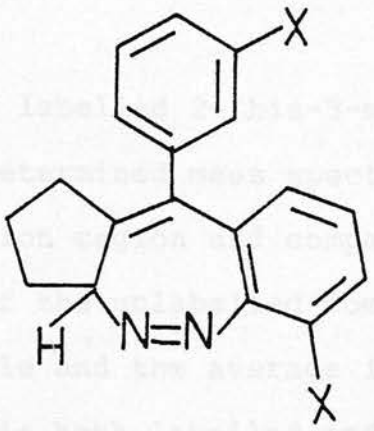


1,2-Benzodiazepines

Mass spectral data

X = $-C(CH_3)_3$	372(4), 245(6), 344(21), 330(8), 329(26), 288(32), 287(100), 231(10).
X = Cl	330(8), 328(10), 302(24), 300(36), 274(36), 272(55), 267(55), 265(100), 237(48), 230(58), 229(41), 215(43), 202(86).
X = OEt	348(15), 321(42), 320(100), 293(13), 292(63), 291(65), 264(23), 263(34), 247(10), 235(20), 236(20), 219(16), 218(12), 189(31), 178(22), 165(18), 152(18).
X = Et	316(6), 288(82), 260(47), 259(100), 231(29), 215(25), 202(14).

Appendix 11



1,2-Benzodiazepines

Mass spectral data

X = Cl 330(<5), 328(<5), 302(11), 300(16), 272(33), 267(34), 265(100), 237(39), 230(39), 229(29), 215(26), 202(70), 200(22), 199(21).

X = OEt 348(13), 321(25), 320(100), 293(6), 292(23), 291(23), 275(17), 264(10), 263(19), 248(19).

X = Et 316(2), 288(100), 260(45), 259(89), 231(22), 215(22), 202(11).

Appendix 12

Determination of Deuterium Content

The deuterium contents of the two labelled 2-(bis-3-methylphenylmethylene)cyclopentanones were determined mass spectrometrically, by scanning the molecular ion region and comparing the relative peak heights with those of the unlabelled compounds. Five scans were recorded for each sample and the average intensities calculated. The peak heights in both labelled and unlabelled samples were measured from spectra run at 12 eV to prevent fragments of mass M-1, M-2 being formed. The spectra were counted using the spectra recorded at 70 eV.

In the spectra of the ketones mentioned above it was found that even at low eV the fragment at M-1 was significant and variable due to the ease of formation of the tropylium ion from a tolyl group. The deuterium content was therefore calculated from the M-15 peak. A typical calculation is shown below. 2-[Bis-(2-^{2}H-3-methylphenyl)methylene]cyclopentanone gave the following peak intensity pattern:

Mass:	261	262	263	264
Intensity:	-	13.9	100	24.2

Peak heights are scaled to give the base peak a value of 100. An unlabelled sample gave the following spectrum:

Mass:	261	262	263	264
Intensity:	100	21.4	2.10	-

In the labelled compound the peak at mass 262 must be due to the mono-deuterio labelled species.

Thus 100 = contribution from di-labelled + (13.9 x 0.214)

∴ Peak Height of di-deuterio labelled species = 97.0

The sum of the corrected intensities is 97.0 + 13.9 = 110.9

∴ % di-deuterio labelled compound = 87.5

∴ % mono-deuterio labelled compound = 12.5

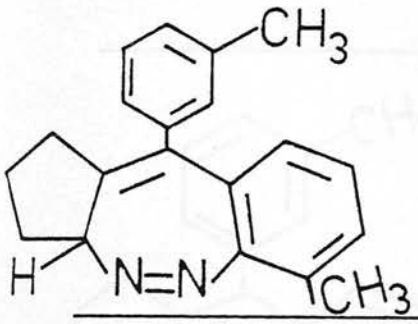
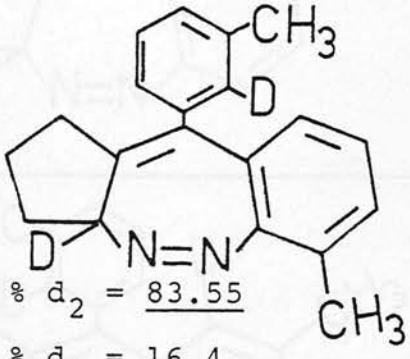
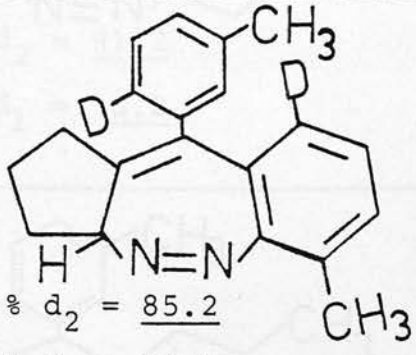
2-[Bis-(2-^{2}H-5-methylphenyl)methylene]cyclopentanone gave the following intensity pattern:

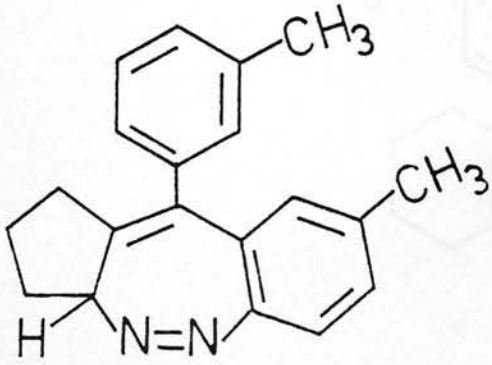
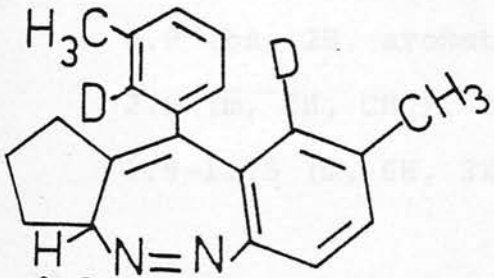
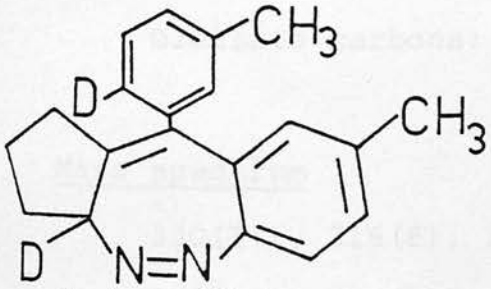
m/e:	261	262	263	264
Intensity:		16.99	100	21.6

∴ % di-deuterio labelled compound = 85.0

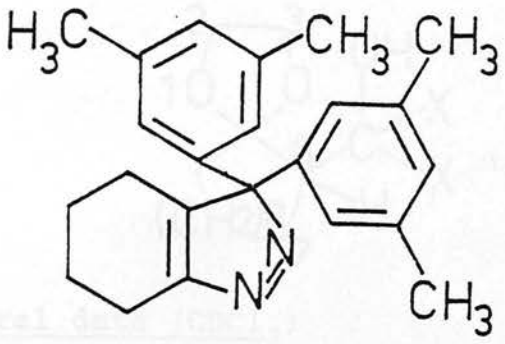
% mono-deuterio labelled compound = 15.0

A similar procedure was used for the deuterio-labelled benzodiazepines:peak heights in both labelled and unlabelled samples were measured from spectra recorded at 70 eV and 14 eV. In the latter case no fragments of M-1, M-2 etc. were formed. The molecular ion peak was used in this case and cross-checks were carried out on the peaks at M-28 and on m/e 291.

m/e	287	288	289	290	291	292
	-	100	26.7	10.2	-	-
 $\therefore$ % d_2 = 83.55 % d_1 = 16.4	-	-	18.7	100	23.4	5.9
 % d_2 = 85.2 % d_1 = 14.8	-	-	16.6	100	23.3	6.6

m/e	287	288	289	290	291	292
	-	100	25.9	8.9	-	-
 % d_2 = 91.2 % d_1 = 8.8	-	-	9.4	100	23.1	7.0
 % d_2 = 64.1 % d_1 = 35.9	-	-	48.9	100	23.0	8.6

Appendix 13



^{1}H N.m.r. spectrum ($CDCl_3$)

6.9 (bs, 2H, aromatic), 6.75 (bs, 4H, aromatic)

2.9 (m, 2H, CH_2), 2.25 (s, 12H, $4XCH_3$),

1.9-1.75 (m, 6H, $3XCH_2$)

^{13}C N.m.r. spectrum ($CDCl_3$)

CH_3: 21.25. C_4-C_7: 22.1, 22.3, 22.7, 23.3. C_3: 104.25.

Aromatic carbons: 215.4, 129.45, 137.2, 137.9

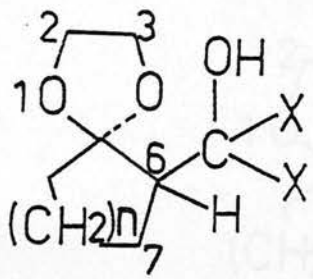
Olefinic carbons: 150.6, 153.4.

Mass spectrum

330(17), 316(8), 303(28), 302(100), 277(30), 263(20),

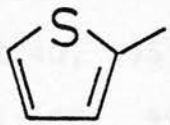
259(17), 196(15), 181(12).

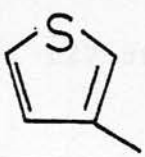
Appendix 14



^{1}H N.m.r. spectral data ($CDCl_3$)

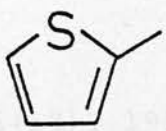
n = 1 X =

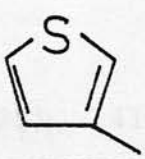




Ar	6.8-7.2(m,6H)	6.8-7.3(m,6H)
OH	5.15(s, 1H)	4.6(s, 1H)
CH_2(2&3) C-H(6)	2.9-3.7(m,5H)	3.7-2.8(m,5H)
CH_2(7,8,9)	1.4-1.9(m,6H)	1.4-1.9(m,6H)

n = 2 X =

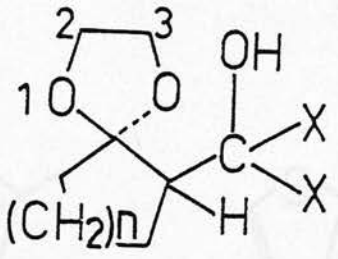




Ar	6.8-7.2(m,6H)	7.0-7.3(m,6H)
OH	6.3(s,1H)	5.38(s,1H)
CH_2(2&3)	3.6-4.0(m,4H)	3.0-3.9(m,4H)
C-H(6)	2.6-2.7(dd,1H)	2.6-2.7(dd,1H)
CH_2(7,8,9&10)	1.2-1.7(m,8H)	1.2-1.9(m,8H)

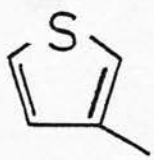
Appendix 15

Mass spectral data



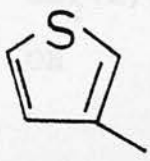
n = 1

X =  322(40, 195(76), 128(80), 127(56), 112(36), 111(100), 99(70), 85(56).

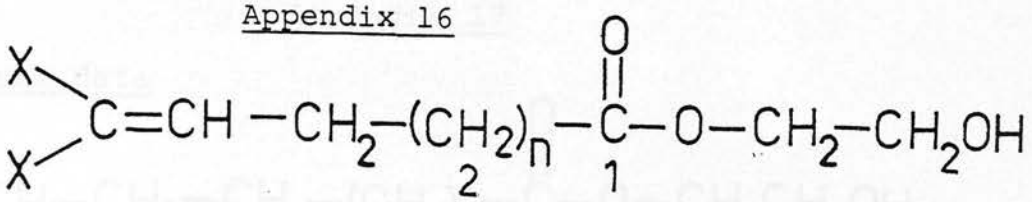
X =  322(24), 218(18), 195(51), 128(72), 127(20), 112(30), 111(100), 99(54), 85(33).

n = 2

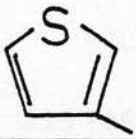
X =  336(13), 195(88), 142(98), 141(66); 111(100); 99(98).

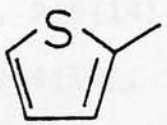
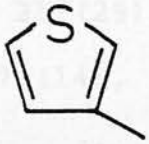
X =  336(83, 275(67), 274(20), 273(46), 205(80), 195(33), 129(40), 111(100), 97(46).

Appendix 16



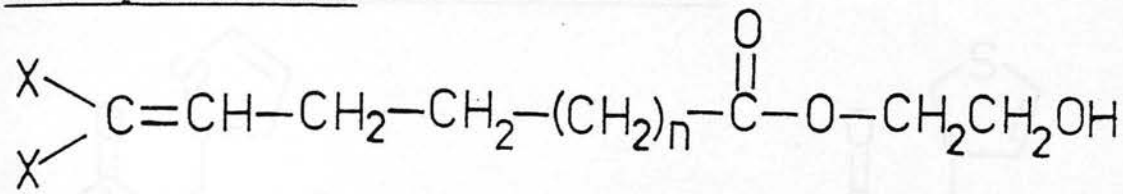
^{1}H N.m.r. spectral data ($CDCl_3$)

n = 2	X		
	Ar	6.7-7.3(m,6H)	6.75-7.3(m,6H)
	C-H(5)	6.1(t,1H J=7.5Hz)	5.1(t,1H J=7.5Hz)
	$-OCH_2CH_2OH$	4.0-4.2(m,2H)	4.1-4.2(m,2H)
		3.6-3.8(m,2H)	3.7-3.8(m,2H)
	CH_2(2,3,4)	1.6-2.4(m,6H)	1.7-2.4(m,6H)
	OH	2.05(s,1H)	2.15(s,1H)

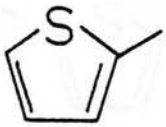
n = 3	X		
	Ar	6.8-7.4(m,6H)	6.8-7.4(m,6H)
	C-H(6)	6.18(t,1H,J=7.5Hz)	6.1(t,1H,J=7.5Hz)
	$-OCH_2CH_2OH$	4.1-4.3(m,2H)	4.15-4.25(m,2H)
		3.6-3.8(m,2H)	3.75-3.85(m,2H)
	CH_2(2,3,4,5)	1.4-2.4(m,8H)	1.3-2.4(m,8H)
	OH	2.0(s,OH)	2.3(s,OH)

Appendix 17

Mass spectral data



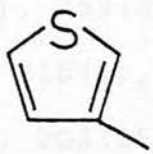
X =



n = 1 322(100), 262(14), 233(16), 220(12), 219(46), 218(17), 207(6), 206(36), 205(10), 98(33).

n = 2 336(100), 275(10), 219(12), 218(32), 217(10), 206(12), 205(75), 192(26), 179(20), 171(16), 121(15), 97(58).

X =

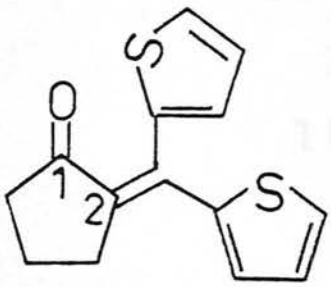


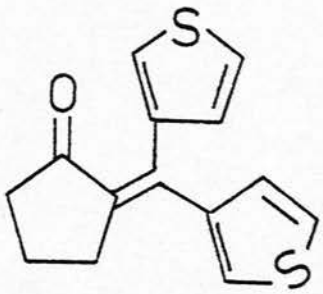
n = 1 322(100), 261(18), 219(14), 218(64), 217(29), 206(7), 205(50), 204(14), 185(21), 171(14), 121(18), 111(24), 97(36).

n = 2 336(100), 292(7), 275(13), 218(10), 205(60), 194(27), 179(24), 173(13), 171(10), 111(40), 97(27).

Appendix 18

2-(Dithienylmethylene)cyclopentanones





a) ^{1}H N.m.r. spectral data ($CDCl_3$)

6.9-7.5(m,6H), 3.1(t,2H), 2.3-2.5(m,2H), 1.9-2.2(m,2H)

6.9-7.5(m,6H), 2.9(t,2H) 2.3-2.5(m,2H), 1.9-2.2 (m,2H).

b) Mass spectral data

260(100), 259(39), 232(5), 231(4), 218(4), 217(5), 204(13), 203(15), 171(5), 115(4), 97(3).

260(100), 259(19), 227(1 218(13), 204(48), 203(35) 199(11), 171(22), 115(9).

c) ^{13}C N.m.r. spectral data ($CDCl_3$)

C_{3-5}: 19.8, 33.3, 39.8.

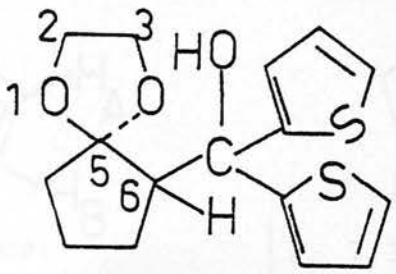
Aromatic C-H's: 125.3, 126.5, 127.3, 128.2, 129.3, 131.4.

Aromatic tertiary carbons: 132.9, 133.5; Olefinic carbons: 140.6, 145.0.

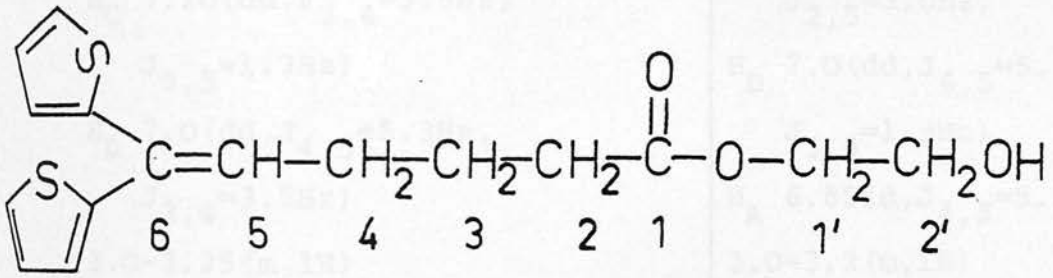
Cl: 205.1.

Appendix 19

^{13}C N.m.r. spectral data ($CDCl_3$)

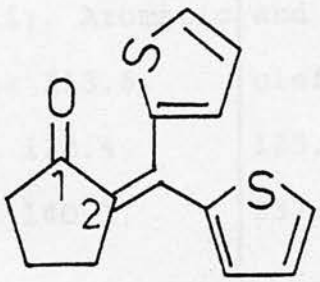


C_7, C_8 & C_9: 21.8, 27.3, 29.9. C(OH): 56.1. C_2 & C_3: 64.0, 64.55. C_5: 77.3. Aromatic carbons: 118.6, 122.3, 122.8, 123.5, 123.7, 126.5, 151.8, 154.05.



C_{2-4}: 24.8, 29.1, 33.6. $C_1{}^1,{}_2{}^1$: 61.6, 66.0

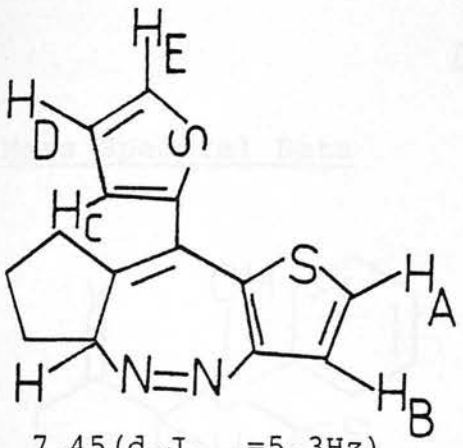
Aromatic and olefinic carbons: 124.1, 125.2, 125.7, 126.75, 127.2, 127.7, 129.45, 130.5, 139.5, 146.45. C_1: 173.7.



C_{3-5}: 19.8, 33.3, 39.9. Aromatic and olefinic carbons: 126.5, 127.3, 218.2, 129.3, 131.5, 133.5, 140.6, 145.0.

C_1: 205.1.

Appendix 21



H_A 7.45(d,$J_{4,5}$=5.3Hz)

H_E 7.35(dd,$J_{4,5}$=5.3Hz, $J_{3,5}$=1.3Hz)

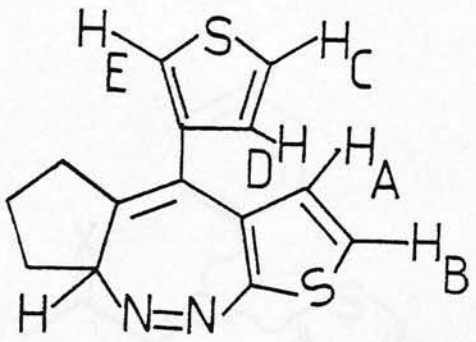
H_B 7.15(d,$J_{4,5}$=5.3Hz)

H_C 7.10(dd,$J_{3,4}$=3.5Hz, $J_{3,5}$=1.3Hz)

H_D 7.0(dd,$J_{4,5}$=5.3Hz, $J_{3,4}$=3.5Hz)

3.0-3.25(m,1H)

2.0-2.8(m,6H,3XCH_2)



H_C 7.35(dd,$J_{4,5}$=5.3Hz, $J_{3,5}$=3.0Hz)

H_B 7.2(d,$J_{4,5}$=5.3Hz)

H_E 7.25(dd,$J_{3,5}$=1.3Hz, $J_{2,5}$=3.0Hz)

H_D 7.0(dd,$J_{4,5}$=5.3Hz, $J_{3,5}$=1.3Hz)

H_A 6.85(d,$J_{4,5}$=5.3Hz)

3.0-3.2(m,1H)

2.0-2.8(m,6H,3XCH_2)

b) ^{13}C N.m.r. spectral data ($CDCl_3$)

C-7, 27.0; C-6 and C-8, 32.7 and 32.9; C-5a, 77.1; Aromatic and olefinic carbons: 213.5, 126.3, 126.6, 126.9, 128.4, 129.2, 135.6, 138.9, 140.1, 153.8.

C-6, 26.8; C-5 and C-7, 32.1 and 32.9; C-7a, 76.3; Aromatic and olefinic carbons: 124.4, 125.0, 125.5, 125.7, 126.4, 128.5, 133.0, 137.6, 138.7, 157.

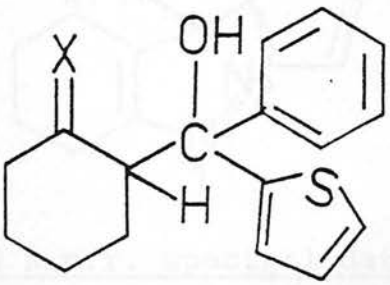
c) Mass spectral data

272(5), 246(6), 245(10), 244(71), 243(10), 218(8), 217(12), 216(100), 211(8), 203(7), 184(8), 171(15)

272(5), 246(8), 245(15), 244(79), 243(15), 218(13), 217(19), 216(100), 211(12), 203(8), 184(13), 171(36).

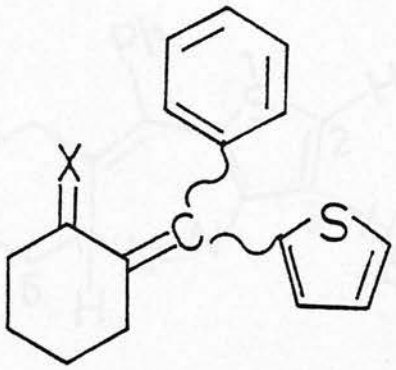
Appendix 22

Mass Spectral Data



X = N-N-Me_2

328(8), 189(36), 188(40), 160(19), 140(78), 139(64), 125(14), 114(16), 111(100), 105(60).



X = O

268(100), 267(62), 240(12), 212(8), 211(10), 197(12), 191(11), 184(8), 179(5), 178(5), 165(6), 115(8), 96(7).

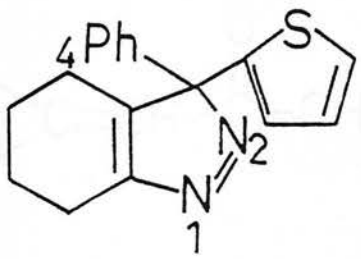
X = O

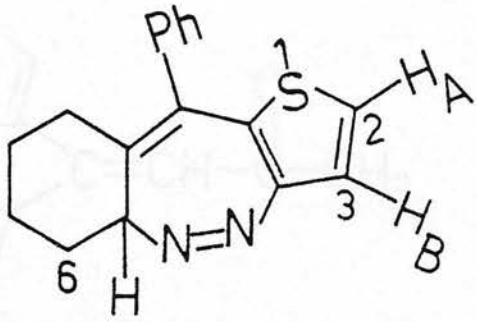
286(4), 190(19), 189(100), 188(19), 111(62), 105(31), 98(13), 77(31)

X = N-NH-Tos

436(3), 435(5), 281(86), 252(67), 224(20), 223(53), 156(40), 139(43), 92(47), 91(100).

Appendix 23





^{1}H N.m.r. spectral data ($CDCl_3$)

6.9-7.4(m,8H)	H_A 7.5(d,J = Hz,1H)
2.8-3.0(m,2H)	H_B 7.2(d,J = Hz,1H)
2.3-2.5(m,2H)	7.25-7.45(m,5H)
1.7-1.9(m,4H)	2.9-3.1(m,1H)
	1.6-2.6(m,8H)

^{13}C N.m.r. spectral data ($CDCl_3$)

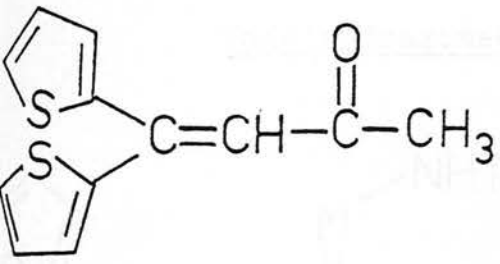
C_4-C_7: 21.9, 22.1, 22.6, 22.8	C_6-C_9: 20.4, 23.4, 27.4, 28.1.
C_3: 100.7. Aromatic carbons:	C_{5a}: 71.9. Aromatic and olefinic
125.4, 126.5, 126.7, 128.1,	carbons: 124.3, 126.4, 126.8,
218.5, 136.5, 137.6.	127.9, 128.5, 129.4, 129.5, 133.9,
Olefinic carbons: 150.3, 153.5.	139.2, 152.2.

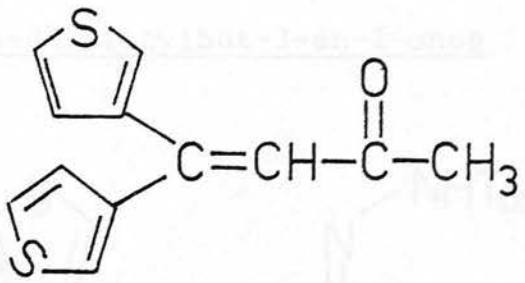
Mass spectral data

280(2), 253(32), 252(100),	280(5), 253(24), 252(100), 251(24),
251(40), 237(10), 224(70),	224(48), 223(98), 211(21), 210(23),
223(98), 211(40), 210(36),	209(15), 208(15), 197(11), 191(14),
209(20), 208(22), 191(24),	184(13), 171(13), 165(16), 152(10),
184(20), 178(22), 168(28),	147(12), 139(8), 115(12), 91(14).
165(26).	

Appendix 24

4,4-Dithienylbut-3-en-2-ones





a) ^{1}H N.m.r. spectral data ($CDCl_3$)

7.6-7.3(m,2H),	7.5-7.25(m,4H)
7.2-7.0(m,4H),	7.2-7.0 (m,2H)
6.6 (s,1H),	6.6 (s,1H)
1.9 (s,3H)	1.9 (s,3H)

b) ^{13}C N.m.r. spectral data ($CDCl_3$)

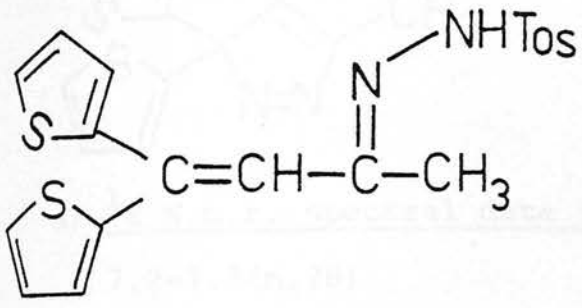
CH_3: 29.65. Aromatic and olefinic carbons 126.6, 126.95, 127.9, 128.4, 129.7, 129.9, 137.9, 139.25, 144.7. Carbonyl: 193.05	CH_3: 29.8. Aromatic and olefinic carbons: 125.5, 125.7, 126.3, 126.5, 127.3, 128.6, 138.4, 142.4, 142.6. Carbonyl: 192.0.

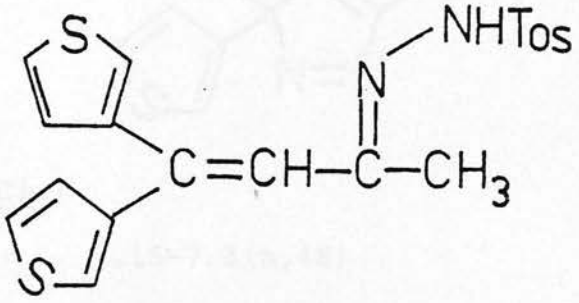
c) Mass spectral data

234(100), 233(44), 219(98), 191(13), 190(33), 158(11), 147(30), 111(78).	234(100), 233(22), 219(98), 191(20), 190(26), 158(7), 147(20), 111(43).

Appendix 25

Tosylhydrazones of 4,4-dithienylbut-3-en-2-ones





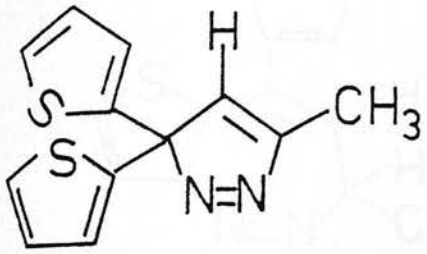
Mass spectral data

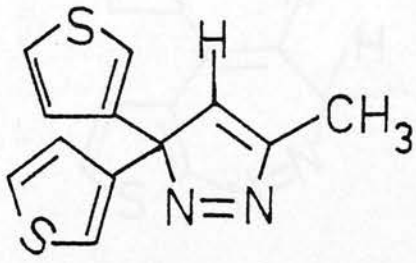
402(2), 401(4), 247(37), 219(37), 218(95), 217(48), 203(100), 185(32), 184(37), 177(16), 171(16), 158(12), 156(26), 92(58), 91(74).

402(21), 247(97), 246(100), 245(54), 231(43), 219(98), 218(98), 203(97), 185(40), 184(43), 177(19), 171(54), 156(96), 139(54), 135(24), 134(26), 92(92), 91(98).

Appendix 26

3,3-Dithienyl-5-methylpyrazoles





a) ^{1}H N.m.r. spectral data ($CDCl_3$)

7.2-7.3(m,2H)

6.9-7.1(m,5H)

2.5(d,J = 1.6Hz, 3H)

7.15-7.3(m,4H)

6.8-7.0(m,3H)

2.5(d,J = 1.6Hz, 3H, Collapsed to a singlet on irradiation at 6.87δ)

b) ^{13}C N.m.r. spectral data ($CDCl_3$)

CH_3: 12.7: C_3: 99.1. Aromatic carbons: 125.6, 126.2, 126.6, 135.8. Olefinic carbons: 137.75, 154.1.

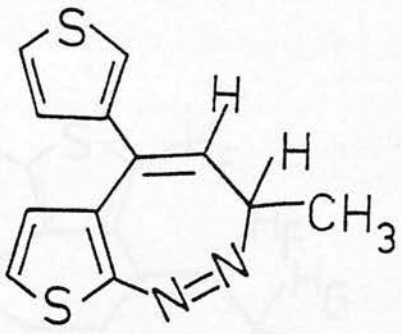
CH_3: 12.7. C_3: 100.6. Aromatic carbons: 122.5, 125.8, 126.7, 135.8. Olefinic carbons: 136.1, 153.6.

c) Mass spectral data

246(3), 219(34), 218(100), 217(80), 204(28), 203(98), 185(44), 184(50), 177(20), 171(26), 134(30).

246(5), 220(10), 219(21), 218(100), 217(42), 205(10), 204(16), 203(89), 185(16), 184(26), 177(7), 171(13) 134(10).

Appendix 27



^{13}C N.m.r. spectral data ($CDCl_3$)

CH_3: 19.15. C_3: 68.5.

Aromatic and olefinic carbons:
120.0, 125.1, 126.1, 126.5, 127.0, 127.4, 130.8, 131.7, 141.0, 155.4.

CH_3: 19.4. C_3: 68.0.

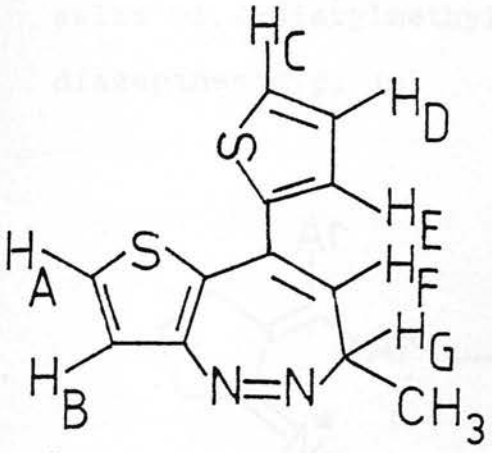
Aromatic and olefinic carbons:
119.7, 123.8, 125.6, 125.8, 125.9, 127.8, 130.8, 133.5, 139.4, 159.1.

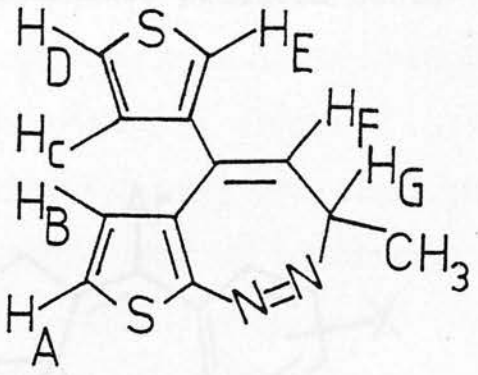
Mass spectral data

246(2), 219(18), 218(100), 217(40), 203(93), 185(26), 184(30), 171(18), 134(12).

246(4), 220(20), 219(36), 218(100), 217(85), 203(96), 191(14), 190(14), 185(52), 184(68), 171(44), 134(28).

Appendix 28





^{1}H N.m.r. spectral data

H_A 7.53(d, $J_{4,5}$= 5.5Hz)

H_B 7.34(d,$J_{4,5}$= 5.5Hz)

H_C 7.30(dd,$J_{4,5}$=5.5Hz, $J_{3,5}$=1.25Hz)

H_E 7.25(m)

H_D 7.0(dd,$J_{4,5}$=5.5Hz, $J_{3,4}$=3.5Hz)

H_F 5.4(d,J=5.5Hz, collapsed to a singlet on irradiation at 2.2δ)

H_G 2.35(m)

CH_3 2.15(d,J=6Hz)

H_A,H_D and H_E 7.4-7.25(m,3H)

H_B & H_C 7.2-7.0(m,2H)

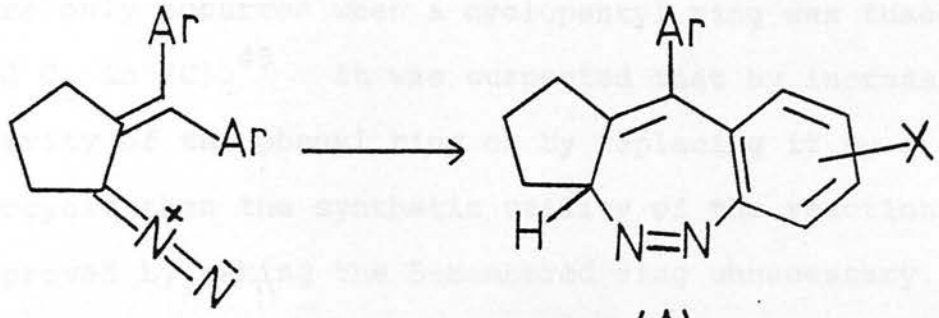
H_F 5.4(d,J=5.5Hz collapsed to a singlet on irradiation at 2.5δ)

H_G 2.5 (m,1H)

CH_3 2.15(d,J = 6Hz,3H)

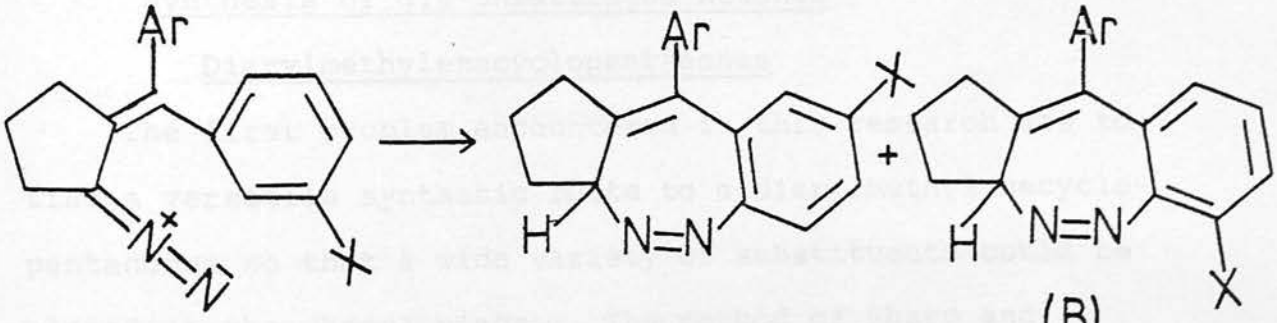
Programme of Research

Thorogood[87] found that the decomposition of the sodium salts of 2-diarylmethylenecyclopentanones produced benzodiazepines e.g. (A)



(A)

Sood[50] repeated some of this work and found that when a substituent X was placed in the 3^1 position of the aryl ring two isomeric benzodiazepines were formed



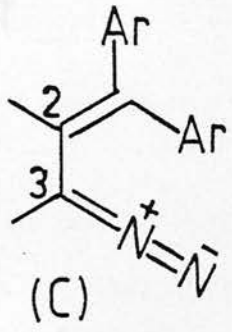
(B)

When X = OMe and Me it was found that (B) the more hindered isomer predominated.

The first objective of this research was to carry out a study of the effect of different substituents on this reaction

and to attempt to rationalise these effects. A study of synthetic routes to the α,β-unsaturated ketones required as starting materials was an integral part of this work.

The second objective was to attempt to increase the scope of this reaction. It had been found that 8π electron 1,7 ring closure only occurred when a cyclopentyl ring was fused between C_2 and C_3 in (C).[45] It was suspected that by increasing the reactivity of the phenyl ring or by replacing it by a suitable heterocycle then the synthetic utility of the reaction could be improved by making the 5-membered ring unnecessary.



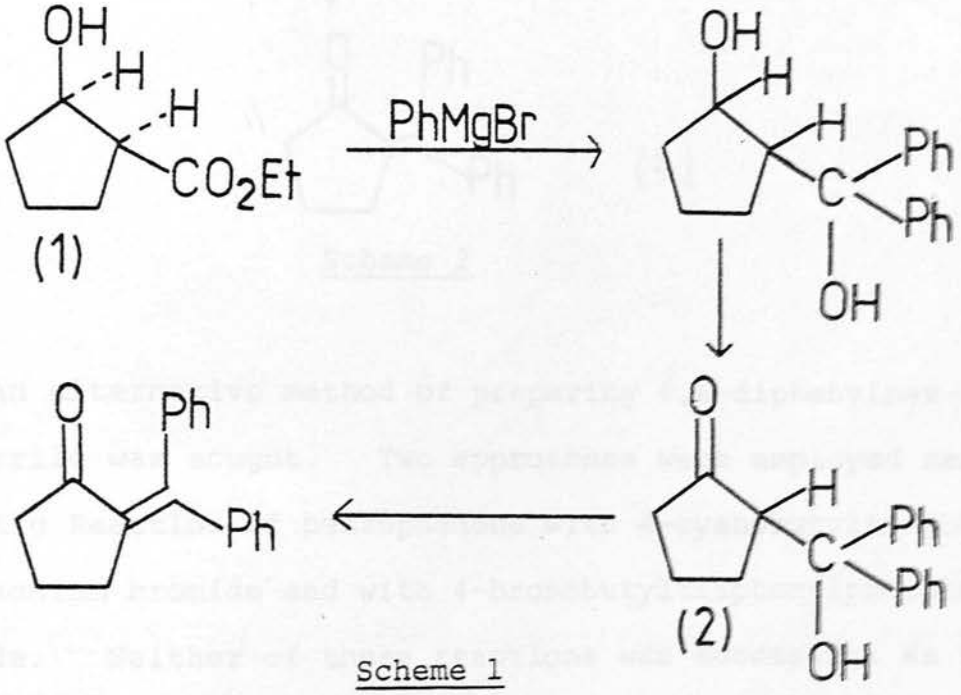
(C)

Synthesis of α,β-Unsaturated Ketones

Diarylmethylenecyclopentanones

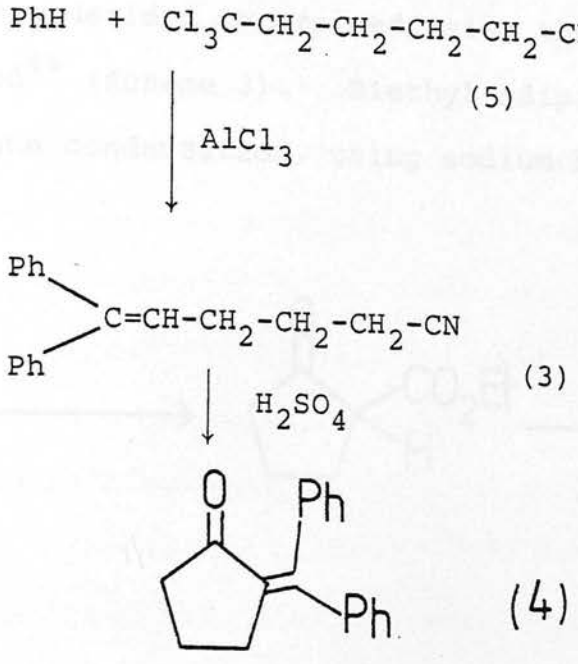
The first problem encountered in this research was to find a versatile synthetic route to α-diarylmethylenecyclopentanones so that a wide variety of substituents could be placed in the phenyl rings. The method of Sharp and Thorogood,[45] which will be discussed in more detail later, involved a Grignard reaction and therefore the choice of substituents in the phenyl rings was limited to those which were unreactive towards Grignard reagents.

Diphenylmethylenecyclopentanone had been prepared by Ghera and Shoua[112] (Scheme 1) by the dehydration of (2-oxocyclopentyl)diphenylmethanol (2) which they had prepared by the reaction of phenyl magnesium bromide on cis-2-hydroxycyclopentanecarboxylic acid ethyl ester (1) followed by a Jones oxidation. This method was considered to offer no advantage over the Thorogood method because it still involved the use of Grignard reagents.



Scheme 1

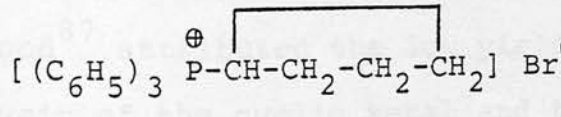
Fujimoto and Hirao[113] reported that 6,6-diphenylhex-5-enenitrile (3) cyclised to give 2-diphenylmethylenecyclopentanone (4) in sulphuric acid at 20° (Scheme 2). Their route to 6,6-diphenylhex-5-enenitrile, however, was not suitable as a general synthetic route since 6,6,6-trichlorohex-5-enenitrile (5) was not readily available by normal laboratory methods and also because substituted benzenes would lead to complications in the Friedel-Crafts alkylation reaction.



Scheme 2

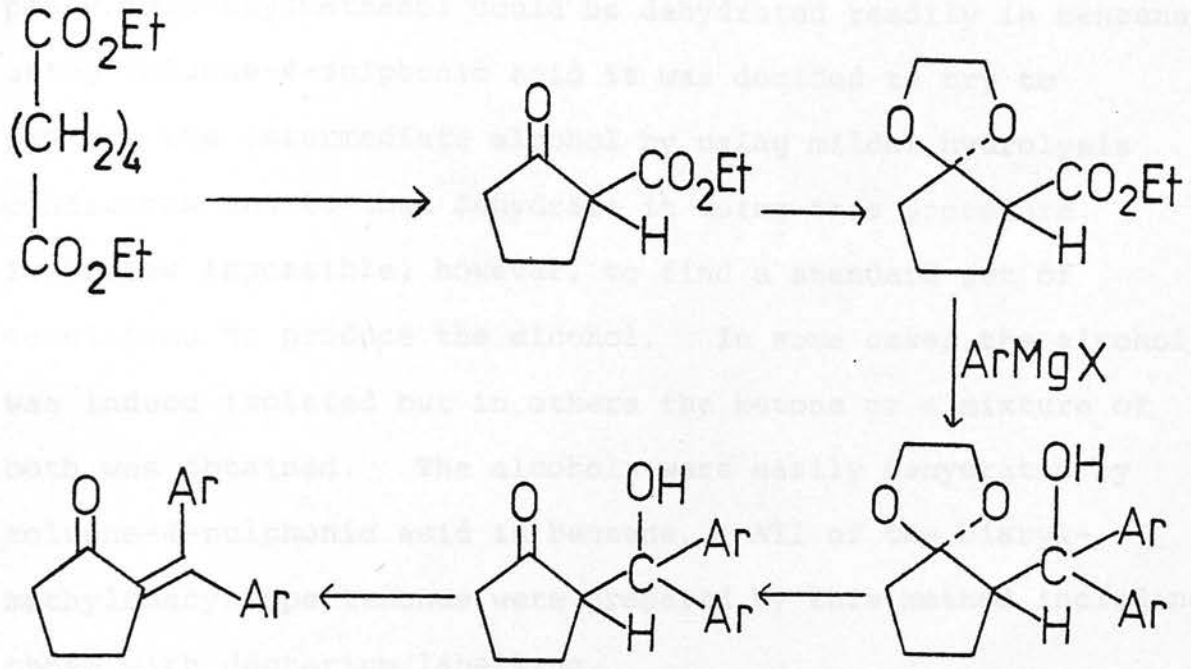
An alternative method of preparing 6,6-diphenylhex-5-enenitrile was sought. Two approaches were employed namely, a Wittig Reaction of benzophenone with 4-cyanobutyltriphenylphosphonium bromide and with 4-bromobutyltriphenylphosphonium bromide. Neither of these reactions was successful as the respective ylides could not be prepared, despite the use of a variety of bases.

Mondon[114] found that reaction of 4-bromobutyltriphenylphosphonium bromide with phenyllithium gave a product of molecular formula $C_{22}H_{22}PBr$ which he suggested was the cyclic phosphonium salt (6). This may explain why the ylide could not be formed in the two cases mentioned earlier.



(6)

At this stage, since no viable alternative had been devised it was decided to proceed using the method of Sharp and Thorogood[45] (Scheme 3). Diethyl adipate was cyclised by a Dieckmann condensation, using sodium hydride as the base,



Scheme 3

to give ethyl-2-cyclopentanonecarboxylate which was reacted with ethylene glycol to protect the carbonyl function. The 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester so produced was then reacted with two molar equivalents of the appropriate aryl Grignard reagent. Hydrolysis and dehydration were achieved by boiling the crude reaction mixture in ethanol with dilute acid.

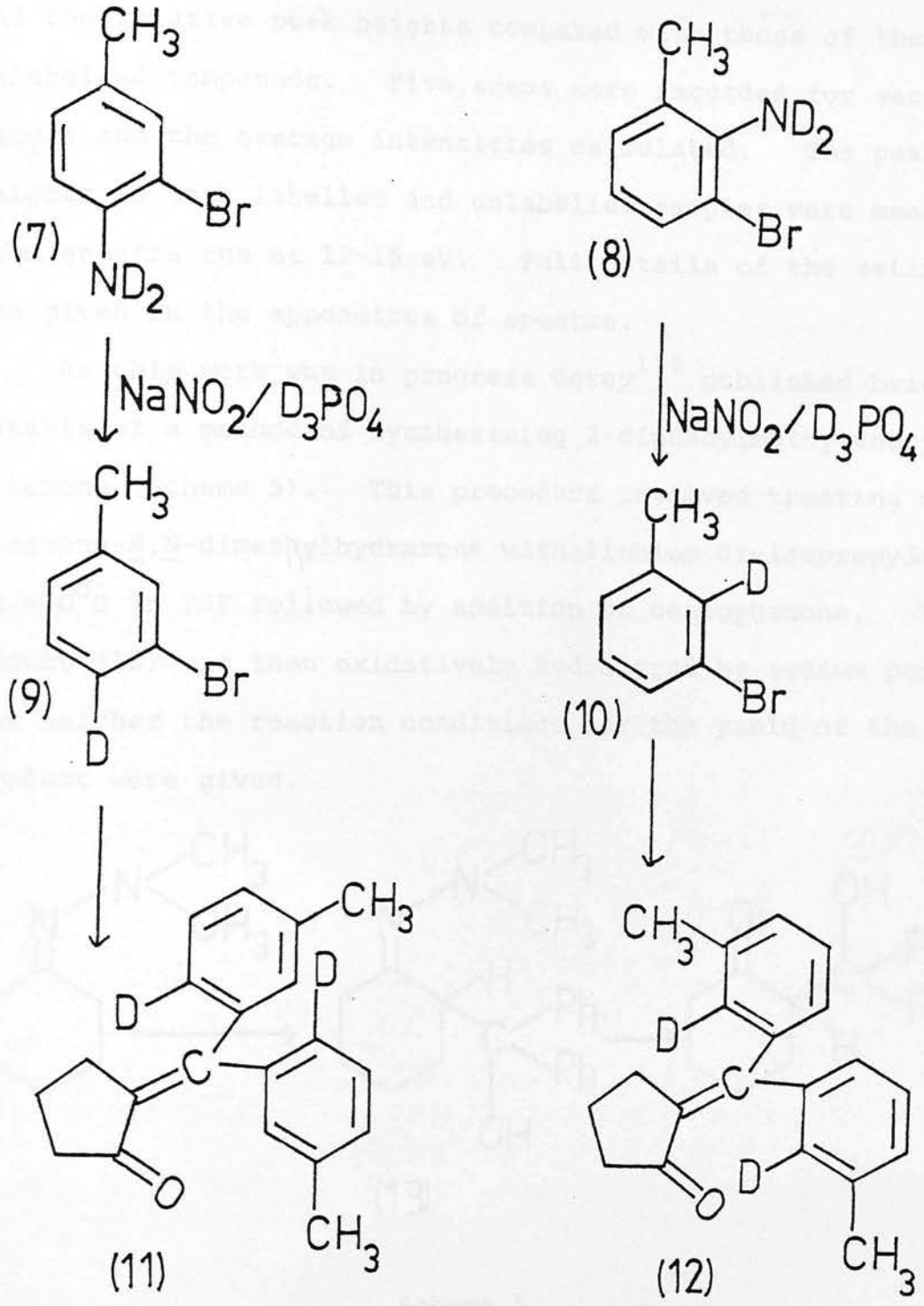
The yield of ketone obtained by this method was normally about 30% based upon the amount of the protected ester used. Thorogood[87] attributed the low yield to polymerisation during the hydrolysis of the cyclic ketal and to the resistance of the ß-keto-tertiary alcohol to dehydration. Another possible reason is that the alcohol can undergo a reverse Aldol reaction

to eliminate benzophenone. In an attempt to dehydrate (2-oxocyclopentyl)(bis-3-chlorophenyl)methanol in acidic ethanol bis-(3-chlorophenyl)methanone was isolated.

Since Ghera and Shoua[112] had shown that (2-oxocyclopentyl)diphenylmethanol could be dehydrated readily in benzene using toluene-4-sulphonic acid it was decided to try to isolate the intermediate alcohol by using milder hydrolysis conditions and to then dehydrate it using this procedure. It proved impossible, however, to find a standard set of conditions to produce the alcohol. In some cases the alcohol was indeed isolated but in others the ketone or a mixture of both was obtained. The alcohols were easily dehydrated by toluene-4-sulphonic acid in benzene. All of the biarylmethylenecyclopentanones were prepared by this method including those with deuterium labelling.

Two dideuteriated ketones (11) and (12) were prepared from the deuterated bromotoluenes (9) and (10). Deuterium was introduced into the bromotoluenes by adaptations of the method of Renaud[101] (Scheme 4) in which the amines (7) and (8) were diazotised by reaction with sodium nitrite in deuteriohypophosphorous acid which was prepared by exchange of hypophosphorous acid with deuterium oxide. This method produced high levels of deuteriation e.g. (11) contained 85% d_2 and 15% d_1.

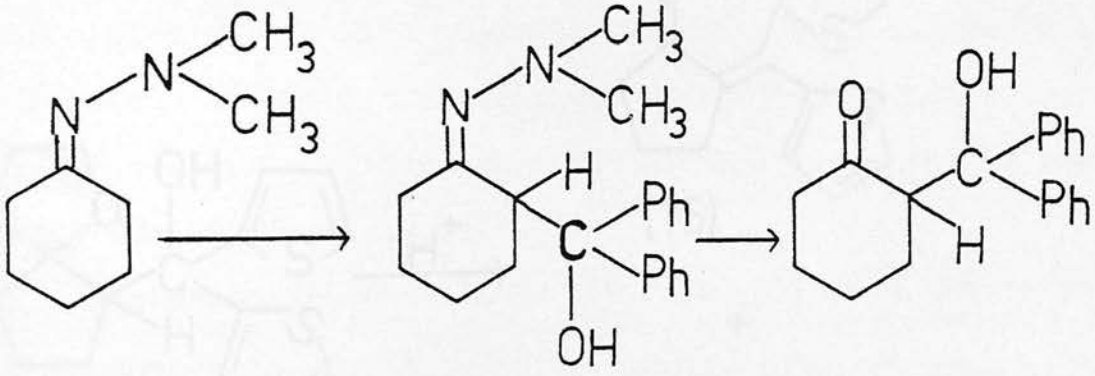
The deuterium contents of the bromotoluenes and of the ketones were estimated by mass spectrometry using the procedure reported by Murray.[115] The molecular weight region was scanned


CH3
Br
(7)
ND2
NaNO2/D3PO4
CH3
Br
(9)
D
CH3
D
D
C
O
CH3
(11)
CH3
ND2
Br
(8)
NaNO2/D3PO4
CH3
D
Br
(10)
CH3
D
C
O
D
CH3
(12)

SCHEME 4

and the relative peak heights compared with those of the unlabelled compounds. Five scans were recorded for each sample and the average intensities calculated. The peak heights in both labelled and unlabelled samples were measured from spectra run at 12-15 eV. Full details of the estimation are given in the appendices of spectra.

As this work was in progress Corey[116] published brief details of a method of synthesising 2-diphenylmethylenecyclohexanone (Scheme 5). This procedure involved treating cyclohexanone-N,N-dimethylhydrazone with lithium di-isopropylamide at -70°C in THF followed by addition of benzophenone. The adduct (13) was then oxidatively hydrolysed by sodium periodate but neither the reaction conditions nor the yield of the product were given.



(13)

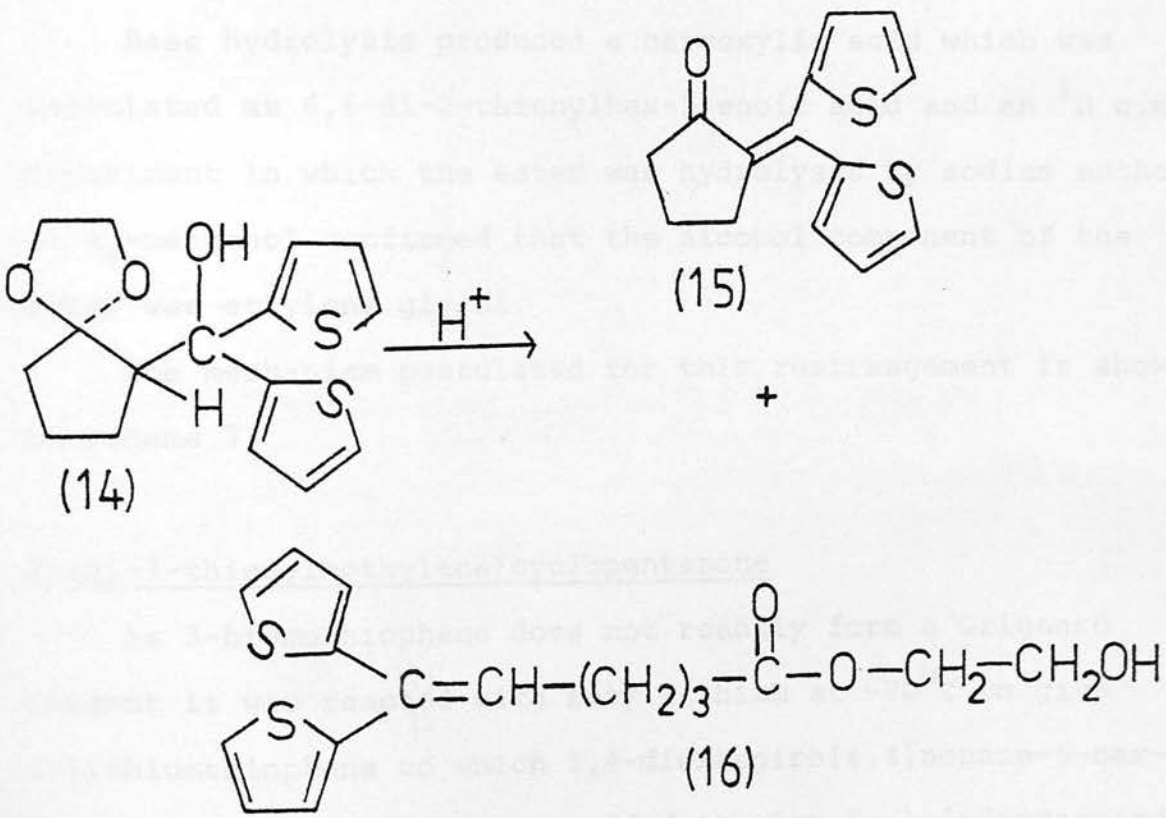
Scheme 5

Although the first part of this procedure was repeated successfully the carbonyl function could not be regenerated by any of the methods outlined by Corey[116-118]. Hydrolysis in acid was successful, however, although the yield was not as high as Corey claimed for his methods. This procedure was extended to cyclopentanone-N,N-dimethylhydrazone but since

the yields were not as high as in the cyclohexanone-N,N-dimethylhydrazone case, it was not extended to substituted benzophenones.

2-(Di-2-thienylmethylene)cyclopentanone

A Grignard reagent was prepared from 2-bromothiophene and reacted with 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester to give 5-(1,4-dioxaspiro[4,4]nonyl)di-2-thienylmethanol (14). Hydrolysis of this compound (Scheme 6) produced 2-(di-2-thienylmethylene) cyclopentanone (15) as expected but in only 33% yield. The major product (51% yield) was identified as 2-hydroxyethyl 6,6-di-2-thienylhex-5-enoate (16) on the basis of chemical and spectroscopic evidence.



Scheme 6

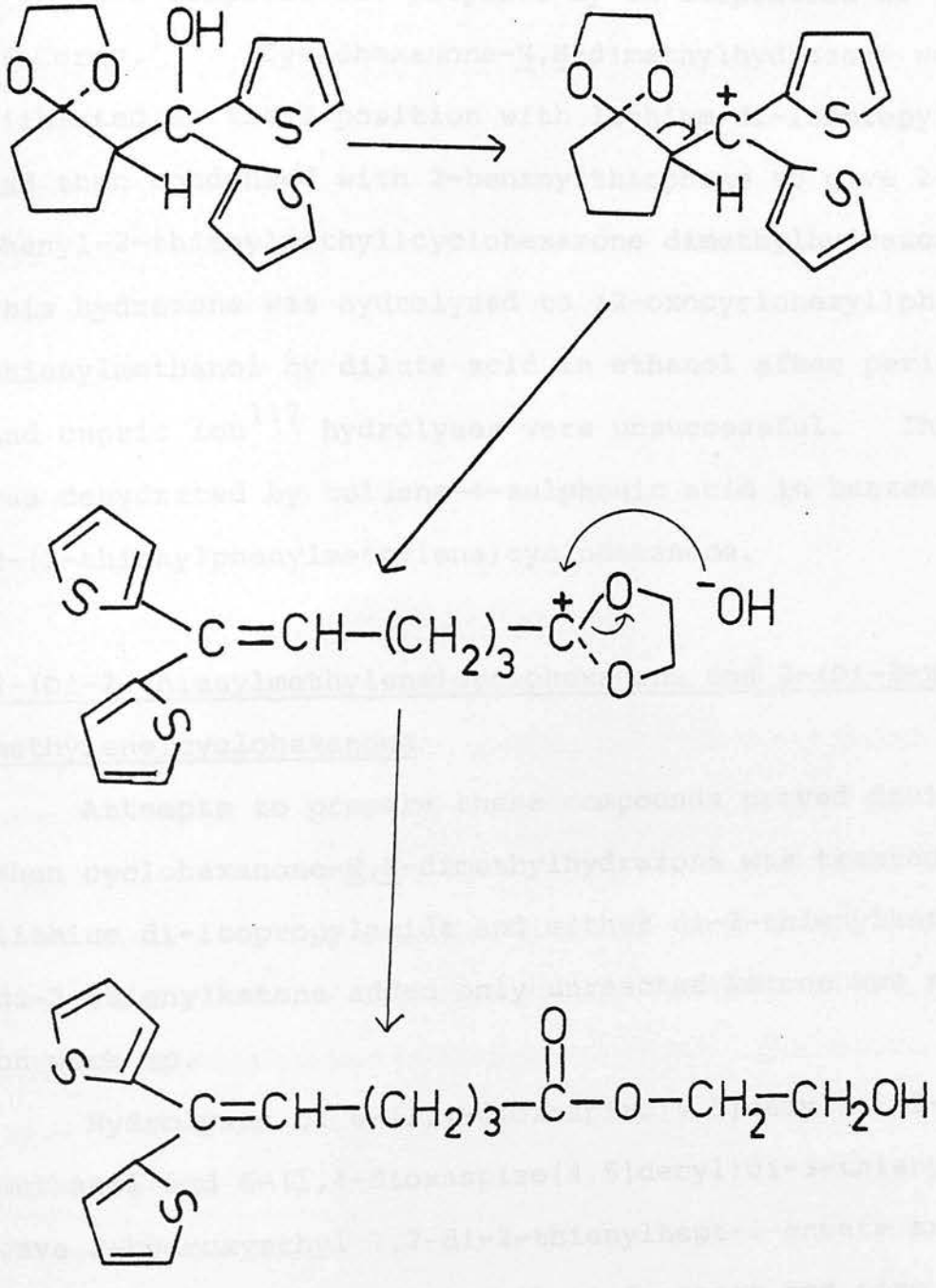
Combustion analysis and high resolution mass spectrometry showed that the molecular formula was $C_{16}H_{18}O_3S_2$, isomeric with the starting material. The i.r. spectrum had two broad bands centred on 3450 and 1730 cm^{-1} indicating a hydroxyl and a carbonyl group. The ^1H n.m.r. spectrum showed six aromatic protons, a triplet at 6.1 δ (J = 7.5 Hz) which collapsed to a singlet on irradiating at 2.2 δ, two multiplets each approximating to a doublet of doublets centred around 4.1 and 3.7 δ respectively and each integrating to 2 protons and a multiplet at 1.6-2.4 δ containing 6 protons and a hydroxyl proton. The ^{13}C n.m.r. spectrum indicated that the carbonyl group was acyclic and the positions of all the other lines was consistent with the assignment of the compound.

Base hydrolysis produced a carboxylic acid which was formulated as 6,6-di-2-thienylhex-5-enoic acid and an ^1H n.m.r. experiment in which the ester was hydrolysed by sodium methoxide in d_4-methanol confirmed that the alcohol component of the ester was ethylene glycol.

The mechanism postulated for this rearrangement is shown in Scheme 7.

2-(Di-3-thienylmethylene)cyclopentanone

As 3-bromothiophene does not readily form a Grignard reagent it was reacted with butyllithium at -70°C to give 3-lithiumthiophene to which 1,4-dioxaspiro[4,4]nonane-6-carboxylic acid ethyl ester was added to give 6-(1,4-dioxaspiro[4,4]nonyl)di-3-thienylmethanol. Hydrolysis of this compound produced 2-(di-3-thienylmethylene)cyclopentanone (22%) and 2-hydroxyethyl 6,6-di-3-thienylhex-5-enoate (46%).



SCHEME 7

2-((2-Thienylphenylmethylene)cyclohexanone

This compound was prepared by an adaptation of the method of Corey.[116] Cyclohexanone-N,N-dimethylhydrazone was lithiated in the 2-position with lithium di-isopropylamide and then condensed with 2-benzoylthiophene to give 2-(hydroxyphenyl-2-thienylmethyl)cyclohexanone dimethylhydrazone. This hydrazone was hydrolysed to (2-oxocyclohexyl)phenyl-2-thienylmethanol by dilute acid in ethanol after periodate[118] and cupric ion[117] hydrolyses were unsuccessful. The alcohol was dehydrated by toluene-4-sulphonic acid in benzene to give 2-(2-thienylphenylmethylene)cyclohexanone.

2-(Di-2-thienylmethylene)cyclohexanone and 2-(Di-3-thienylmethylene)cyclohexanone

Attempts to prepare these compounds proved fruitless. When cyclohexanone-N,N-dimethylhydrazone was treated with lithium di-isopropylamide and either di-2-thienylketone or di-3-thienylketone added only unreacted ketone was recovered on work up.

Hydrolyses of 6-(1,4-dioxaspiro[4,5]decyl)di-2-thienylmethanol and 6-(1,4-dioxaspiro[4,5]decyl)di-3-thienylmethanol gave 2-hydroxyethyl 7,7-di-2-thienylhept-6-enoate and 2-hydroxyethyl 7,7-di-3-thienylhept-6-enoate and none of the required products.

4,4-Di-2-thienylbut-3-en-2-one and 4,4-di-3-thienylbut-3-en-2-one

These compounds were prepared by adaptations of Corey's method. Acetone-N,N-dimethylhydrazone was treated with n-butyllithium and condensed with di-2-thienylketone and di-3-thienylketone respectively and the crude reaction mixtures hydrolysed

by dilute acid in ethanol to give the required products.

Tosylhydrazones of α,β-Unsaturated Carbonyl Compounds

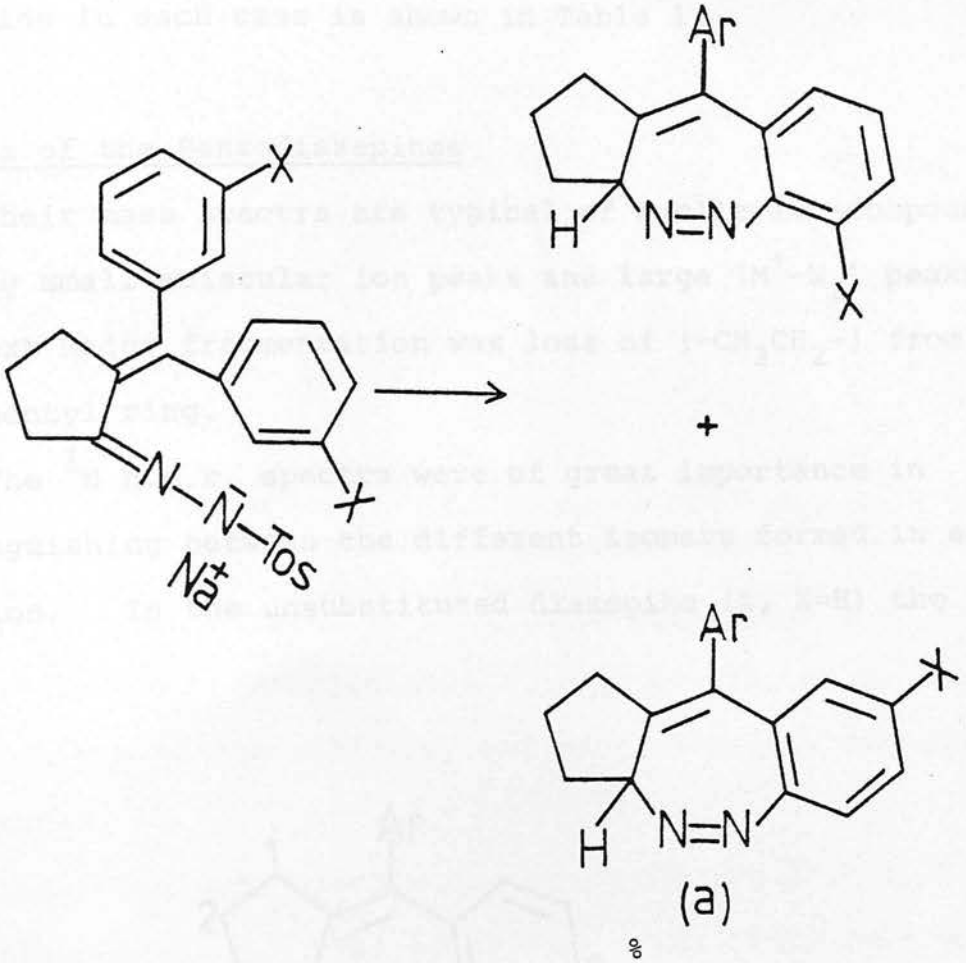
The tosylhydrazones were prepared by admixture of warm ethanolic solutions of the unsaturated ketone and 4-tolylsulphonylhydrazine with the addition of concentrated hydrochloric acid. The products crystallised out overnight and were identified by their i.r. and ^{1}H n.m.r. spectra.

Base Induced Cyclisation of the Toluene-4-sulphonylhydrazones of α-Diarylmethylene Cyclic Ketones

1) Diarylmethylenecyclopentanones

In this series of reactions the anhydrous sodium salt of the 2-diarylmethylenecyclopentanone toluene-4-sulphonylhydrazone was heated at 80° in 1,2-dimethoxyethane until the reaction appeared to be complete by t.l.c.. Almost immediately the temperature of the reaction mixture reached 80° a red colouration was observed which gradually faded to give a yellow solution and a colourless precipitate. The colourless precipitate of sodium p-toluenesulphinate was filtered off, and the filtrate evaporated down. The products were separated by medium pressure chromatography and identified on the basis of spectroscopic and analytical evidence.

The benzodiazepines isolated were all yellow crystalline solids or oils stable at room temperature but sensitive to light. Two isomeric benzodiazepines were isolated for each substituent-X with the exception of the t-butyl case where only one isomer (a) was obtained. In each reaction small quantities of unidentified hydrocarbons were also obtained and in the case of the trifluoromethyl substituent a small



(a)

X =		%
	t-Butyl	64
	Chloro	78
	Ethoxy	75
	Ethyl	74
	Methoxy	70
	Methyl	74
	Trifluoromethyl	62

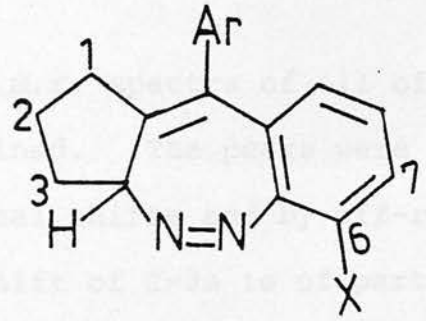
Table 1

amount of azine was also isolated. The total yield of diazepine in each case is shown in Table 1.

Spectra of the Benzodiazepines

Their mass spectra are typical of cyclic azo-compounds in showing small molecular ion peaks and large (M^+-N_2) peaks. The next major fragmentation was loss of [$-CH_2CH_2-$] from the cyclopentyl ring.

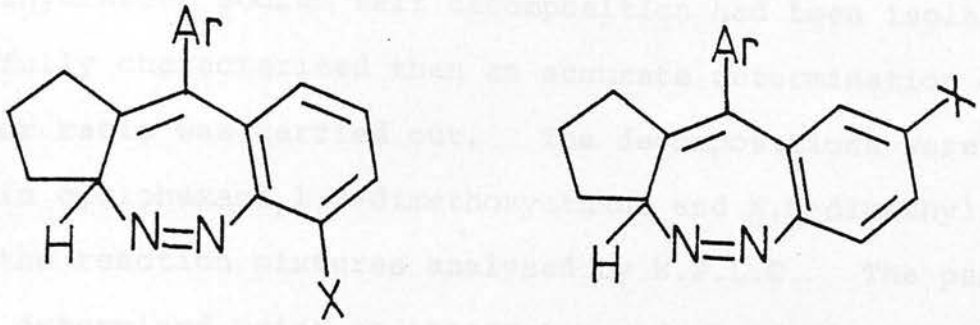
The ^1H n.m.r. spectra were of great importance in distinguishing between the different isomers formed in each reaction. In the unsubstituted diazepine (A, X=H) the



(A)

aromatic 6-proton absorbs at lower field (δ 7.78) than the other aromatic protons giving a broad doublet (J_o = 8Hz). A similar effect is observed in azobenzene where the ortho-protons are more deshielded than the meta- and para-protons. In compounds in which C-7 carried a non-coupling substituent the 6-proton gave a broad singlet.

The absence of this low-field aromatic absorption in the spectra of the reaction products allowed a differentiation between the two possible isomers.



The ^{1}H n.m.r. spectra of all the diazepines also showed a broad distorted doublet at δ 3.1-3.2 attributed to the 3-proton cis to the azo-group and subject to its deshielding influences.

The ^{13}C n.m.r. spectra of all of the benzodiazepines were also obtained. The peaks were identified where possible, by their chemical shifts and by off-resonance decoupling. The chemical shift of C-3a is of particular interest in that it absorbed in the range 73-77 p.p.m. from Me_4Si whereas in 3H-pyrazoles, which are the five-membered analogues of this system, the saturated carbon atom (C-3) is more strongly deshielded by the azo-group absorbing at 93-105 p.p.m. from Me_4Si. Ring size has a similar but less marked effect in the hydrocarbon analogues.[45]

Measurement of Isomer Ratio

Once the two isomeric benzodiazepines from a particular tosylhydrazone sodium salt decomposition had been isolated and fully characterised then an accurate determination of the isomer ratio was carried out. The decompositions were carried out in cyclohexane, 1,2-dimethoxyethane and N,N-dimethylformamide and the reaction mixtures analysed by H.P.L.C.. The peak areas were determined using an integrator and standard solutions of the authentic benzodiazepines were injected to obtain a correction factor to allow conversion of the peak area ratio into a molar ratio. The results are shown in Table 2.

Table 2

O/P Ratios

Substitutent	Solvent		
	CYCLOHEXANE	D.M.E.	D.M.F.
Cl	1.86	2.73	2.95
OEt	1.35	1.49	1.94
Et	3.5	3.2	2.85
CF_3	0.5	0.64	0.96
OCH_3	1.2	1.35	2.35
CH_3	4.3	3.6	3.6

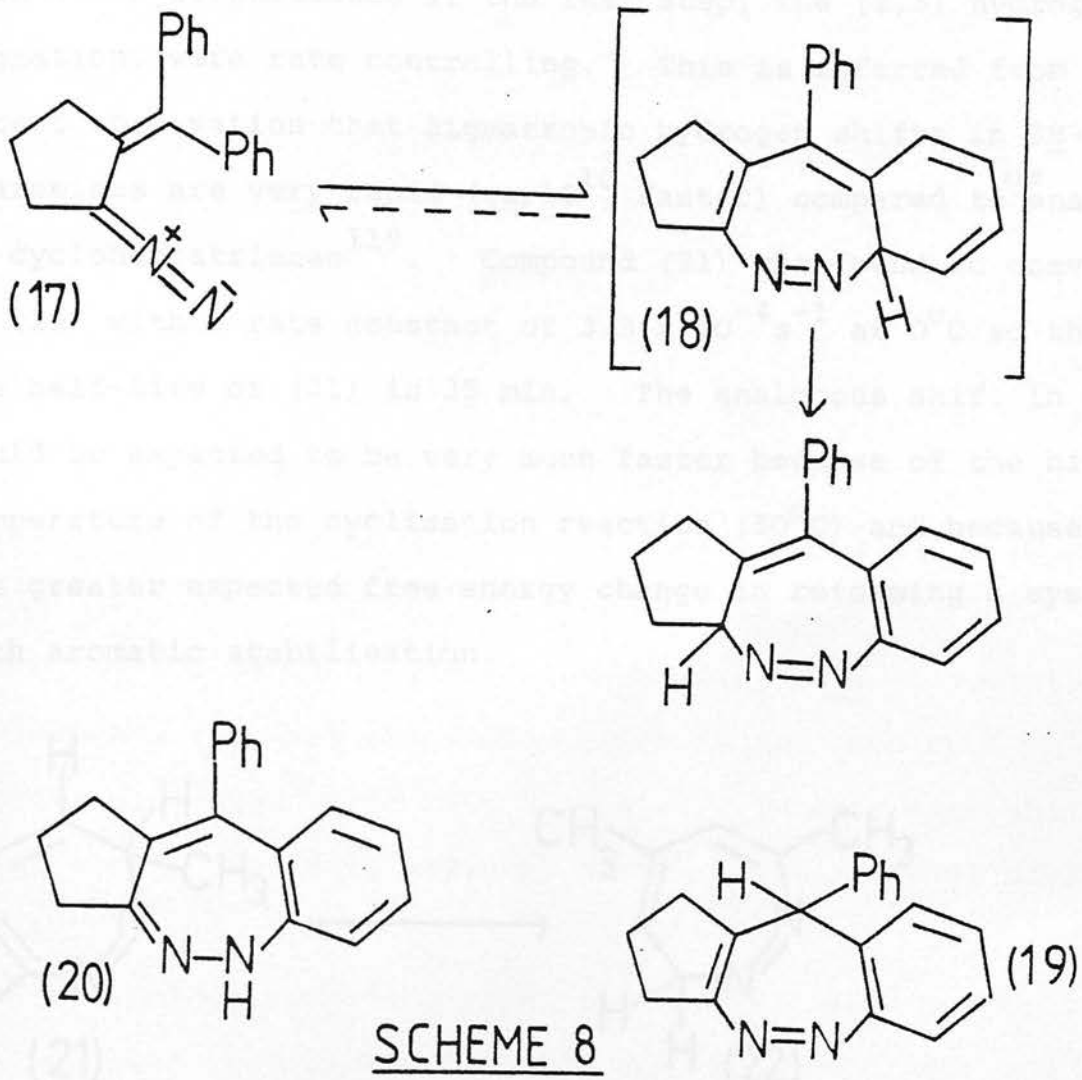
The first striking feature is that the greatest effects are obtained with electron releasing methyl and ethyl groups which direct predominantly ortho. A similar but less pronounced effect is observed with ethoxy and methoxy substituents which are considered to have a net electron releasing effect in electrophilic aromatic substitution, whereas the electron withdrawing trifluoromethyl group directs predominantly para.

Each individual benzodiazepine was heated at 80° in solution and monitored by H.P.L.C. to ensure that interconversion with its isomer was not occurring at this temperature. This was necessary since it was shown that this interconversion does occur at higher temperatures for some of the diazepines as will be discussed later.

Before a rationalisation of these substituent effects could be attempted it was necessary to study the reaction mechanism in more detail to ascertain at which stage of the reaction the substituents were exerting their directive influence.

Mechanism

The mechanism proposed for this reaction[45] is that the diazoalkane (17) undergoes a 1,7 conrotatory ring closure to give (18) Scheme 8 followed by a hydrogen shift which restores aromatic stabilisation. This hydrogen migration may best be rationalised as a concerted sigmatropic shift since only a [1,5] suprafacial migration is observed and not the sterically impossible [1,3] or [1,7] antarafacial migrations which would have given (19) or the more stable (20). A base catalysed hydrogen shift would be expected to give (20), the most thermodynamically stable isomer. This isomer can readily be prepared by the acid or base catalysed isomerisation of the product.



SCHEME 8

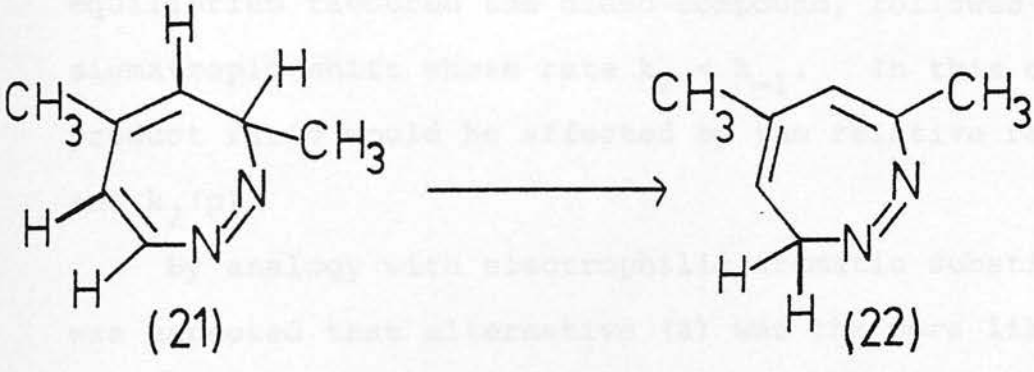
It was necessary therefore to find out more about the relative rates of the two steps and to determine whether they are reversible under the reaction conditions before an attempt could be made to rationalise the substituent effects.

Some preliminary conclusions can be drawn from general observation of the system and by analogy with similar steps in related systems:

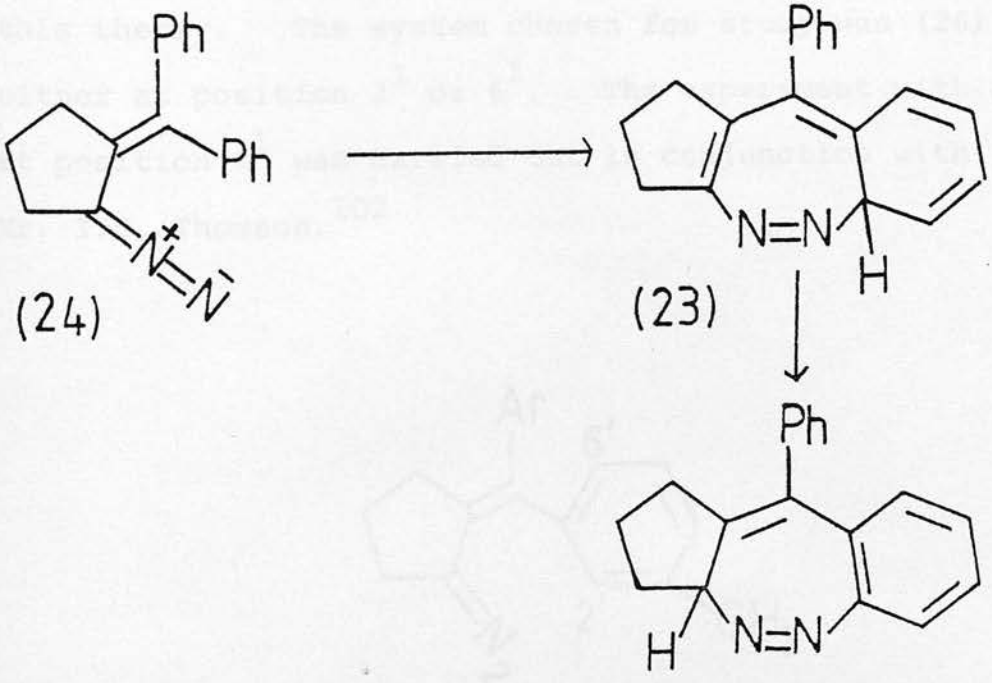
I) The rate of production of the diazo-compound from its precursor is much greater than the rate of cyclisation. This is inferred from the rapid build up of the red colour of the diazo-compound at the start of the reaction and its slow disappearance over two to five hours.

II) The overall rate of diazepine formation is much slower

than would be predicted if the last step, the [1,5] hydrogen migration, were rate controlling. This is inferred from the recent observation that sigmatropic hydrogen shifts in 3H-1,2-diazepines are very rapid (ca. 10^{10} faster) compared to the analogous shift in cycloheptatrienes[119]. Compound (21) was found to convert to (22) with a rate constant of $3.3 \times 10^{-4} s^{-1}$ at 0°C so that the half-life of (21) is 35 min. The analogous shift in (23) would be expected to be very much faster because of the higher temperature of the cyclisation reaction (80°C) and because of the greater expected free energy change in reforming a system with aromatic stabilisation.



(21) (22)



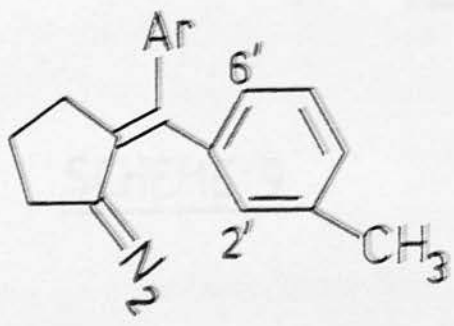
(24) (23)

It can be concluded from this that the net rate of conversion of the diazo-compound (24) to the intermediate (23) is much slower than the subsequent hydrogen shift. If we now consider the implications of this for the cyclisation of the substituted diazo-compound (25) in Scheme 9 then two extreme situations can be visualised:

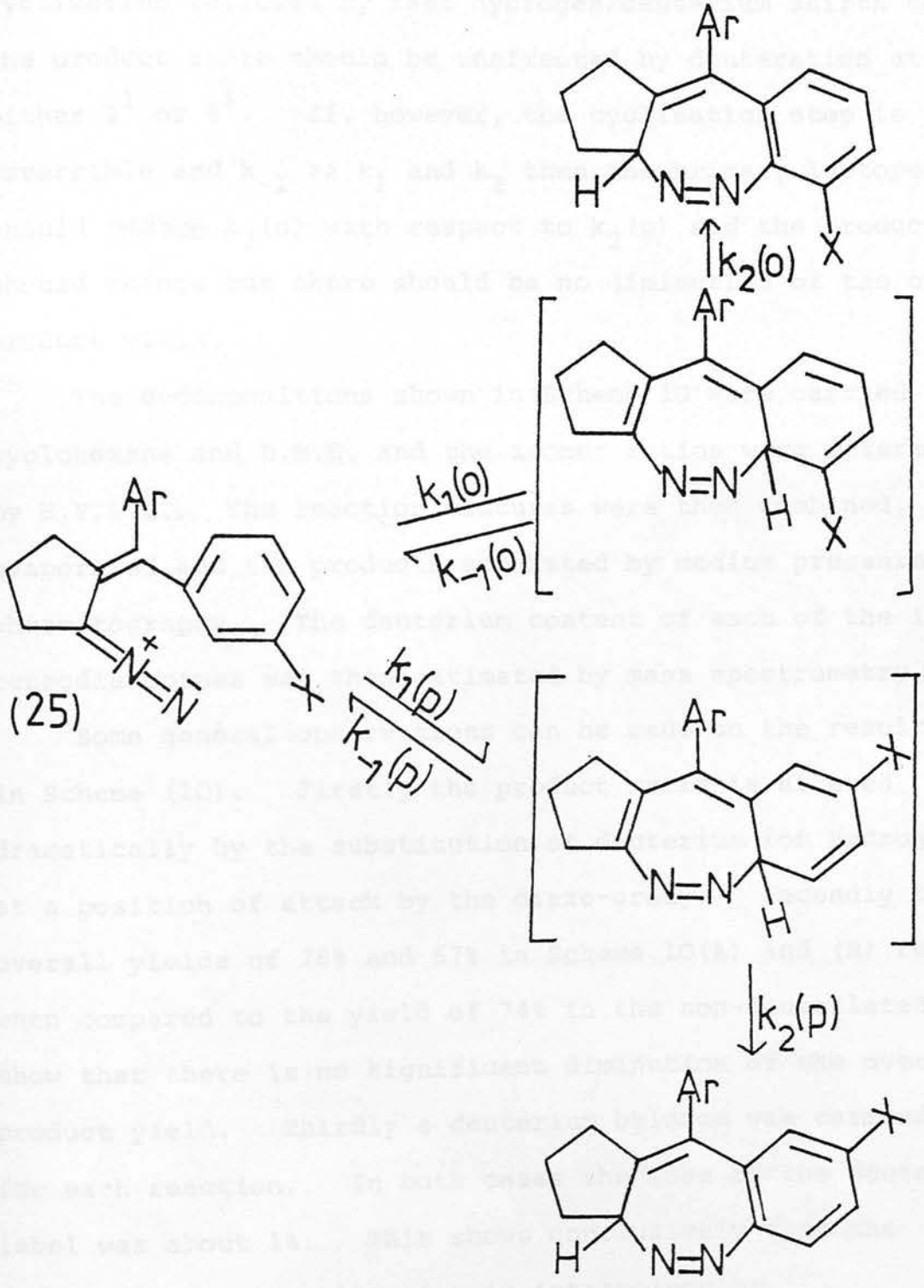
a) A slow non-reversible cyclisation step (k_1) followed by a fast hydrogen shift (k_2). The product ratio would then reflect the $k_1(o):k_1(p)$ ratio i.e. the relative rates of cyclisation on to the two positions in the aromatic ring.

b) A reversible cyclisation step with $k_{-1} > k_1$ so that the equilibrium favoured the diazo-compound, followed by a sigmatropic shift whose rate $k_2 < k_{-1}$. In this case the product ratio would be affected by the relative rates of $k_2(o)$ and $k_2(p)$.

By analogy with electrophilic aromatic substitution it was expected that alternative (a) was the more likely and some experiments with deuterated substrates were designed to test this theory. The system chosen for study was (26) deuteriated either at position 2^1 or 6^1. The experiment with deuterium at position 6^1 was carried out in conjunction with Mr. I.D. Thomson.[102]



(26)



SCHEME 9

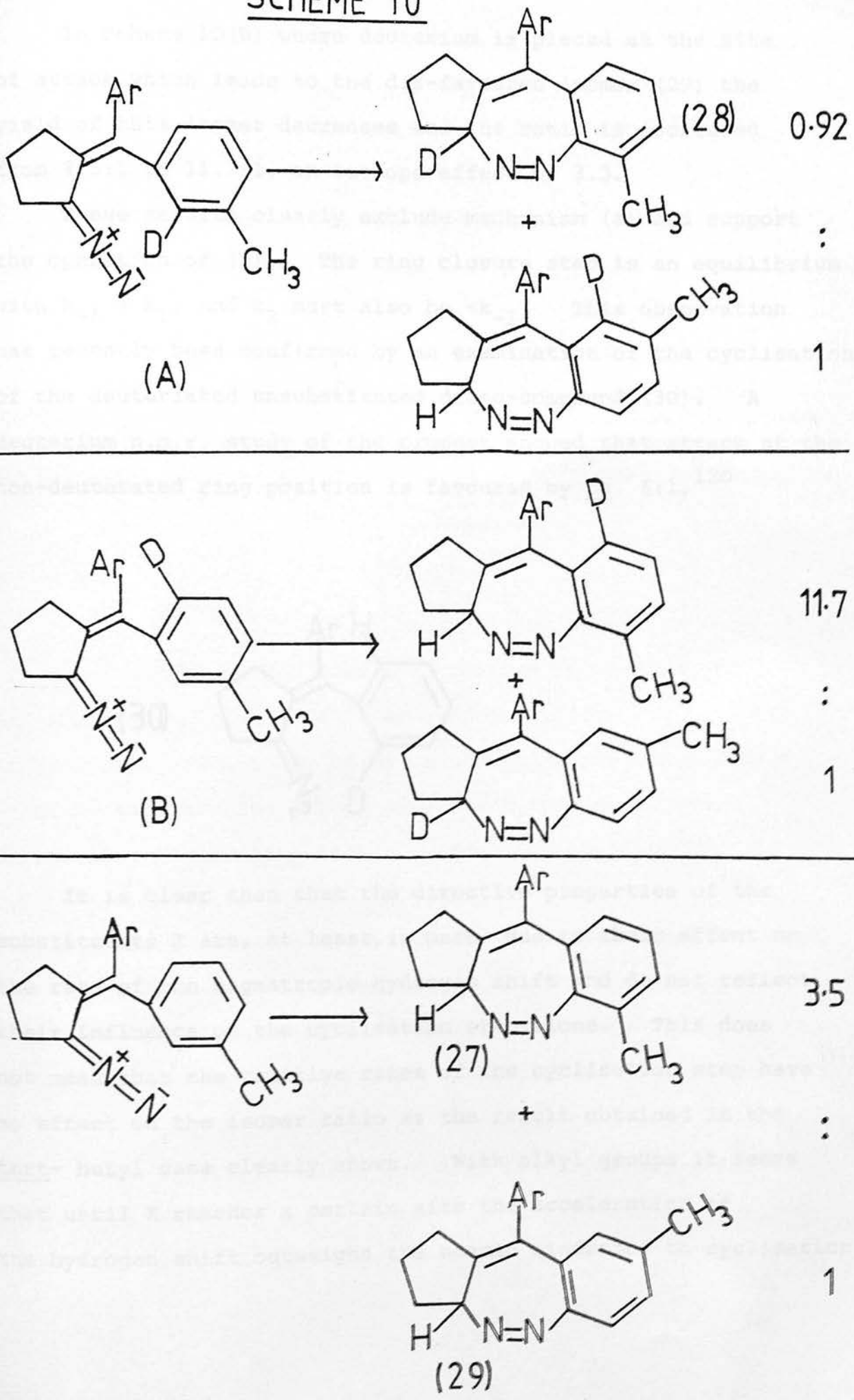
If mechanism (a) applies i.e. slow irreversible cyclisation followed by fast hydrogen/deuterium shifts then the product ratio should be unaffected by deuteration at either 2^1 or 6^1. If, however, the cyclisation step is reversible and $k_{-1} >> k_1$ and k_2 then the primary isotope effect should reduce $k_2(o)$ with respect to $k_2(p)$ and the product ratio should change but there should be no diminution of the overall product yield.

The decompositions shown in Scheme 10 were carried out in cyclohexane and D.M.E. and the isomer ratios were determined by H.P.L.C.. The reaction mixtures were then combined, filtered, evaporated and the products separated by medium pressure chromatography. The deuterium content of each of the isolated benzodiazepines was then estimated by mass spectrometry.

Some general observations can be made on the results shown in Scheme (10). Firstly the product ratio is altered dramatically by the substitution of deuterium for hydrogen at a position of attack by the diazo-group. Secondly the overall yields of 78% and 67% in Scheme 10(A) and (B) respectivel when compared to the yield of 74% in the non-deuteriated case show that there is no significant diminution of the overall product yield. Thirdly a deuterium balance was carried out for each reaction. In both cases the loss of the deuterium label was about 1%. This shows conclusively that the hydrogen/deuterium migration is intramolecular.

In Scheme 10(A) where deuterium is placed at the site of attack which leads to the favoured isomer (27) the ratio is decreased from 3.5:1 to 0.92:1, an isotope effect of 3.8, and (28) becomes the predominant isomer.

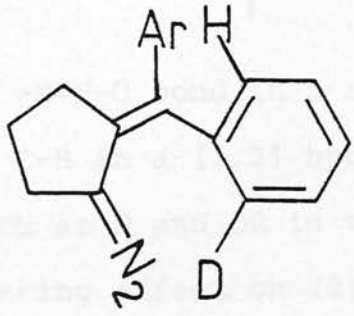
SCHEME 10



In Scheme 10(B) where deuterium is placed at the site of attack which leads to the dis-favoured isomer (29) the yield of this isomer decreases and the ratio is increased from 3.5:1 to 11.7:1, an isotope effect of 3.3.

These results clearly exclude mechanism (a) and support the operation of (b). The ring closure step is an equilibrium with $k_{-1} > k_1$, and k_2 must also be $< k_{-1}$. This observation has recently been confirmed by an examination of the cyclisation of the deuteriated unsubstituted diazo-compound (30). A deuterium n.m.r. study of the product showed that attack at the non-deuterated ring position is favoured by ca. 6:1.[120]

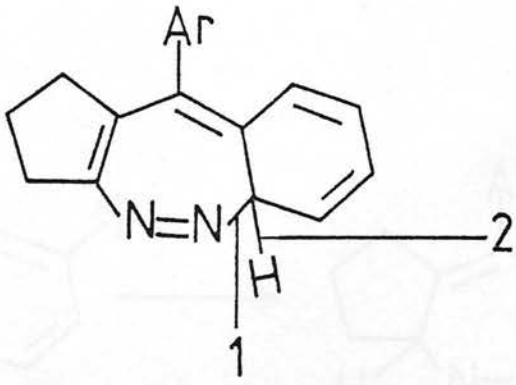
(30)



It is clear then that the directive properties of the substituents X are, at least in part, due to their effect on the rate of the sigmatropic hydrogen shift and do not reflect their influence on the cyclisation step alone. This does not mean that the relative rates of the cyclisation step have no effect on the isomer ratio as the result obtained in the tert- butyl case clearly shows. With alkyl groups it seems that until X reaches a certain size the acceleration of the hydrogen shift outweighs the steric hindrance to cyclisation

and the steric destabilisation of the product. The observed isomer ratio may be a superimposition of the effect which X has on the cyclisation step and the effect which it has on the hydrogen shift.

Once the intermediate has been formed it is subject to two competing bond cleavage processes:



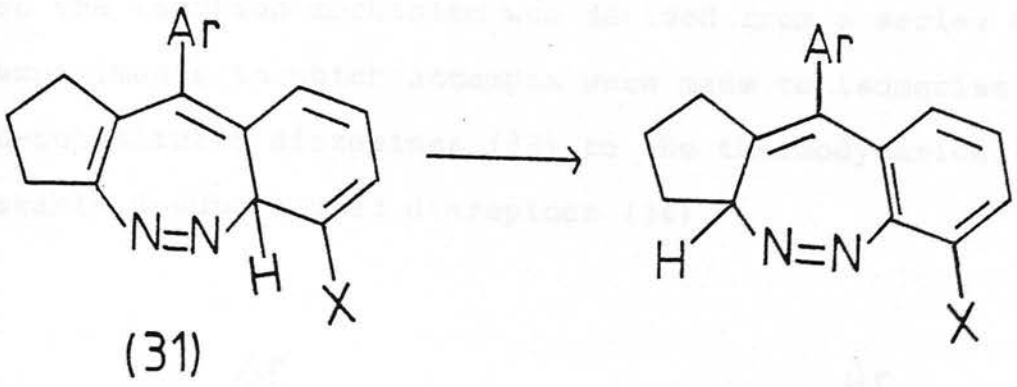
1) cleavage of -N=N-C bond in a retro-cyclisation.

2) cleavage of C-H in a [1,5] hydrogen shift.

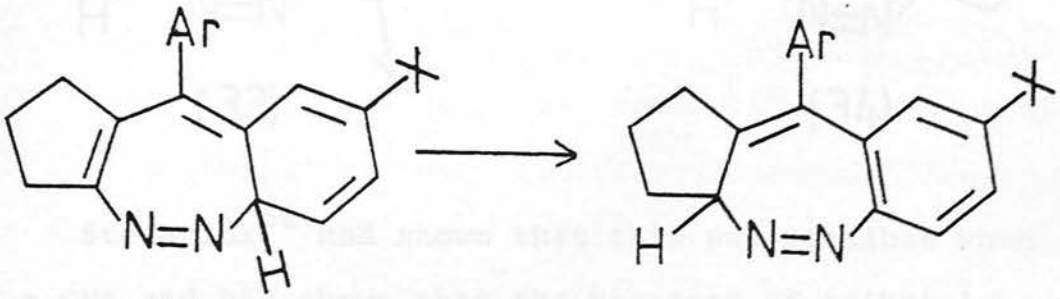
Substituents such as R and OR in the ortho position clearly have an accelerating effect on (2) and thus encourage formation of the ortho isomer.

On inspecting the two intermediates for the reaction it is difficult to see why an electronic effect could account for the differences observed in the rate of hydrogen migration since one would expect little difference between an ortho and a para electronic effect by the substituent.

Construction of a model of these intermediates reveals that there is slight steric crowding in (31) which does not exist in (32). It seems likely that the rates of these two reactions reflects the differences in the steric interaction



(31)

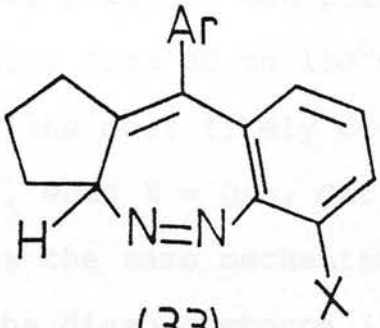


(32)

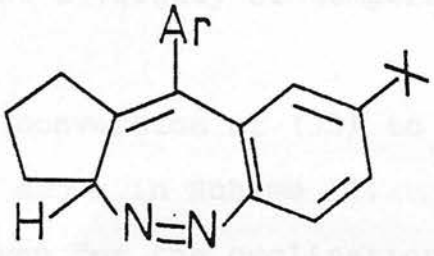
between the migrating hydrogen and the substituent group although an electronic effect cannot be completely ruled out.

If one studies the difference in free energy between equatorial and axial substituents on the cyclohexane ring, for monosubstituted cyclohexanes, which provide a measure of the steric requirements of these groups, then the results show a similar trend to the o/p ratios observed in the benzodiazepine system. The order is Me > Et > OEt > OMe > Cl in the cyclohexane series whereas in the o/p ratios the order is Me > Et > Cl > OEt > OMe. With the exception of chlorine there is a similar trend.

More information about the effect of the substituents on the reaction mechanism was derived from a series of experiments in which attempts were made to isomerise the 6-substituted diazepines (33) to the thermodynamically more stable 8-substituted diazepines (34).



(33)



(34)

Stefaniuk[55] had shown that this was possible when X = OMe and had shown that the presence of tributylphosphine inhibited the conversion suggesting that the mechanism involved the diazo-intermediate.

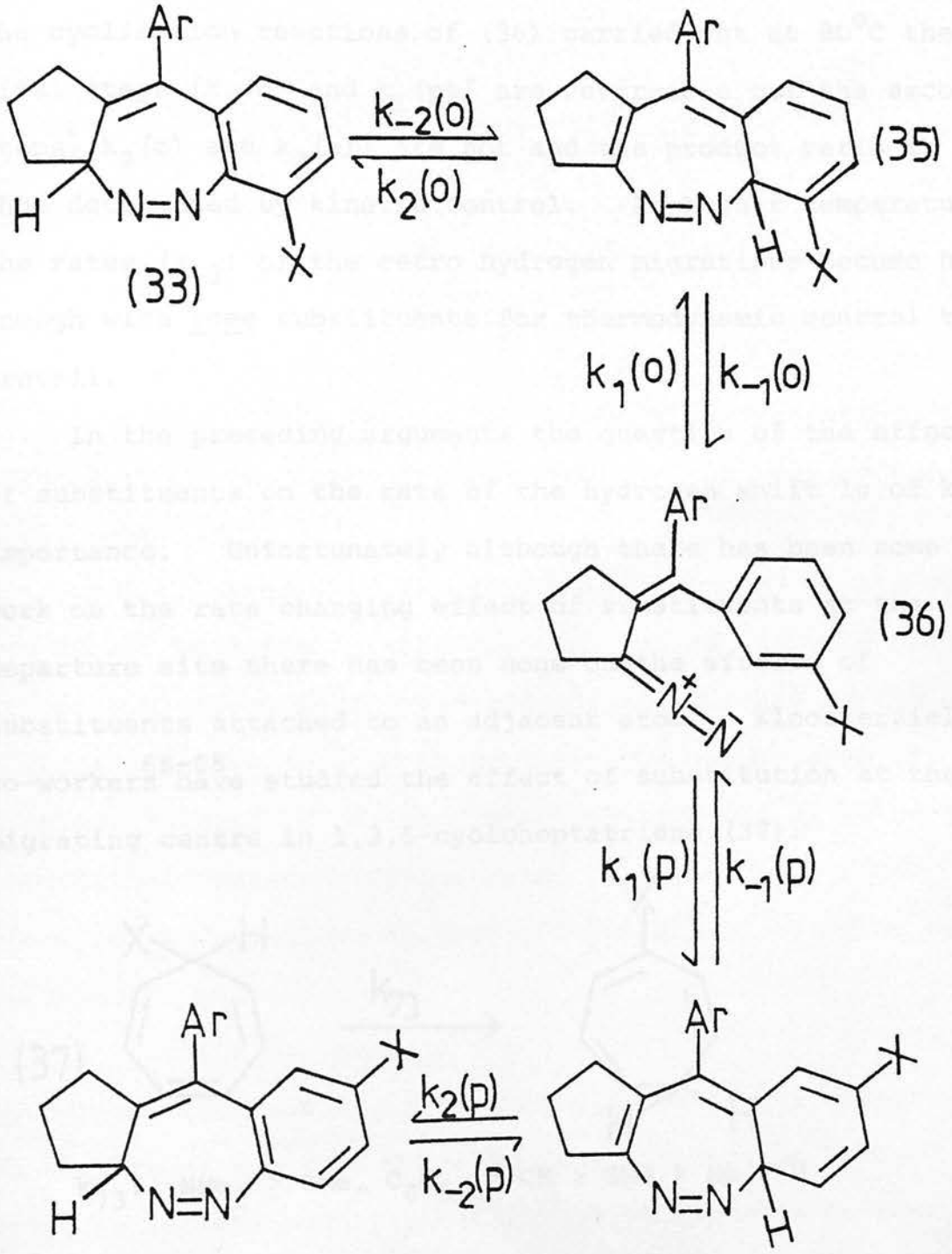
A complicating factor, however, is that at higher temperatures benzodiazepines are known to isomerise to 3H-indazoles and also to decompose via loss of nitrogen to give hydrocarbons.[53,54]

Isomerisation reactions were carried out for X = OMe, OEt, Cl, Me in (33). The 6-substituted diazepine was boiled under reflux in a variety of different solvents at increasing temperatures until either isomerisation or decomposition occurred. The reactions were monitored by H.P.L.C. and the presence of the 8-substituted diazepine was deduced by

a comparison of retention time with an authentic sample. It was found that when X = OMe, OEt and Cl in (33) isomerisation occurred readily in toluene. In a larger scale experiment the 8-ethoxy isomer (34, X = OEt) was isolated and fully characterised.

When X = Me in (33) isomerisation did not occur in either polar or non-polar solvents at a variety of temperatures ranging from 80 to 150°C.

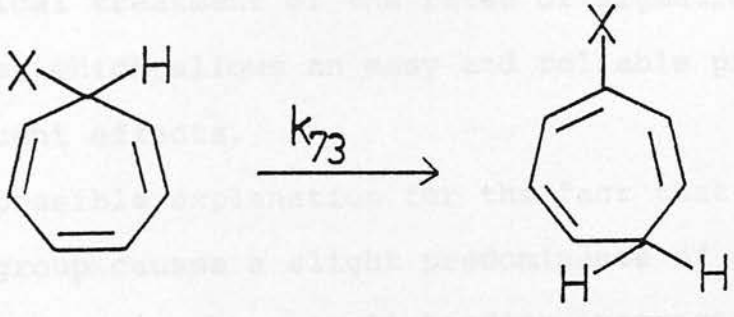
The most likely course for the conversion of (33) to (34), when X = OMe, OEt, and Cl, is shown in Scheme 11. It is the same mechanism as that given for the cyclisation of the diazo-compound (36) [cf. Scheme (9)] except that the [1,5] sigmatropic hydrogen shifts have become effectively reversible ($k_{-2} \neq 0$) at the higher temperature of the isomerisation reactions. Thus a reverse hydrogen shift in (33) [$k_{-2}(\underline{o})$] generates (35) which undergoes electrocyclic ring opening to give (36) which can then cyclise to give either (33) again or (34). Since all the steps are reversible the less hindered, more thermodynamically stable product (34) is favoured. The failure of the (33) → (34) isomerisation when X = Me is consistent with its having the strongest <u>ortho</u> directing effect in the cyclisation of (36). It was argued earlier that this was most likely due to the strong accelerating effect of the methyl group on $k_2(o)$ cf. $k_2(p)$. If the methyl group enhances $k_2(o)$ then it seems reasonable to argue that it will retard $k_{-2}(o)$ and so inhibit the conversion of (33) to (35) which is the first step in the isomerisation process.



SCHEME 11

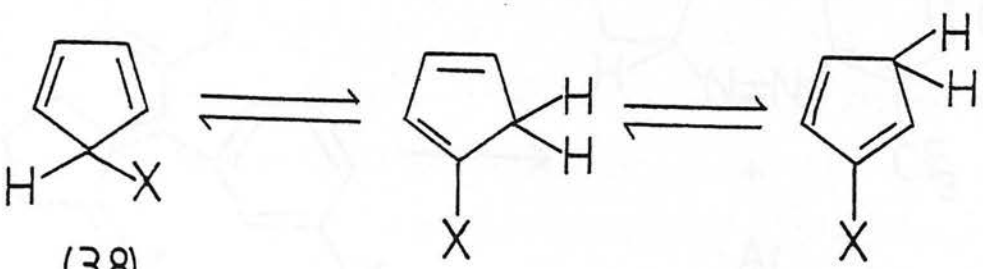
Thus to sum up the results so far it appears that in the cyclisation reactions of (36) carried out at 80°C the first steps [k_1(o) and k_1(p)] are reversible but the second steps [k_2(o) and k_2(p)] are not and the product ratio is thus determined by kinetic control. At higher temperatures the rates (k_{-2}) of the retro hydrogen migrations become high enough with <u>some</u> substituents for thermodynamic control to prevail.

In the preceding arguments the question of the effect of substituents on the rate of the hydrogen shift is of key importance. Unfortunately although there has been some work on the rate changing effect of substituents at the departure site there has been none on the effects of substituents attached to an adjacent atom. Kloosterziel and co-workers[65-68] have studied the effect of substitution at the migrating centre in 1,3,5-cycloheptatriene (37).

(37) 

k_{73}: NMe_2 > OMe, C_6H_5, > CN > SMe > Me > H

Breslow[70] has studied the effect of halogen substitution on [1,5] hydrogen migration in cyclopentadiene (38). He has found that halogen substitution decreases the rate of hydrogen migration compared to the parent hydrocarbon with iodine having the greatest effect (H > Cl > Br > I).

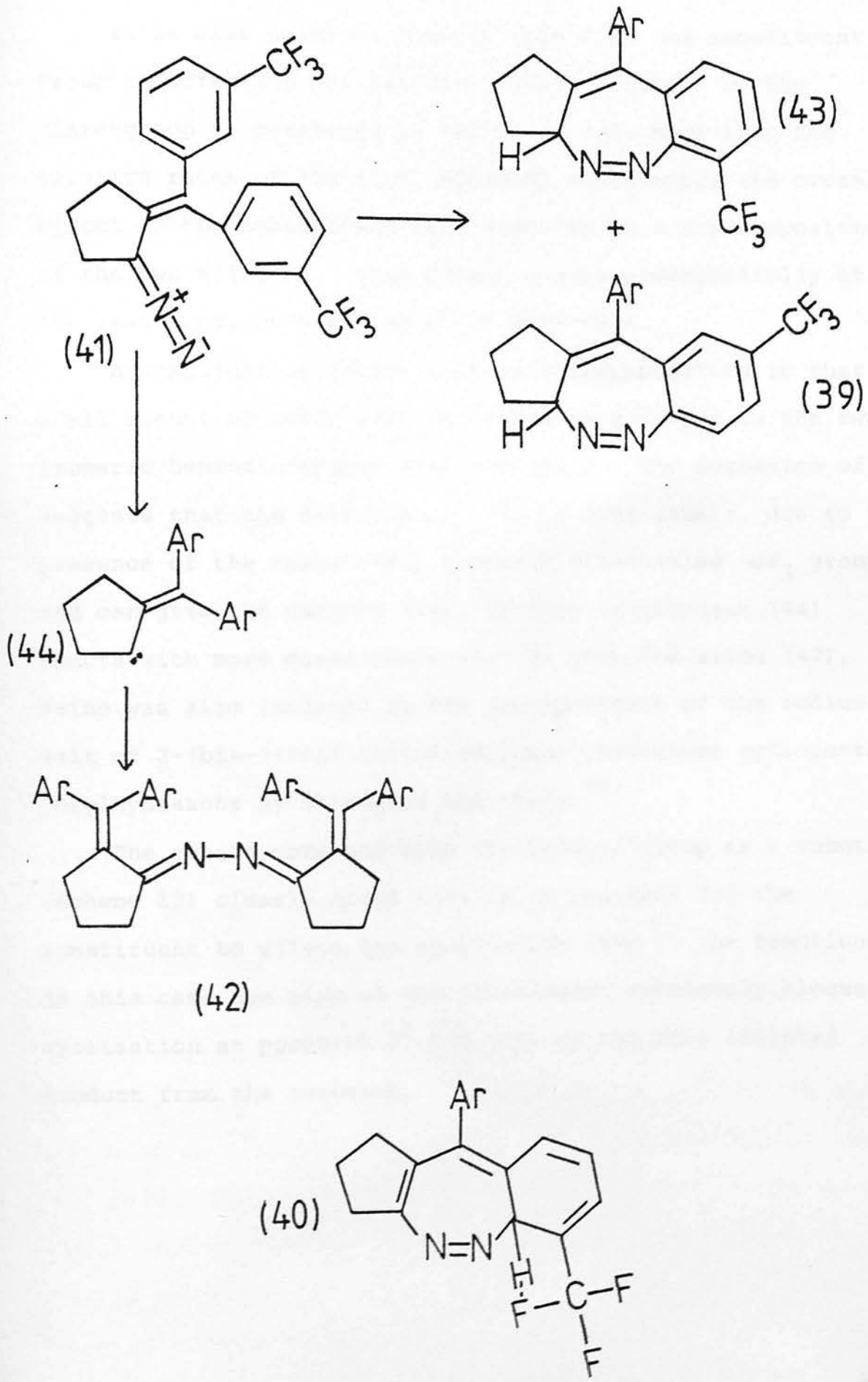


(38)

Breslow rationalised this behaviour as indicating that local positive charges on carbon must be involved in the [1,5] transition state.

Both of these systems are uncomplicated by steric effects and do not have the further complication of aromatic stabilisation. Also, since the substituent is attached to the migrating centre in both these cases the comparisons are not directly relevant. At the moment there seems to be no general theoretical treatment of the rates of sigmatropic shift processes which allows an easy and reliable prediction of substituent effects.

A possible explanation for the fact that the trifluoromethyl group causes a slight predominance of (39) (Scheme 12) is that there may be a small bonding interaction between the hydrogen and the highly electronegative fluorine counteracting the steric repulsion between them. This would decrease the rate of the [1,5] hydrogen shift in (40) and hence could account for the observed result.

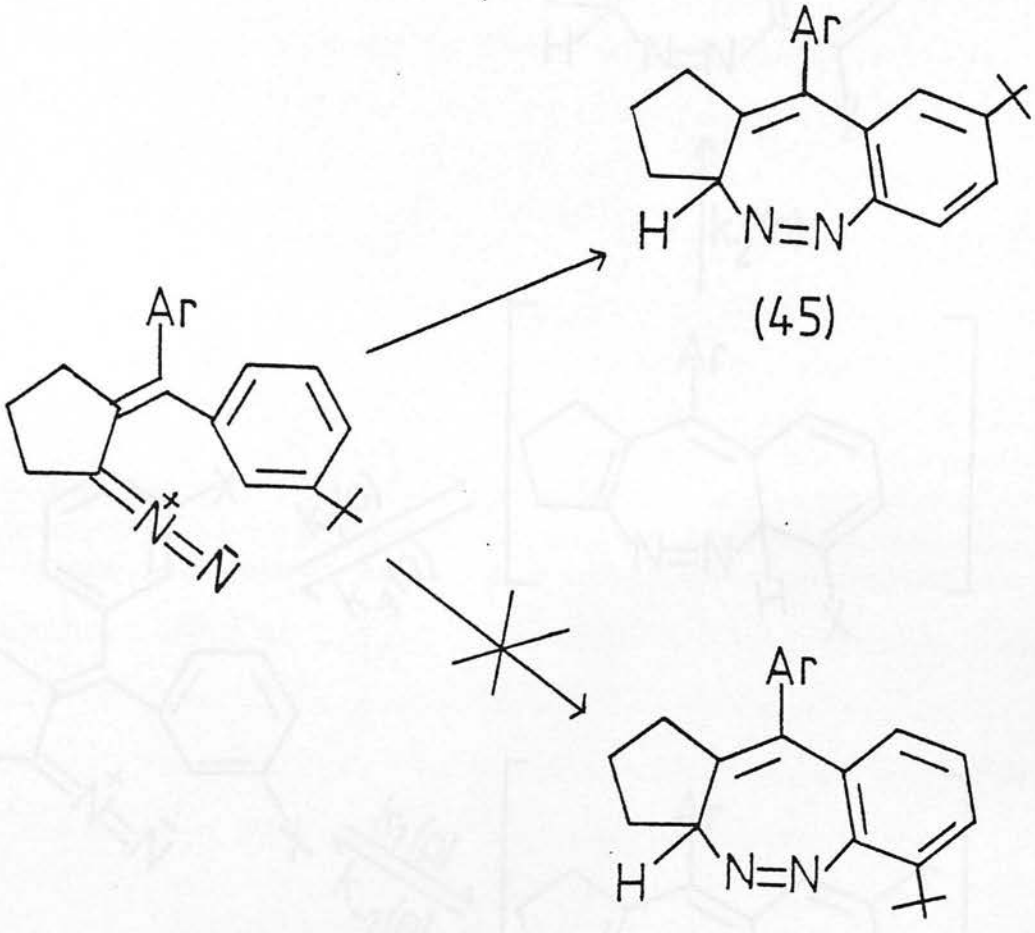

CF3
CF3
N+
N
(41)
Ar
H
N=N
(43)
CF3
+
Ar
CF3
H
N=N
(39)
Ar
Ar
(44)
Ar
Ar
Ar
Ar
N–N
(42)
Ar
(40)
N=N
H
F
C
F
F

SCHEME 12

It is also possible that in this case the substituent group is affecting the relative rates of attack by the diazo-group at positions 2^1 and 6^1 in (41) more than the relative rates of the [1,5] hydrogen shift since the overall effect of the substituent is thought to be a superimposition of the two effects. Thus attack occurs preferentially at the less hindered position 6^1 in this case.

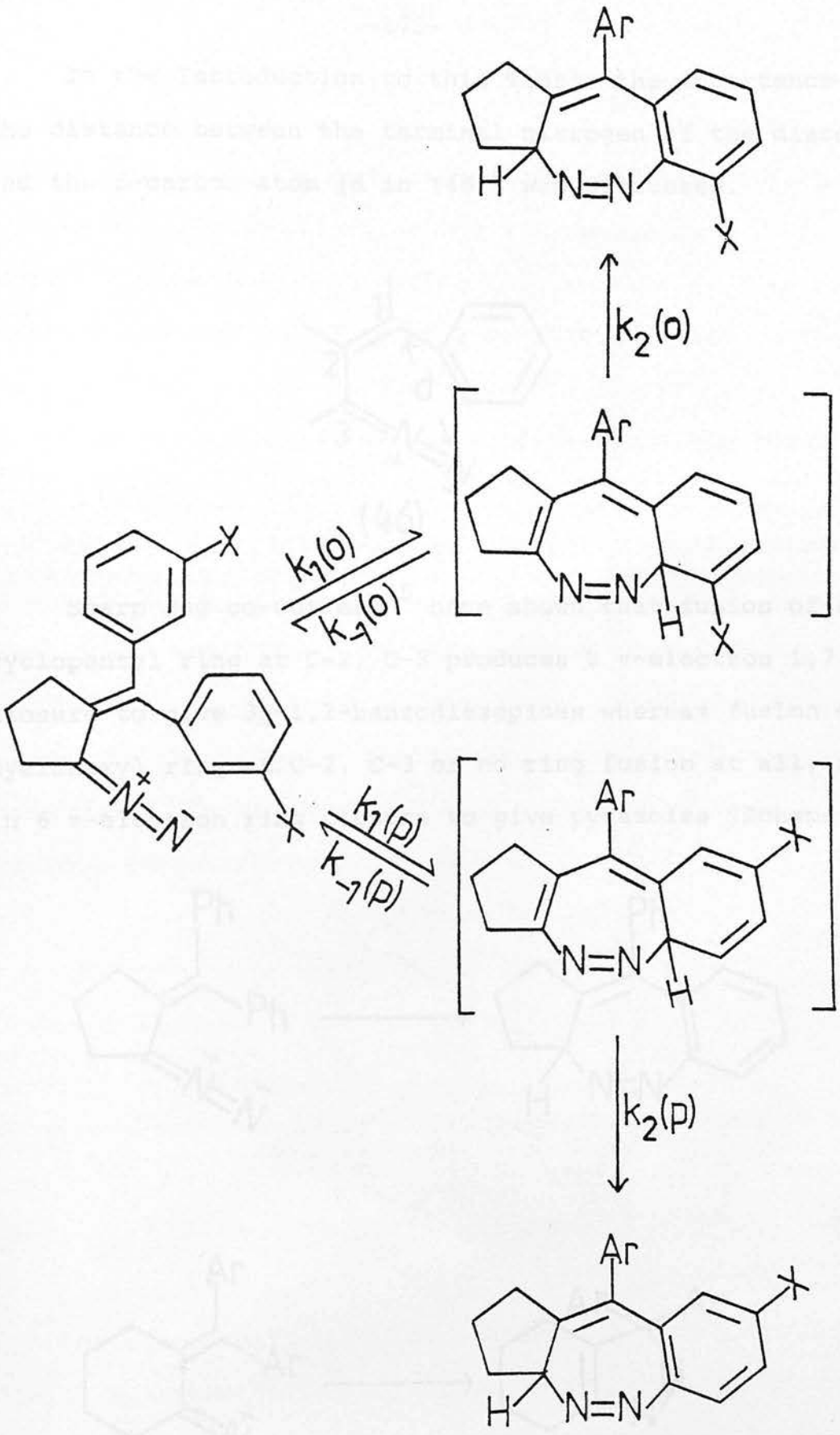
A complicating factor with this decomposition is that a small amount of azine (42) is formed in addition to the two isomeric benzodiazepines (39) and (43). The formation of azine suggests that the diazoalkane (41) is less stable, due to the presence of the inductively electron withdrawing $-CF_3$ group, and can give the carbene (44), by loss of nitrogen (44) reacts with more diazoalkane (41) to give the azine (42). Azine was also isolated in the decomposition of the sodium salt of 2-(bis-4-trifluoromethylphenyl)methylene cyclopentanone tosylhydrazone by Thorogood and Sharp.[45]

The result obtained with the t-butyl group as a substituent (Scheme 13) clearly shows that it is possible for the substituent to affect the cyclisation step in the reaction. In this case the size of the substituent completely blocks cyclisation at position 2^1 and (45) is the only isolated product from the reaction.



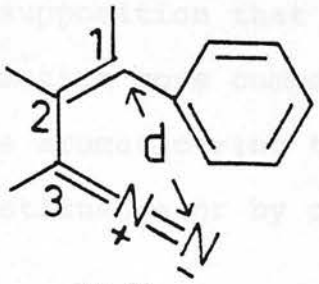
SCHEME 13

To sum up, the effect of substituents on the mechanism of benzodiazepine formation is complicated. The overall effect is a combination of the effects on the cyclisation step and on the subsequent [1,5] hydrogen migration. On the basis of these results the most likely mechanism is that the cyclisation is an equilibrium with $k_{-1} >> k_1$ (Scheme 14) and that the second step k_2 is fast cf. k_1 and probably of the same order of magnitude but slower than k_{-1}. The substituent exerts its effect mainly on k_2 unless X is large e.g. t-butyl when it affects k_1 more strongly. The probably explanation of the substituent effect on k_2 is that a combination of steric and electronic effects accelerate $k_2(o)$ with respect to $k_2(p)$.



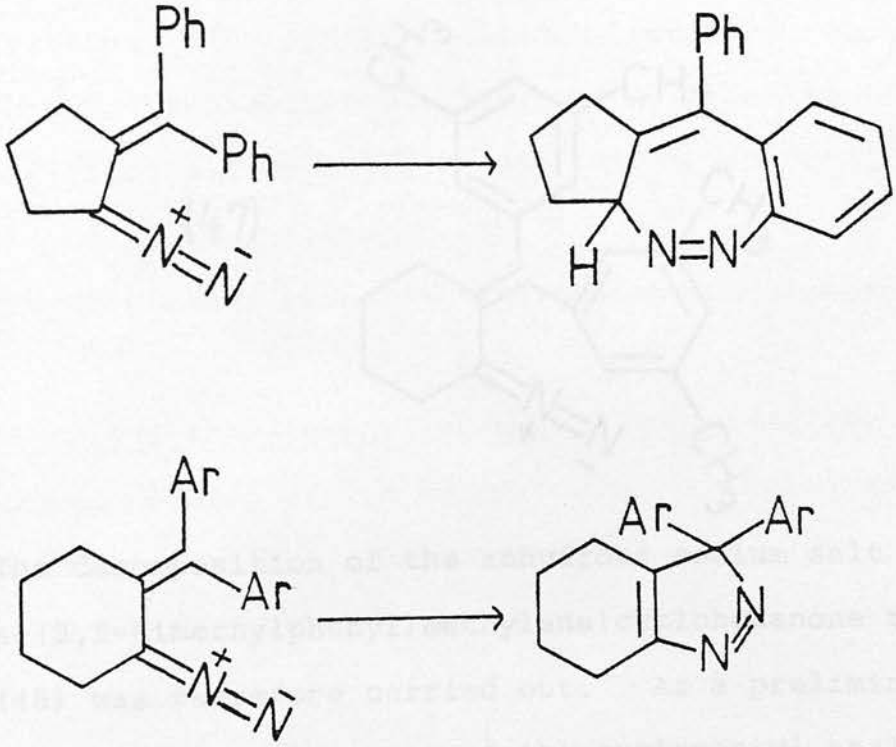
SCHEME 14

In the Introduction to this Thesis the importance of the distance between the terminal nitrogen of the diazo-group and the β-carbon atom [d in (46)] was discussed.



(46)

Sharp and co-workers[45] have shown that fusion of a cyclopentyl ring at C-2, C-3 produces 8 π-electron 1,7 ring closure to give 3H-1,2-benzodiazepines whereas fusion of a cyclohexyl ring at C-2, C-3 or no ring fusion at all, results in 6 π-electron ring closure to give pyrazoles (Scheme 15).

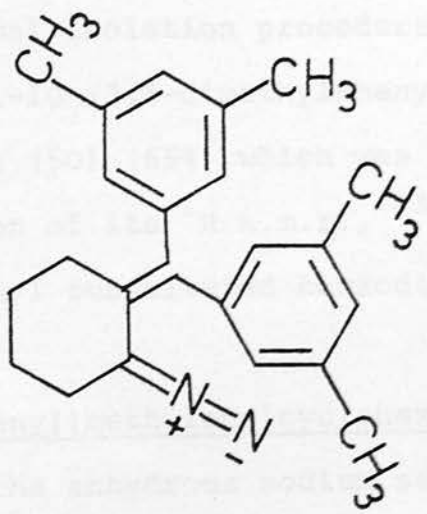


SCHEME 15

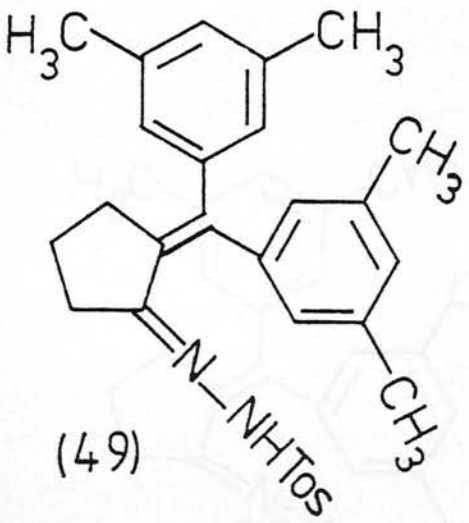
The effectiveness of the cyclopentyl ring in promoting diazepine formation is thought to be due to its inhibiting effect on the usually dominating 6π ring closure rather than to an accelerating effect on the 8π cyclisation. It therefore seemed a reasonable supposition that an alternative way of making diazepine formation more competitive might be to increase the reactivity of the aromatic ring to electrocyclic attack either by use of substituents or by changing the nature of the ring system.

Since a methyl substituent has the greatest directing effect of the substituents studied so far in this type of reaction it was hoped that the presence of two methyl groups in the 3 and 5 positions of the phenyl ring might be sufficiently activating to produce a benzodiazepine from (47) despite the presence of the six membered ring which would normally lead to pyrazole formation.

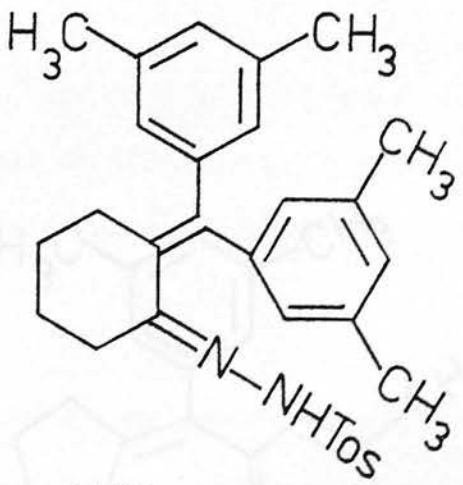
(47)



The decomposition of the anhydrous sodium salt of 2-[bis-(3,5-dimethylphenyl)methylene]cyclohexanone tosylhydrazone (48) was therefore carried out. As a preliminary control experiment the decomposition of the cyclopentyl analogue 2-[bis-(3,5-dimethylphenyl)methylene]cyclopentanone tosylhydrazone (49) was performed in conjunction with Mr. C.B. Argo.[94]



(49)



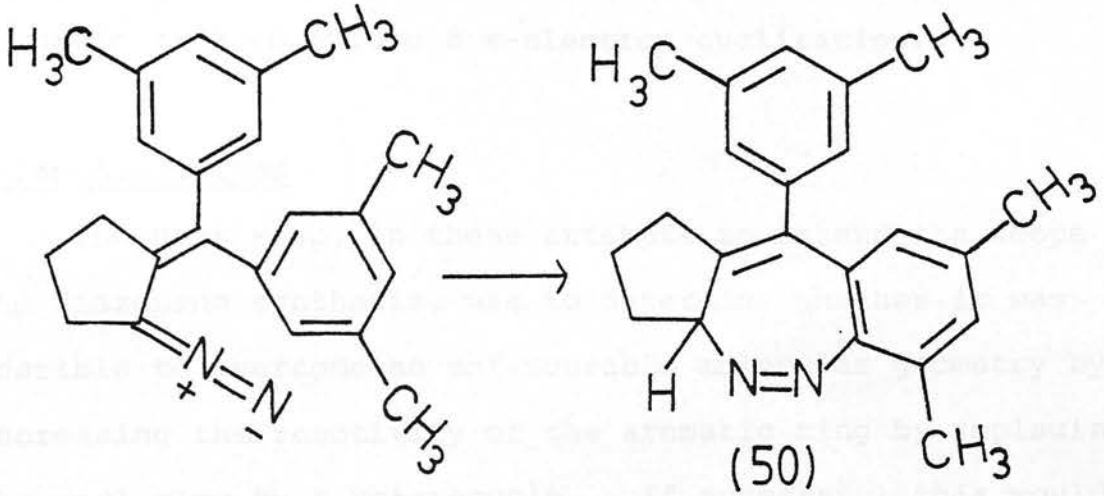
(48)

2-[Bis-(3,5-dimethylphenyl)methylene]cyclopentanone tosylhydrazon

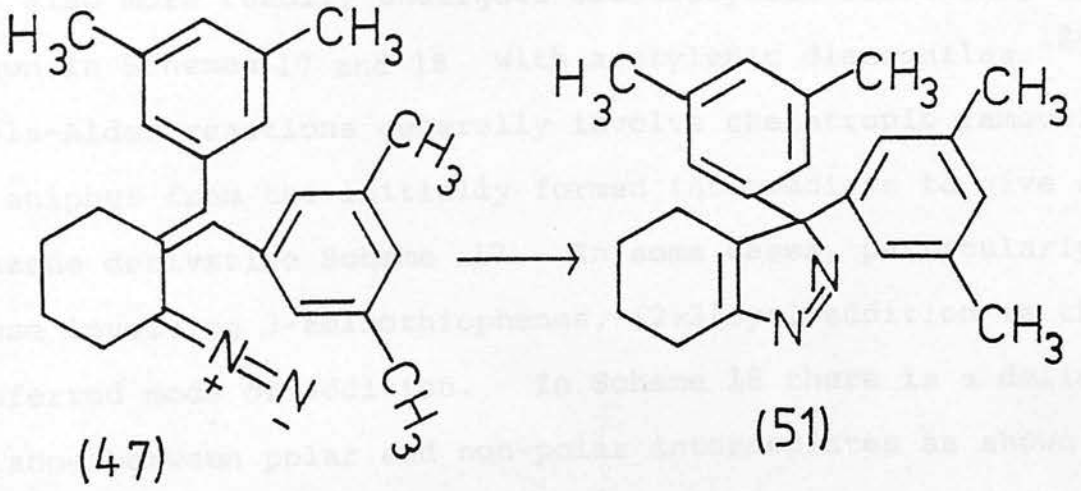
The anhydrous sodium salt (Scheme 16) was heated under reflux in DME for 1.5 hours. Initially a red colouration was visible but this faded to give a yellow solution with a white precipitate. The normal isolation procedure produced 1,2,3,3a-tetrahydro-6,8-dimethyl-10-(3,5-dimethylphenyl)benzo[c]cyclopenta[f][1,2] diazepine (50) (66%) which was readily identified by comparison of its ^{1}H n.m.r., ^{13}C n.m.r. and mass spectra with other methyl substituted benzodiazepines.

2-[Bis-(3,5-dimethylphenyl)methylene]cyclohexanone tosylhydrazone

Decomposition of the anhydrous sodium salt in DME (Scheme 16a) gave 4,5,6,7-tetrahydro-3,3-bis-(3,5-dimethylphenyl)indazole (51) (44%) as the only product after medium pressure chromatography. The reaction mixture was examined by H.P.L.C. which confirmed that the indazole was the only reaction product. No red colouration was observed in the early stages of the reaction, implying a very fast consumption of the



SCHEME 16



SCHEME 16a

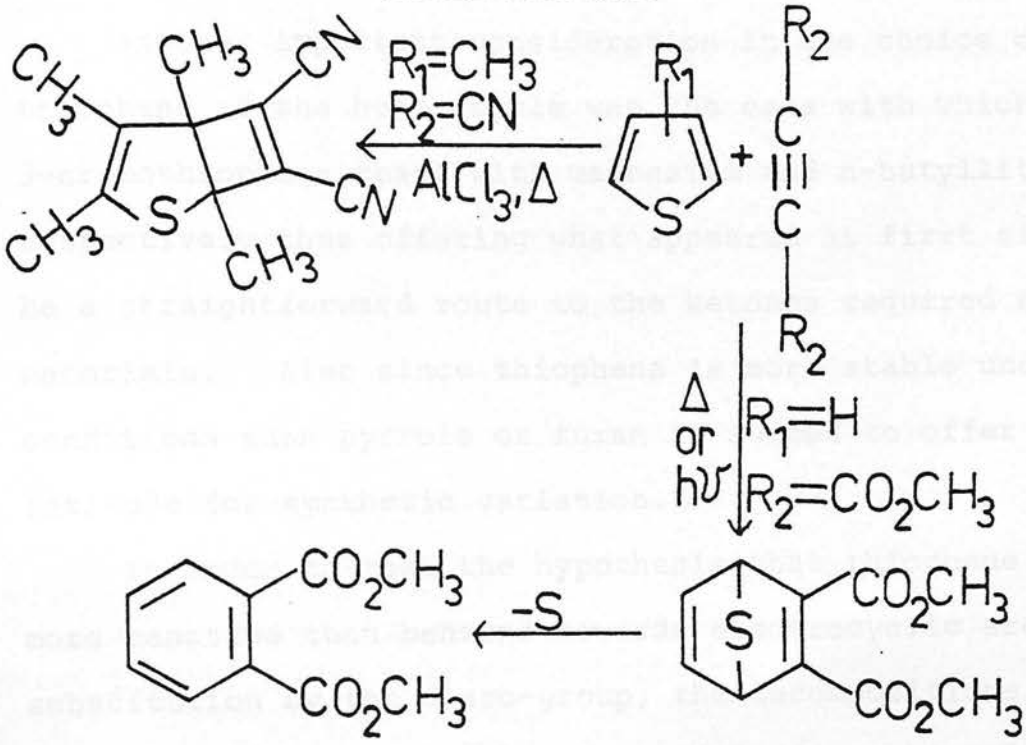
diazo-compound in the 6 π cyclisation. The identity of (51) was deduced by comparing its spectra with those of other tetrahydro-3H-indazoles.[46]

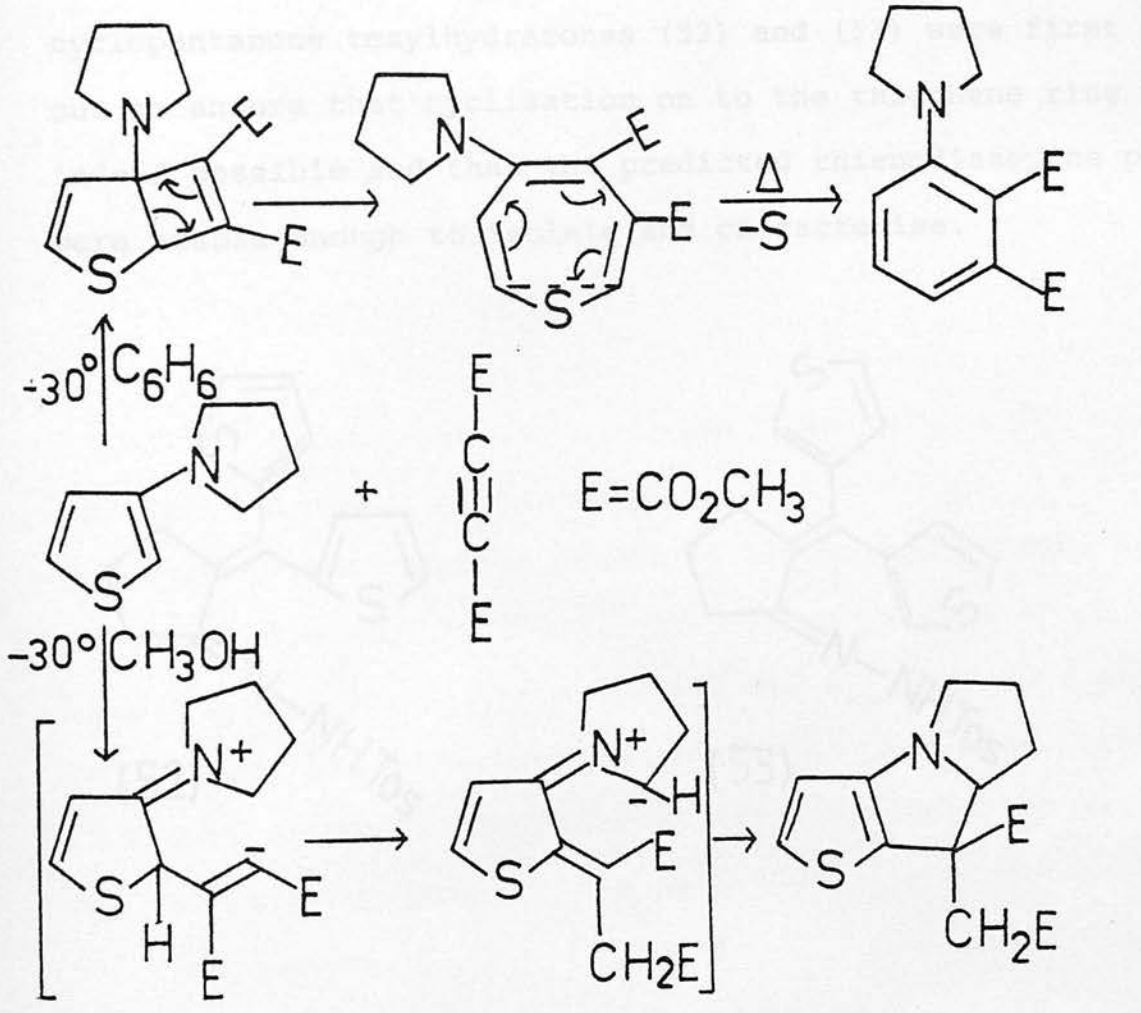
These experiments show that the presence of two methyl groups in the phenyl ring does not sufficiently activate the aromatic ring to induce 8 π-electron cyclisation.

Thienodiazepines

The next step, in these attempts to extend the scope of the diazepine synthesis, was to determine whether it was possible to overcome an unfavourable molecular geometry by increasing the reactivity of the aromatic ring by replacing the aryl ring by a heterocycle. If successful this would lead to novel heterocyclic systems. Thiophene was chosen as the heterocycle since it is more reactive than benzene towards electrophilic and nucleophilic substitution[122,123] and also more readily undergoes electrocyclic reactions, as shown in Schemes 17 and 18 with acetylenic dienophiles.[124,125] Diels-Alder reactions generally involve cheletropic removal of sulphur from the initially formed intermediate to give a benzene derivative Scheme 17. In some cases, particularly those involving 3-aminothiophenes, [2+2]cycloaddition is the preferred mode of addition. In Scheme 18 there is a delicate balance between polar and non-polar intermediates as shown by the change in the course of the cycloadditions in different solvents.

SCHEME 17

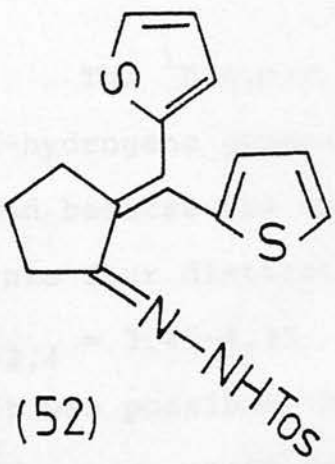




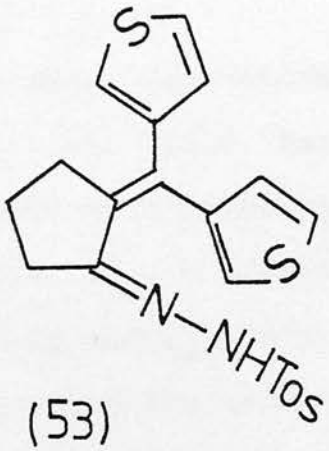
SCHEME 18

Another important consideration in the choice of thiophene as the heterocycle was the ease with which 2- and 3-bromothiophene react with magnesium and n-butyllithium respectively thus offering what appeared at first sight to be a straightforward route to the ketones required as starting materials. Also since thiophene is more stable under acidic conditions than pyrrole or furan it seemed to offer a greater latitude for synthetic variation.

In order to test the hypothesis that thiophene should be more reactive than benzene towards electrocyclic aromatic substitution by the diazo-group, the decompositions of 2-(di-2-thienylmethylene)cyclopentanone and 2-(di-3-thienylmethylene) cyclopentanone tosylhydrazones (52) and (53) were first carried out to ensure that cyclisation on to the thiophene ring was indeed possible and that the predicted thienodiazepine products were stable enough to isolate and characterise.



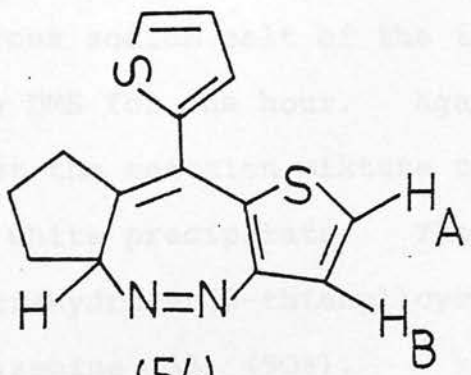
(52)



(53)

2-(Di-2-thienylmethylene)cyclopentanone tosylhydrazone

The anhydrous sodium salt of the tosylhydrazone (52) was heated under reflux in DME for one hour, at the end of which all the starting material had been consumed. In contrast to the aryl analogues no red colouration was observed but the reaction mixture consisted of a yellow solution and a white precipitate. The standard isolation procedure produced a yellow crystalline solid which was identified as 5a, 6, 7, 8-tetrahydro-9-(2-thienyl)cyclopenta[f]thieno[3,2-c][1,2] diazepine (85%) (54) on the basis of spectroscopic evidence.



(54)

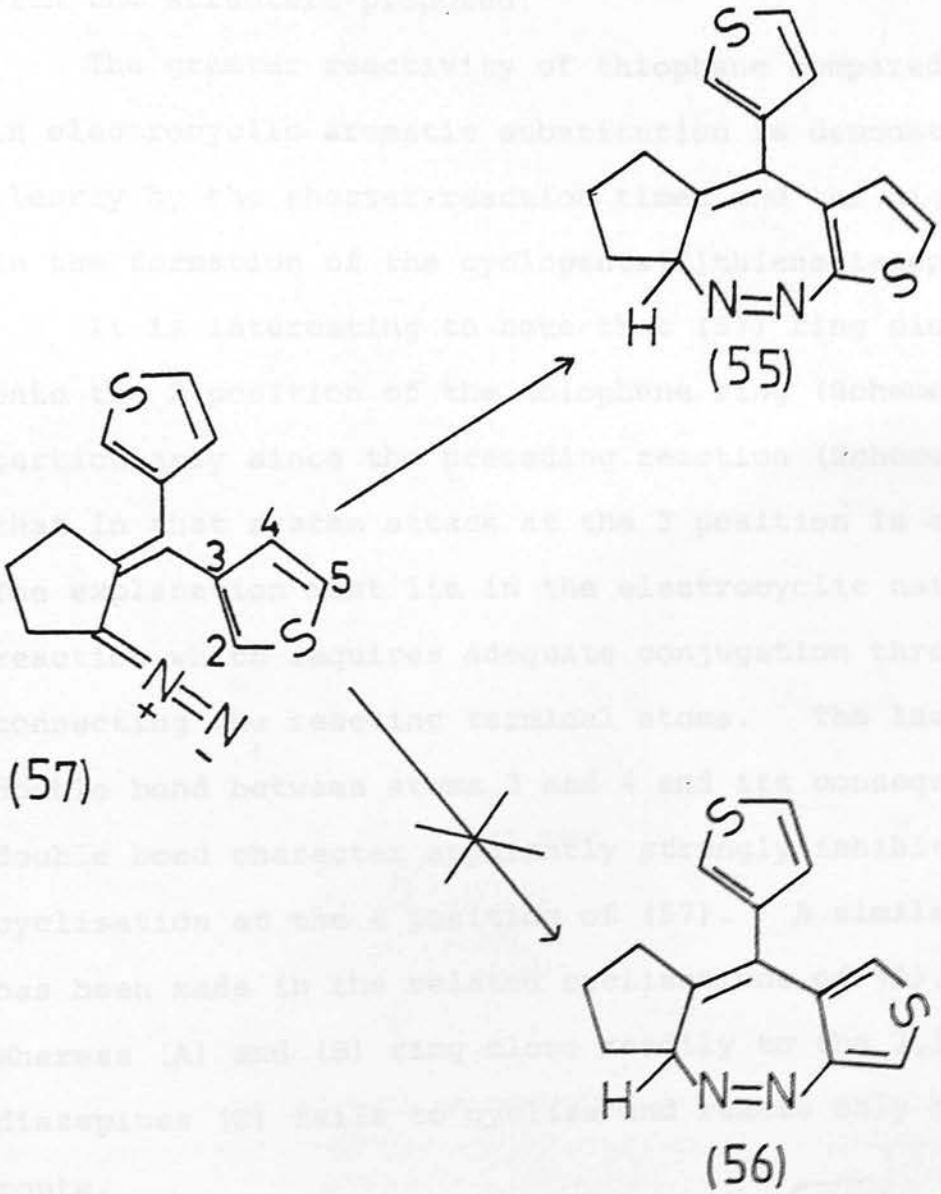
The ^1H n.m.r. spectrum was very informative since the α-hydrogens generally absorb at lower field than the β-hydrogens and because the coupling constants of thienyl protons fall into four distinct regions[122] i.e. $J_{2,3}$ = 4.80-5.80, $J_{3,4}$ = 3.45-4.35, $J_{2,4}$ = 1.25-1.70 and $J_{2,5}$ = 3.20-3.65 Hz. It was possible to completely analyse the aromatic region of the ^1H n.m.r. spectrum and this analysis was consistent with the structure proposed. The most significant feature was the two doublets ($J_{4,5}$ = 5.3 Hz) at 7.45 and 7.15 δ attributable to H_A and H_B in (54).

The ^{13}C n.m.r. and mass spectra showed good agreement with those of 1,2,3,3a-tetrahydro-10-phenylbenzo[c]cyclopenta[f][1,2]diazepine.[45] The ^{13}C n.m.r. spectrum showed a peak at 77.1 p.p.m. diagnostic for a carbon atom deshielded by the azo-group in a seven membered ring. The mass spectrum showed the characteristic small molecular ion peak at m/e 272 (5%), a large (M^+-28) peak at m/e 244 (71%) corresponding to loss of nitrogen and the base peak at m/e 216 corresponding to further loss of [$-CH_2-CH_2-$] from the cyclopentyl ring.

2-(Di-3-thienylmethylene)cyclopentanone tosylhydrazone

The anhydrous sodium salt of the tosylhydrazone was heated under reflux in DME for one hour. Again no red colouration was observed but the reaction mixture consisted of a yellow solution and a white precipitate. The product was identified as 4,5,7,7a-tetrahydro-9-(3-thienyl)cyclopenta[f]thieno[2,3-c][1,2]diazepine (55) (90%).

This structure was proposed after a detailed examination of the spectroscopic evidence since in this case another isomer could be formed if cyclisation occurred at the 4-position instead of the 2-position (Scheme 19). A priori it should be relatively easy to distinguish between structures (55) and (56) since (55) contains 3 hydrogens α to the sulphur and two β whereas (56) contains 4 α-hydrogens and only one β. The ^1H n.m.r. spectrum of the product showed three downfield and two upfield protons and a full analysis of the coupling constants confirmed that the structure of the product was (55).

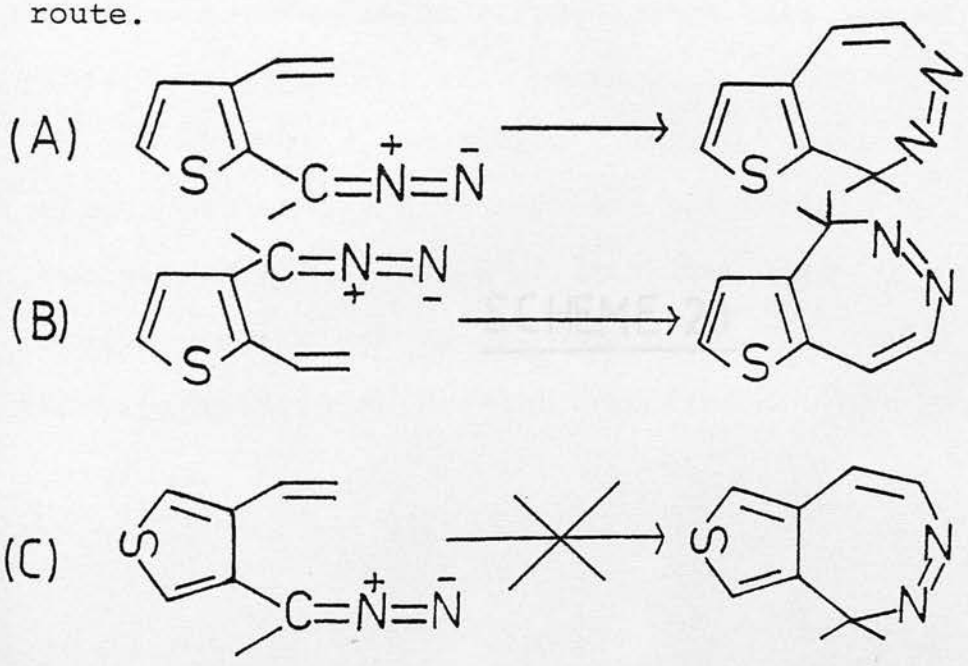


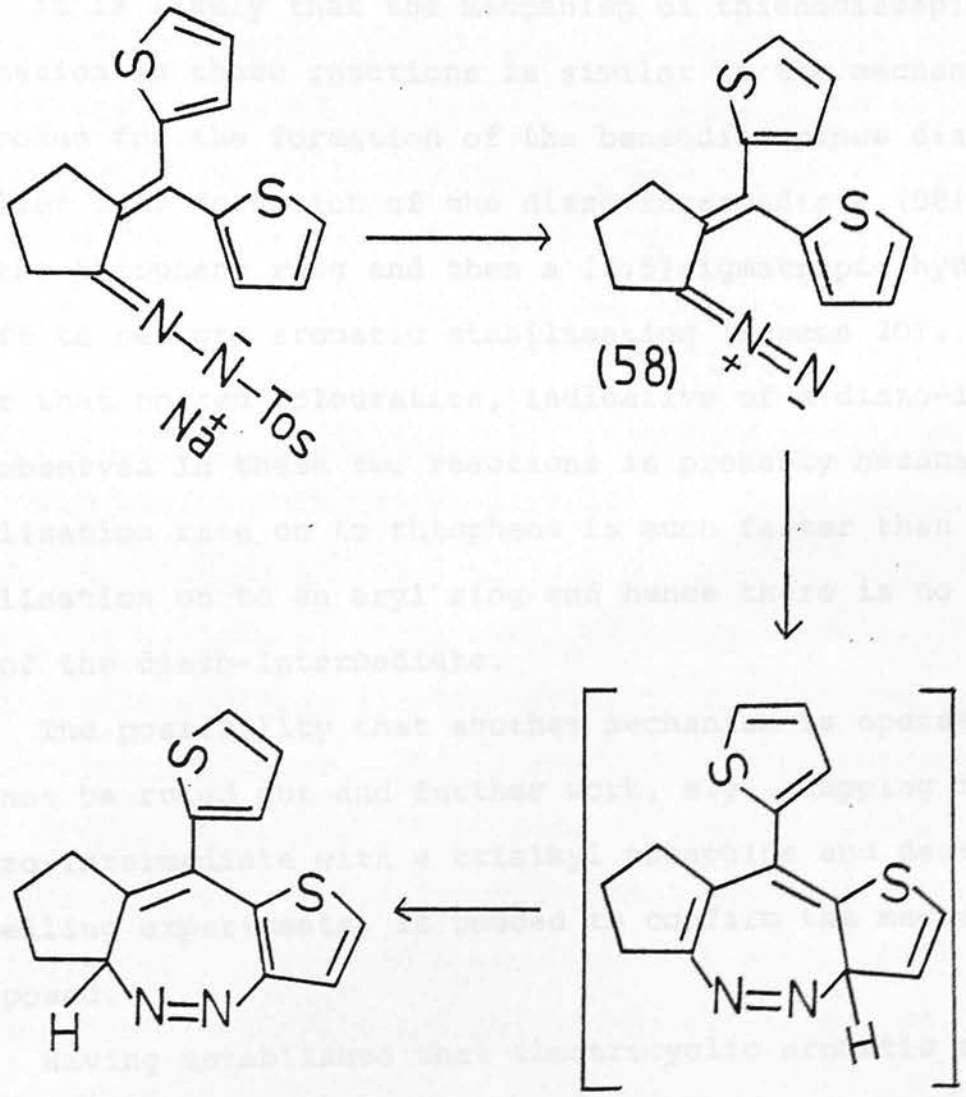
SCHEME 19

The ^{13}C n.m.r. spectrum showed a peak at 76.3 p.p.m. consistent with C_{7a} and the mass spectrum was consistent with the structure proposed.

The greater reactivity of thiophene compared to benzene in electrocyclic aromatic substitution is demonstrated quite clearly by the shorter reaction times and the higher yields in the formation of the cyclopenta[f]thienodiazepines.

It is interesting to note that (57) ring closes only onto the 2 position of the thiophene ring (Scheme 19) particularly since the preceding reaction (Scheme 20) shows that in that system attack at the 3 position is equally rapid. The explanation must lie in the electrocyclic nature of the reaction which requires adequate conjugation through the chain connecting the reacting terminal atoms. The lack of a formal double bond between atoms 3 and 4 and its consequent lower double bond character apparently strongly inhibits the cyclisation at the 4 position of (57). A similar observation[126] has been made in the related cyclisations of (A),(B) and (C). Whereas (A) and (B) ring close readily to the 2,3-thienodiazepines (C) fails to cyclise and reacts only by a carbenic route.





SCHEME 20

Mechanism

It is likely that the mechanism of thienodiazepine formation in these reactions is similar to the mechanism proposed for the formation of the benzodiazepines discussed earlier i.e. formation of the diazo-intermediate (58) attack on the thiophene ring and then a [1,5]sigmatropic hydrogen shift to restore aromatic stabilisation (Scheme 20). The fact that no red colouration, indicative of a diazo-intermediate, is observed in these two reactions is probably because the cyclisation rate on to thiophene is much faster than for cyclisation on to an aryl ring and hence there is no build up of the diazo-intermediate.

The possibility that another mechanism is operating cannot be ruled out and further work, e.g. trapping the diazo-intermediate with a trialkyl phosphine and deuterium labelling experiments, is needed to confirm the mechanism proposed.

Having established that electrocyclic aromatic substitution by the diazo-group occurs more readily with thiophene than with benzene it was then of interest to ascertain whether the fusion of a cyclopentyl ring was as necessary with thiophene as it was with benzene. The first objective was to see whether 8 π-electron 1,7 ring closure would occur when a cyclohexyl ring replaced the cyclopentyl ring thus decreasing the distance between the diazo-group and the olefinic methylene double bond hence increasing the competitiveness of 6 π-electron ring closure to give a pyrazole.

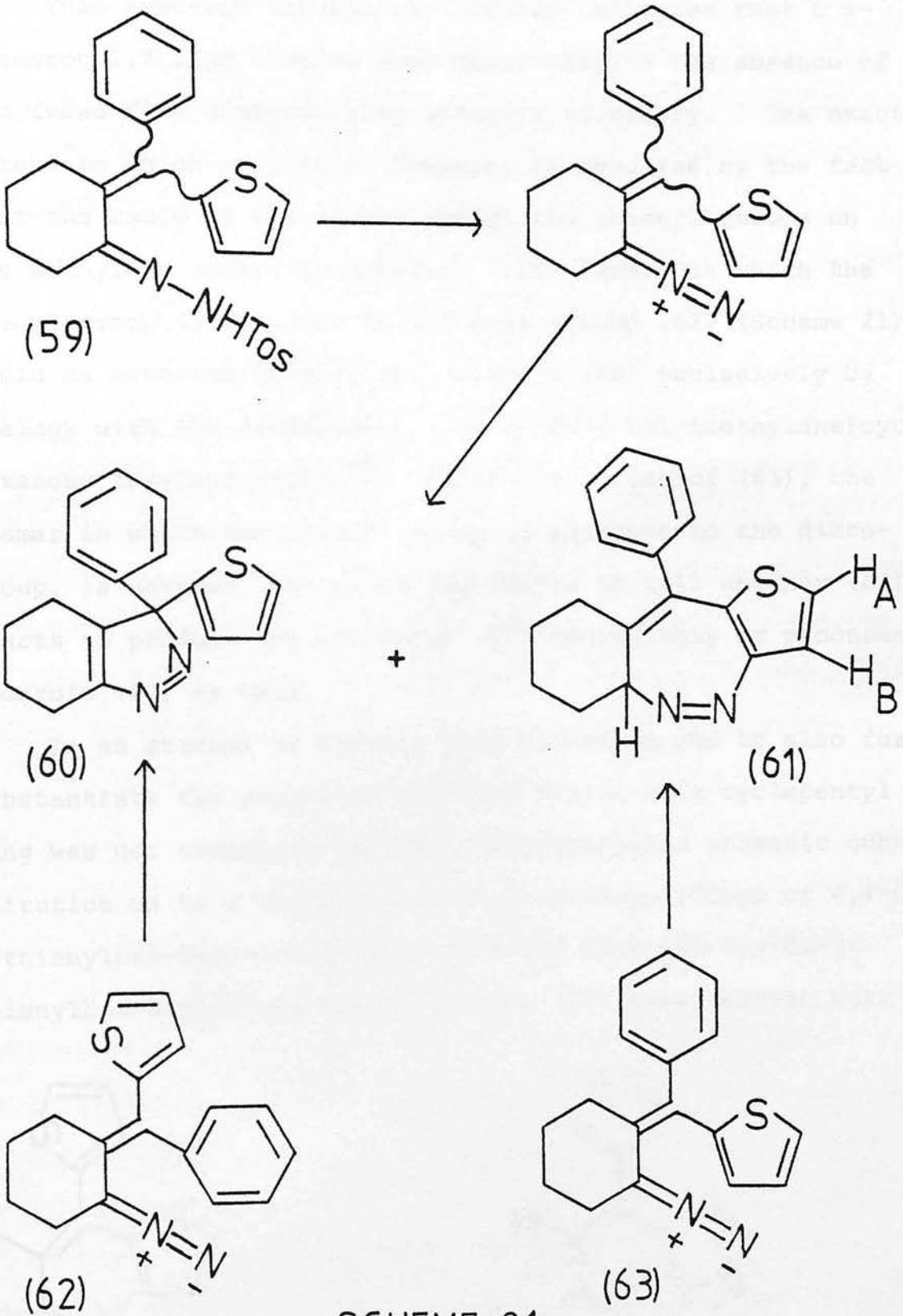
Unfortunately the first systems chosen for study i.e. the tosylhydrazones of dithienylmethylenecyclohexanones could not be prepared due to the unforeseen synthetic problems which were discussed earlier. The synthesis of 2-(phenyl-2-thienylmethylene)cyclohexanone tosylhydrazone (59) was, however, possible and the decomposition of its sodium salt carried out. (Scheme 21).

2-(Phenyl-2-thienylmethylene)cyclohexanone tosylhydrazone

The sodium salt was prepared in the usual way from the tosylhydrazone which was a mixture of cis and trans isomers, about the methylene double bond, of unknown ratio. The sodium salt was heated under reflux in DME for one hour and after work-up, two compounds were obtained by chromatography.

The major product (85%) a colourless crystalline solid, was identified as 4,5,6,7-tetrahydro-3-phenyl-3-(2-thienyl) indazole (60). The ^{13}C n.m.r. spectrum was typical of a tetrahydro-3H-indazole and had an absorption at 100.7 p.p.m. characteristic of C_3 in that system.

The other product (9.5%), a yellow crystalline solid, was identified as 6,7,8,9-tetrahydro-10-(2-thienyl)cyclohexa[f] thieno[3,2-c][1,2]diazepine (61) since the ^{13}C n.m.r. spectrum showed an absorption at 71.9 p.p.m. attributable to C_{5a} and the ^{1}H n.m.r. spectrum showed a doublet (J = 5Hz) on each side of the phenyl protons attributable to H_A and H_B in (61). The mass spectrum was also consistent with this assignment.



SCHEME 21

4,4-Di-2-thienylbut-3-en-2-one tosylhydrazone

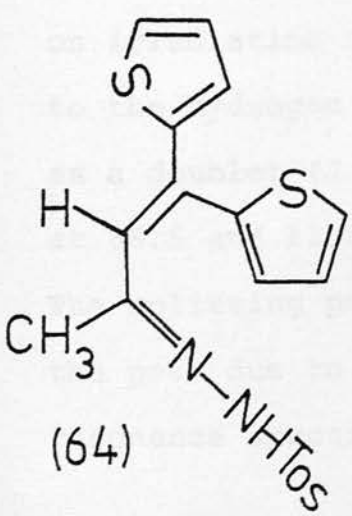
The sodium salt was prepared in the usual way but additional precautions were taken to ensure that all the ethanol had been removed since it has been shown that traces of protic solvent can cause rearrangement of the initial product in the analogous diphenylbut-3-en-2-one tosylhydrazone decomposition.[45] DME was added and the mixture heated under reflux for thirty minutes. After the normal work-up procedure two products were isolated by chromatography.

The major product (49%), a colourless crystalline solid, was identified as 3,3-di-2-thienyl-5-methylpyrazole (66) (Scheme 22). The ^{1}H n.m.r. spectrum showed the methyl group as a doublet (J = 1.6 Hz) and the ^{13}C n.m.r. showed an absorption at 99.0 p.p.m. attributable to C_3. Both spectra were closely analogous to those reported for 3,3-diphenyl-5-methylpyrazole.[45]

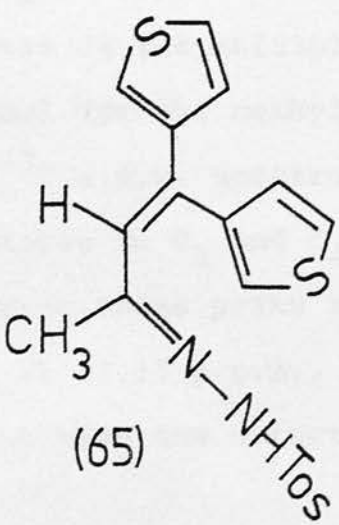
The other product (19%) was identified as 3-methyl-5-(2-thienyl)thieno[3,2-c][1,2]diazepine (67) by ^{1}H and ^{13}C n.m.r. spectroscopy. In the ^{1}H n.m.r. spectrum a complete analysis of the aromatic protons was consistent with the structure proposed. In addition the doublet at 5.4 δ ($J_{4,5}$= 5.5Hz) attributable to the hydrogen on C_4 collapsed to a singlet on irradiation at 2.4 δ, the centre of the multiplet attributable to the hydrogen at C_3. The signal for the methyl group appeared as a doublet (J = 5.5 Hz). The ^{13}C n.m.r. spectrum showed peaks at 68.5 and 120.0 p.p.m. attributable to C_3 and C_4 respectively. The splitting patterns obtained from these peaks and also from the peak due to the methyl group at 19.15 p.p.m., in the off-resonance spectrum were consistent with the structure proposed.

This reaction (Scheme 21) clearly indicates that 8 π-electron 1,7 ring closure does occur despite the absence of the fused five membered ring normally necessary. The exact extent to which it occurs, however, is obscured by the fact that the ratio of E:Z of the phenyl and thienyl groups on the methylene carbon is unknown. The isomer in which the phenyl group is adjacent to the diazo-group (62) (Scheme 21) would be expected to give the indazole (60) exclusively by analogy with the decomposition of 2-(di-p-tolylmethylene)cyclohexanone tosylhydrazone.[45] Since the amount of (63), the isomer in which the thienyl group is adjacent to the diazo-group, is unknown then it is impossible to tell whether (63) reacts to produce the diazepine (61) exclusively or produces indazole (60) as well.

In an attempt to clarify this situation and to also further substantiate the postulate that the fusion of a cyclopentyl ring was not necessary to induce electrocyclic aromatic substitution on to a thiophene ring the decompositions of 4,4-di-2-thienylbut-3-en-2-one tosylhydrazone (64) and 4,4-di-3-thienylbut-3-en-2-one tosylhydrazone (65) were carried out.



(64)



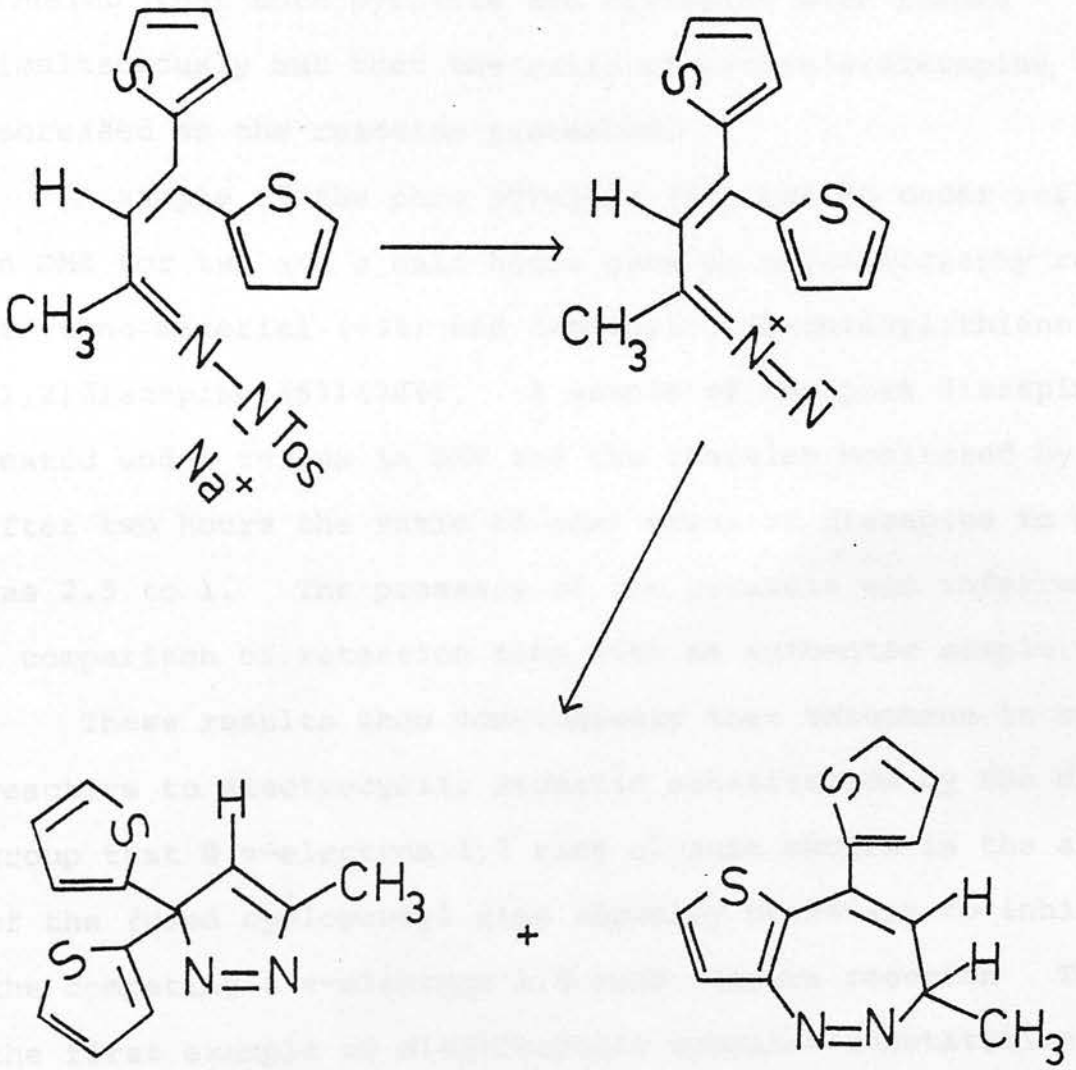
(65)

4,4-Di-2-thienylbut-3-en-2-one tosylhydrazone

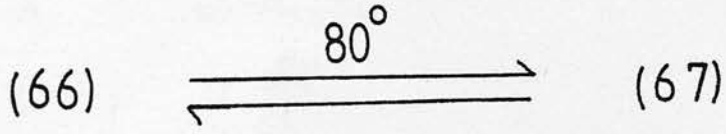
The sodium salt was prepared in the usual way but additional precautions were taken to ensure that all the ethanol had been removed since it has been shown that traces of protic solvent can cause rearrangement of the initial product in the analogous diphenylbut-3-en-2-one tosylhydrazone decomposition.[45] DME was added and the mixture heated under reflux for thirty minutes. After the normal work-up procedure two products were isolated by chromatography.

The major product (49%), a colourless crystalline solid, was identified as 3,3-di-2-thienyl-5-methylpyrazole (66) (Scheme 22). The ^{1}H n.m.r. spectrum showed the methyl group as a doublet (J = 1.6 Hz) and the ^{13}C n.m.r. showed an absorption at 99.0 p.p.m. attributable to C_3. Both spectra were closely analogous to those reported for 3,3-diphenyl-5-methylpyrazole.[45]

The other product (19%) was identified as 3-methyl-5-(2-thienyl)thieno[3,2-c][1,2]diazepine (67) by ^{1}H and ^{13}C n.m.r. spectroscopy. In the ^{1}H n.m.r. spectrum a complete analysis of the aromatic protons was consistent with the structure proposed. In addition the doublet at 5.4 δ ($J_{4,5}$= 5.5Hz) attributable to the hydrogen on C_4 collapsed to a singlet on irradiation at 2.4 δ, the centre of the multiplet attributable to the hydrogen at C_3. The signal for the methyl group appeared as a doublet (J = 5.5 Hz). The ^{13}C n.m.r. spectrum showed peaks at 68.5 and 120.0 p.p.m. attributable to C_3 and C_4 respectively. The splitting patterns obtained from these peaks and also from the peak due to the methyl group at 19.15 p.p.m., in the off-resonance spectrum were consistent with the structure proposed.



(66) + (67)

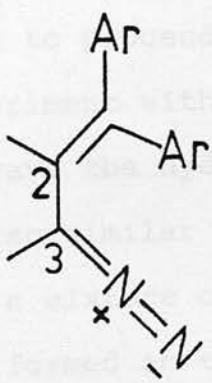


SCHEME 22

A repeat decomposition was monitored by H.P.L.C. and revealed that both pyrazole and diazepine were formed simultaneously but that the ratio of pyrazole:diazepine decreased as the reaction proceeded.

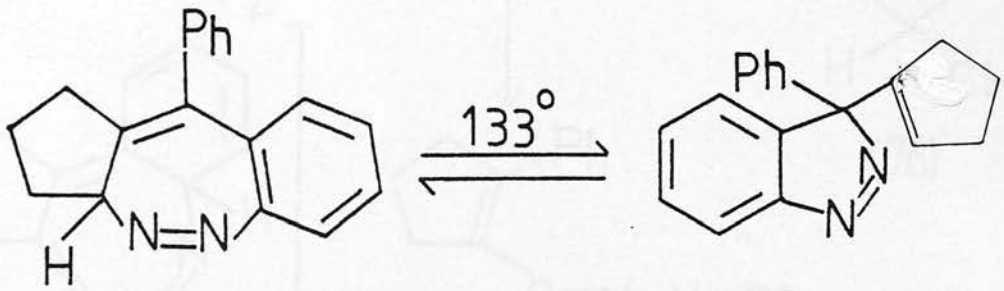
A sample of the pure pyrazole (66) heated under reflux in DME for two and a half hours gave on chromatography recovered starting material (43%) and 3-methyl-5-(2-thienyl)thieno[3,2-c][1,2]diazepine (67)(28%). A sample of the pure diazepine was heated under reflux in DME and the reaction monitored by H.P.L.C.. After two hours the ratio of peak areas of diazepine to pyrazole was 2.5 to 1. The presence of the pyrazole was inferred from a comparison of retention time with an authentic sample.

These results show conclusively that thiophene is sufficiently reactive to electrocyclic aromatic substitution by the diazo-group that 8 π-electron 1,7 ring closure occurs in the absence of the fused cyclopentyl ring normally necessary to inhibit the competing 6 π-electron 1,5 ring closure reaction This is the first example of electrocyclic aromatic substitution by the diazo-group in which there is no fusion of a carbocyclic ring at C-2,C-3 in (68).



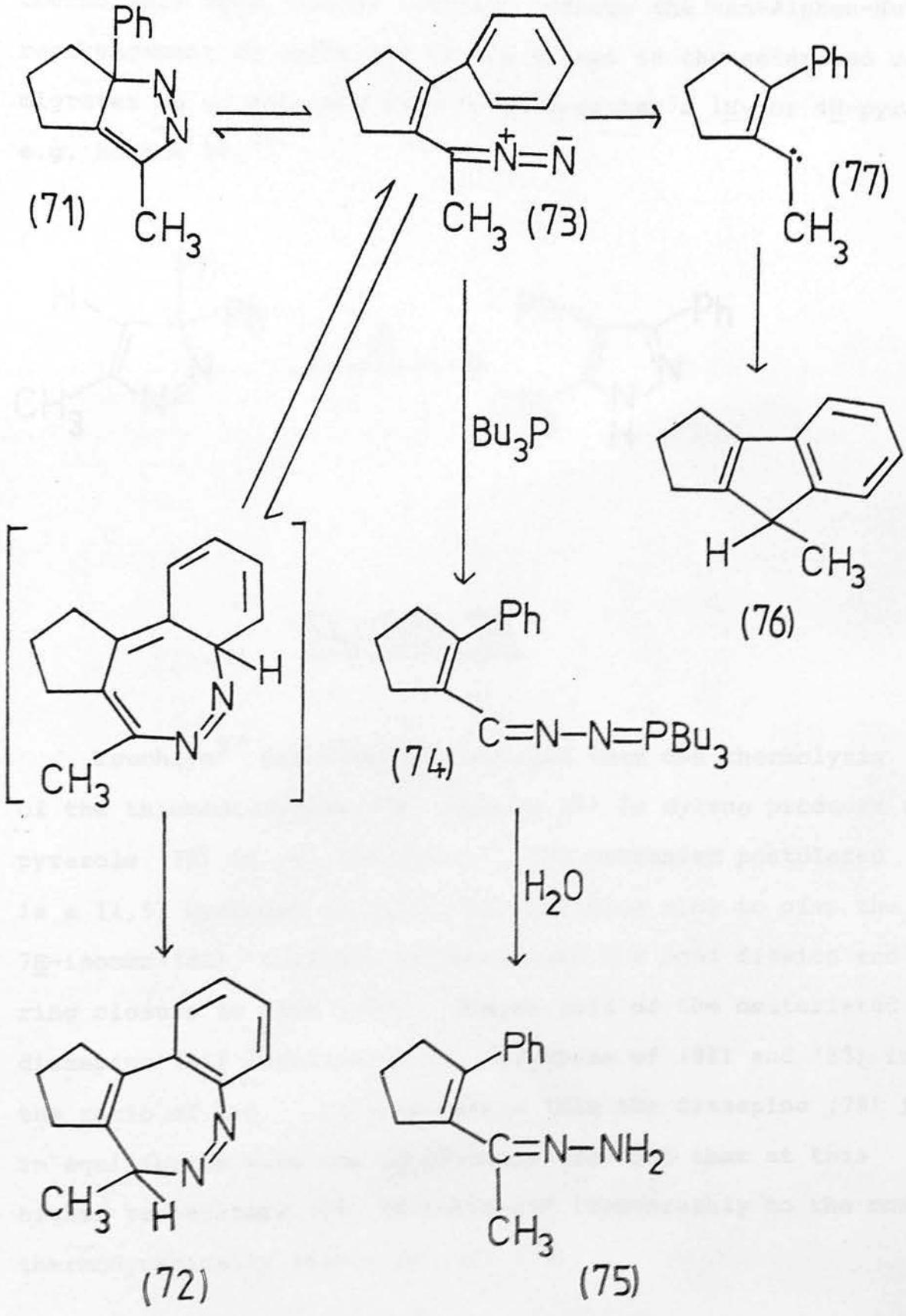
(68)

It is also interesting that the thermolysis of the pyrazole (66) and the diazepine (67) leads to an equilibrium mixture of the two compounds. Two other examples of a five to seven membered ring transformation involving the formal 1,3-migration of an azo group have been reported by Sharp and his co-workers[54,127]. In the first case the decomposition of the 3H-1,2-benzodiazepine (69) was accompanied by a fast equilibrium with the 3H-indazole (70) in which the ratio of (70) to (69) was ca. 2:1.[54]



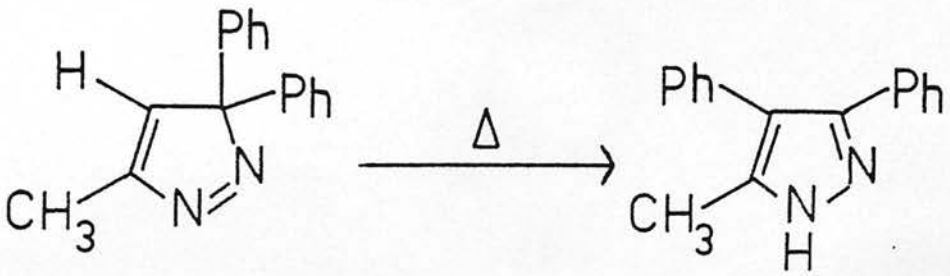
(69) (70)

The second case involved the irreversible conversion of the pyrazole (71) (Scheme 23) into the diazepine (72). This reaction was shown to proceed via the diazo-intermediate (73) by a trapping experiment with tributylphosphine in which the phosphazine (74) gave the hydrazone (75) on hydrolytic work up. This system was also similar to the reaction presently being discussed in that a mixture of the diazepine (72) and the pyrazole (71) was formed in the decomposition of the tosyl-hydrazone sodium salt. In addition the cyclopentaindene (76) derived from the carbene (77). (79) was also formed in the thermolysis of (71).


Ph
N
N
(71)
CH3
+N=N
CH3 (73)
Ph
(77)
CH3
Bu3P
H
CH3
(76)
H
N
N
CH3
Ph
C=N–N=PBu3
(74)
H2O
N
N
CH3
H
(72)
Ph
C=N–NH2
CH3
(75)

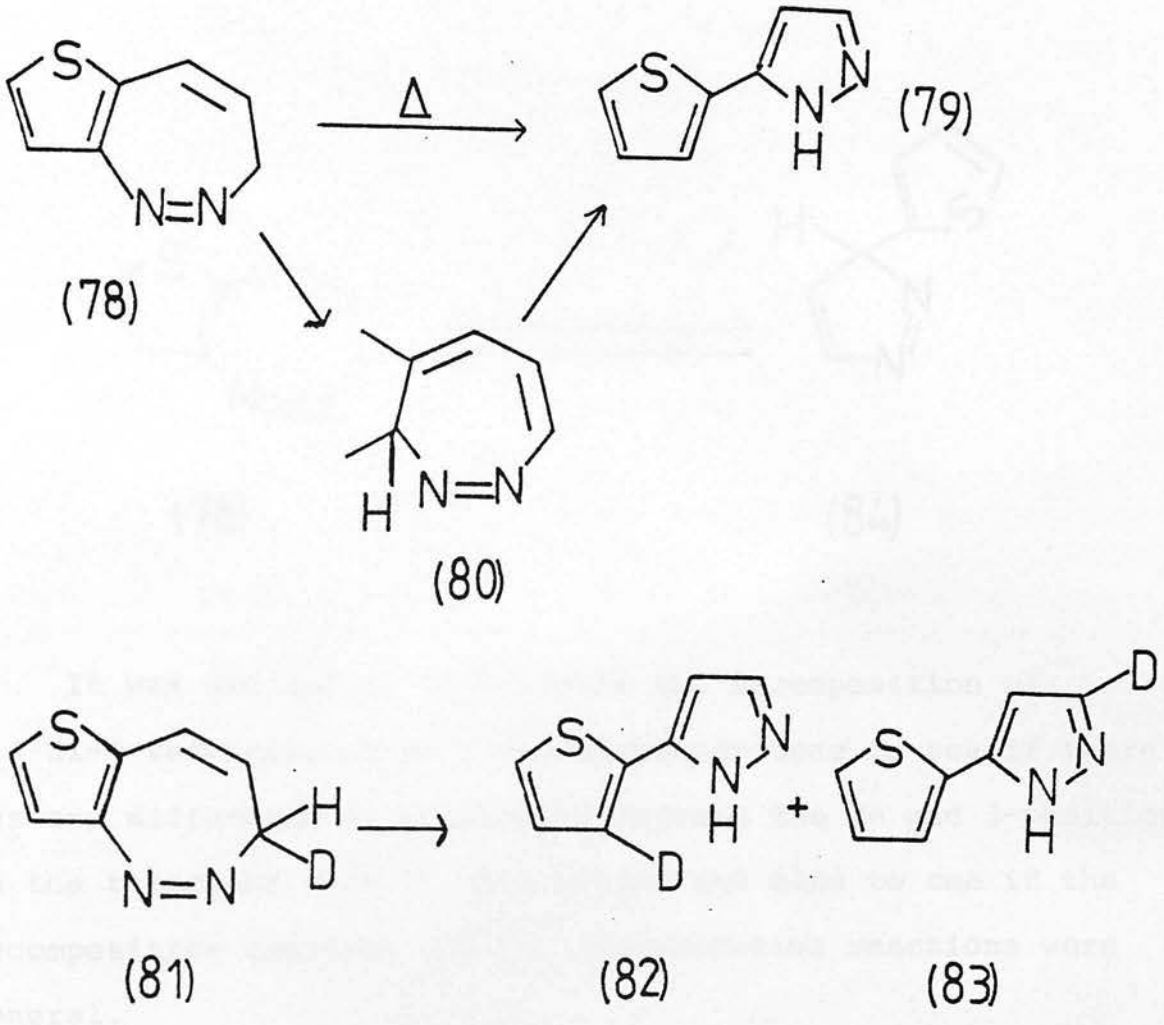
SCHEME 23

These reactions are of further interest because on thermolysis 3H-pyrazoles normally undergo the van-Alphen-Huttel rearrangement in which one of the groups on the saturated carbon migrates to an adjacent atom to give either a 1H- or 4H-pyrazole e.g. Scheme 24.[45]

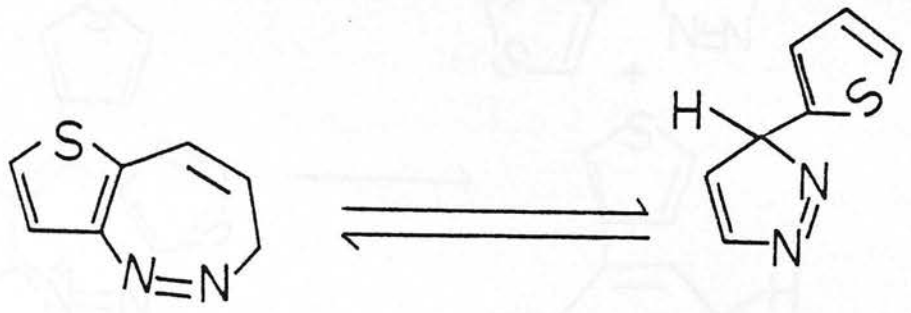


SCHEME 24

Tsuchiya[57] has recently reported that the thermolysis of the thienodiazepine (78) (Scheme 25) in xylene produces the pyrazole (79) in ca. 55% yield. The mechanism postulated is a [1,5] hydrogen shift in the diazepine ring to give the 7H-isomer (80), followed by successive C-N bond fission and ring closure to give (79). Thermolysis of the deuteriated diazepine (81) resulted in the formation of (82) and (83) in the ratio of 1:3. It is possible that the diazepine (78) is in equilibrium with the 3H-pyrazole (84) but that at this higher temperature (84) is converted irreversibly to the most thermodynamically stable product (79).



SCHEME 25



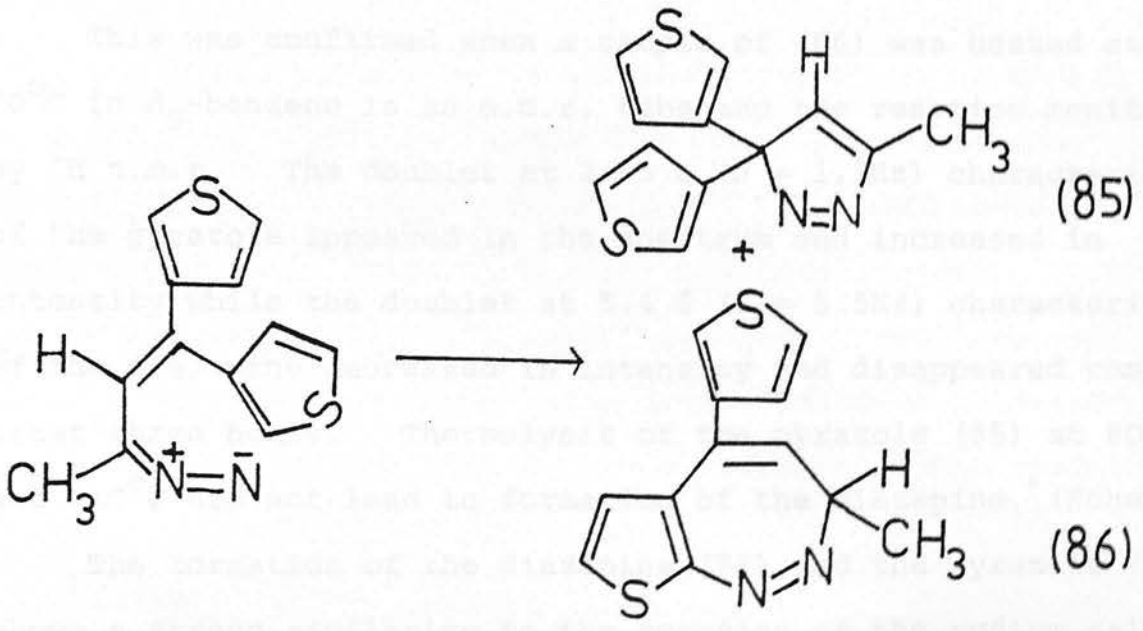
(78) (84)

It was decided to investigate the decomposition of 4,4-di-3-thienylbut-3-en-2-one tosylhydrazone to see if there was any difference in reactivity between the 2- and 3-positions on the thiophene ring in this system and also to see if the decomposition reaction and the isomerisation reactions were general.

4,4-Di-3-thienylbut-3-en-2-one tosylhydrazone

The ethanol-free anhydrous sodium salt was heated under reflux in DME for thirty minutes. After work-up two products were isolated by chromatography. The major product (43%) was identified as 3,3-di-3-thienyl-5-methylpyrazole (85)(Scheme 26) on inspection of the spectroscopic evidence.

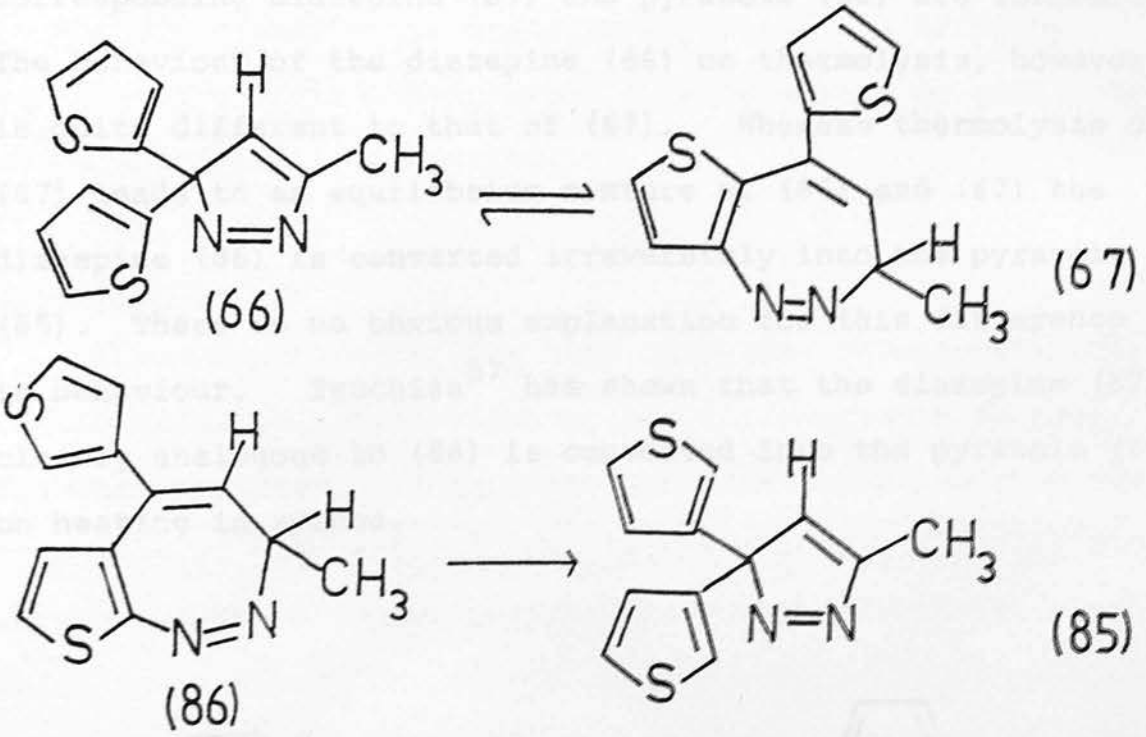
The minor product (8%) was identified as 3-methyl-5-(3-thienyl)thieno[2,3-c][1,2]diazepine (86) by comparison of its ^{13}C n.m.r. and ^{1}H n.m.r. spectra with those of thieno-diazepines previously prepared. This compound was difficult to obtain pure i.e. free from the pyrazole (85), and it was suspected that isomerisation was taking place.



(85)

(86)

SCHEME 26



(66)

(67)

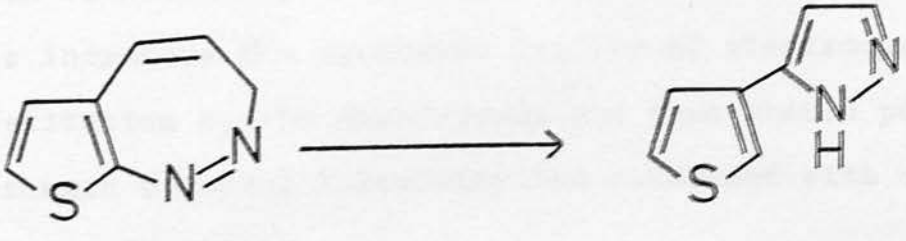
(86)

(85)

SCHEME 27

This was confirmed when a sample of (86) was heated at 80°C in d_6-benzene in an n.m.r. tube and the reaction monitored by ^1H n.m.r. The doublet at 2.45 δ (J = 1.5Hz) characteristic of the pyrazole appeared in the spectrum and increased in intensity while the doublet at 5.4 δ (J = 5.5Hz) characteristic of the diazepine decreased in intensity and disappeared completely after three hours. Thermolysis of the pyrazole (85) at 80°C and 110°C did not lead to formation of the diazepine. (Scheme 27).

The formation of the diazepine (86) and the pyrazole (85) shows a strong similarity to the reaction of the sodium salt of 4,4-di-2-thienylbut-3-en-2-one tosylhydrazone in which the corresponding diazepine (67) and pyrazole (66) are formed. The behaviour of the diazepine (86) on thermolysis, however, is quite different to that of (67). Whereas thermolysis of (67) leads to an equilibrium mixture of (66) and (67) the diazepine (86) is converted irreversibly into the pyrazole (85). There is no obvious explanation for this difference in behaviour. Tsuchiza[57] has shown that the diazepine (87) closely analogous to (86) is converted into the pyrazole (88) on heating in xylene.



(87) (88)

Mechanism

The formation of the thienodiazepines from the sodium salts of 4,4-di-2-thienyl- and 4,4-di-3-thienylbut-3-en-2-one probably occurs by attack of the diazo-intermediate on the thiophene ring followed by a [1,5] hydrogen migration which restores aromaticity. The short reaction times involved in these reactions make it unlikely that a build-up of diazo-compound would be observed by the appearance of the characteristic red colouration.

Further research is required to confirm the mechanism proposed since the formation of both pyrazoles and diazepine could be rationalised on the basis of a concerted mechanism in which the sulphinate anion is expelled. A trapping experiment with tributylphosphine is necessary to elucidate which mechanism is operating.

Conclusions

These experiments show that thiophene undergoes electrocyclic aromatic substitution by the diazo-group more readily than benzene does. This increased reactivity leads to the formation of thienodiazepines *via* 8 π electron 1,7 ring closure in systems which do not contain the fused cyclopentyl ring which is necessary to produce benzodiazepines in similar systems. This increases the synthetic utility of electrocyclic aromatic substitution by the diazo-group and thus should permit the synthesis of novel 1,2-diazepines condensed with various heterocyclic rings.

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