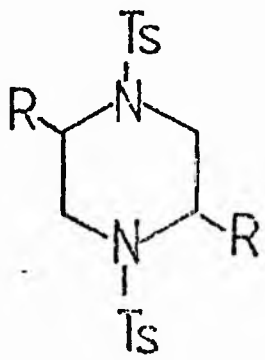
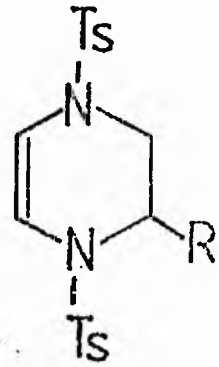
ANTHONY JOHN WILLIAMS

ABSTRACT

The present work explores the chemistry of the little known 1,2,3,4-tetrahydropyrazines and the possibility of their conversion into the 8π electron 1,4-dihydropyrazines by means of β-elimination reactions.

The cyclisation of p-toluenesulphonylaminoacetals, $p\text{-}CH_3C_6H_4SO_2NHCH_2CH(OR)_2$, under various conditions was found to give either the 2,5-disubstituted piperazines (1-3) or the 2-substituted-1,2,3,4-tetrahydropyrazines (5-7). These two systems could be interconverted by elimination - addition reactions of water and/or alcohols. The hydroxy and alkoxy groups in (1-3) and (5-7) were also





(1) R = OMe

(2) R = OEt

(3) R = OH

(4) R = Cl

(5) R = OMe

(6) R = OEt

(7) R = OH

(8) R = SPh

(9) R = Cl

(10) R = SePh

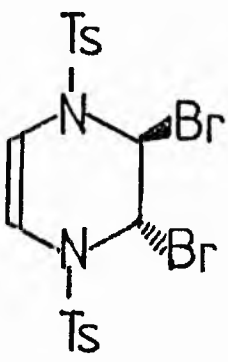
(11) R = H

interconvertible by reaction with the appropriate reagent; an analogous reaction with thiophenol led to the synthesis of the 2-phenylthio-1,2,3,4-tetrahydropyrazine (8) which was oxidised to the corresponding sulphoxide.

Attempts to form esters of the 2-hydroxy-1,2,3,4-tetrahydropyrazine (7) are described and the reasons for their failure discussed.

The 2,5-dichloropiperazine (4) was prepared from both (3) and (7) and was converted into the 2-chloro-1,2,3,4-tetrahydropyrazine (9) by thermal elimination of one mole of HCl. Both the chloro compounds (4) and (9) were very reactive towards nucleophiles, and a range of nucleophilic substitution reactions of the 2-chloro-1,2,3,4-tetrahydropyrazine (9) was carried out to give interesting new products including e.g. (10) and (11).

Access to the 2,3-disubstituted-1,2,3,4-tetrahydropyrazines such as (12) was provided by bromination of (7) or (9).



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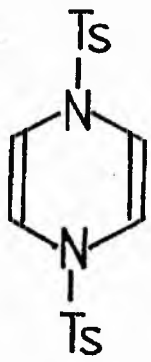

(13)

The reactions of the 2,3-dibromo-1,2,3,4-tetrahydropyrazine (12) are reported; these include formation of hydrolysis and alcoholysis products, a novel trans-cis isomerisation, and conversion into a new fused heterocycle.

A related heterocyclic system was obtained by [4+2] cycloaddition of the tetrahydropyrazine (11) with tetrachloro-o-benzoquinone.

Oxidation of the 2-hydroxy- 1,2,3,4-tetrahydropyrazine (7) was carried out under various conditions; Jones reagent unexpectedly led to hydroxylation of the double bond.

Attempts to synthesise the 1,4-dihydropyrazine (13) by a variety of methods, including elimination of water, hydrogen chloride, bromine and phenylseleninic acid from the appropriate substrates are described. Evidence for the transient formation of a 1,4-dihydropyrazine is presented and the reasons for the failure to isolate the desired product are discussed.

SYNTHESIS AND REACTIONS OF

REDUCED PYRAZINES

being a thesis submitted in support of candidature
for the degree of Doctor of Philosophy of the
Council for National Academic Awards.

by

ANTHONY JOHN WILLIAMS, B.Sc.

Trent Polytechnic, Nottingham

April, 1979.

To my Parents

and

Pep

ACKNOWLEDGEMENTS

I should like to express my sincere thanks to Dr. U. Eisner for her help and encouragement throughout this work. I am also grateful to all members of the synthetic group for assistance and useful discussions and to them and the many other colleagues at Trent Polytechnic who made my stay so enjoyable.

Finally I wish to thank Mrs. Anne Ager for typing this thesis and James Shipstone for sustenance.

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The present work explores the chemistry of the little known 1,2,3,4-tetrahydropyrazines and the possibility of their conversion into the 8π electron 1,4-dihydropyrazines by means of β-elimination reactions.

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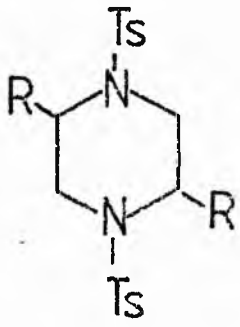

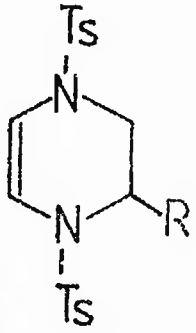

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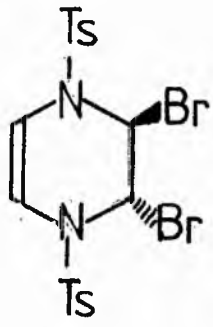

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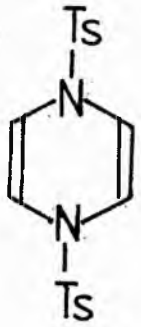

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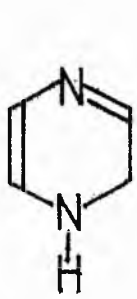
CONTENTS

INTRODUCTION

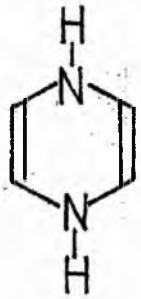
There are seven types of reduced pyrazine:

DIHYDROPYRAZINES



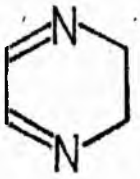
1,2-dihydropyrazine

(I)



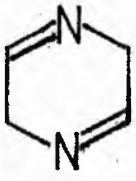
1,4-dihydropyrazine

(II)



2,3-dihydropyrazine

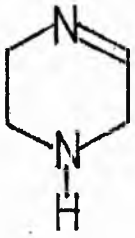
(III)



2,5-dihydropyrazine

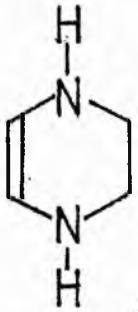
(IV)

TETRAHYDRO-PYRAZINES



3,4,5,6-tetrahydro-pyrazine

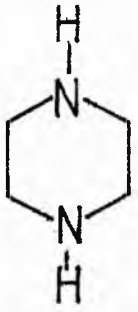
(V)



1,2,3,4-tetrahydro-pyrazine

(VI)

HEXAHYDRO-PYRAZINE



Piperazine

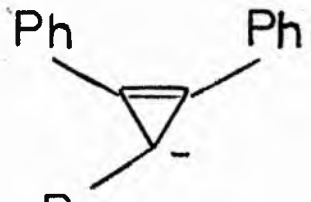
(VII)

With the exception of the piperazines little is known about the chemistry of these systems; much of what has been published deals with the 2,3- and 2,5-dihydropyrazines (III)[1-3] and (IV)[4-9], and the 3,4,5,6-tetrahydropyrazines (V)[10-13]. The present work seeks partially to remedy this situation by exploring the chemistry of the 1,2,3,4-tetrahydropyrazines (VI) and their possible conversion into the 1,4-dihydropyrazines (II).

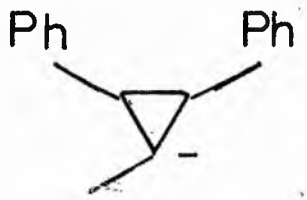
Two aspects of the ring system (II) are of particular interest:

it possesses 8π electrons, and it occurs in some important natural products.

According to Hückel only planar, conjugated, cyclic molecules containing $(4n+2)\pi$ electrons are aromatic; they are stabilised by the overlap of p-orbitals resulting in delocalisation. $4n\pi$ Electron systems such as (II) would therefore not be expected to have aromatic properties and might behave like their acyclic analogues. Breslow[14,15], however, has developed the concept of anti-aromatic compounds which are defined as those in which cyclic electron delocalisation raises the energy relative to the acyclic analogue and results in destabilisation. This has been demonstrated experimentally to apply to some molecules containing 4π electrons. Thus, for example, the cyclopropenyl anion (VIII) was shown to be destabilised relative to (IX) by a determination of the relative rates of proton exchange of the parent hydrocarbons, which were found to be in the ratio 1:6000.



(VIII)

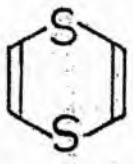


(IX)

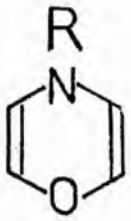
The earliest known 8π electron system is cyclooctatetraene which behaves as a typical olefin; X-ray analysis[16] has shown that to avoid strain the molecule adopts a non-planar conformation in which orbital overlap is greatly diminished and single and double bond distances are 1.46A and 1.33A , respectively. This is as expected for a non-aromatic conjugated polyene.

Sulphur and oxygen analogues of 1,4-dihydropyrazines are known, e.g., 1,4-dioxin[17], 1,4-dithiin[18] and N-substituted 1,4-oxazines[19] and -thiazines[20] .

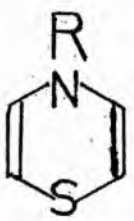
1,4-dioxin
(X)



1,4-dithiin
(XI)



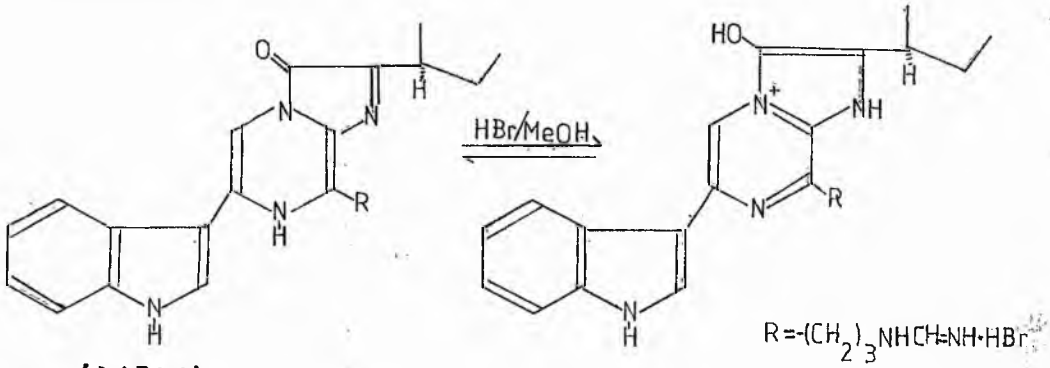
1,4-oxazine
(XII)



1,4-thiazine
(XIII)

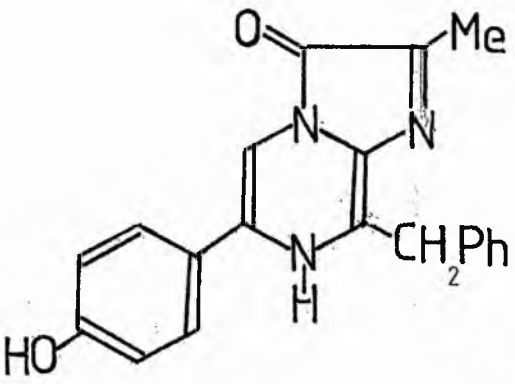
1,4-Dioxin contains symmetrically placed double bonds and its properties are those of an unsaturated ether. 1,4-Dithiin behaves as a non-aromatic compound; an X-ray analysis of the 2,5-diphenyl derivative showed it to have a boat conformation with bond lengths of 1.79A and 1.29A for the single and double bonds, respectively[21]. A more recent X-ray analysis of 1,4-dithiin-1-oxide[22,23] confirms that it, too, has a boat conformation. Thus although 8π electron systems are potentially anti-aromatic the evidence for the sulphur and oxygen analogues (X) and (XI) indicates that 1,4-dihydropyrazines are unlikely to exhibit such behaviour. This was recently confirmed by Schmidt[24] who reported an X-ray analysis of a substituted 1,4-dihydropyrazine which shows that it, also, has a boat conformation (for a discussion of Schmidt's work see page 15).

The 1,4-dihydropyrazine ring system occurs in nature in the Cypridina and Renella luciferins. Shimomura[25] and co-workers proposed structures (XIV) or (XV) for the chromophore of Cypridina luciferin, the two species being in equilibrium in solution with the position dependent on the acidity of the solution.

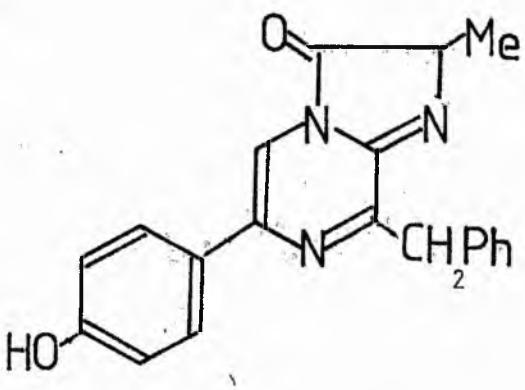


(XIV) (XV)

There is conflicting evidence concerning the structure of Renella luciferin which was regarded as (XVI) by Hori[26] but as (XVII) by McCapra[27].

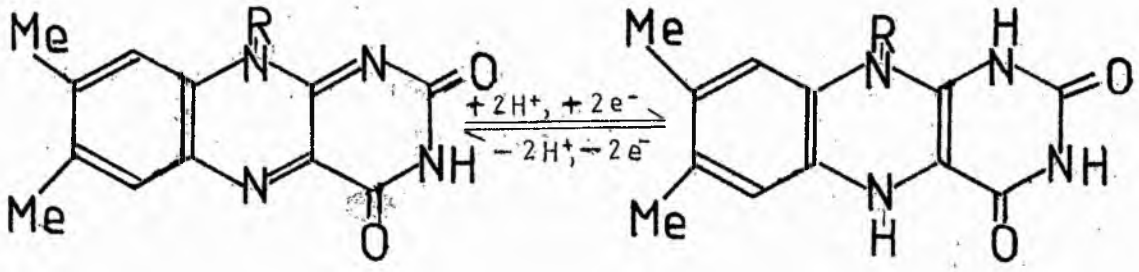


(XVI)



(XVII)

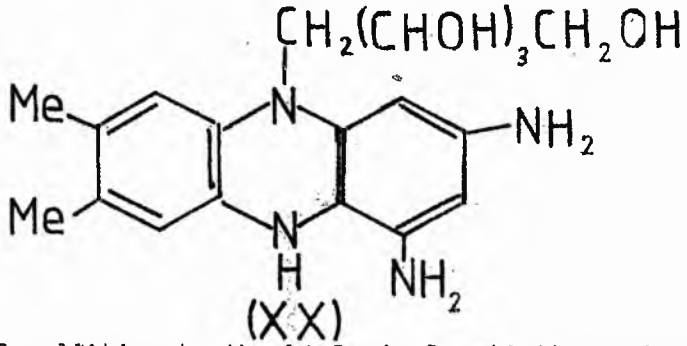
The 1,4-dihydropyrazine system also occurs in the riboflavin derivatives flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which play an important role as co-enzymes in many biological processes where they act as electron carriers in oxidation/reduction involving the pyrazine ring as shown.



(XVIII)

(XIX)

An example of this catalysis occurs in the oxidation of glucose-6-phosphate to 6-phosphogluconolactone, the co-enzyme here being FMN (XVlll; R=$-CH_2(CHOH)_3CH_2O\overset{O}{\overset{\|}{P}}(OH)_2$). While riboflavin and its derivatives are growth stimulators some analogues have been used as growth inhibitors, e.g. 2,4-diamino-7,8-dimethyl-10-ribityl-5,10-dihydrophenazine (XX)[28].

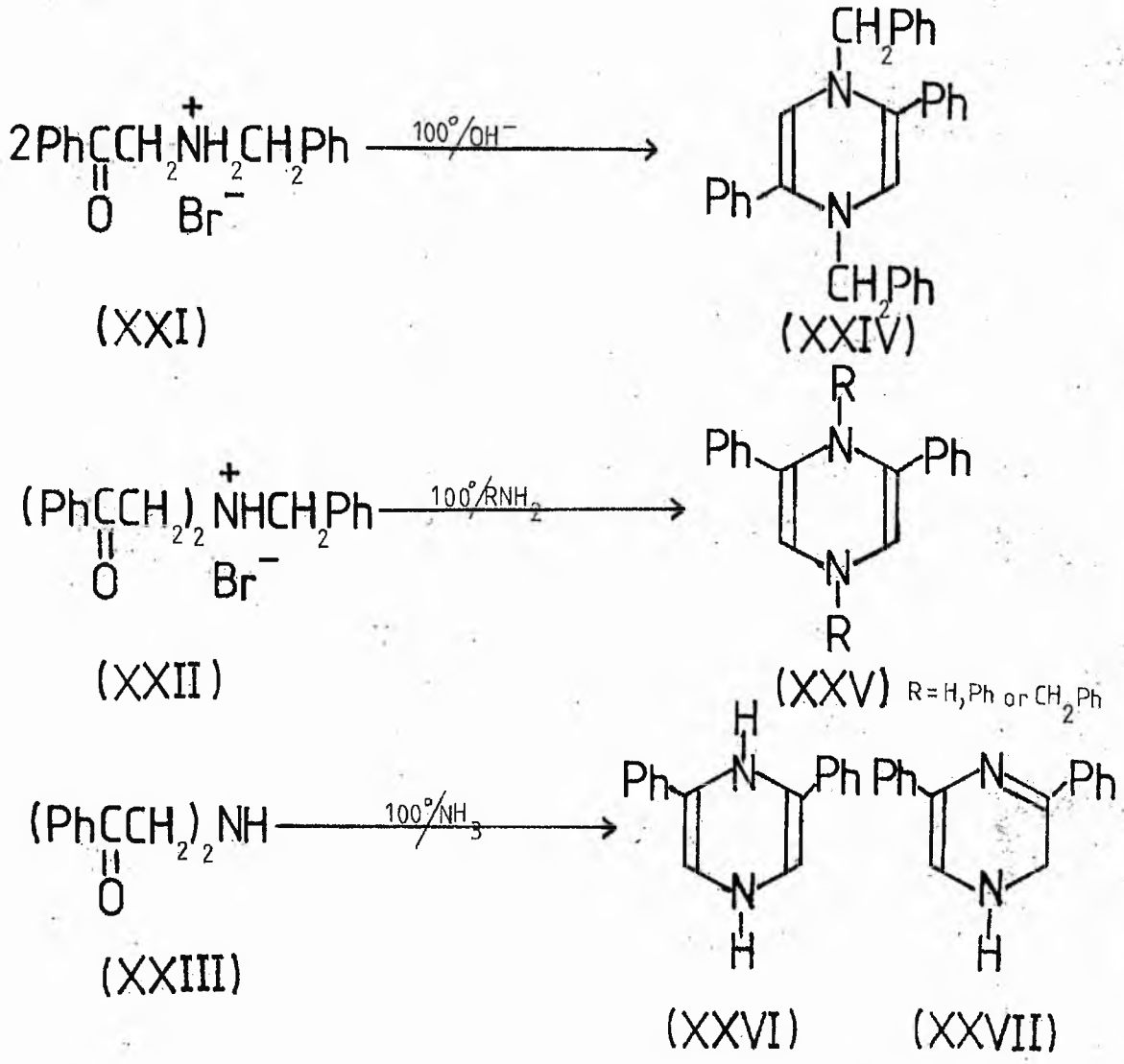


(XX)

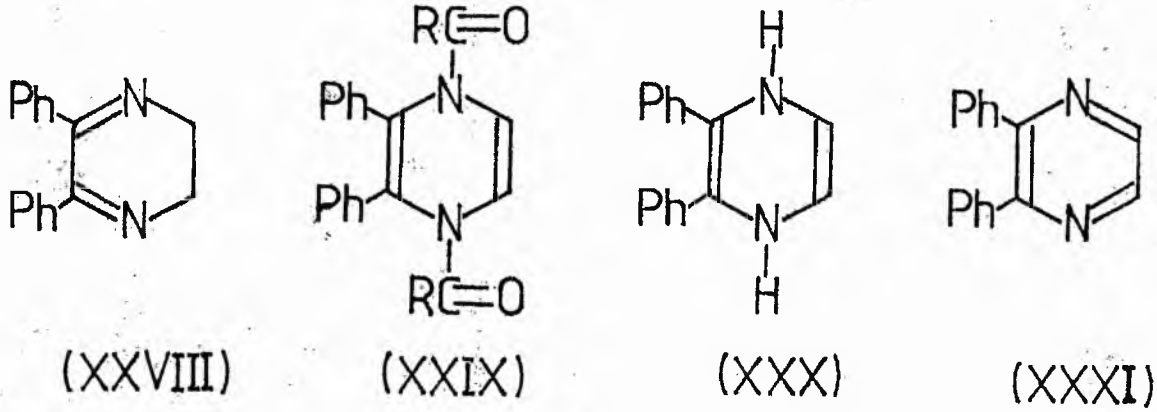
In addition to the biological activity mentioned above, it should be noted that pyrazines are known to possess anti-bacterial, anti-tuberculosis, anti-depressant, diuretic, pesticidal and herbicidal activity[29], while the piperazines also exhibit a wide range of useful pharmacological properties[30].

1,4-Dihydropyrazines were described as early as 1893 when Mason and Winder[31] reported that base-catalysed cyclodehydration of N-benzylphenacylamine hydrobromide (XXl) gave 1,4-dibenzyl-2,5-diphenyl-1,4-dihydropyrazine (XXlV), and that the reaction of N-benzyldiphenacylamine hydrobromide (XXll) with ammonia or primary amines yielded the 2,6-diphenyl-1,4-dihydropyrazines (XXV). Later Gabriel[32] reported an N-unsubstituted dihydropyrazine by treatment of diphenacylamine (XXlll) with ammonia and proposed two possible structures (XXVl) or (XXVll) for it.

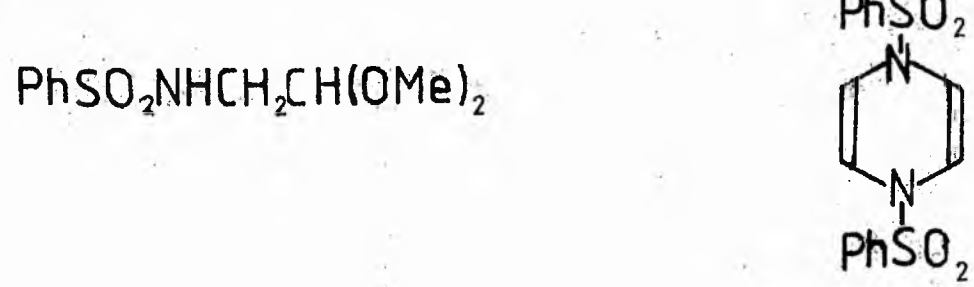
Mason and Dryfoos[33] reported that on heating 5,6-diphenyl-2,3-dihydropyrazine (XXVlll) with benzoic or acetic anhydride a 1,4-dihydropyrazine derivative (XXlX) was obtained. Heating (XXVlll)



at 200° was alleged to isomerise it to (XXX) which underwent oxidation to 2,3-diphenylpyrazine (XXXI), the isolated product.



Marckwald and Ellinger[34] found that acid treatment of benzenesulphonylaminoacetal (XXXII) apparently gave the 1,4-dihydropyrazine (XXXIII).

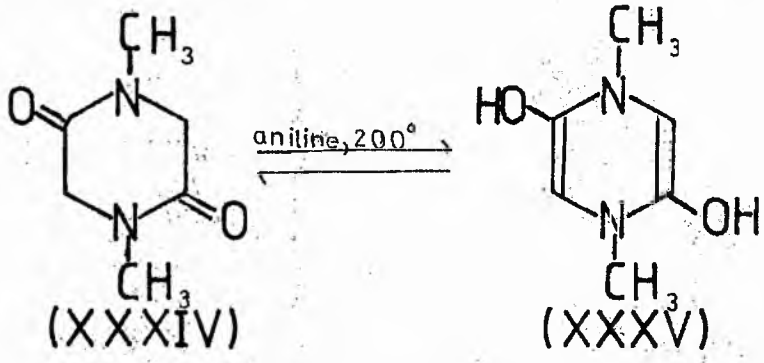


(XXXII)

(XXXIII)

All these early examples have been re-investigated in recent years and the structural assignments shown to be incorrect; for a full discussion of this work see page 10.

Abderhalden[35] and co-workers heated diketopiperazines with tyrosine in glycerol or with aniline at 200° and postulated, with little supporting evidence, that enolisation of (XXXIV) to (XXXV) was occurring as shown below.

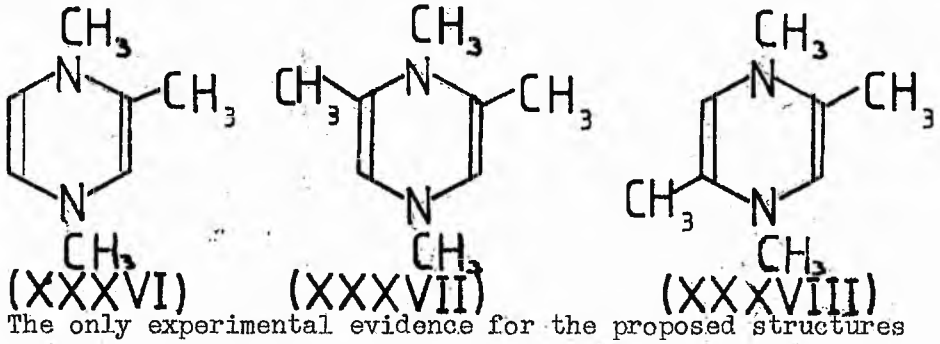


(XXXIV) (XXXV)

A structure of this type, however, seems extremely unlikely as there is no precedent for such an enolisation of amide carbonyl groups.

Jezo[36,37] and Grimett[38] isolated a number of supposed 1,4-dihydropyrazine derivatives (e.g. XXXVI-XXXVIII).

from the aminolysis of sugars; these compounds were unstable to light and air as might be expected of 1,4-dihydropyrazines.

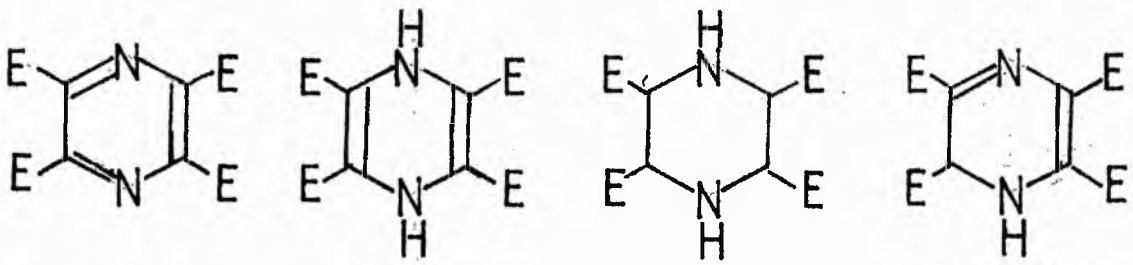


(XXXVI) (XXXVII) (XXXVIII)

The only experimental evidence for the proposed structures is that on catalytic hydrogenation 2 moles of hydrogen were taken up to give piperazines; these were identified by a comparison of their infra-red spectra and the physical properties of their picrates with those of authentic samples. However, this evidence is inconclusive since it does not eliminate e.g. a 1,2-dihydropyrazine structure.

Both in this work and in that of Abdehalden temperatures of about 200° are involved; in view of recent work demonstrating the thermal instability of 1,4-dihydropyrazines (see below) the assigned structures appear unlikely.

Mager and Berends[39,40] reported that catalytic hydrogenation or treatment with alkaline sodium dithionite of the 2,3,5,6-tetraethoxycarbonylpyrazine (XXXIX) gave the 1,4-dihydropyrazine (XL) rather than the expected piperazine (XLI).

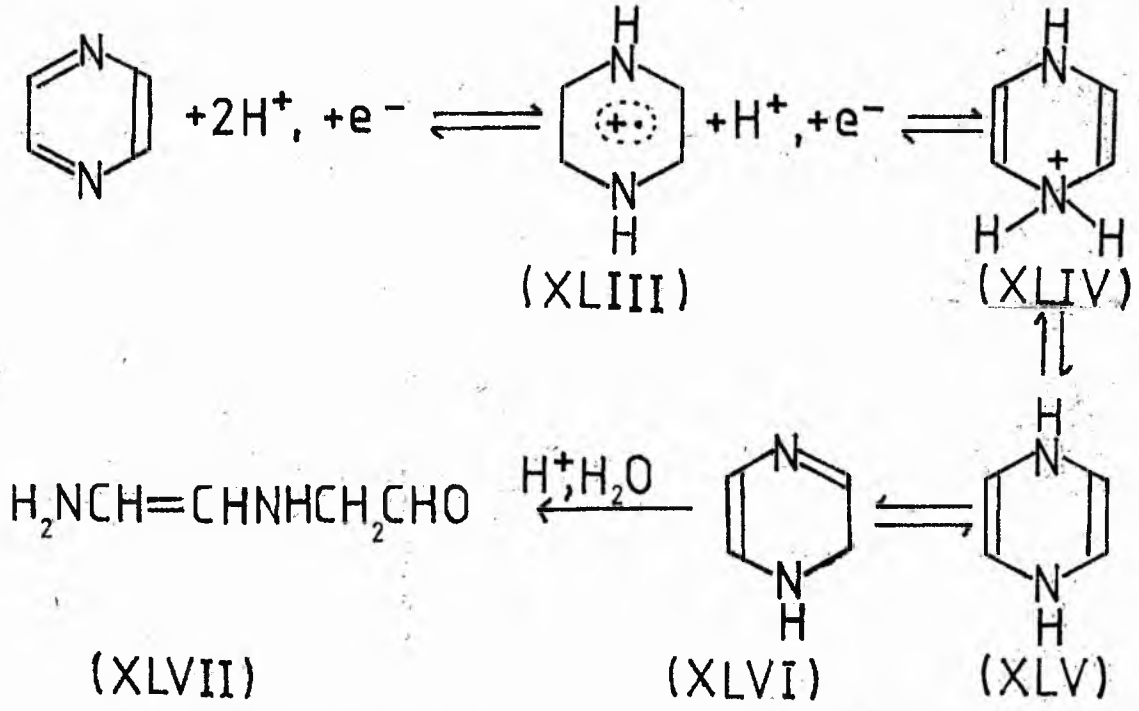


(XXXIX) (XL) (XLI) (XLII)

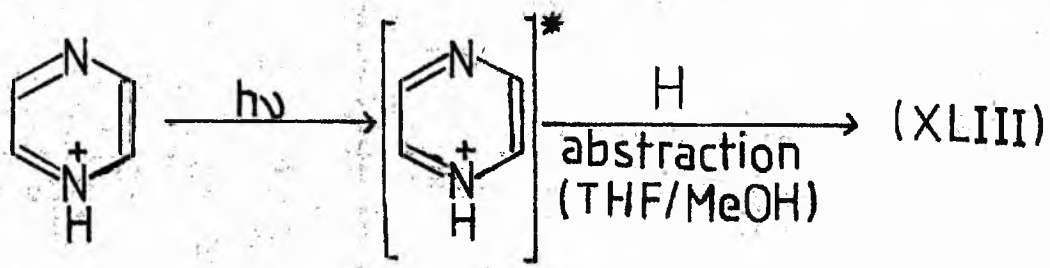
E = COOEt

This work was reinvestigated by J.R. Williams[41] who found that the above assignments were erroneous, the sole product formed in these reactions being the 1,2-dihydropyrazine (XLII), the structure of which was elucidated by means of NMR spectroscopy.

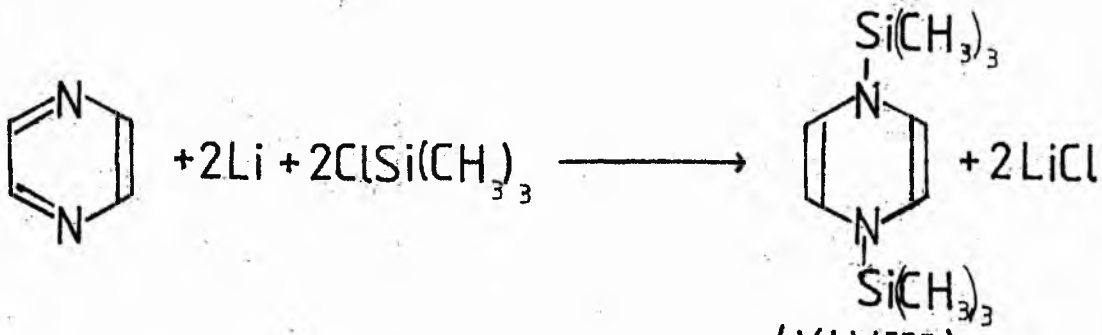
Another approach to dihydropyrazines has been the electrochemical reduction of pyrazines. Thus Katt and Rouseff[42] found that on reduction of pyrazine the isolated product was (XLVII) which they suggested was formed by the pathway shown below.



Polarographic evidence was cited to support this hypothesis. Knowing 1,2-dihydropyrazines to be unstable under acid conditions Armand[43] performed electrochemical reductions on a variety of substituted pyrazines under alkaline conditions and obtained a number of 1,2-dihydropyrazines which he postulated were produced by a rapid hydrogen shift from the initially formed 1,4-isomer. The cation radical (XLIII) has also been prepared photochemically as shown below and its e.s.r. spectrum recorded.



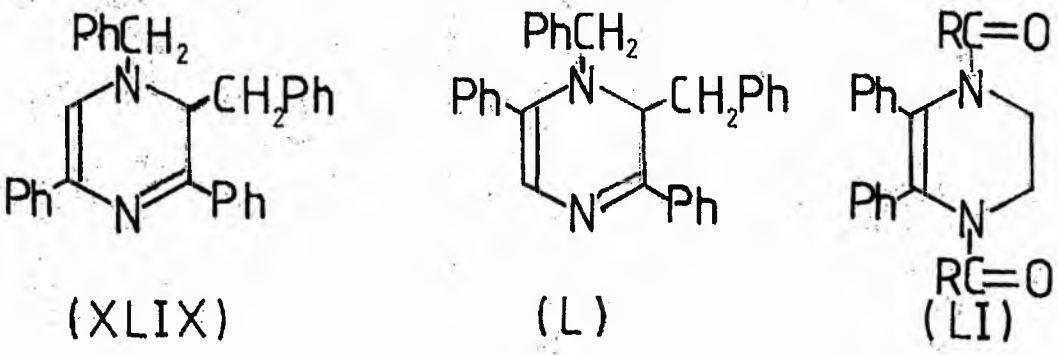
In recent years interest in 1,4-dihydropyrazines has revived and structural assignments have been made more secure by the use of modern physical techniques. Sulzbach[45] obtained compound (XLVIII) by the reaction shown.



(XLVIII)

Further examples of 1,4-dihydropyrazines have been reported as a result of reinvestigations of earlier work. Chen and Fowler[46] found that the product of condensation of benzylamine and N-benzyl-diphenacylamine hydrobromide (XXII) was not the reported[31] 1,4-dihydropyrazine (XXV) but the 1,2-dihydropyrazine (XLIX).

Similarly, self-condensation of (XXI) gave the 1,2-dihydropyrazine (L) and not (XXIV) as claimed by the original workers[31].

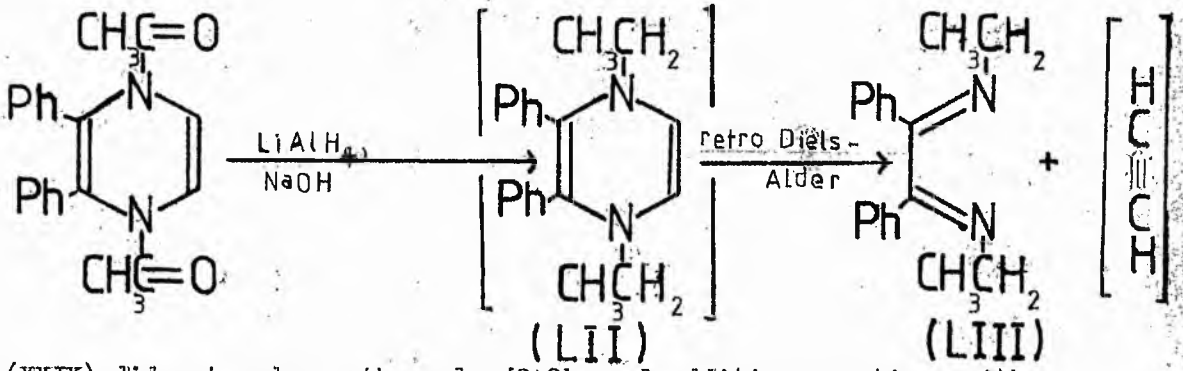


(XLIX) (L) (LI)

On re-examining the work of Mason and Dryfoos[33], Chen and Fowler[47] discovered that heating 2,3-diphenyl-5,6-dihydropyrazine with acetic anhydride did not yield the reported 1,4-dihydropyrazine (XXIX), but

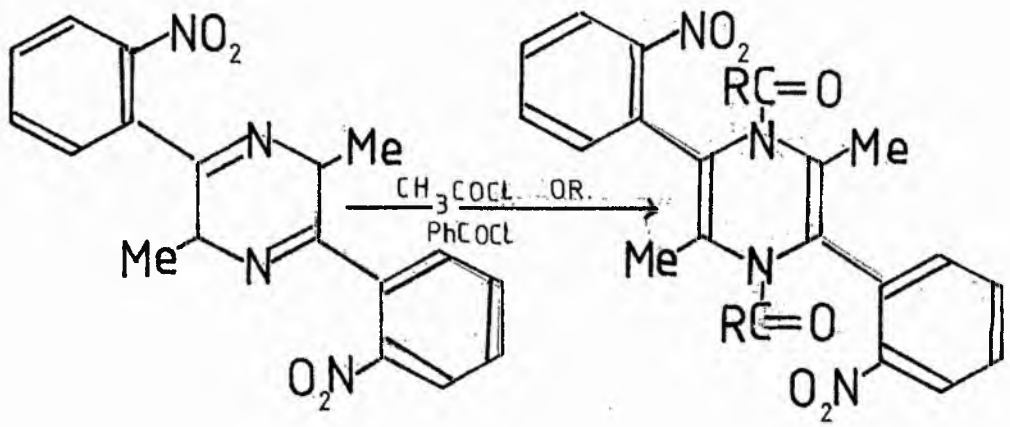
instead a mixture of 2,3-diphenylpyrazine (XXXI) and the 1,2,3,4-tetrahydropyrazine (LI). However, the synthesis of (XXIX; R=Me) was achieved[47] by the reaction of 5,6-diphenyl-2,3-dihydropyrazine (XXVIII) with acetyl chloride in benzene containing two equivalents of pyridine; (XXXI) and (LI) were also produced.

The structure of (XXIX) was confirmed by catalytic hydrogenation, one mole of hydrogen being taken up to form (LI). Attempted reduction of (XXIX, R = Me) to the N,N-diethyl derivative (LII) with lithium aluminium hydride was unsuccessful, N,N-diethylbenzilimine (LIII) being the major product. This was unexpected as the tetrahydropyrazine (LI) was readily reduced to its diethyl analogue under the same conditions; it was suggested by the authors that due to the instability caused by the presence of a fully conjugated 8π electron system, the expected 1,4-dihydropyrazine underwent a retro Diels-Alder reaction as shown below. It was also discovered that



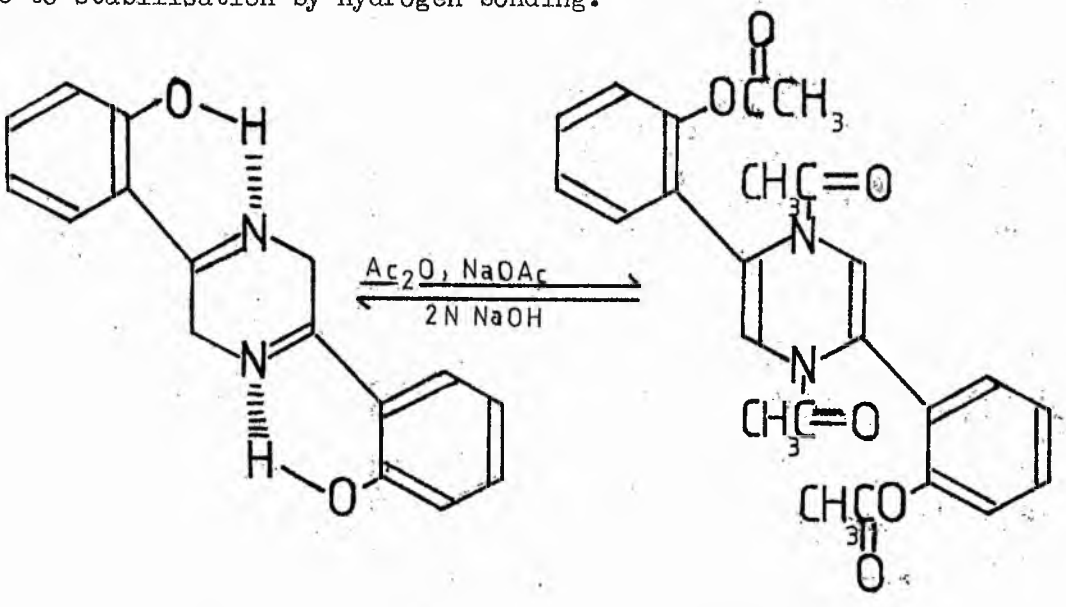
(XXIX) did not undergo thermal [2+2] cycloaddition reactions with either dimethyl acetylenedicarboxylate or tetracyanoethylene; an attempted photochemical cycloaddition with the former reagent was also unsuccessful.

The fact that the electron withdrawing acetyl group appears to stabilise the 2,3-diphenyl-1,4-dihydropyrazine system adds credibility to two early reports of 2,5-diaryl-1,4-diacyl-1,4-dihydropyrazines. Neber[48] found that on treatment of 2,5-dimethyl-3,6-bis(2'-nitrophenyl)-2,5-dihydropyrazine (LIV) with acetyl or benzoyl chloride the 3,6-diaryl-1,4-dihydropyrazines (LV) were obtained.



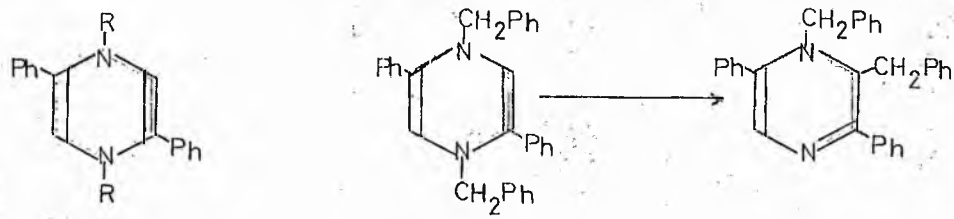
(LIV) (LV)

Kappe[49] reported that treatment of 3,6-bis(2'-hydroxyphenyl)-2,5-dihydropyrazine (LVI) with sodium acetate in acetic anhydride gave the 1,4-dihydropyrazine (LVII). Hydrolysis with sodium hydroxide gave back the starting 2,5-dihydropyrazine; it was proposed that in this case the 2,5-isomer was the preferred form due to stabilisation by hydrogen bonding.



(LVI) (LVII)

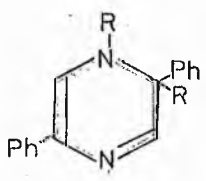
The work of Mason and Winder[31] was further elucidated in a series of papers by Lown and Akhtar[50-53], who showed[50] that self-condensation of N-alkylphenacylamines and subsequent rearrangement of the extremely labile intermediate 1,4-dialkyl-2,5-diphenyl-1,4-dihydropyrazines (XXIVa) gave the 1,2-dihydropyrazines (LVIII). This appeared to contradict the reported[47] rearrangement of 1,4-dibenzyl-2,5-diphenyl-1,4-dihydropyrazine (XXIV) to (L) which



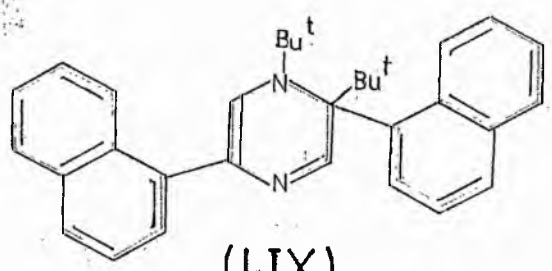
(XXIVa) R = alkyl (XXIV) (L)

involves the migration of the benzyl group to an unsubstituted carbon atom.

Reinvestigation[51] of this case showed that (L) (which had only been isolated[47] in 20% yield) was a minor product of the reaction, the major product being the isomer (LVIII, R=CH_2Ph) in which the benzyl group had migrated to the phenyl substituted carbon atom. For all other alkyl groups studied, migration occurred solely to this substituted position. Further evidence for the regiospecificity of this rearrangement was provided by reaction of 1-bromoacetylnaphthalene with t-butylamine and thermolysis of the resulting α-aminoketone in toluene at 110° to give the 1,2-dihydropyrazine (LIX). Despite substantially increased steric crowding at the 1- and 2- positions of the product, migration of the alkyl group was found to proceed solely to the substituted position.

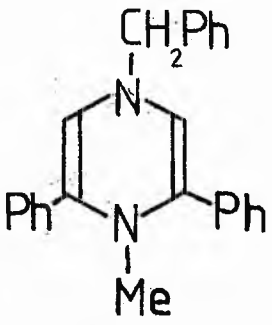


(LVIII)

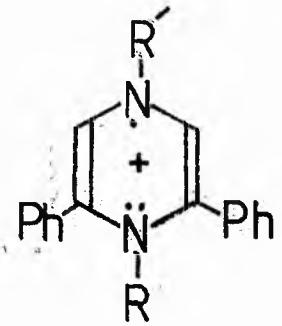


(LIX)

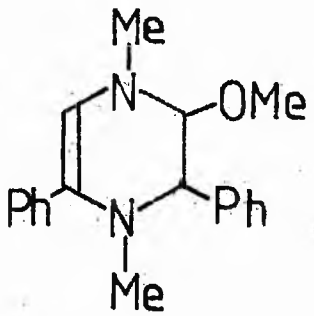
On reaction of primary aliphatic amines with N-benzyldiphenacylamine (XXII) a series of 1,4-dialkyl-1,4-dihydropyrazines, e.g. (LX), was obtained in excellent yield. These compounds were orange-red solids which were sensitive to light and atmospheric oxygen; in solution they were rapidly oxidised by air to give stable 7π electron paramagnetic species (LXI) identified by their e.s.r. spectra. Because of this oxidation the n.m.r. spectra of these 1,4-dialkyl-1,4-dihydropyrazines exhibited considerable paramagnetic line broadening and were difficult to reproduce. However, the structural assignments were supported by elemental analysis, catalytic hydrogenation to the expected 1,2,3,4-tetrahydropyrazines, and by formation of a methanol adduct (LXII); the latter compound had normal n.m.r. spectrum.[51,52]



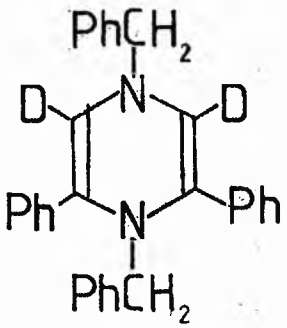
(LX)



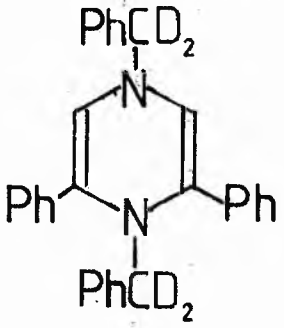
(LXI)



(LXII)



(LXIII)

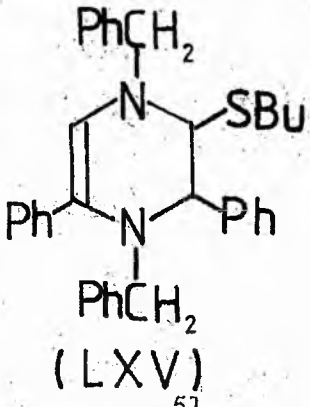


(LXIV)

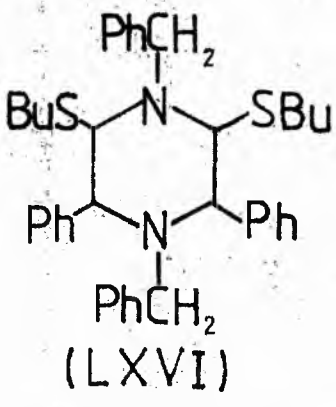
It was also discovered that a highly reactive 1,4-dibenzyl-1,4-dihydropyrazine (XXV, R=CH_2Ph) which had been postulated[46] as an

intermediate in the formation of the 1,2-dihydropyrazine (XLIX) from benzylamine and N-benzylphenacylamine hydrobromide (XXI) could be isolated by lowering the reaction temperature; this compound (XXV) rearranged rapidly in degassed benzene at 55° to give (XLIX) by means of a 1,3-benzyl shift. This migration was established as a largely intramolecular free radical process by a series of crossover recombination experiments using the deuterated derivatives (LXIII) and (LXIV).[15]

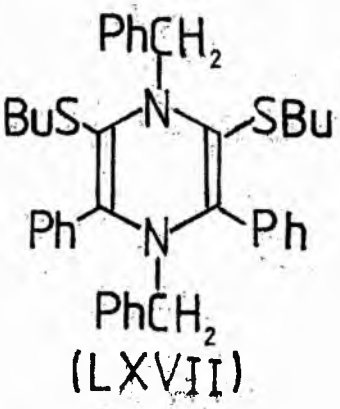
In the course of this work it was discovered that butanethiol slowly added to the dihydropyrazine (XXV, R=CH_2Ph) to give (LXVII) rather than (LXV) or (LXVI) as might have been expected.



(LXV)



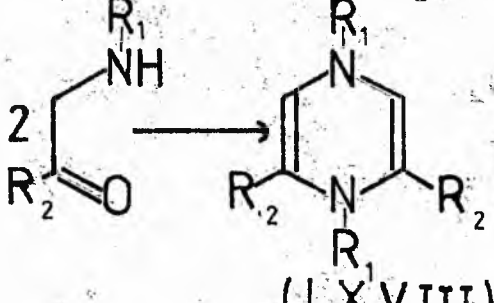
(LXVI)



(LXVII)

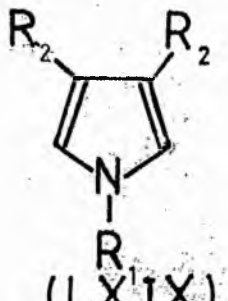
Lown[51] postulates that the 1,4-dialkyl-2,6-diphenyl-1,4-dihydropyrazines such as (LX) owe their relative stability to their substitution pattern which imposes restrictions on full conjugation, possibly owing to steric interactions at 1-, 2-, and 6- positions.

Schmidt[24] extended Lown's work to the synthesis of the 1,2,4,6-tetraaryl-1,4-dihydropyrazines (LXVIII). One electron oxidation of these compounds gave radical cations with characteristic e.s.r. spectra, while on heating at 300° the pyrroles (LXIX) were formed.



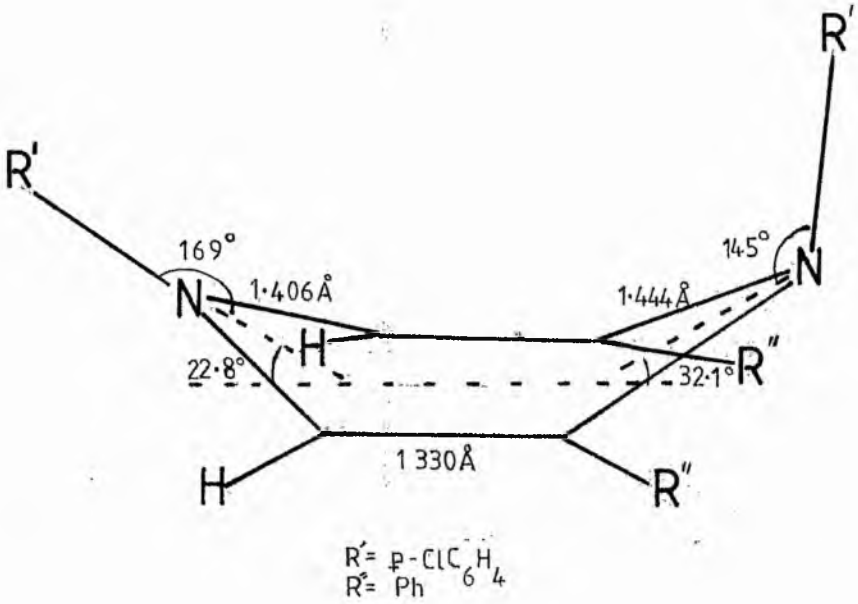
(LXVIII)

R_1	R_2
a) p-ClC_6H_4	C_6H_5
b) "	p-$CH_3C_6H_4$
c) "	p-ClC_6H_4
d) p-$CH_3C_6H_4$	"



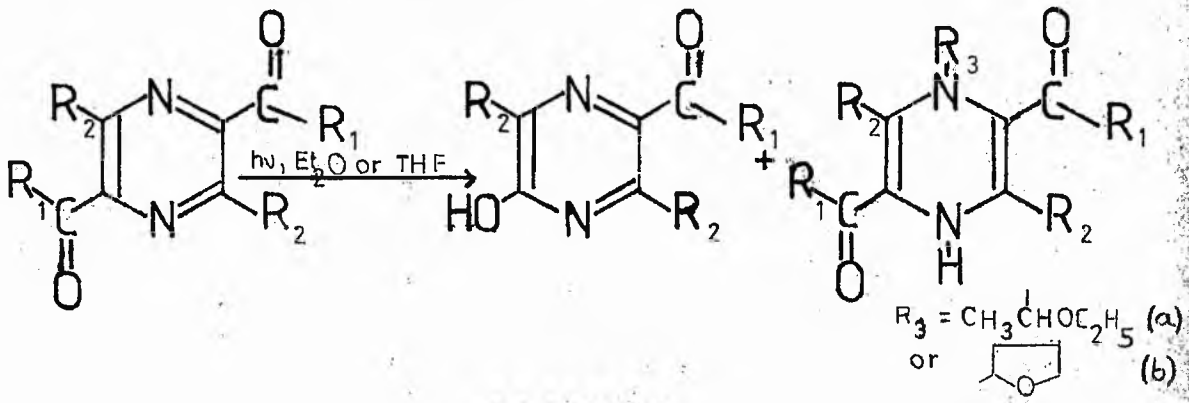
(LXIX)

An X-ray analysis of 1,4-bis-p-chlorophenyl-2,6-diphenyl-1,4-dihydropyrazine (LXVIIIa) showed it to possess a boat conformation thus accounting for the lack of anti-aromatic properties in 1,4-dihydropyrazines (see above).



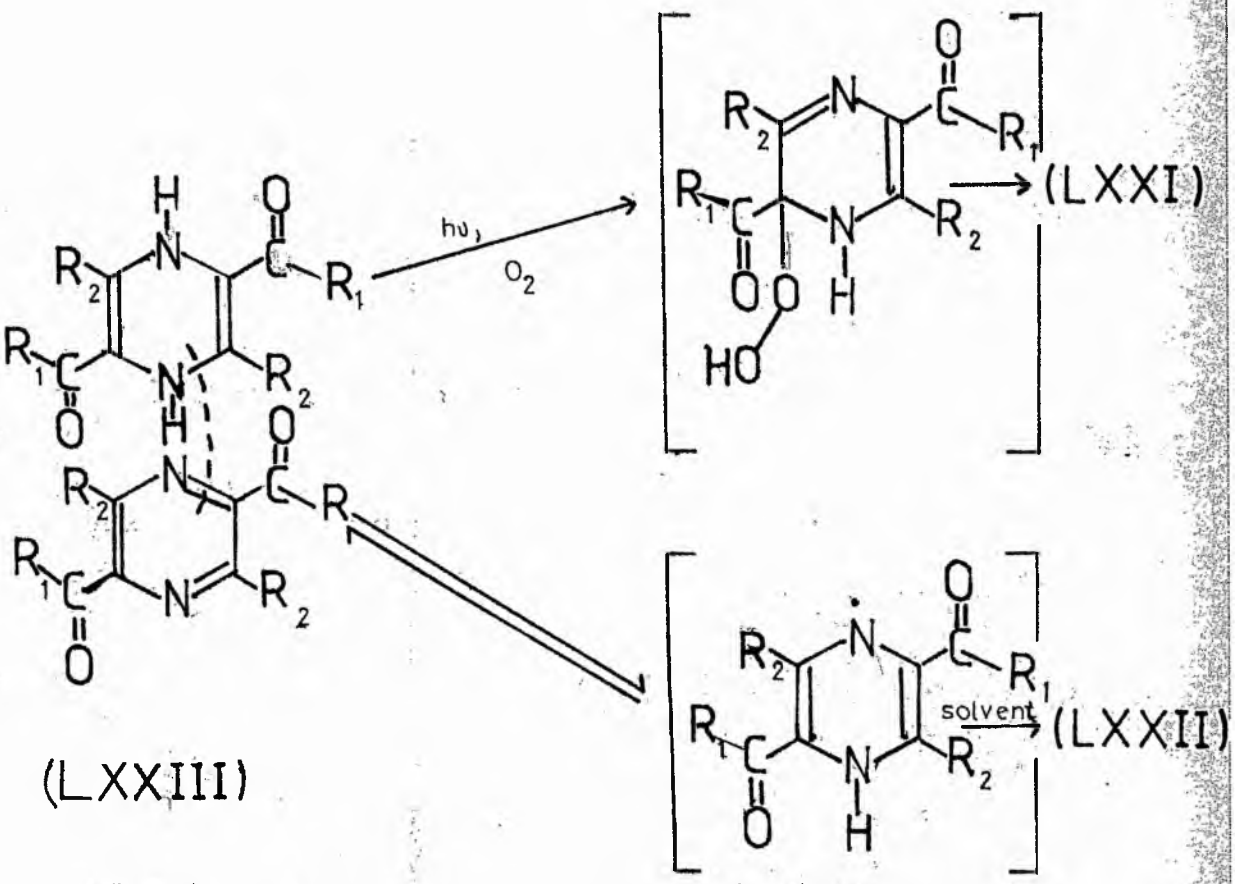
(LXVIIIa)

Yamada and co-workers[55] irradiated the pyrazines (LXX) at 330 nm in diethyl ether and obtained two photoproducts, an alkyl 3,6-dialkyl-5-hydroxypyrazine-2-carboxylate (LXXI) and a solvent adduct (LXXIIa). When the reaction was carried out in tetrahydrofuran the products were (LXXI) and the adduct (LXXIIb). The structures



(LXX) (LXXI) (LXXII)

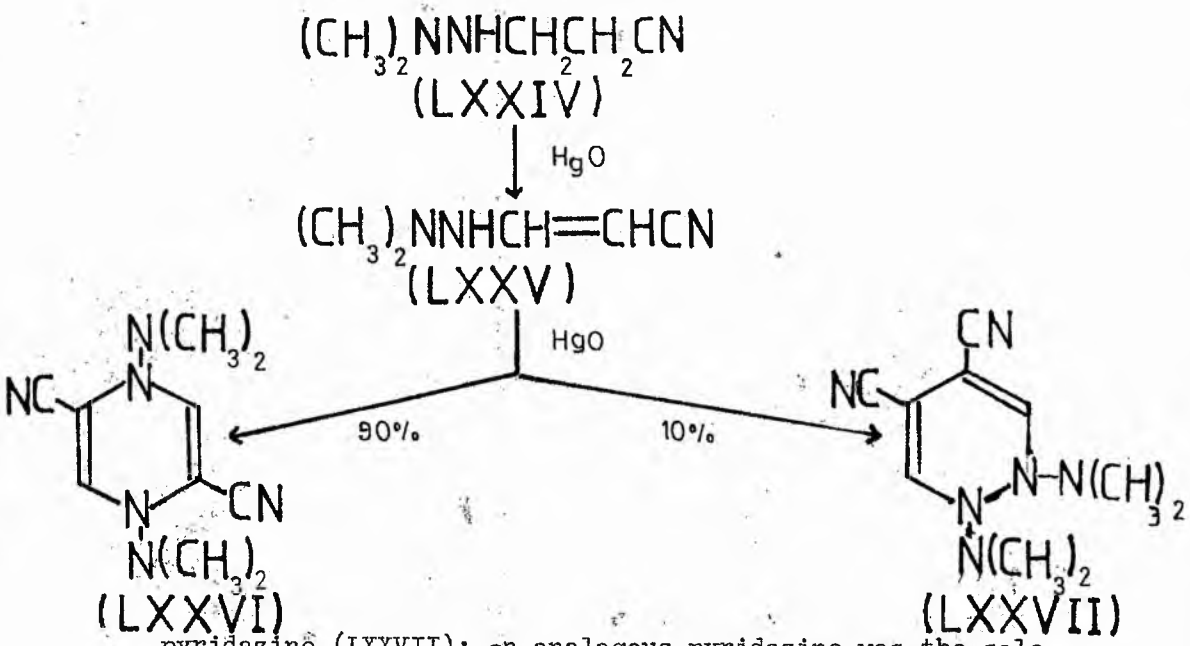
of the adducts (LXXII) were deduced from their infra-red and n.m.r. spectra. The formation of these products was explained by the two alternative modes of reaction of an intermediate charge-transfer complex (LXXIII). Evidence for the existence of this compound was provided by U.V. spectroscopy; in the case where $R_1 = R_2 = CH_2Bu^t$ (LXXI) and (LXXII) were not formed, the complex (LXXIII) actually being isolated as it was precipitated from solution. Mass spectral and n.m.r. data support the identity of (LXXIII).



(LXXIII)

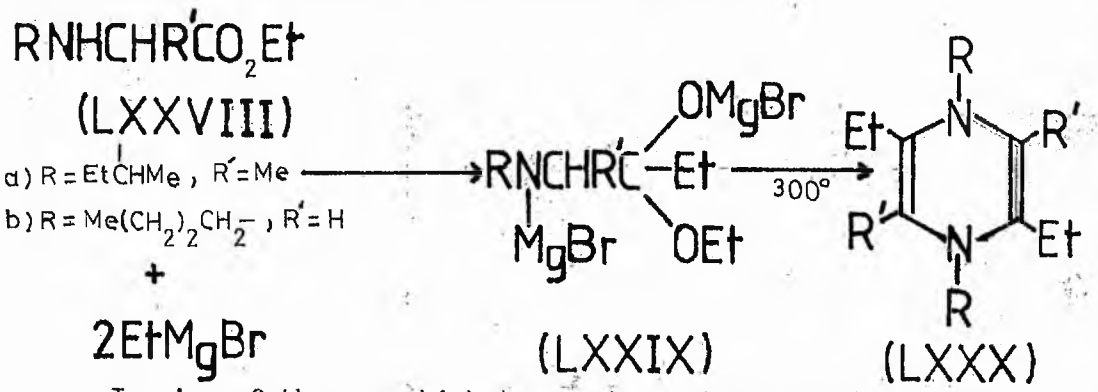
Recently the oxidation of the hydrazine (LXXIV) with yellow mercuric oxide has been shown[56] to form a mixture of two products in the ratio 9:1 and the 1,4-dihydropyrazine structure (LXXVI) was assigned to the major of these on the basis of dipole moment measurements and ^1H and ^{13}C n.m.r. spectra. Similar results were

obtained on oxidation of the hydrazone (LXXV) with one equivalent of mercuric oxide. The minor product of the reaction was the



pyridazine (LXXVII); an analagous pyridazine was the sole product when a methoxycarbonyl group was substituted for cyanide in the starting hydrazine.

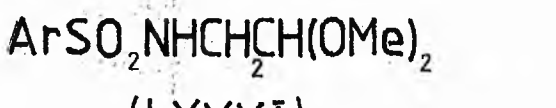
Gololobov[57] claimed that on treating the aminoesters (LXXVIII) with ethylmagnesium bromide followed by cyclisation at 250-300°/1mmHg he obtained the 1,4-dihydropyrazine derivatives (LXXX).



In view of the very high temperatures involved this seems an unlikely route to 1,4-dihydopyrazines.

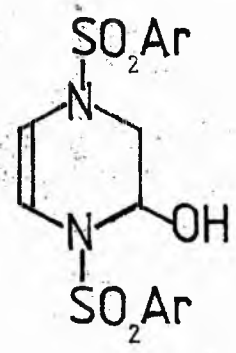
Eisner and Pashayan[58] reinvestigated the work of Marckwald and Elinger[34], who had claimed that treatment of benzenesulphonyl-aminoacetaldehyde dimethyl acetal (LXXXIa) with hydrochloric acid produced the 1,4-dihydropyrazine (XXXIII). Later Takata[59] reported

a similar reaction; during attempted acid hydrolysis of the p-nitrobenzenesulphonylaminoacetal (LXXXId) to the corresponding aldehyde a yellow solid was isolated to which a 1,4-dihydropyrazine structure was assigned. In the course of reinvestigation[58] a range of substituted aminoacetals (LXXXI) was prepared; on repeating the work of Marckwald and Ellinger[34] it was found that a mixture of two components was obtained, neither of which corresponded to the 1,4-dihydropyrazine (XXXIII). They were identified as the 2-hydroxy- and 2-methoxy-1,2,3,4-tetrahydropyrazines (LXXXIIa) and (LXXXIIIa), respectively; the structures were confirmed by elemental analysis and

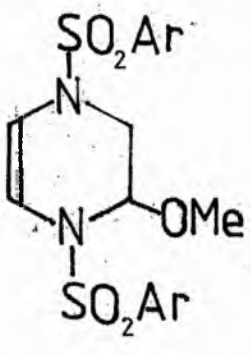


(LXXXI)

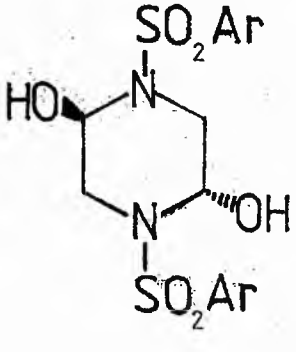
a) Ar = Ph c) Ar = p-BrC_6H_4
b) Ar = p-MeC_6H_4 d) Ar = p-$NO_2C_6H_4$



(LXXXII)



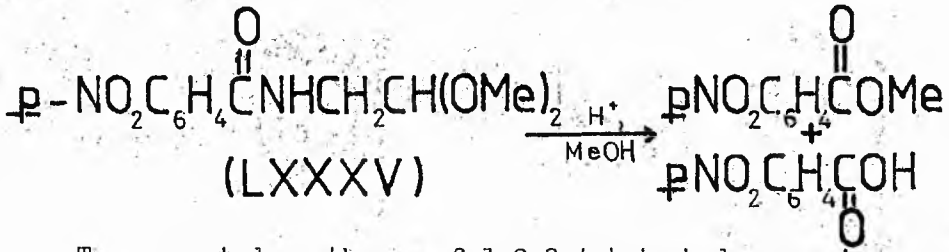
(LXXXIII)



(LXXXIV)

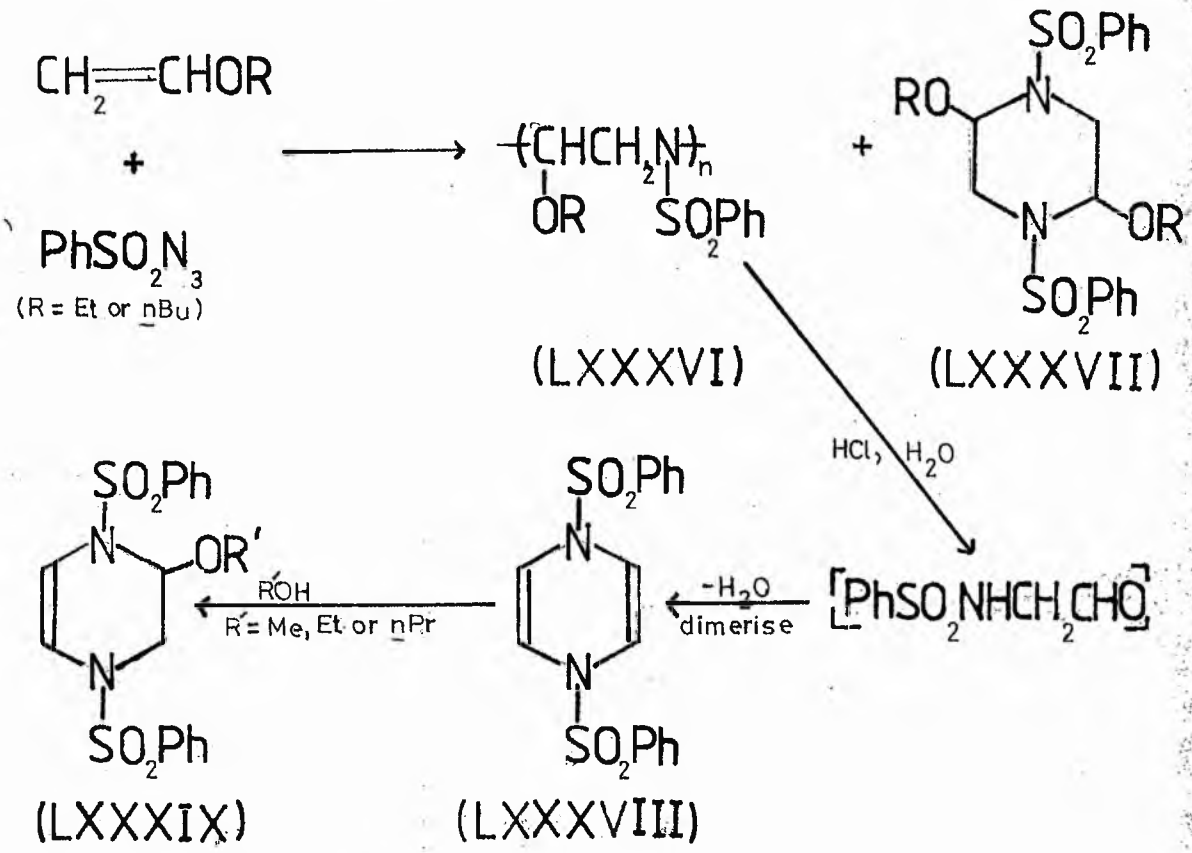
spectral data. Compound (LXXXIIIa) was more conveniently prepared by treating (LXXXIa) with aqueous acidic methanol, being formed as the sole product in high yield. On treating (LXXXIa) with aqueous

acetic acid-hydrochloric acid at room temperature, the 2,5-dihydroxypiperazine (LXXXIVa)was formed; this was very insoluble but the structure was confirmed by X-ray analysis[60] which showed the molecule to have a chair conformation with the hydroxyl groups trans and diaxial with intermolecular hydrogen bonding. Heating this compound in aqueous acetic acid-hydrochloric acid gave the 2-hydroxy compound (LXXXIIa)in good yield while heating in methanolic hydrochloric acid afforded (LXXXIIIa). The p-toluenesulphonyl and p-bromobenzenesulphonyl analogues (LXXXIIIb and c) were prepared by heating the respective aminoacetals in aqueous acidified methanol; treatment of p-nitrobenzenesulphonylaminoacetal in this way gave an insoluble product, the elemental analysis of which corresponded to a dimethoxypiperazine rather than the expected 1,2,3,4-tetrahydropyrazine. With aqueous acetic acid containing HCl this latter aminoacetal afforded the 2-hydroxy-1,2,3,4-tetrahydropyrazine (LXXXIIc)which had a melting point almost identical with that of the alleged 1,4-dihydropyrazine prepared by Takata[59]. When p-nitrobenzoylamino-acetal (LXXXV) was warmed with aqueous acidic methanol a totally different result was obtained, the products being methyl p-nitrobenzoate and p-nitrobenzoic acid with no cyclised products being isolated.



Two reported syntheses of 1,2,3,4-tetrahydropyrazines are of particular interest because of their connection with the above work. Franz[61] found that on treatment of benzenesulphonyl azide with either ethyl or n-butyl vinyl ether at moderate temperatures the 1:1 polymer (LXXXVI) was produced together with small quantities of the

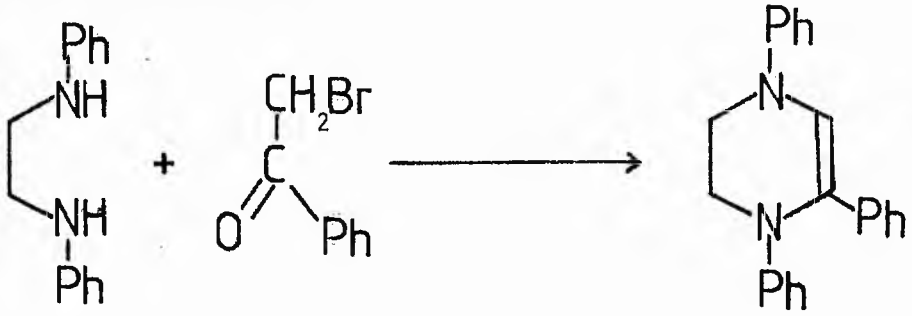
2,5-dialkoxypiperazines (LXXXVII). On treating the polymer (LXXXVI) with hot concentrated hydrochloric acid in the presence of an alcohol excellent yields of the corresponding 2-alkoxy-1,2,3,4-tetrahydropyrazines (LXXXIX) were produced. The suggested reaction pathway was via the 1,4-dihydropyrazine (LXXXVIII). On heating (LXXXIX) above its melting point alcohol was evolved and a dark oil was formed, presumably by conversion into (LXXXVIII) followed by polymerisation. The course of these reactions was summarised as shown.



In a similar reaction Oglobin[62] obtained the 2-ethoxy and 2-methoxy-1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines.

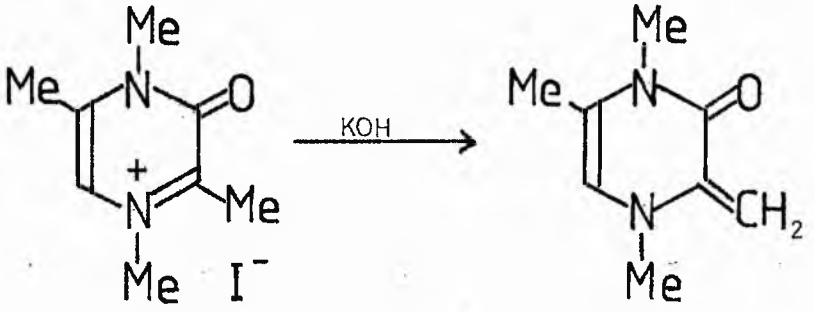
Apart from the examples already mentioned[47,50-52,60,61] 1,2,3,4-tetrahydropyrazines have been reported only infrequently in the literature. Garzino[63] obtained a compound which he

formulated as (XC) by condensing N,N'-diphenylethylenediamine with phenacyl bromide as shown.



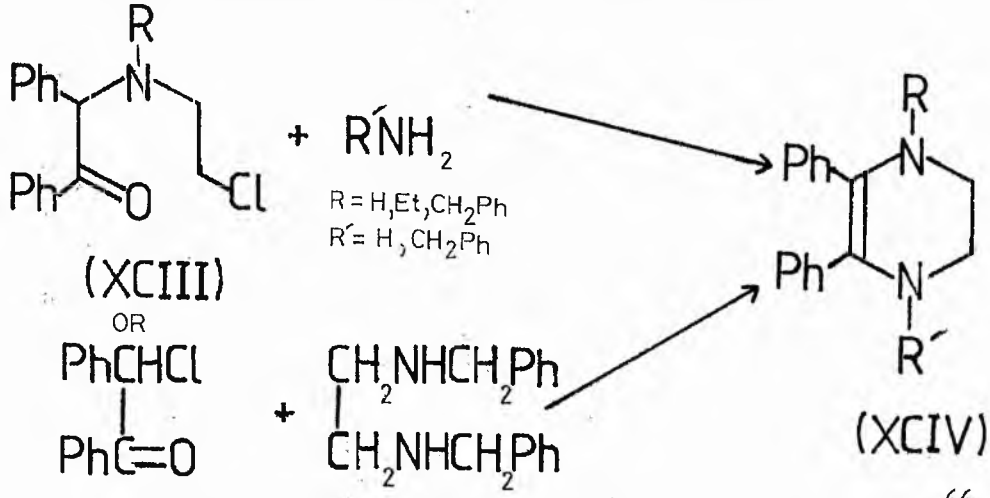
(XC)

The tetrahydropyrazine ring system is present in the anhydro base (XCII) obtained[64] by the action of alkali on the quaternary salt of the 1,2-dihydropyrazine (XCI). Lunsford, Lutz and Bourden[65] prepared the 1,2,3,4-tetrahydropyrazines (XCIV) by



(XCI) (XCII)

condensation of (XCIII) with ammonia or primary amines and also by reaction of desyl chloride with dibenzylethylenediamine.

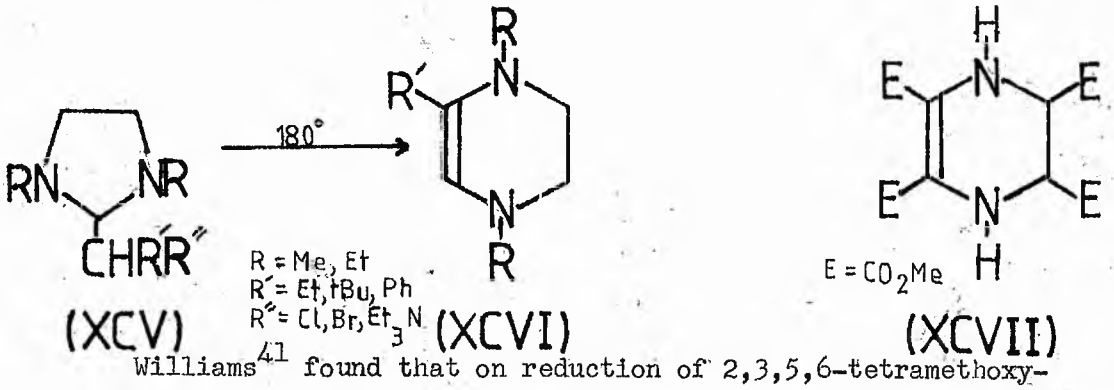


(XCIII)

(XCIV)

The parent compound (XCIV;R=R'=H) has been prepared[66] by the electrochemical reduction of the corresponding 2,3-dihydropyrazine. Duhamel and co-workers[67] obtained a range of tetrahydropyrazines

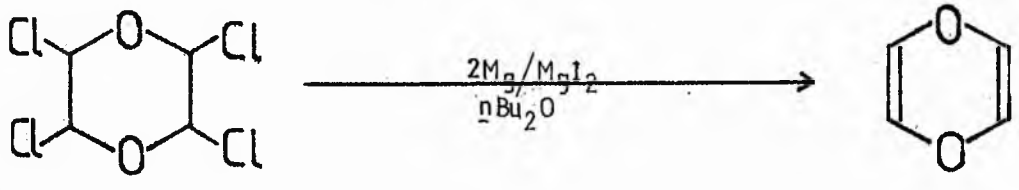
by heating the aminal (XCV) to 180°.



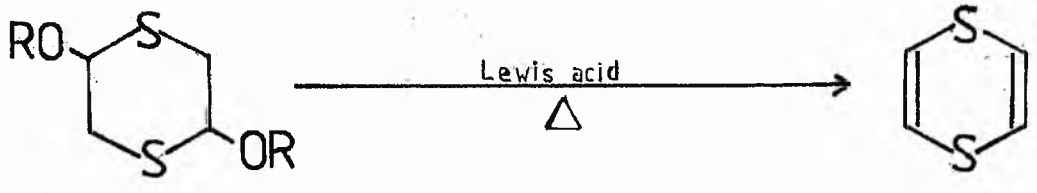
(XCV) (XCVI) (XCVII)

Williams[41] found that on reduction of 2,3,5,6-tetramethoxycarbonylpyrazine he obtained not only the methoxycarbonyl analogue of the 1,2-dihydropyrazine (XLII) but also the 1,2,3,4-tetrahydropyrazine (XCVII).

The availability of functionalised tetrahydropyrazines opens up a possible synthetic route to 1,4-dihydropyrazines via elimination reactions. There are precedents for such syntheses in the formation of the oxygen and sulphur analogues 1,4-dioxin[17] and 1,4-dithiin[18] as shown below.

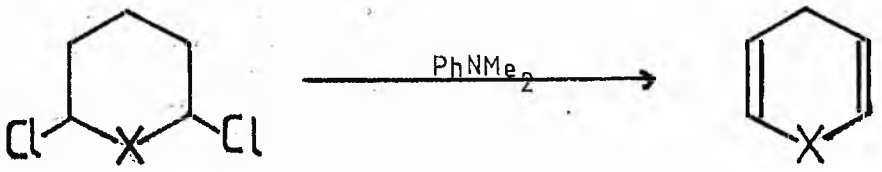


(X)



(XI)

Another example of the synthesis of a heterocycle by this means is the preparation of 4 H-pyran (XCVIIIa) and -thiopyran (XCVIIIb).



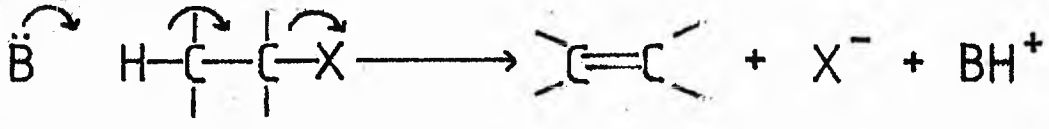
(XCVIII) a) X = O
b) X = S

In view of the above syntheses it is appropriate to briefly discuss elimination reactions. The type of elimination which occurs in these reactions is known as β -elimination where two groups (one usually, but not always, hydrogen) are lost from adjacent carbon atoms with the formation of a double bond. This may be represented in the most general sense as:

Most of the examples discussed here will deal with the case where X is hydrogen. β -Eliminations may be divided into two categories, those taking place in solution and those (pyrolytic eliminations) which usually occur in the gas phase. A wide variety of leaving groups has been utilised in elimination reactions; these include : $\overset{+}{N}R_3$, $\overset{+}{P}R_3$ $\overset{+}{S}R_2$, $\overset{+}{O}H_2$, $\overset{+}{O}HR$, SO_2R, SOR, SeOR, OSO_2R, OCOR, OOH, OOR, Cl, Br, I, CN and $\overset{+}{N}_2$.

Reactions occurring in solution proceed by one of three major mechanistic types: E_1, E_2 and E_{1cb}. It should be noted, however, that these represent extremes of a continuum of possibilities and many eliminations occur via mechanisms which are borderline cases.

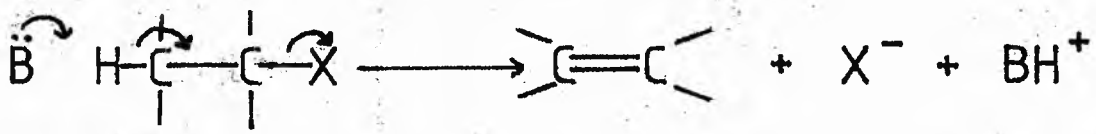
In the case of the E_2 mechanism the two groups leave simultaneously, the proton (or other group) being pulled off by a base as shown.



E_2 reactions show second order kinetics being first order in both substrate and base. They are similar to S_N2 reactions with which they compete, the difference between the reactions being that the species with the unshared pair attacks either the carbon (acting as a nucleophile) or the hydrogen (acting as a base).

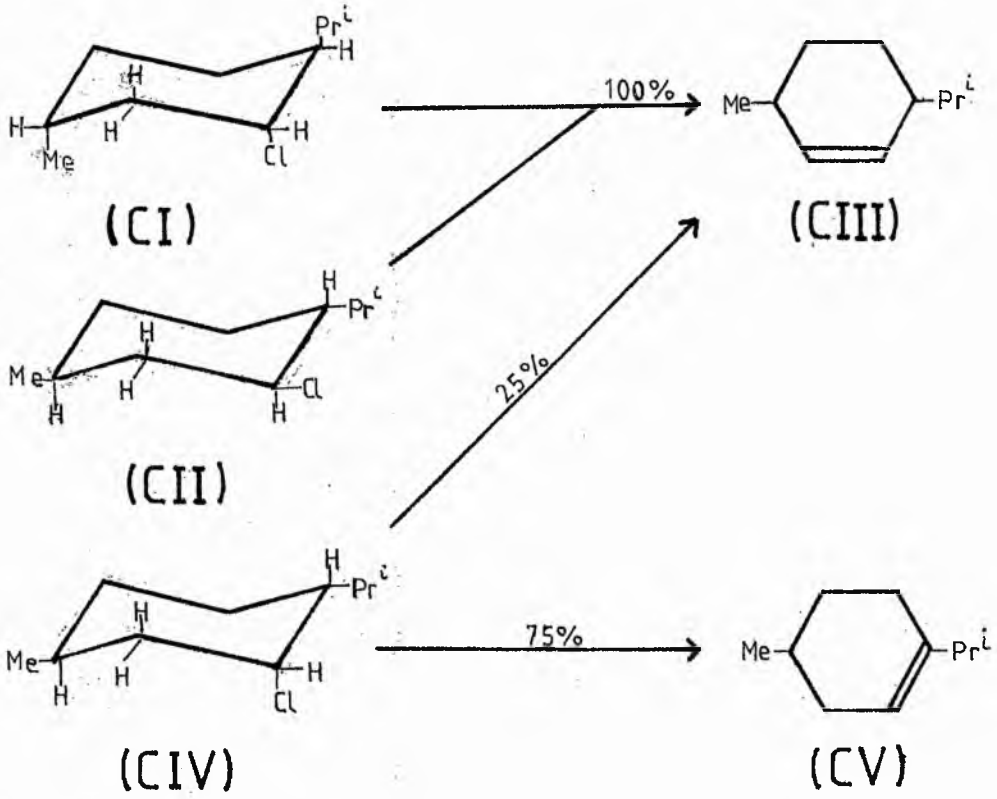
The E_2 mechanism is stereospecific; in the transition state the five atoms involved must be in one plane.

There are two ways in which this can occur: either the hydrogen and the leaving group are <u>trans</u> to each other with a dihedral angle of 180° (XCIX), or <u>cis</u> with a dihedral angle of 0°(C). Conformation (XCIX) is called anti-periplanar and the resulting reaction <u>anti</u> - elimination, while (C) is known as <u>syn</u> periplanar and hence the corresponding process is <u>syn</u> - elimination. <u>Anti</u>-elimination is greatly favoured in most cases as (XCIX) is a staggered conformation and is of lower energy than (C). In six-



membered rings an additional restriction occurs; adjacent <u>trans</u> groups may be diaxial or diequatorial and the molecule is often free to adopt either conformation, though one may be of higher energy. <u>Anti</u>-periplanarity of the leaving groups requires them to be diaxial even if this is the conformation of higher energy. An illustration of this point is the elimination of hydrogen chloride from menthyl and neomenthyl chlorides[69]. The former has two chair conformations (CI) and (CII), of which the more stable is (CII). The most stable conformation of neomenthyl chloride is (CIV). The latter undergoes

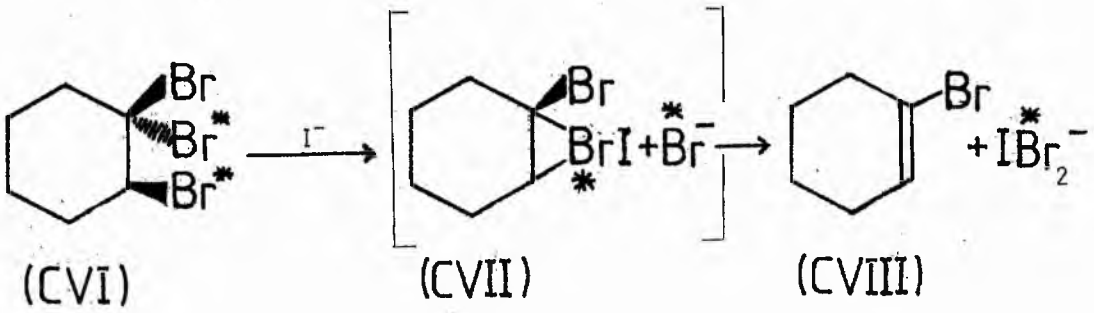
rapid E_2 elimination on treatment with base to give a mixture of (CIII) and (CV), because an axial hydrogen is available on either side of the chlorine. In the case of menthyl chloride, however, elimination is slow since it involves the unfavourable conformation (CI), and (CIII) is the sole product as only one axial hydrogen is available.



In some rare cases syn - elimination may occur and even predominate; this may be due to a variety of factors such as steric effects (inability to form an anti-periplanar transition state), conformational influences and ion pairing.

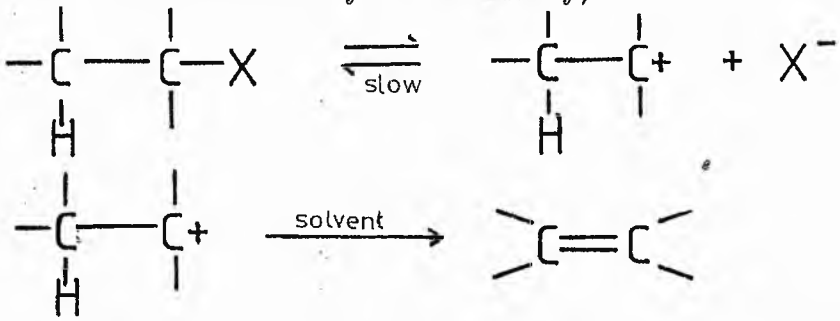
An example of an E_2 mechanism where hydrogen is not one of the departing groups is the action of iodide ion on the tribromocyclohexane (CVI)[70], which was found to give exclusive anti-elimination, probably via the bridged intermediate (CVII). The course of the reaction was

determined by using material labelled with ^{82}Br as shown.



(CVI) (CVII) (CVIII)

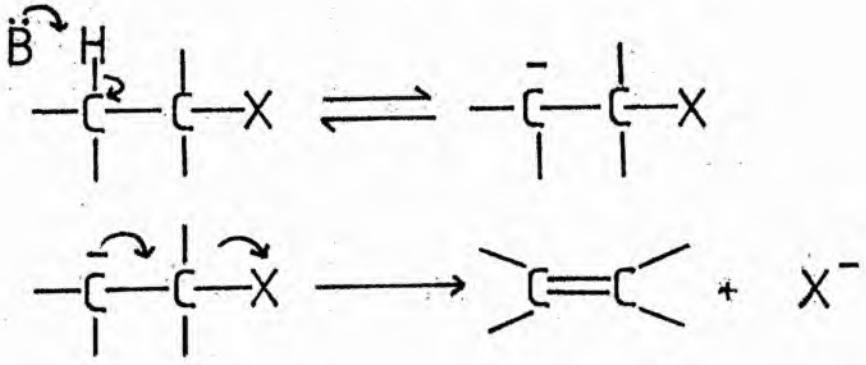
The E1 mechanism is a two-step process in which the rate-determining step is ionisation of the substrate to a carbonium ion. This rapidly loses a β-proton to a base, which is usually the solvent (addition of base is normally not necessary).



The kinetics are first order (in substrate) as expected.

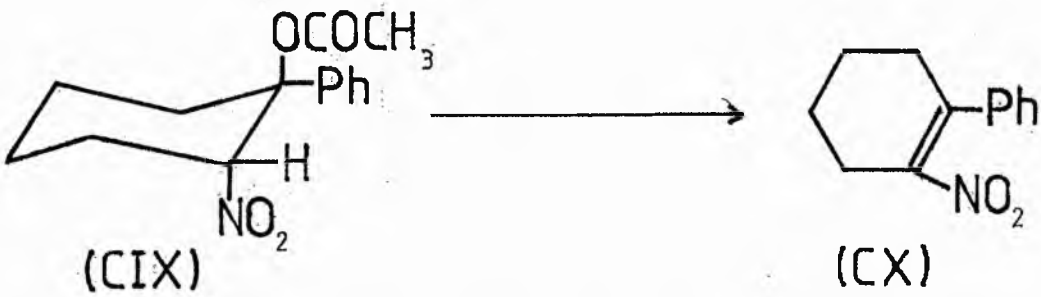
The first step here is exactly the same as that in the S_N1 mechanism; whether elimination or substitution predominates depends on whether the solvent pulls a proton from the β-carbon of the carbonium ion or attacks at the positively charged carbon. A pure E_1 reaction is completely non-stereospecific as the carbonium ion can adopt its most stable conformation before giving up the proton. However, there is abundant evidence[71] that many carbonium ion reactions involve ion pair intermediates, and show some stereospecificity.

The E_{1cb} mechanism, also known as the carbanion mechanism, represents the third possible order of departure of proton and leaving group, where the proton leaves first.



This is a second order mechanism as both base and substrate are involved in the rate-determining step. Reactions proceeding in this way are limited to those substrates with substituents which can stabilise the intermediate carbanion, e.g., where the leaving group is β - to a nitro group.

An example of this mechanism[72] occurs in the elimination of acetic acid from (CIX) where the carbanion is stabilised by the electron withdrawing nitro group.



(CIX) (CX)

There are four factors which may affect the course of elimination reactions in solution by altering the overall reactivity of the molecule, shifting the mechanism to left or right of the E_1-E_2-E_{1cb} continuum and by influencing the ratio of elimination to substitution. These factors are: the structure of the substrate, the nature of the base, the kind of leaving group and the type of reaction medium; each of these will be discussed in turn.

Groups attached to the ∝-carbon bearing the leaving group or to the β-carbon which loses the proton may affect overall reactivity

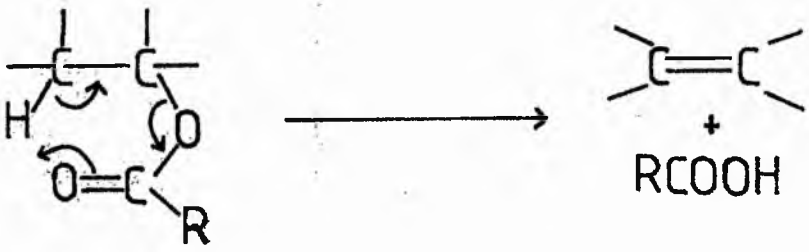
by stabilising or destabilising an incipient carbonium ion (α-groups only) or carbanion (β-groups only), by exerting steric effects and by affecting the stability of an incipient double bond.

The addition of base to a reaction mixture shifts the mechanism towards the E_2 limit as external base is not required for E_1 reactions. Stronger bases increase the likelihood of the E_{1cb} mechanism and also favour elimination over substitution. Thus under moderately to strongly basic conditions the E_2 mechanism predominates over the S_N2 while under weakly basic or neutral conditions S_N1 predominates over E_1.

The E_1 mechanism is favoured by good leaving groups (e.g. Br, I) as they facilitate ionisation. Poor leaving groups and those carrying a positive charge favour E_{1cb} elimination as the strong electron withdrawing effects increase the acidity of the β-hydrogen. In a pure E_1 reaction (i.e. one in which ion pairs do not occur) the leaving group plays no part in the competition between elimination and substitution, whereas in reactions proceeding by the other two mechanisms positively charged leaving groups increase the amount of elimination.

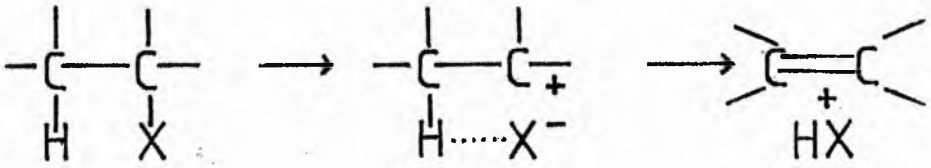
The reaction medium plays an important part in determining the reaction mechanism. A polar environment stabilises ionic intermediates and thus favours the E_1 and E_{1cb} mechanisms. Increasing solvent polarity also favours S_N2 reactions at the expense of E_2, while in most solvents S_N1 predominates over E_1. The latter competes best in polar solvents which are poor nucleophiles, e.g. dipolar aprotic solvents. Elimination is favoured over substitution by increasing temperature, irrespective of the mechanism by which it occurs or the solvent used.

Pyrolytic eliminations may proceed via three mechanisms. The first of these, known as E_i, involves a cyclic transition state as shown:



Elimination is <u>syn</u> and for four and five-membered transition states the atoms making up the ring must be co-planar.

A second mechanism, closely related to E_i, involves loss of the negative group as the first step leaving a carbonium ion, which then loses its β-proton to the negative ion which has just left. With nothing to solvate the negative ion, an ion pair is formed as an intermediate.

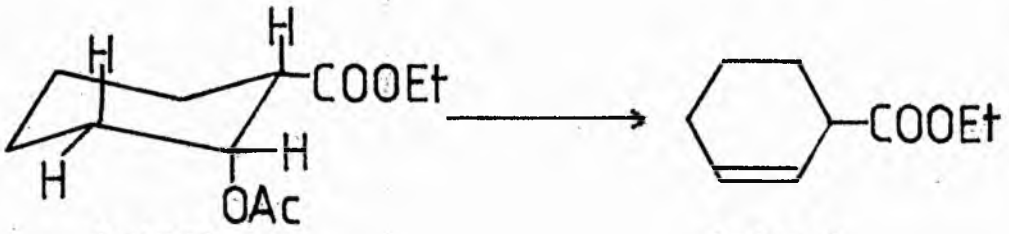


This is known as the ion pair mechanism. In fact a spectrum of pyrolytic mechanisms probably occurs with the above ion pair mechanism at one end, and at the other a mechanism where a proton leaves first.

A pure E_i situation with simultaneous cleavage will be between those extreme cases.

The E_i mechanism is supported by first order kinetics, exclusive <u>syn</u>-elimination, negative entropies of activation (indicating a more ordered transition state than the starting material) and the fact that free radical inhibitors do not slow

down the reaction. Important leaving groups in this type of elimination are Cl, Br, I, OCOR, $OCH{=}CH_2$, OCS_2CH_3, OH, NH_2 and OCOCl. A <u>cis</u> β-hydrogen is essential for reaction to occur. An example of a reaction proceeding by this mechanism is given below[73].



(CXI) (CXII)

The third mechanism found in pyrolytic reactions involves free radicals with initiation occurring by pyrolytic homolytic cleavage.

$$R_2CHCH_2X \longrightarrow R_2CHCH_2\cdot + X\cdot$$

$$R_2CHCH_2X + X\cdot \longrightarrow R_2\dot{C}CH_2X + HX$$

$$R_2\dot{C}CH_2X \longrightarrow R_2C{=}CH_2 + X\cdot$$

This mechanism is only known for primary alkyl bromides, primary esters and certain polyhalides; little is known about its detailed course.

DISCUSSION

The preliminary work of Eisner and Pashayan[58] provides ready access to functionalised 1,2,3,4 -tetrahydropyrazines. The object of the present work was to extend this investigation and, in particular, to explore the chemistry of the little known 1,2,3,4-tetrahydropyrazines and to attempt their conversion into 1,4-dihydropyrazines.

Preparation and Cyclisation of Arenesulphonylaminoacetals.

The arenesulphonylaminoacetals (I-VI) were prepared in high yield by the standard method previously used[58]; of these (II), (V) and (VI) are new compounds. The original method is time-consuming and it was found that the addition of the phase-transfer catalyst benzyltriethylammonium chloride greatly increased the rate of reaction without diminishing the yield. The substituted aminoacetals were obtained as low melting crystalline solids; their structures were established by elemental analysis, the presence of a sharp infra-red absorption at ~ 3200cm^{-1} (NH), and their p.m.r. spectra (see Experimental).

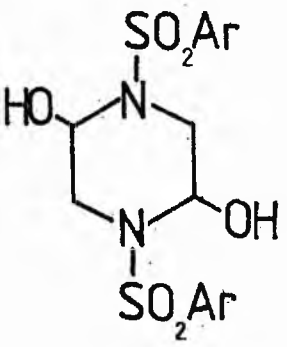
$$ArSO_2Cl + H_2NCH_2CH(OR)_2 \longrightarrow ArSO_2NHCH_2CH(OR)_2$$

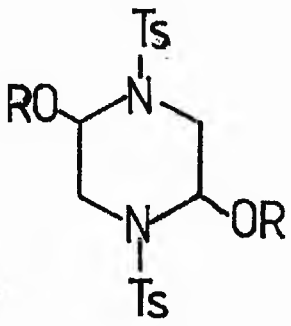
(I) Ar = C_6H_5, R = Me (IV) Ar = p-$NO_2C_6H_4$, R = Me

(II) Ar = p-$CH_3C_6H_4$, R = Me (V) Ar = p-$CH_3C_6H_4$, R = Et

(III) Ar = p-BrC_6H_4, R = Me (VI) Ar = p-BrC_6H_4, R = Et

The synthesis of the 2,5-dihydroxypiperazine (VII)[58] by cyclisation of the substituted aminoacetal (I) was repeated; the reaction was extended to the preparation of the previously unknown analogues (VIII) and (IX) from (II) and (III), respectively.





(VII) Ar=C_6H_5

(VIII) Ar=p-$CH_3C_6H_4$

(IX) Ar=p-BrC_6H_4

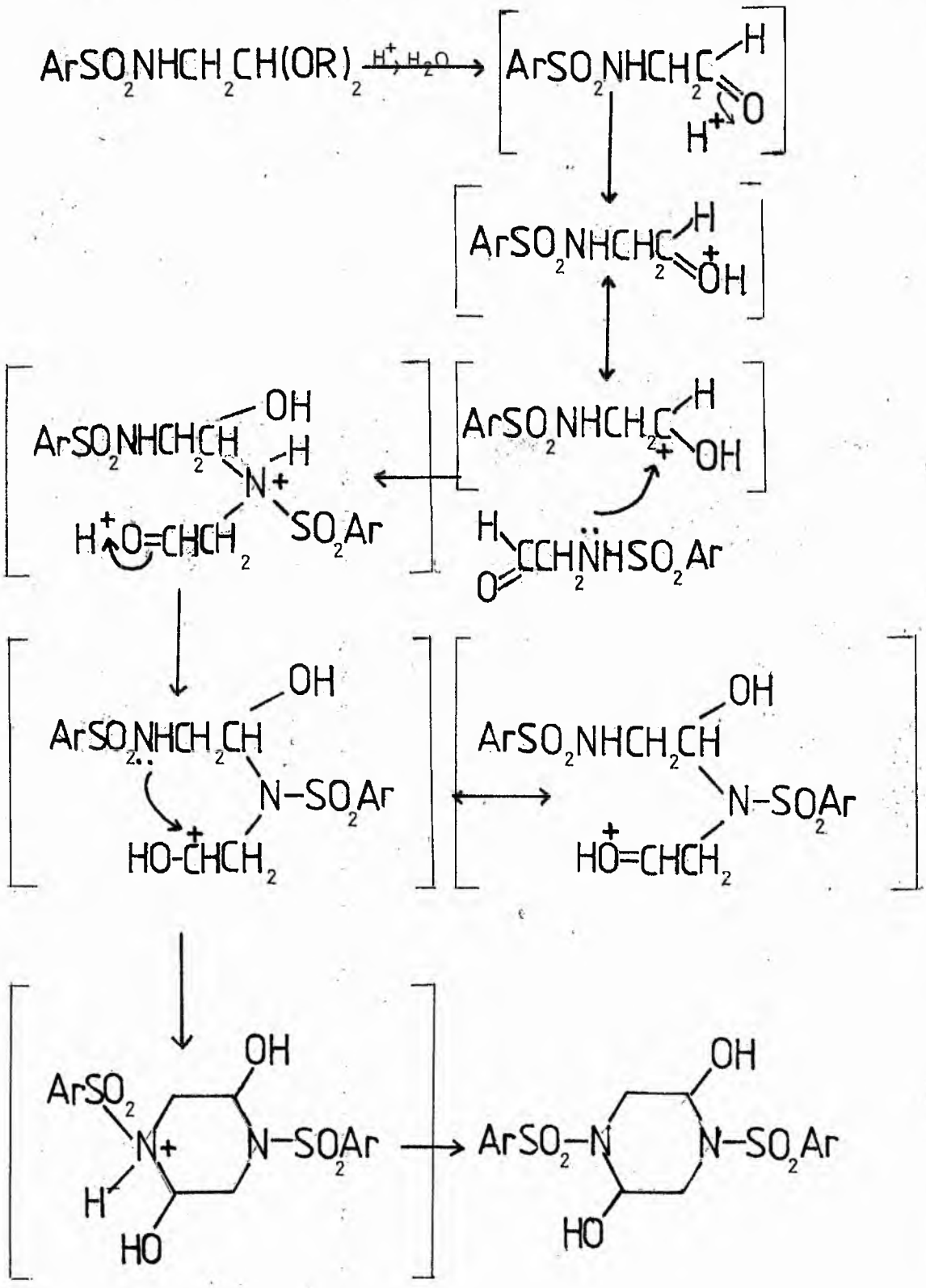
(X) R=Me

(XI) R=Et

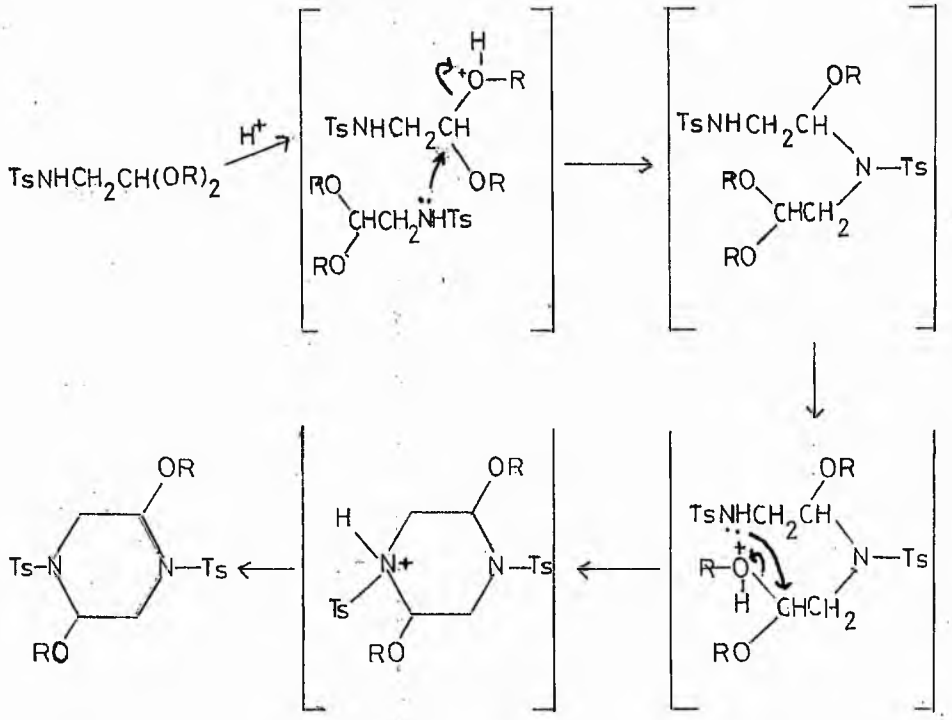
Like (VII), and presumably for the same reason (intermolecular hydrogen bonding, see p.20), these compounds are highly insoluble; their structures were confirmed by elemental analysis and by strong OH absorptions at ~ 3500cm^{-1} in the infra-red.

The mechanism of formation of (VII-IX) probably entails initial hydrolysis of the aminoacetals (I-III) to the corresponding aldehyde, which then cyclises to the observed product as shown (p.34).

Some of these steps may be reversible. In acidified methanol at room temperature the dimethyl acetal (II) cyclised to give the previously unknown 2,5-dimethoxypiperazine (X) in good yield, while in a similar reaction the diethyl acetal (V) gave the known[62] 2,5-diethoxy analogue (XI) with ethanol. These compounds were identified by their spectral characteristics and elemental analysis (for a discussion of their p.m.r. spectra see below). The mechanism



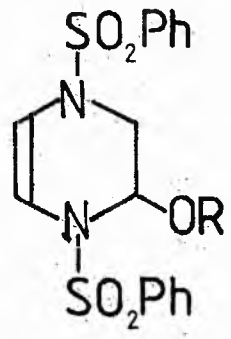
of this reaction is probably as shown.



It was found earlier[58] that under more severe conditions ($HOAc/HCl/H_2O$ at 100°) the substituted aminoacetal (I) afforded not a piperazine but the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVI). Similarly, heating the aminoacetals (I) or (II) in acidified methanol or ethanol yielded[58] the corresponding 2-alkoxy-1,2,3,4-tetrahydropyrazines (XII-XIV). These syntheses were repeated and excellent yields were obtained; the p-toluenesulphonyl derivatives (XIV) and (XV) were also prepared starting from the diethyl acetal (V).

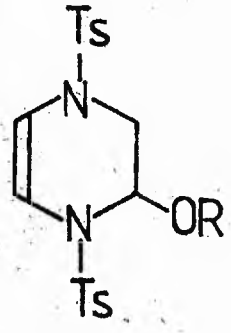
The physical properties of the 2-alkoxy-1,2,3,4-tetrahydropyrazines (XII-XV) were in good agreement with the literature values[58,61,62].

These compounds are presumably formed by a facile elimination of 1 mole of alcohol from the initially formed dialkoxypiperazines (for a full mechanistic discussion see below).



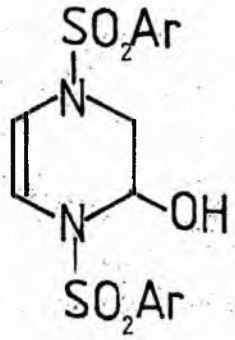
(XII) R=Me

(XIII) R=Et



(XIV) R=Me

(XV) R=Et



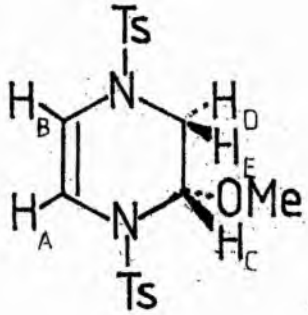
(XVI) Ar=C_6H_5

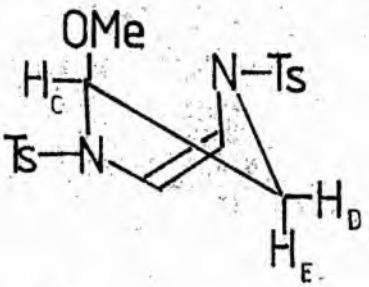
(XVII) Ar=p-$CH_3C_6H_4$

(XVIII) Ar=p-BrC_6H_4

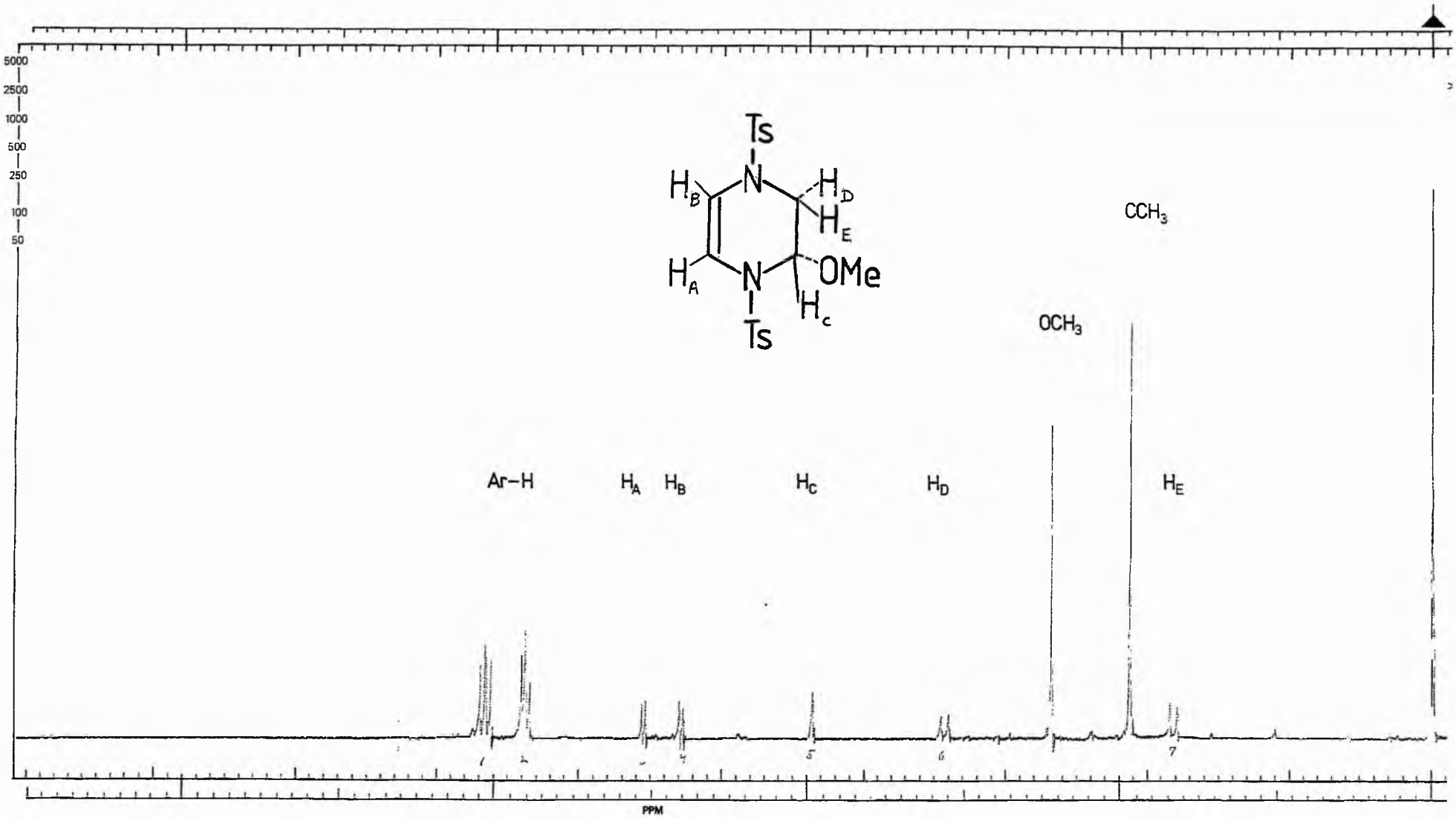
Spectral Characteristics of the Tetra- and Hexa-hydropyrazines.

The 2-substituted 1,4-bis(arenesulphonyl)-1,2,3,4-tetrahydropyrazines possess very characteristic n.m.r. spectra which vary only slightly with the substituent group in the 2-position. Previous work[74] using double irradiation on 1,4-bis(p-toluenesulphonyl)-2-methoxy-1,2,3,4-tetrahydropyrazine (XIV) (see Spectrum A) had permitted the assignment of chemical shifts and coupling constants as shown.





(XIX) [≡ (XIV)]



N.M.R. Spectrum A(at 220 MHz)

1,4-bis(p-toluenesulphonyl)-2-methoxy-1,2,3,4-tetrahydropyrazine (XIV)

From models, the methoxy group of (XIV), and hence H_E, are axial, H_D and H_C are equatorial and H_D therefore resonates at lower field than H_E.

Double Irradiation Experiments (at 220 MHz)

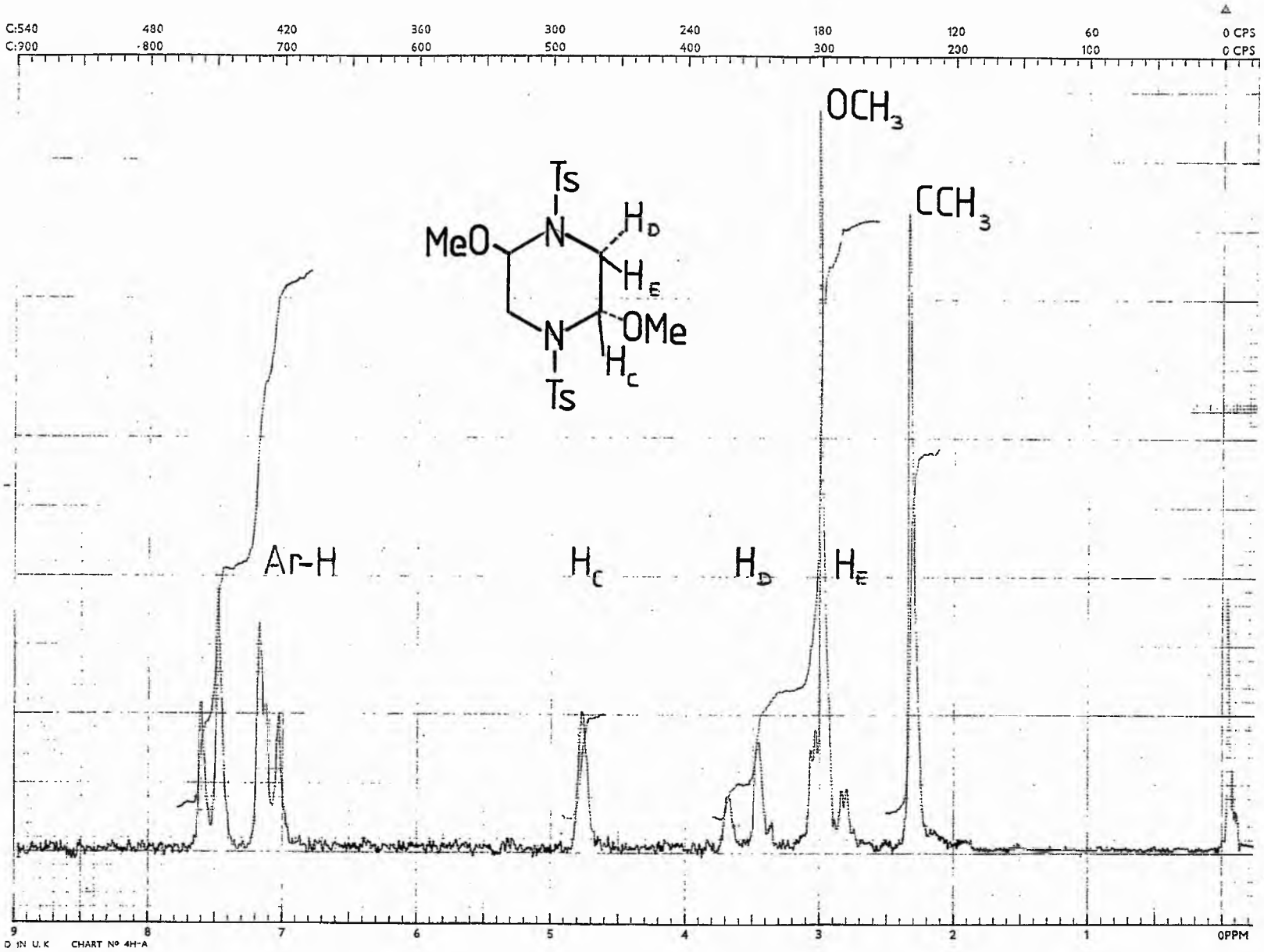
Assignment	Chemical Shift	Coupling Constants (Hz)
H_E	2.1	J_{DE}=13.2; J_{CE}=1.7; J_{AE}= 0.3
H_D	3.9	J_{CD}=2.2; J_{AD}=1.4
H_C	5.0	J_{BC}=1.6
H_B	6.0	J_{AB}=6.6
H_A	6.35	

These results are broadly in agreement with those reported by Franz[61] for the tetrahydropyrazine (XIII).

The spectra of other 2-substituted 1,4-bis-(arenesulphonyl)-1,2,3,4-tetrahydropyrazines are similar to the one shown, the chief differences being variation in the chemical shift of H_C (see (XIX)) due to the differing electronegativity, and hence shielding effect, of the substituting group in the 2-position. Thus in the 2-hydroxy compound (XVII) H_C resonates at 5.5 δ as the hydroxyl group is more electronegative than the methoxy group (H_C is at 5.0 in (XIV)).

In the 2-ethoxy compounds (XIII)and (XV) the methylene protons give a complex signal (which is in agreement with the spectrum reported by Franz[61] for (XIII); this is explained by the fact that these protons are diastereotopic. This behaviour is also observed for the diethyl acetals (V) and (VI).

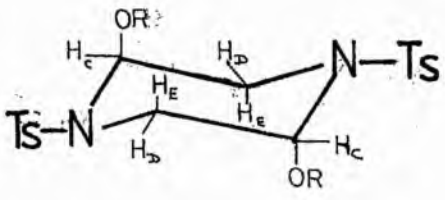
The spectra of the 2,5-dialkoxypiperazines (X) and (XI) are the first recorded for this type of compound; although Oglobin[62] refers to the spectrum of (XI) and Franz[61] to that of its benzenesulphonyl



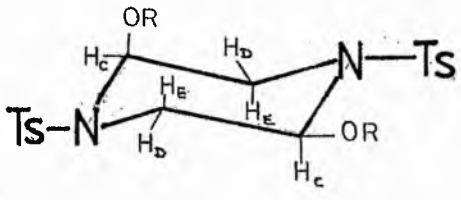
N.M.R. Spectrum B (at 60 MHz)

1,4-bis(p-toluenesulphonyl)-2,5-dimethoxypiperazine (X)

analogue they do not report the actual data. Assignments in the present work were made assuming the molecules to possess chair conformations with the alkoxy groups trans - diaxial to each other (see (XXa)); this assumption is based on the fact that the 2,5-dihydroxypiperazine (VII), prepared from (II) by a similar reaction, is known to have this stereochemistry from X-ray analysis[60]. The simplicity of the spectra obtained for (X) and (XI) (see spectrum B) which show only three types of protons, H_C, H_D and H_E, would also support the trans - configuration (XXa). The cis-isomer (XXb) would be expected to show a more complex spectrum.



(XXa)



(XXb)

In conformation (XXa) both H_E and H_D are deshielded by the alkoxy groups; H_D will be expected to resonate in a similar position to the corresponding proton in the 1,2,3,4-tetrahydropyrazines (XIV) and (XV) discussed earlier. H_E will resonate at lower field in the piperazines (X) and (XI) than in (XIV) and (XV) as in the former it is deshielded.

This is observed; the shifts for the relevant protons are tabulated below.

Proton	Shift (δ)	
	2-alkoxy-1,2,3,4-tetrahydropyrazines	2,5-dialkoxypiperazines
H_C	5.0	5.0
H_D	3.9	3.7
H_E	2.1	3.15

Further evidence for the structure of the 2-methoxy- and 2-hydroxy-1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines (XIV) and (XVII) was provided by their C^{13} n.m.r. spectra (see Appendix).

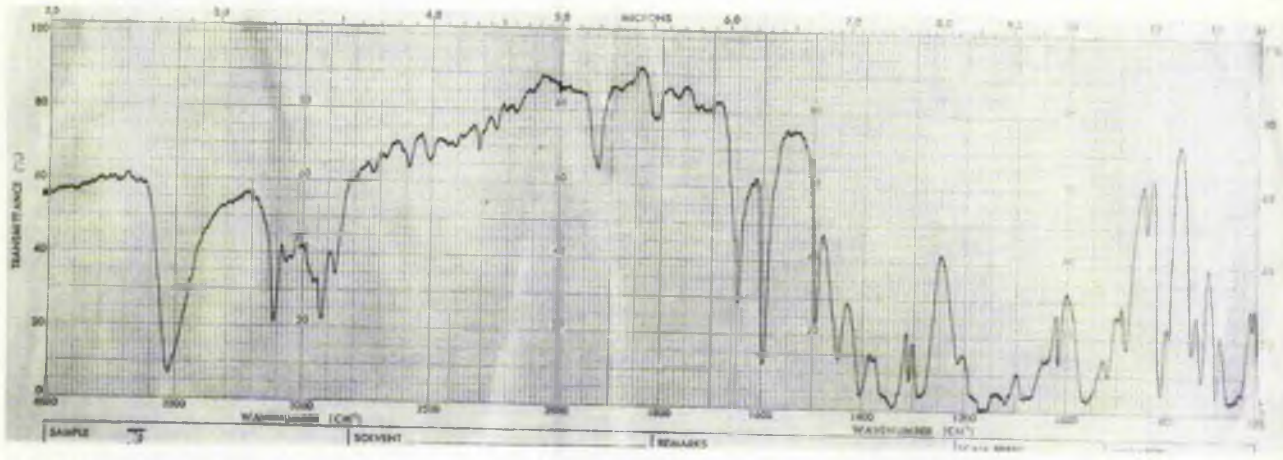
The piperazines and tetrahydropyrazines prepared in the course of this work possess very characteristic infra-red spectra, notably in the region of $\sim 3000 cm^{-1}$, and it is possible to distinguish nearly all the compounds prepared by a comparison of their infra-red spectra.

Another useful feature of these spectra is the reasonably strong signal at $\sim 1650 cm^{-1}$ for the double bond of the tetrahydropyrazines; this enables them to be readily distinguished from the piperazines. As an example the spectrum of the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) and the 2,5-dihydroxypiperazine (VIII) are shown overleaf.

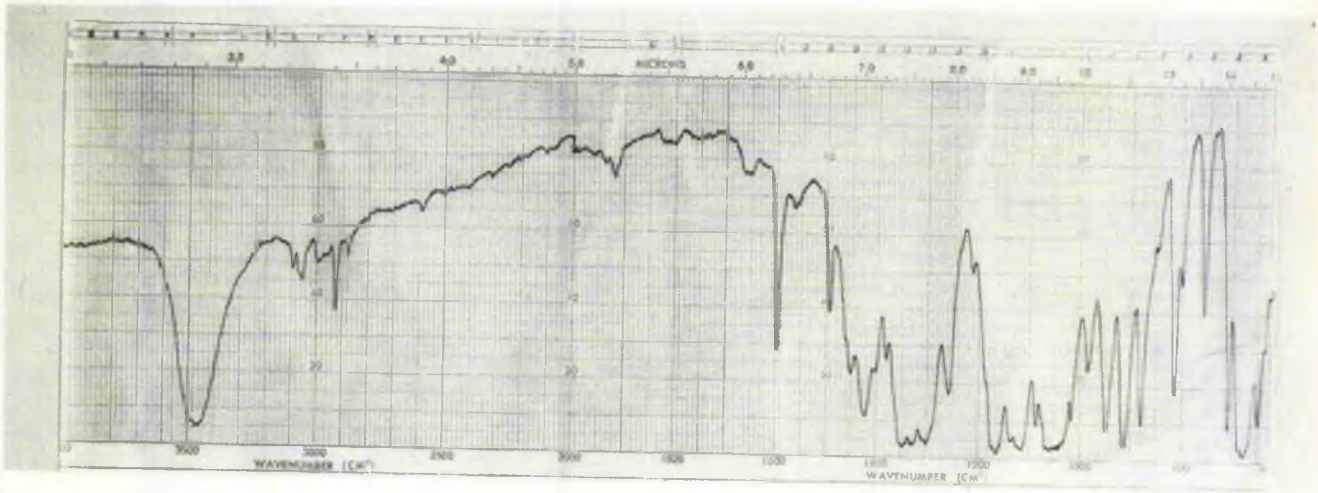
Interconversions of Cyclisation Products.

The various cyclisation products of the p-toluenesulphonyl-aminoacetals (II) and (V) were found to be readily interconvertible.

It had been discovered[58] that on heating the 2,5-dihydroxy-piperazine (VII) in aqueous acetic acid containing conc. hydrochloric acid the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVI) was obtained.

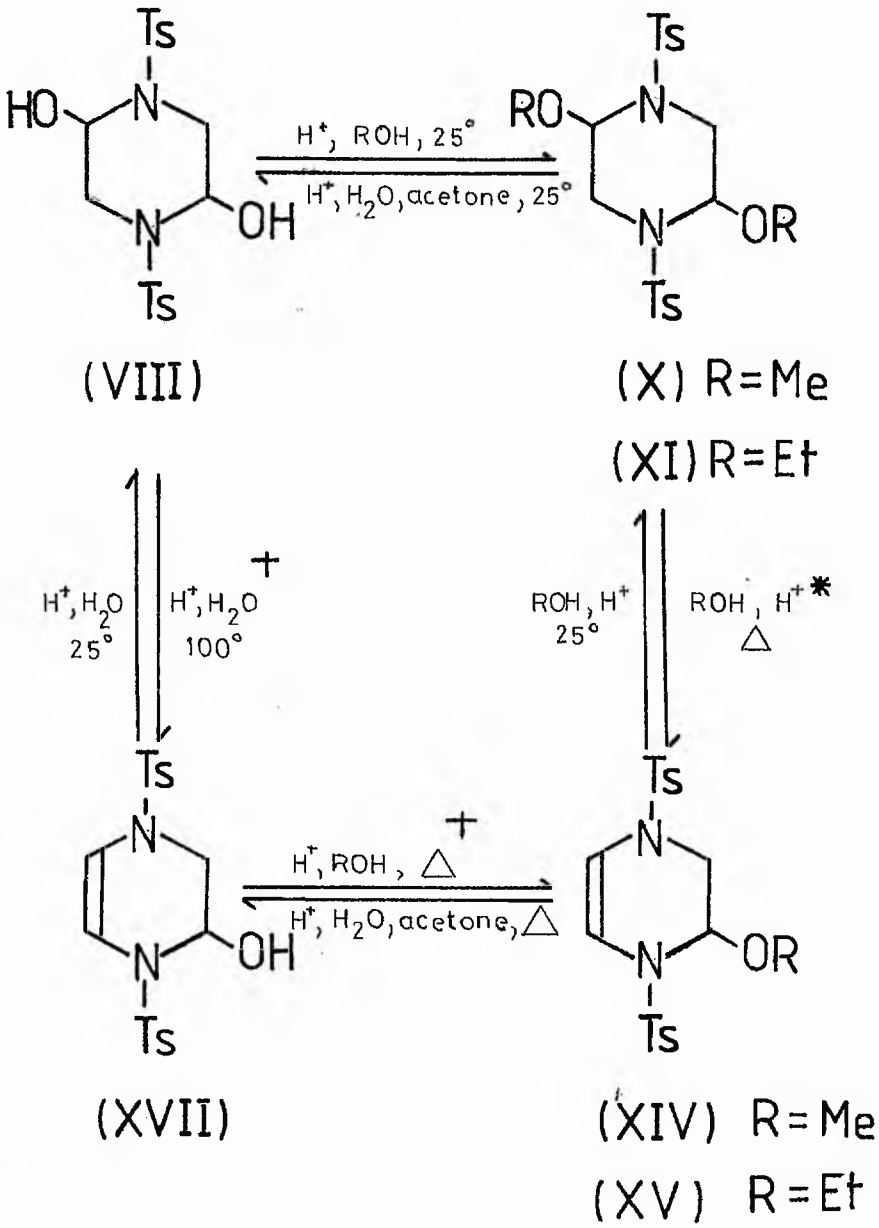


1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine



Trans-1,4-bis(p-toluenesulphonyl)-2,5-dihydroxypiperazine

Infra-red spectra of some reduced pyrazine derivatives (KBr disc)



+ Also carried out by Eisner and Pashayan[58]

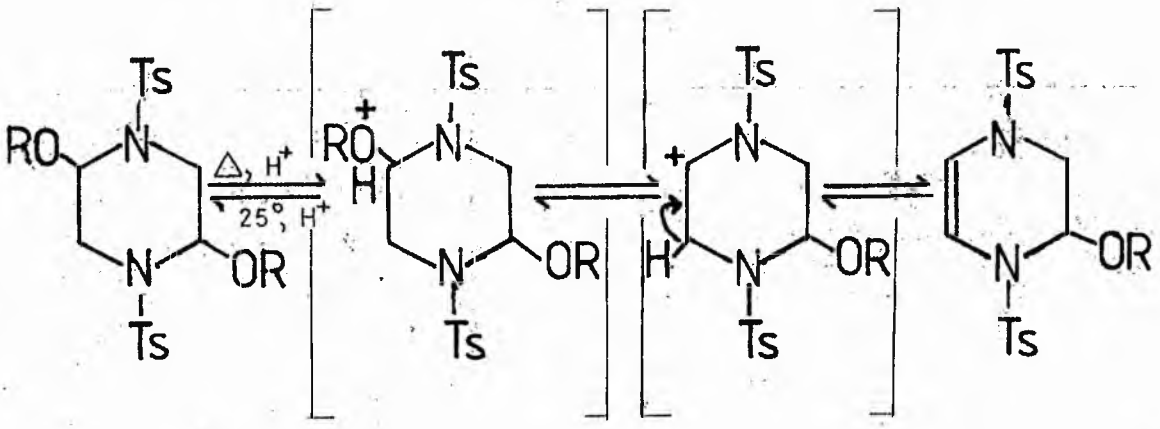
* Also carried out by Oglobin[62] with (XI).

Two new compounds, the analogues (XVII) and (XVIII) were similarly prepared in the present work from (VIII) and (IX). When the 2-hydroxy compound (XVII) was treated with water in aqueous acidified acetone the reverse reaction was observed, a mole of water being added to give (VIII). This latter reaction was demonstrated to be an electrophilic addition since it occurred only under acidic but not neutral or basic conditions.

On warming the 2,5-dialkoxypiperazines (X) and (XI) in acidified alcohol they readily eliminated one mole of alcohol to give the 2-alkoxy-1,2,3,4-tetrahydropyrazines (XIV) and (XV), respectively (a reaction already reported for (XI) by Oglobin[62]).

When (XIV) and (XV) were allowed to stand in cold acidified alcohol a slow addition of alcohol took place with reversion to the 2,5-dialkoxypiperazines (X) and (XI) (see p. 43).

The mechanism of these elimination/addition reactions is almost certainly as shown below.



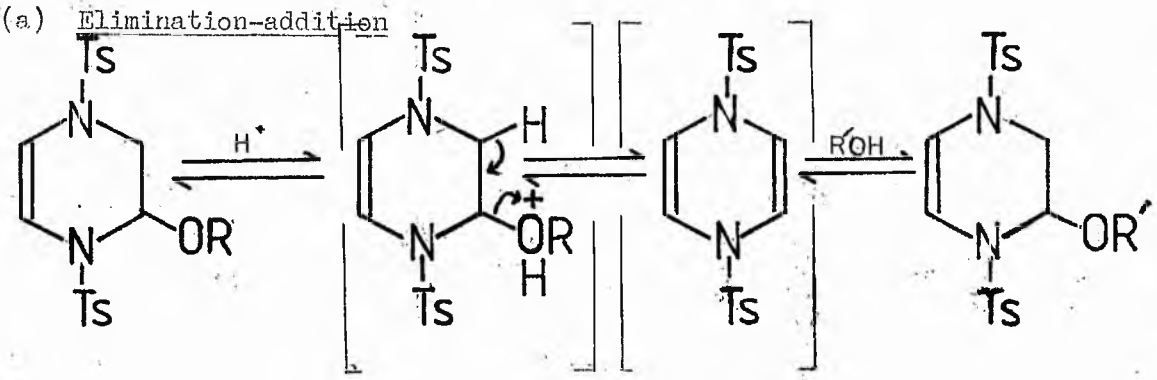
Eisner and Pashayan[58] had found that the hydroxy compound (XVI) could be converted into the alkoxy derivatives (XII) and (XIII) by refluxing in the appropriate acidified alcohol. Franz[61] had reported a similar reaction, converting the 2-ethoxy compound (XIII) into its 2-isopropoxy analogue by refluxing in isopropanol

containing boron trifluoride etherate.

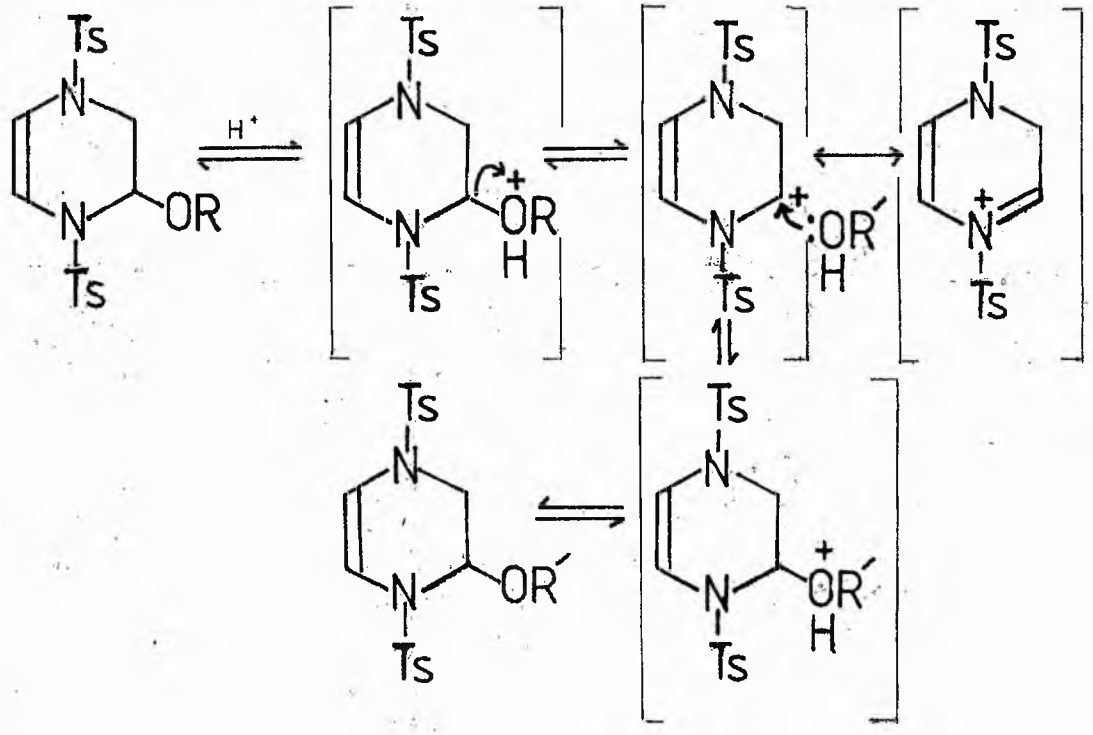
When the 2-hydroxy compound (XVII) was refluxed in acidified methanol, the 2-methoxy compound (XIV) was obtained (cf ref 58); on refluxing (XIV) in acidified aqueous acetone the reverse reaction was accomplished. The action of cold acidified methanol on the 2,5-dihydroxypiperazine (VIII) gave the 2,5-dialkoxy compound (X) and here, too, the reverse reaction could be carried out by stirring (X) in aqueous acidified acetone.

The interconversion of the 2-hydroxy and 2-methoxy-1,2,3,4-tetrahydropyrazines (XVII) and (XIV) may proceed by one of the following mechanistic routes.

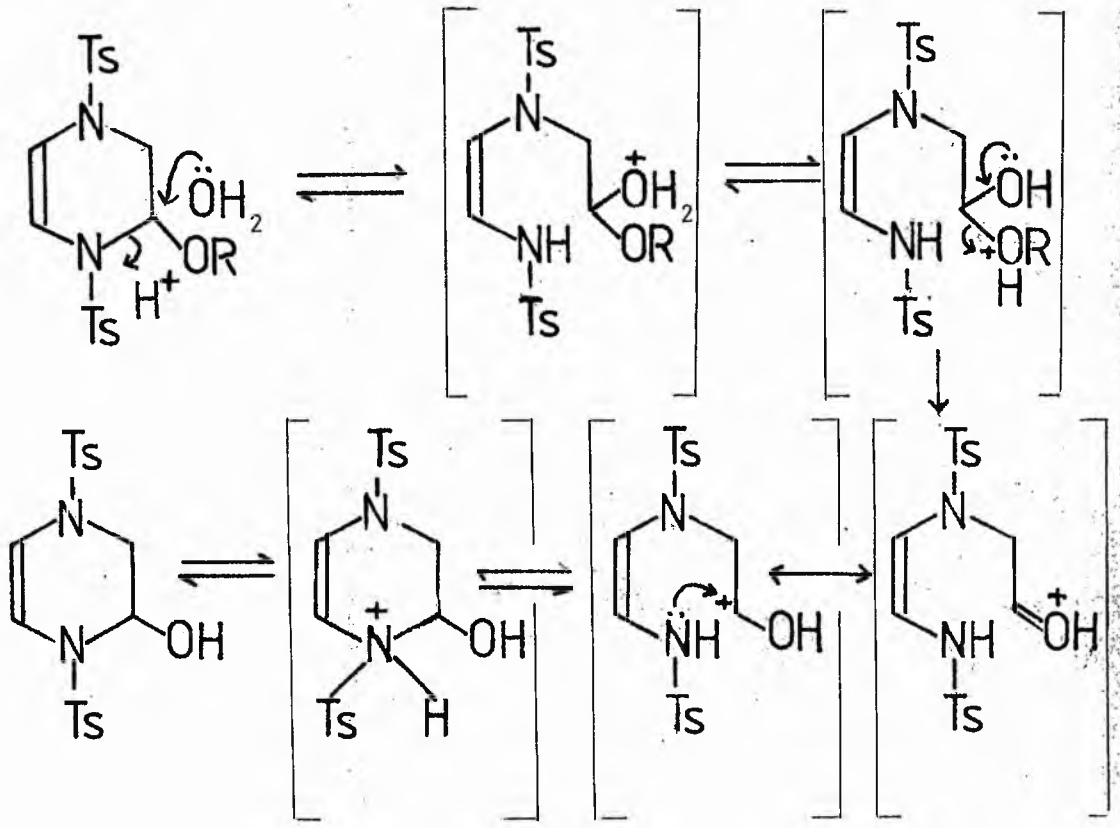
(a) Elimination-addition



(b) Carbonium ion mechanism



(C) Ring Opening

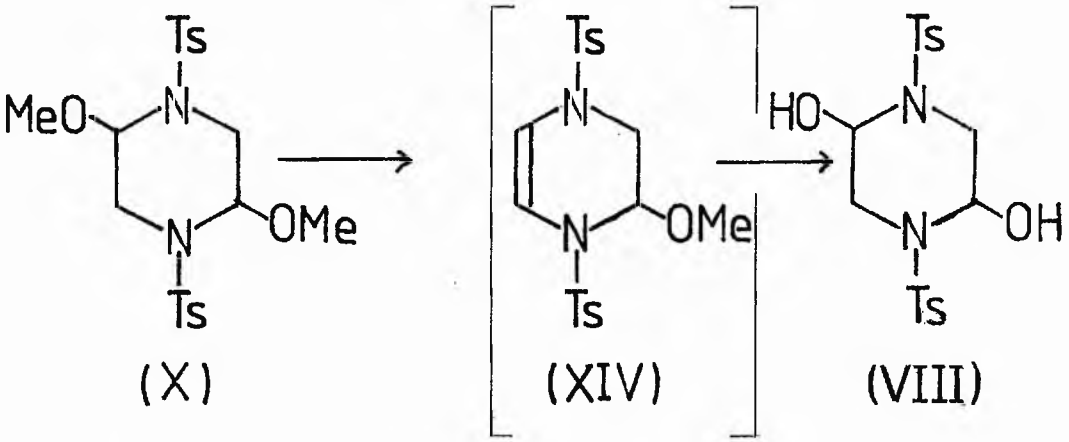


Deuteration experiments were carried out which showed that H_D and H_E (see (XIX), p.36) were exchanged when the 2-hydroxy compound (XVII) was refluxed with D_2O under neutral conditions but not in acid solution. This excludes the elimination-addition mechanism (which was proposed by Franz[61] for similar reactions) since if the reaction had occurred in this way deuterium would have been incorporated at C_3 even under acid conditions. Attempts were made to trap an aldehyde intermediate by refluxing the 2-hydroxy compound (XVII) with 2,4-dinitrophenylhydrazine in methanol and also with hydroxylamine hydrochloride-sodium acetate in acetonitrile, without any success, unchanged starting material being recovered.

This would suggest that ring opening does not occur and the

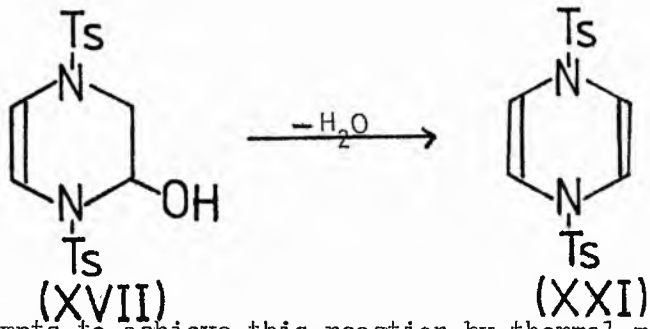
most likely pathway for exchange is via a carbonium ion which is stabilised by the lone pair on the adjacent nitrogen atom. The fact that exchange does occur in neutral solution, however, is difficult to explain without invoking a ring-opened intermediate; the failure to trap such a product conflicts with this hypothesis and further experiments are needed to clarify this point.

By carrying out the conversion of the 2,5-dimethoxypiperazine (X) to the 2,5-dihydroxypiperazine (VIII) in $CD_3COCD_3/H_2O/HCl$ and following the reaction by n.m.r. it was possible to identify the 2-methoxy compound (XIV) as an intermediate by the appearance of the characteristic quartet for the olefinic protons. This indicates that the reaction occurs via elimination of one mole of alcohol followed by exchange of the remaining methoxy group by the mechanism outlined earlier and addition of one mole of water (although not necessarily in that order).



Attempted Dehydration of 1,4-bis-(p-toluenesulphonyl)-2-hydroxy-1,2,3,4,-tetrahydropyrazine and related reactions

The 2-hydroxy compound (XVII) appeared to be a suitable substrate for effecting the synthesis of the 1,4-dihydropyrazine (XXI) as shown.



(XVII) (XXI)

Attempts to achieve this reaction by thermal means were unsuccessful. On heating (XVII) (neat) above 100° in vacuo, gradual decomposition to an oily mixture occurred; refluxing (XVII) in toluene or xylene led to the recovery of starting material, while on raising the temperature by using decalin as a solvent tars were produced. Iodine[75] has been used as a catalyst in dehydration reactions but the addition of iodine to a solution of (XVII) in refluxing toluene led to the recovery of unchanged starting material, whereas iodine in refluxing xylene afforded tars. In dimethylsulphoxide solution (XVII) was slowly transformed into other materials; this reaction was accelerated on warming. An attempt was made to follow it by n.m.r. in DMSO-d_6 but there was no sign of (XXI) being formed at any stage and the resulting spectrum could not be interpreted.

The use of acid catalysts was equally fruitless. Continued heating of a solution of (XVII) in aqueous acetic acid containing conc. hydrochloric acid led only to tars. Attempted dehydration using phosphorus pentoxide in toluene was unsuccessful, no reaction occurring in the cold and mixtures being produced on warming. No reaction occurred when (XVII) was refluxed with p-toluenesulphonic acid in toluene.

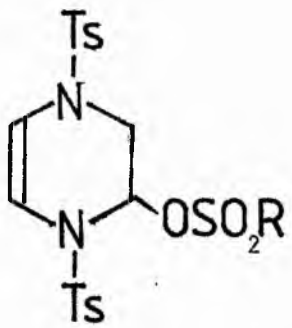
Two useful reagents which bring about dehydration are thionyl chloride/pyridine and phosphoryl chloride/pyridine, the first being the more powerful while the latter is advantageous for increased stereoselectivity[76]. Reaction of the 2-hydroxy-1,2,3,4-tetrahydropyrazine

(XVII) with either of these reagents in pyridine at room temperature gave only complex mixtures.

Two methods which have been used to prepare olefins from ethers are heating the latter in vacuo with ammonium bromide[77] or in dimethylformamide with lithium chloride[78]. These were tried in an attempt to convert the 2-methoxy compound (XIV) into (XXI). In the former case tars were produced while in the latter instance only the 2-hydroxy compound (XVII) could be isolated.

Ester Formation.

The failure to eliminate water from (XVII) suggested that a better leaving group than OH would be needed to synthesise (XXI). The most obvious choice appeared to be the sulphonic esters (XXII) and (XXIII). Under standard conditions (reaction of the alcohol



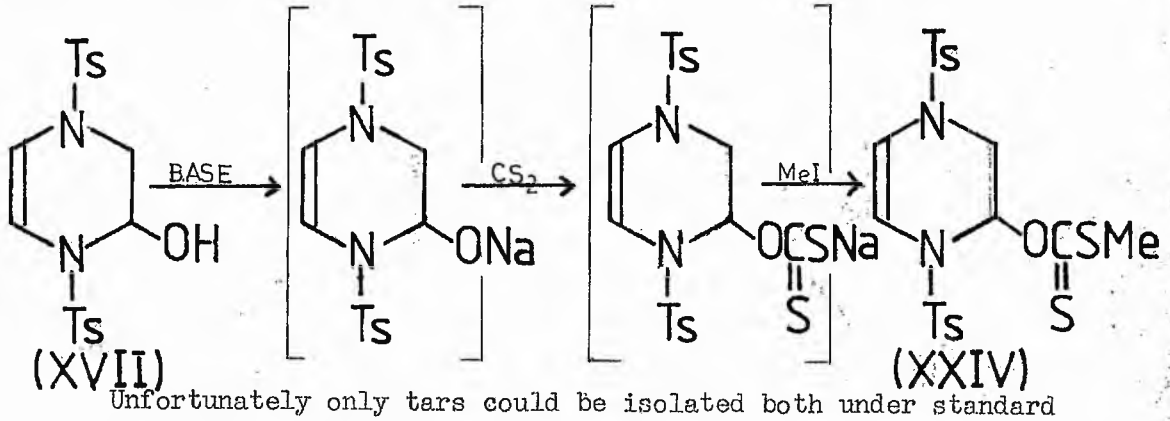
(XXII) R=p-MeC$_6$H$_4$

(XXIII) R=Me

with one equivalent of acid chloride in pyridine) no reaction occurred between (XVII) and p-toluenesulphonyl chloride at temperatures up to 100°. In refluxing pyridine intractable tars were formed. With the more reactive methanesulphonyl chloride a gradual reaction occurred at room temperature to give a complex mixture. An attempt to form the ester (XXIII) by reacting (XVII) with methanesulphonyl chloride in methylene chloride containing triethylamine led to the recovery of starting material. Attempted reaction by phase-transfer catalysis (in chloroform with benzyltriethylammonium chloride) with either p-toluenesulphonyl or methanesulphonyl chloride gave unchanged starting material when potassium carbonate was used as the base.

Reaction of methanesulphonic anhydride either neat at 111° or in pyridine at 100° afforded mixtures.

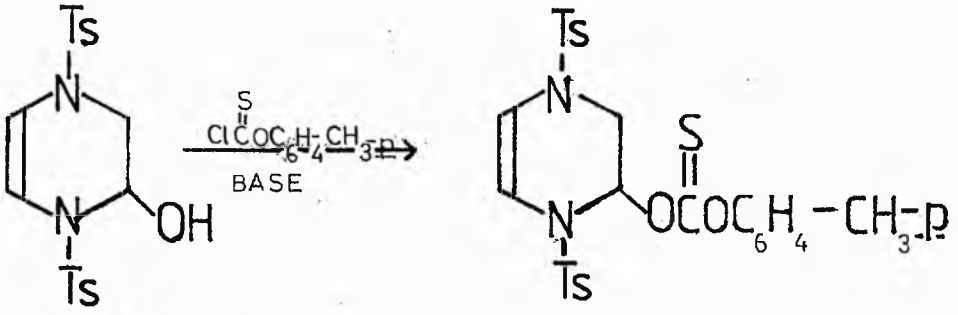
The Chugaev reaction (pyrolysis of xanthates)[79] has been successfully employed for the synthesis of many olefins, and accordingly an attempt was made to convert (XVII) into the xanthate (XXIV) as shown below.



(XVII) (XXIV)

Unfortunately only tars could be isolated both under standard conditions and using dimsyl sodium as the base.

p-Tolyl chlorothionoformate[80] was used in an attempt to prepare the thioester (XXV) but mixtures were obtained when either pyridine or triethylamine were used as the base even at room temperature.

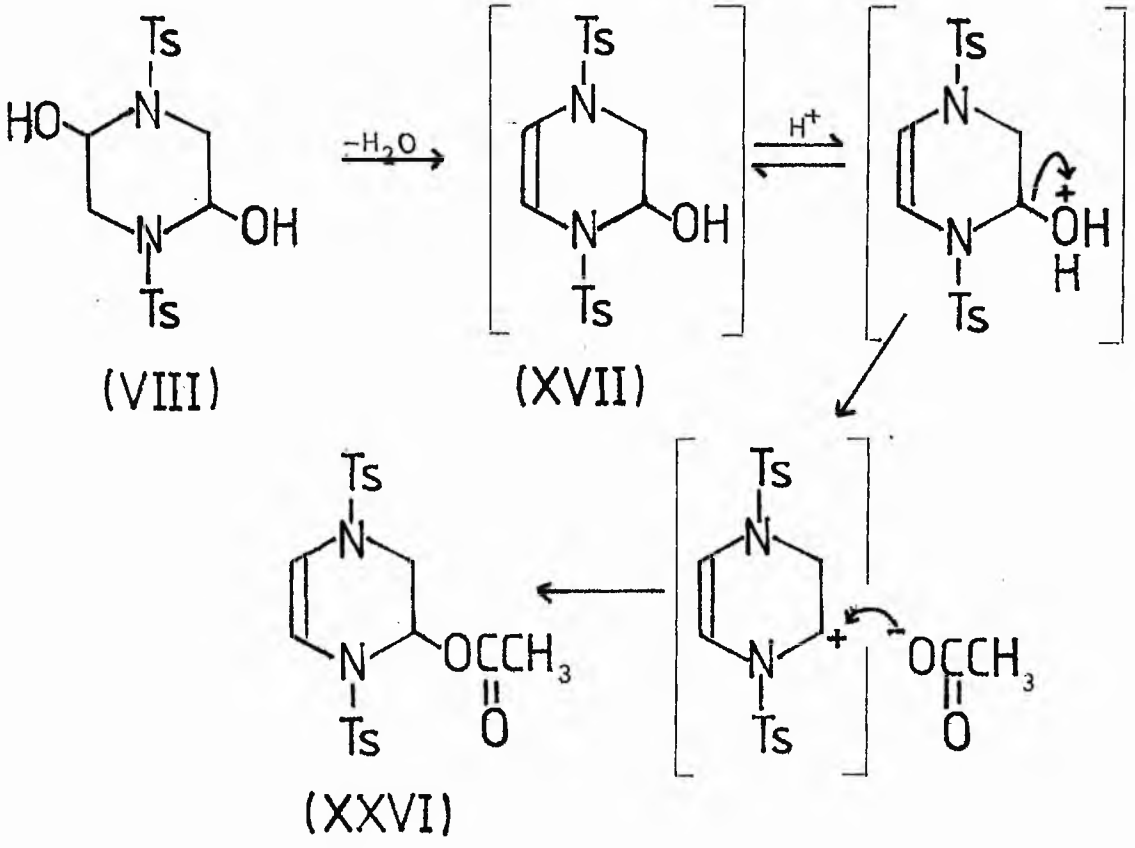


(XVII) (XXV)

The attempted preparation of the 2-acetoxy compound (XXVI) from (XVII) and acetic anhydride in pyridine was unsuccessful, no reaction occurring at room temperature and mixtures being produced at 100°. However, compound (XXVI) was formed on heating the

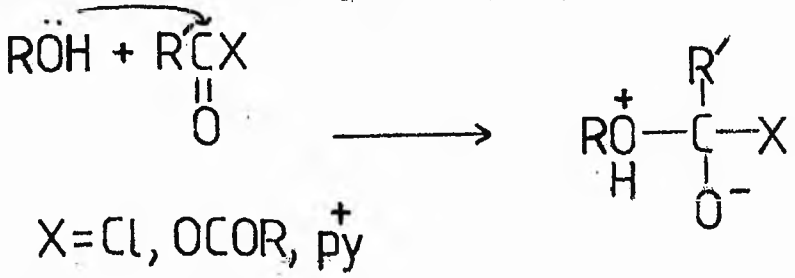
2,5-dihydroxypiperazine (VIII) in acetic anhydride containing conc. hydrochloric acid, a method successfully employed by Eisner and Pashayan[58] for the preparation of the benzenesulphonyl analogue.

In view of the fact that the dihydroxypiperazine (VIII) is known to eliminate water very readily to give (XVII), and that acetic anhydride is a well-known dehydrating agent, it seems likely that the mechanism of formation of (XXVI) from (VIII) is initial elimination of a mole of water followed by the formation of (XVII) as shown.



This mechanism is analogous to that proposed for the interconversion of the 2-hydroxy- and 2-methoxy compounds (XVII) and (XIV) (p. 45). The reaction is assumed to proceed in this way rather than by the more normal tetrahedral mechanism shown below

because if the latter were operative (XXVI) would also be produced



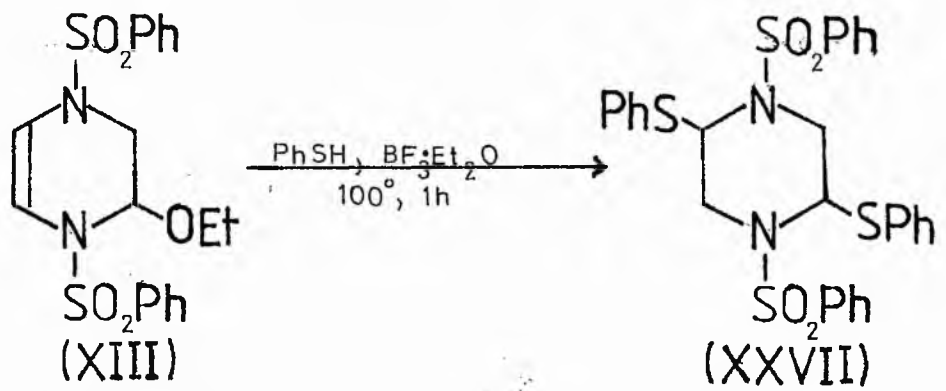
in pyridine. Pyrolysis of acetates being a well known method for the synthesis of olefins, attempts were made to accomplish such a reaction using (XXVI). However, only tars were obtained both on dry heating in vacuo at 100° and on prolonged refluxing in acetic anhydride.

In view of the ready formation of (XXVI) under acidic conditions the synthesis of the analogous trifluoroacetate with trifluoroacetic anhydride was attempted. The trifluoroacetoxy group is a better leaving group and might facilitate the synthesis of (XXI). Treatment of (VIII) with trifluoroacetic anhydride produced a yellow oil which may have contained the desired product. However, it had the same R_F as (XVII) on t.l.c., and on work-up only this compound (XVII) was isolated. It seems likely that the trifluoroacetate was formed but hydrolysed very readily even on t.l.c.. The 2-acetoxy compound (XXVI) also showed a tendency to hydrolyse when kept in air for several weeks and the more reactive trifluoroacetoxy group would be expected to hydrolyse even more easily.

The failure to synthesise any ester of (XVII) under basic conditions leads to speculation on a possible reason for this. The most likely explanation is that the powerful electron withdrawing p-toluenesulphonylamino group reduces the electron density on the oxygen atom of the hydroxyl group to such an extent that it is no longer sufficiently nucleophilic for ester formation.

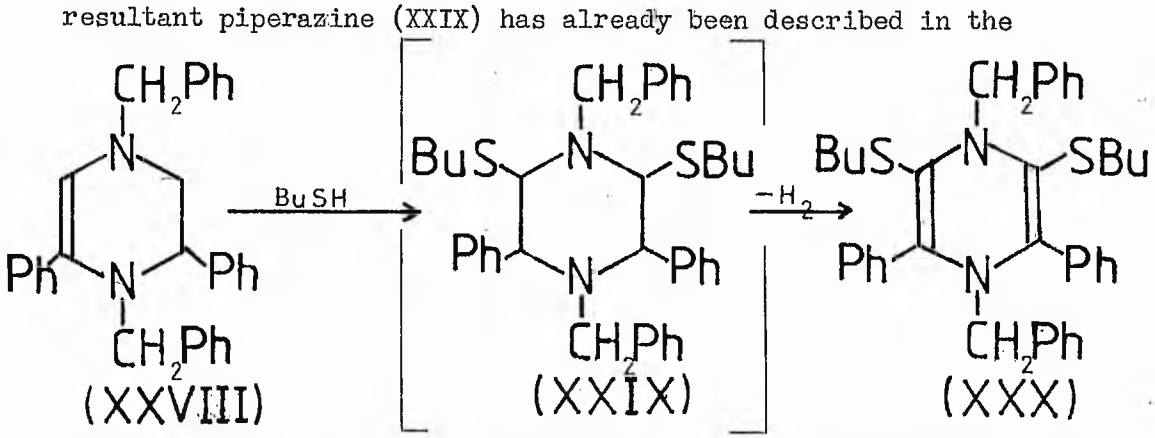
Sulphur Derivatives of 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-Tetrahydropyrazine.

The fact that the 2-hydroxy compound (XVII) readily reacts with alcohols to give 2-alkoxy derivatives suggested that it might be possible to synthesise thioethers by reaction of (XVII) with thiols under similar conditions. Such thioethers have been reported in the literature; Franz[61] obtained the 2,5-bis-(phenylthio)-piperazine (XXVII) by the reaction of the 2-ethoxy compound (XIII) with thiophenol in the presence of boron trifluoride etherate.



(XIII) (XXVII)

The preparation of (XXX) by addition of butanethiol to the 1,4-dihydropyrazine (XXVIII) followed by dehydrogenation of the resultant piperazine (XXIX) has already been described in the

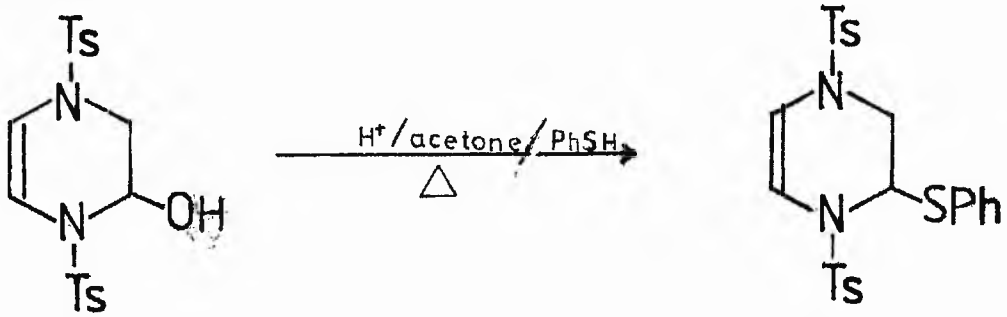


(XXVIII) (XXIX) (XXX)

introduction (p. 15). This extraordinary result does not appear to have any precedent and reinvestigation would seem desirable.

When (XVII) was refluxed in acetone containing conc. HCl and excess thiophenol, 1,4-bis-(p-toluenesulphonyl)-2-phenylthio-

1,2,3,4-tetrahydropyrazine (XXXI) was isolated in almost quantitative yield. Its structure was established by spectral data and elemental analysis.

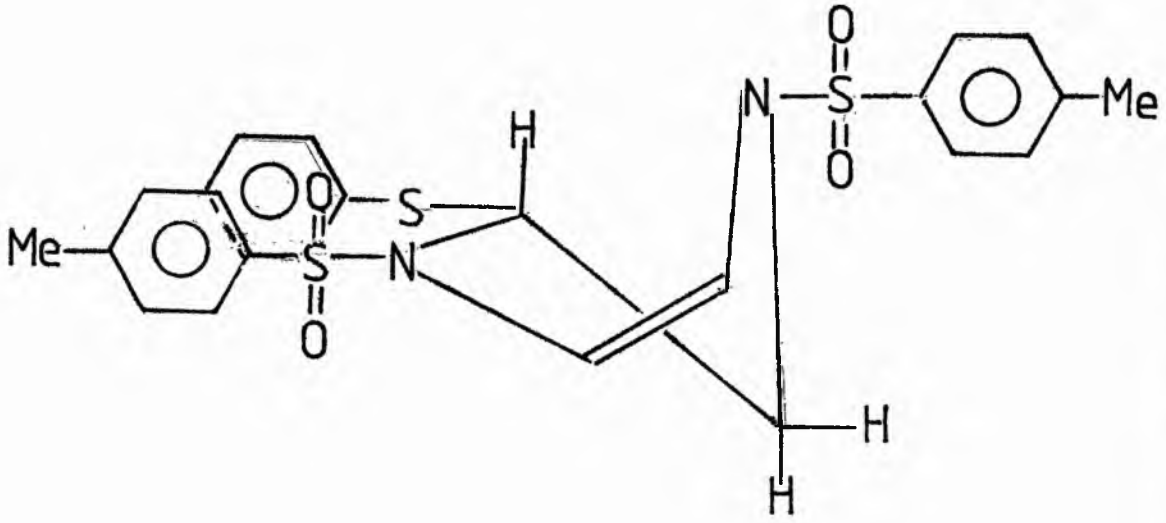


(XVII) (XXXI)

The mechanism of formation of (XXXI) is likely to be the same as that discussed earlier for the 2-alkoxy-1,2,3,4-tetrahydropyrazines (p. 45).

The n.m.r. spectrum of (XXXI) is unusual in that two individual signals are observed for the two aryl methyl groups. This may be due to the fact that one of the p-toluenesulphonyl groups is in the same plane as, and adjacent to, the aromatic ring of the substituent group as shown in (XXXII). This places the two methyl groups in different environments and hence gives rise to different shifts.

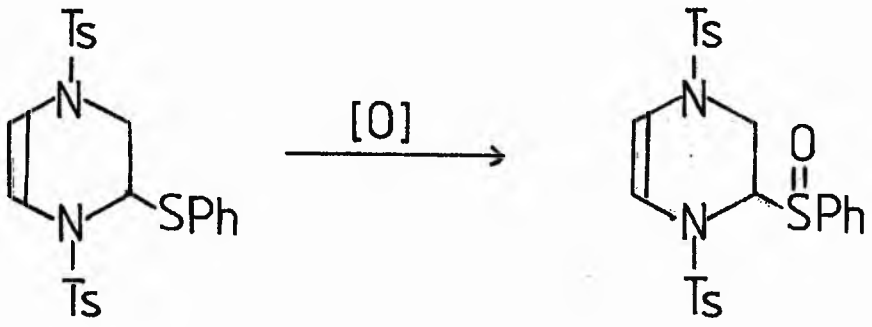
It was decided to attempt the preparation of a sulphonium salt from (XXXI) in order to introduce a good leaving group for elimination. Unfortunately methylation of (XXXI) could not be achieved either with methyl iodide (neat or in various solvents up to 43°) or dimethyl sulphate (heating alone or in dimethylformamide at 100°). In the case of the latter reagent silver tetrafluoroborate was tried as a catalyst[81] but again no reaction took place. It is known that the sulphur of thioethers like (XXXI) is deactivated by a phenyl group and a stronger



(XXXII)

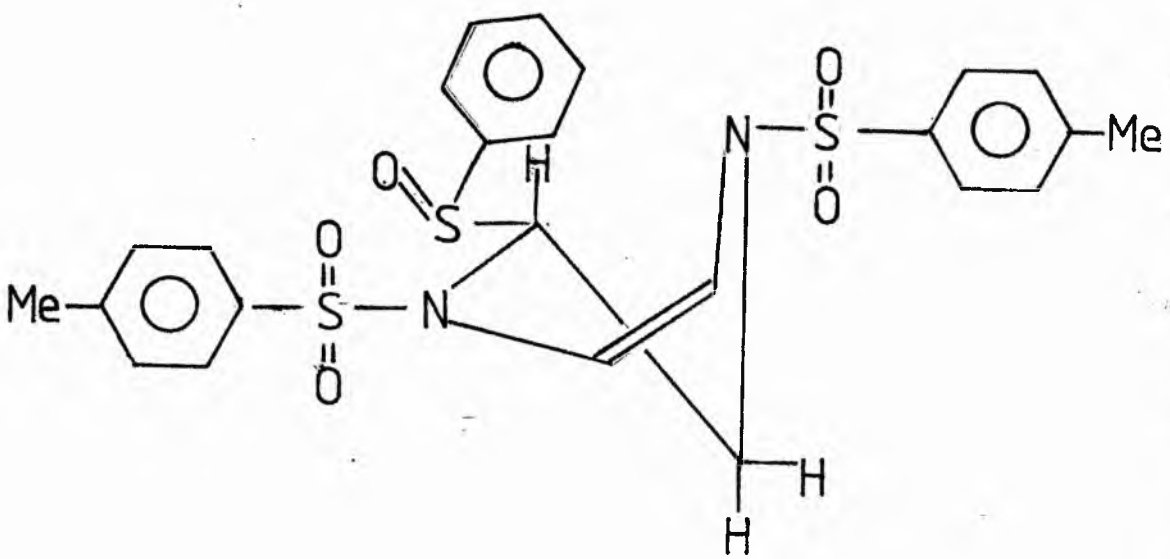
methylating agent (e.g. trimethyloxonium tetrafluoroborate) is probably necessary to accomplish the desired transformation. It is also possible that the formation of a salt is not favoured because of the steric crowding that methylation would create.

Another possible approach to olefin synthesis is the pyrolysis of sulphoxides. Accordingly the 2-phenylthio compound (XXXI) was oxidised; this reaction was successfully accomplished using hydrogen peroxide in acetic acid, m-chloroperbenzoic acid, lithium periodate and iodosobenzene. In all cases the compound isolated was identified as the sulphoxide (XXXIII) by elemental analysis and spectral characteristics. Further oxidation to a sulphone was unsuccessful, unchanged starting material being recovered. When more severe conditions were used mixtures were



(XXXI) (XXXIII)

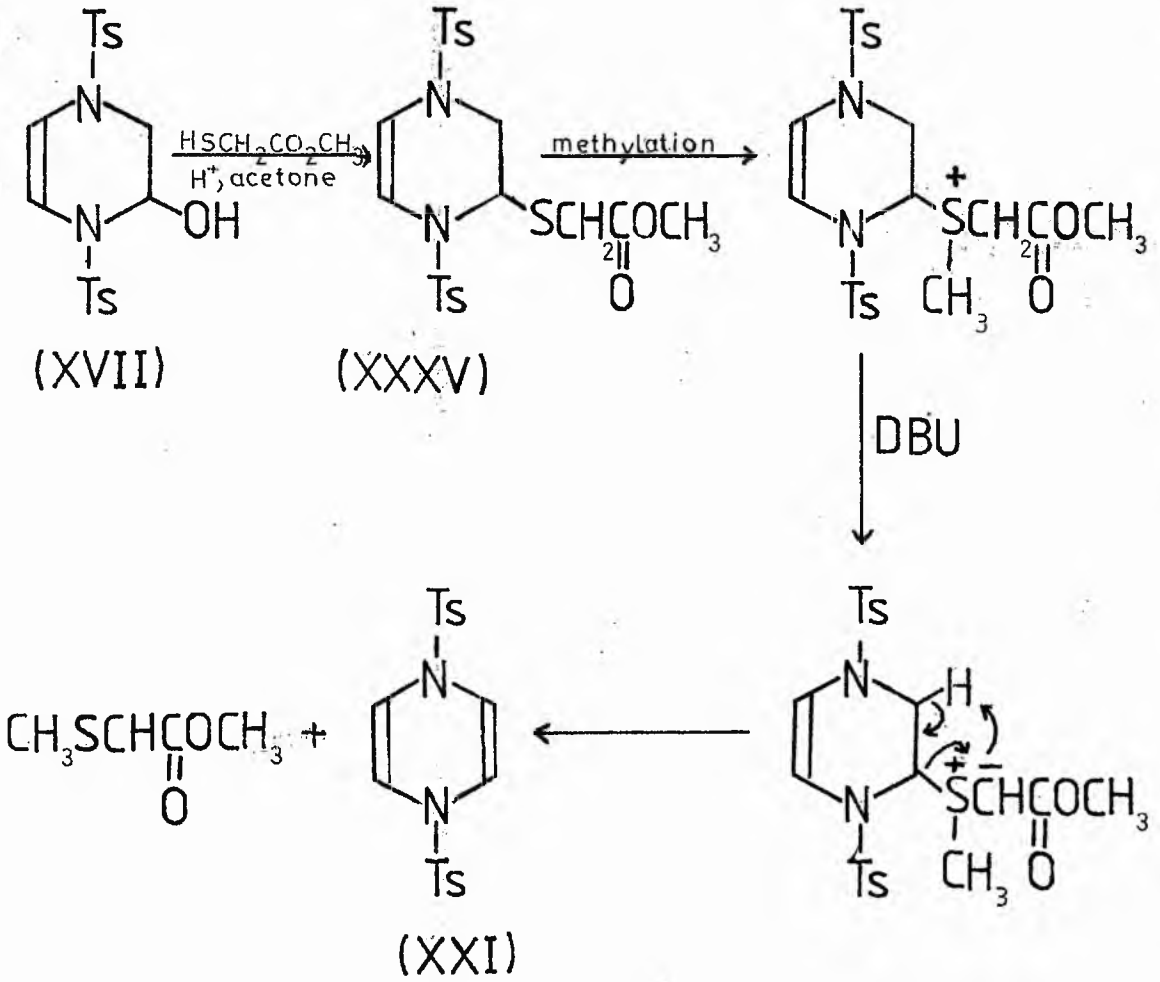
produced. The reason for this is probably steric in origin; it can be seen from (XXXIV) that the introduction of a further oxygen atom would create a very crowded situation.



(XXXIV)

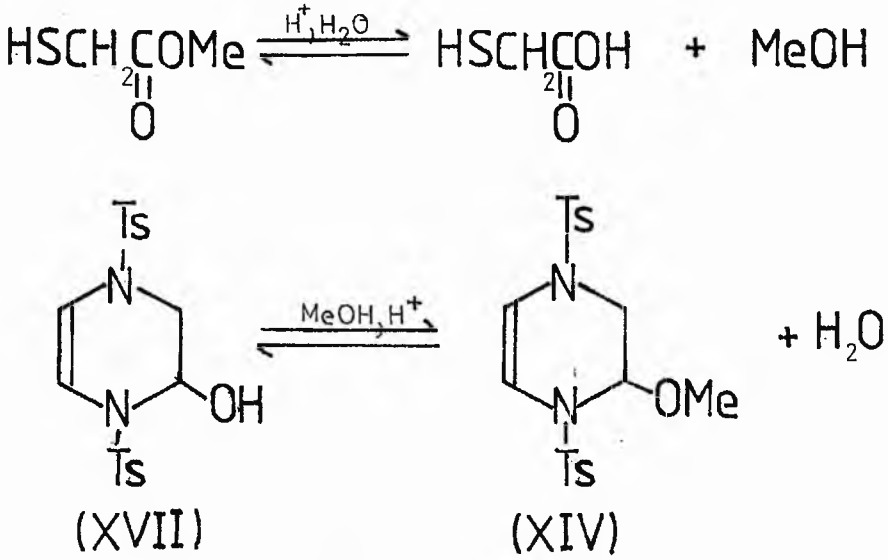
Like the 2-phenylthio compound (XXXI) the sulphoxide (XXXIII) shows two tolyl methyl peaks in the n.m.r. spectrum. An unusual feature is that the proton at C-2(H_C - see earlier

discussion on n.m.r., p. 36) resonates at considerably higher fieldthan that in (XXXI) or indeed any other 2-substituted-1,4-bis-(p-toluenesulphonyl)-2-substituted-1,2,3,4-tetrahydropyrazine prepared in the course of this work. This may be because this proton lies within the shielding zone of the sulphoxide group. Attempts to pyrolyse (XXXIII) either by heating it alone in vacuo or in dry toluene led to intractable mixtures. An attempt was made to react the 2-hydroxy compound (XVII) with methyl thioglycolate to form (XXXV); olefins have been synthesised[82] (via ylids as shown) from such compounds and this could provide a route to (XXI).



(XVII) (XXXV) (XXI)

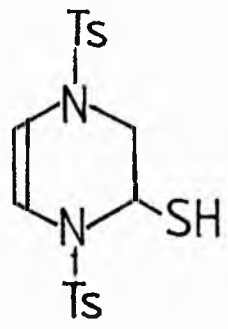
However, attempts to prepare (XXXV) by treating (XVII) in the manner shown failed; instead of the desired product the 2-methoxy compound (XIV) was obtained in excellent yield. This is probably explained by partial hydrolysis of the methyl thioglycolate (by the conc. HCl) to produce methanol. This methanol will react with (XVII) to give the 2-methoxy derivative (XIV) (as described earlier, see p. 45). The other product of this reaction is a mole of water which hydrolyses further methyl thioglycolate the reaction proceeding in this way until total



(XVII) (XIV)

conversion of (XVII) to (XIV) has occurred.

Attempts were made to prepare the thiol (XXXVa) by reaction of (XVII) with hydrogen sulphide in acidified acetone. It was thought possible that this compound might react further to give



(XXXVa)

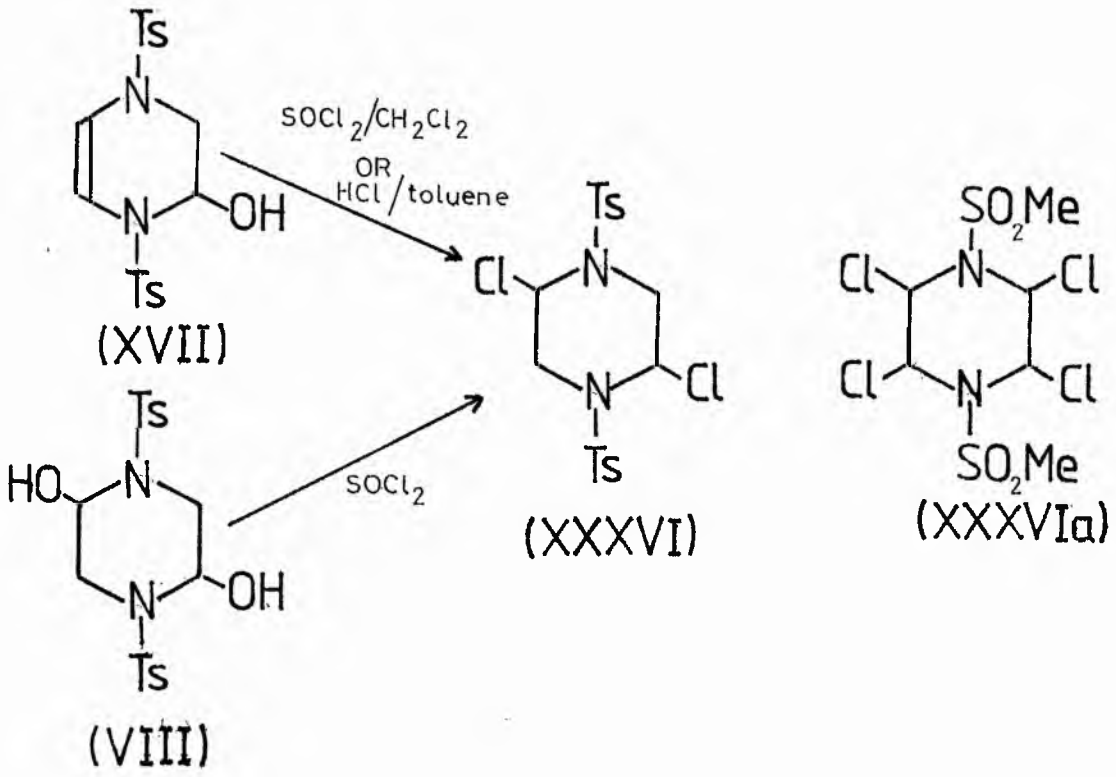
(XXXVb)

the bridged structure(XXXVb), similar compounds to which have been shown to possess considerable biological activity.

Halogen derivatives of 1,4-bis-(p-toluenesulphonyl)-1,2,3,4 - tetrahydropyrazine.

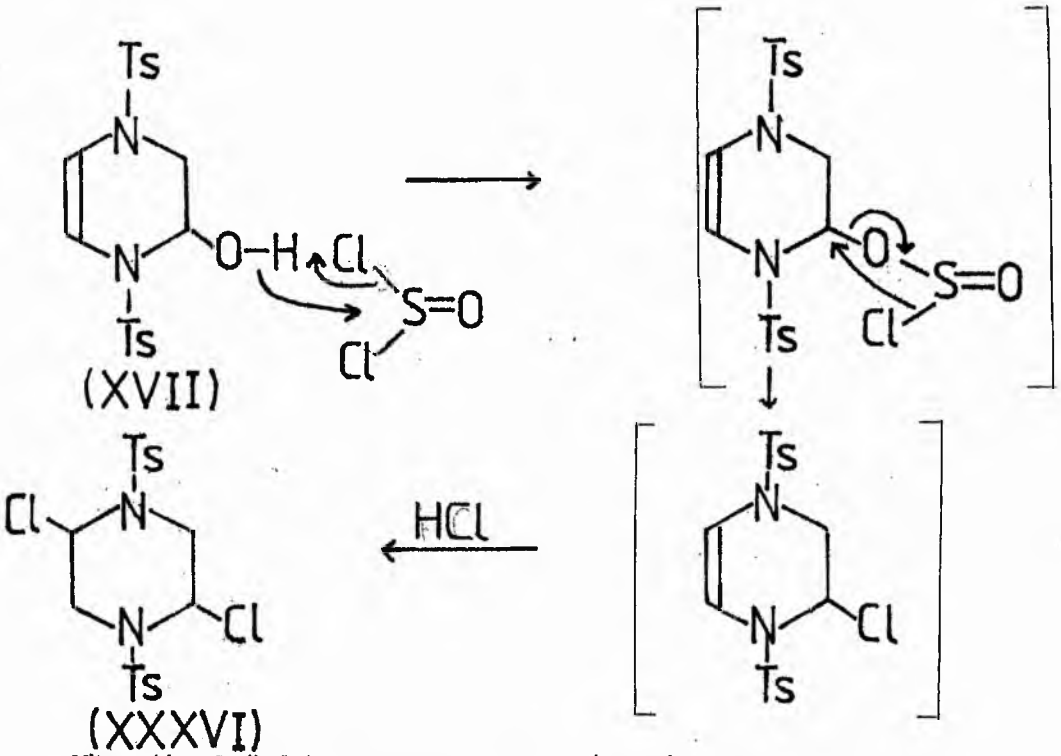
It was decided to attempt the synthesis of a 2-halo substituted-1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine as such a compound would appear to provide easy access to the 1,4-dihydropyrazine (XXI) by elimination of hydrogen halide.

When the 2-hydroxy compound (XVII) was treated with thionyl chloride in methylene chloride, or the 2,5-dihydroxypiperazine (VIII) with thionyl chloride alone, a highly insoluble new compound was formed which was identified as the 2,5-dichloropiperazine (XXXVI) by elemental analysis and its chemical transformations. The same compound (XXXVI) was also formed when (XVII) was treated with dry HCl gas in toluene although this method gave much lower yields than the others.



The surprising lack of solubility of (XXXVI) is paralleled by that reported by Currie et al.[83] for the tetrachloropiperazine (XXXVIa).

The mechanism of formation of (XXXVI) from (XVII) and thionyl chloride is probably as show below although the sequence of chloride formation and addition of HCl is not necessarily as indicated.



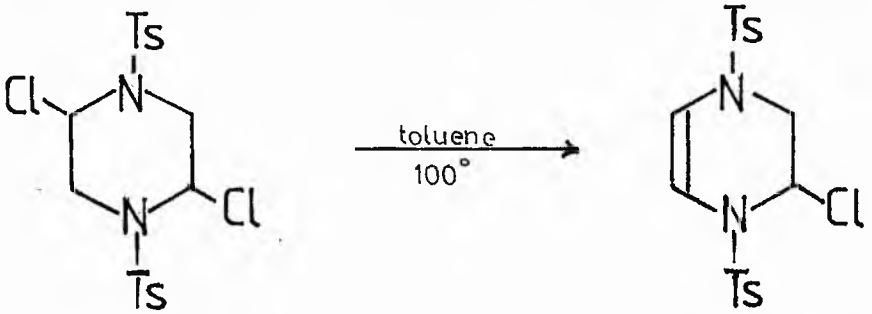
When the 2,5-dihydroxypiperazine (VIII) is the starting material there are two possibilities:

a) direct conversion of the hydroxyl groups into (XXXVI) without going via an olefinic intermediate or,

b) elimination of a mole of water to give (XVII) followed by the reaction shown above. The fact that the interconversion between the 2,5-dimethoxypiperazine (X) and 2,5-dihydroxy analogue (VIII) was shown (see p.47) to proceed via an olefinic intermediate might favour the latter mechanism, but more experimental evidence is required. The reaction of thionyl

chloride with alcohols proceeds with retention of configuration so that if mechanism a) operates the product will have the same trans-configuration as the starting material (see p.20). If an olefinic intermediate is involved then the stereochemistry of (XXXVI) is uncertain.

When (XXXVI) was briefly heated in dry toluene at 100° a new compound, 1,4-bis-(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine (XXXVII), was formed in good yield. Its structure was established from spectral data and elemental analysis. The n.m.r. spectrum of (XXXVII) shows the proton



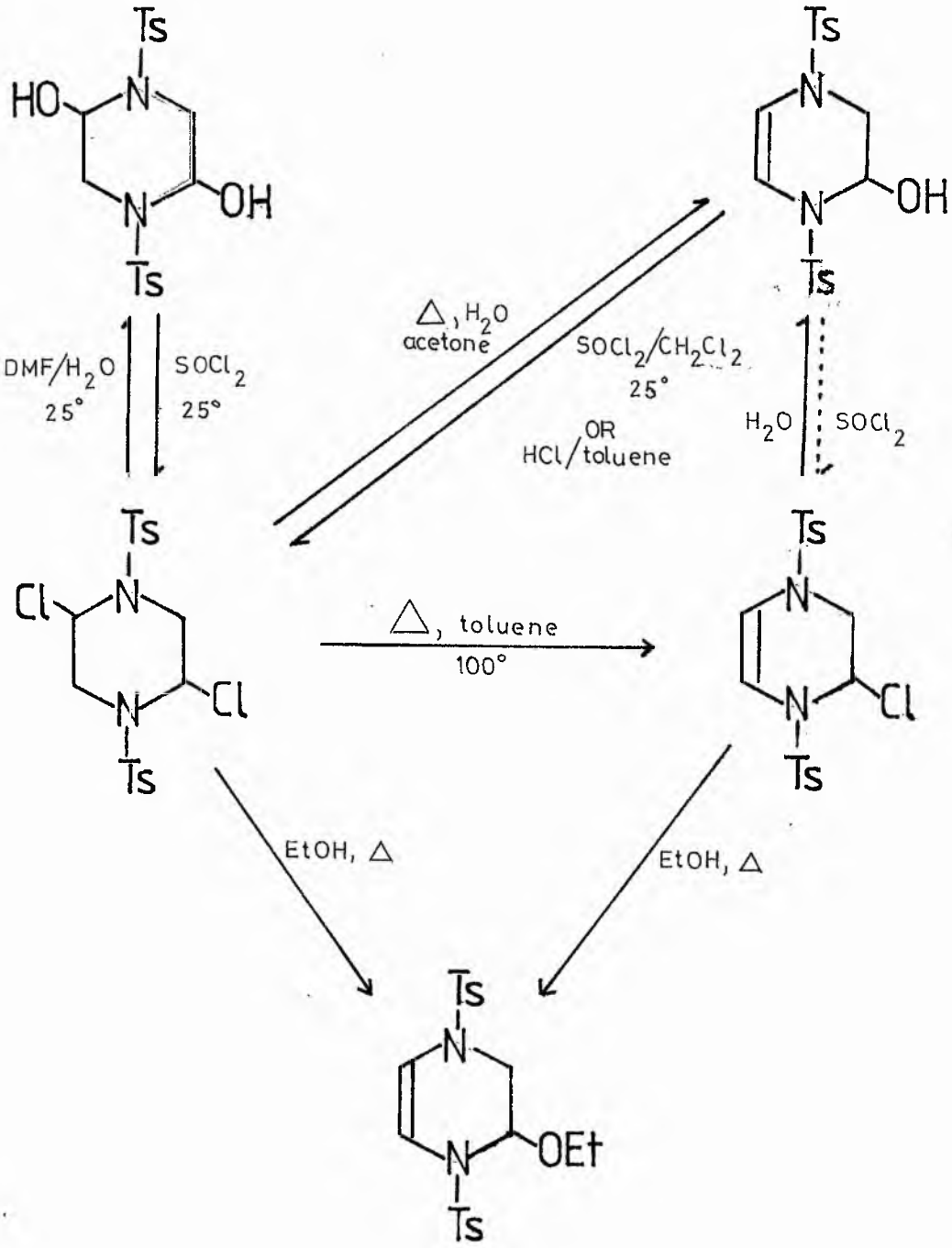
(XXXVI) (XXXVII)

at C_2 (H_C) to resonate at much lower field (6.2δ) than the corresponding proton in other 2-substituted 1,4-bis-(p-toluene-sulphonyl)-1,2,3,4-tetrahydropyrazines; this is attributed to deshielding by the very electronegative chlorine atom.

The benzenesulphonyl- and p-bromobenzenesulphonyl analogues of (XXXVI) and (XXXVII) were similarly prepared.

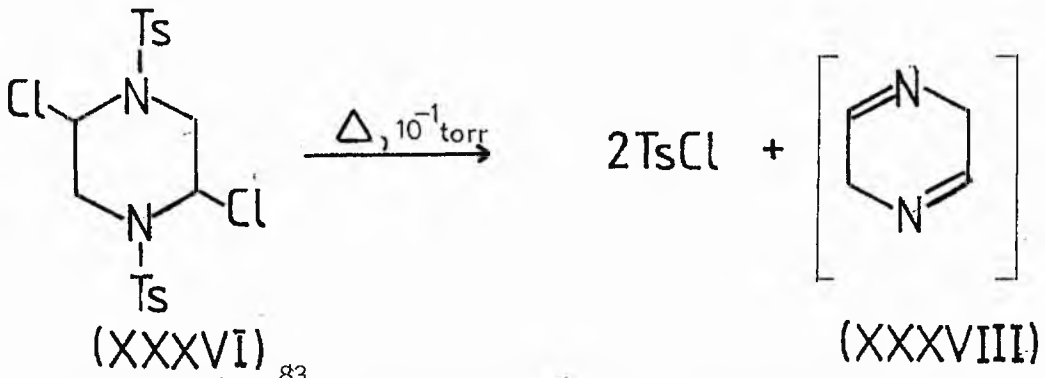
The 2,5-dichloropiperazine (XXXVI) was found to be very reactive towards water and alcohols. It was hydrolysed to the 2,5-dihydroxypiperazine (VIII) by aqueous dimethylformamide at room temperature. On heating in aqueous acetone the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) was formed, while heating (XXXVI) in chloroform gave the 2-ethoxy compound (XV) by reaction

Transformations of halogen derivatives of 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines



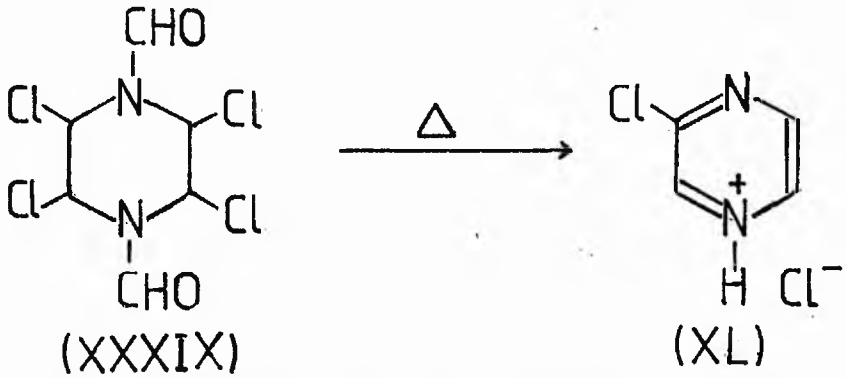
with the stabilising ethanol in the solvent. These reactions involve elimination and hydrolysis or alcoholysis; no experiments have been performed to determine the order of these. The 2-chloro compound (XXXVII) is also easily hydrolysed (see next section). The reactions are summed up in the flow chart (p. 62) . It should be possible to convert (XVII) into (XXXVII) although this particular experiment was not carried out.

On heating (XXXVI) alone in vacuo two equivalents of p-toluenesulphonyl chloride were obtained; the other product may be the 2,5-dihydropyrazine (XXXVIII) but no attempt was made to isolate it.



(XXXVI) (XXXVIII)

Currie et al.[83] report an apparently similar reaction; on heating the tetrachloropiperazine (XXXIX) they obtained (XL).



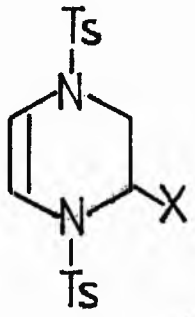
(XXXIX) (XL)

On heating the 2-chloro compound (XXXVII) in toluene at 111° it decomposed to a mixture, one of the components of which was identified as p-toluenesulphonyl chloride.

This type of elimination, the mechanism of which is not clear, may explain the failure of previous attempts to obtain a 1,4-dihydropyrazine by thermal means; it is possible that the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) (p. 47), 2-acetoxy compound (XXVI) (p. 52) and sulphoxide (XXXIII) (p 57) undergo similar reactions.

Prior to the successful preparation of (XXXVI) and (XXXVII) a number of other methods were tried to synthesise halogen derivatives of 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine.

Reaction of (XVII) with triphenylphosphine in carbon tetrachloride[84] was unsuccessful, starting material being recovered. This was attributed to the lack of solubility of (XVII) in the solvent. The reaction of (XVII) with Vilsmeier reagent[85] in dimethylformamide was also unsuccessful, unchanged starting material being recovered. No reaction was observed when (XVII) was treated with either triphenylphosphine/iodine in dimethylformamide[86] or iodine in acetic acid[87] at 100° in an attempt to prepare the 2-iodo compounds (XLI). A method which has been used in the



(XXXVII) X=Cl

(XLI) X=I

preparation of olefins is the reaction of alcohols with methyl-triphenoxyphosphonium iodide to form an iodide which is spontaneously converted into the olefinic product[88]. The 2-hydroxy compound (XVII) was treated with this reagent but no reaction occurred even at 100°; on raising the temperature to 120° tars were produced.

Reactions of 1,4-bis-(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine.

(a) Nucleophilic Substitution*

Since the chlorine in (XXXVII) appeared to be very reactive, presumably because it is ∝ to a nitrogen atom, it was of interest to investigate its nucleophilic substitution reactions.

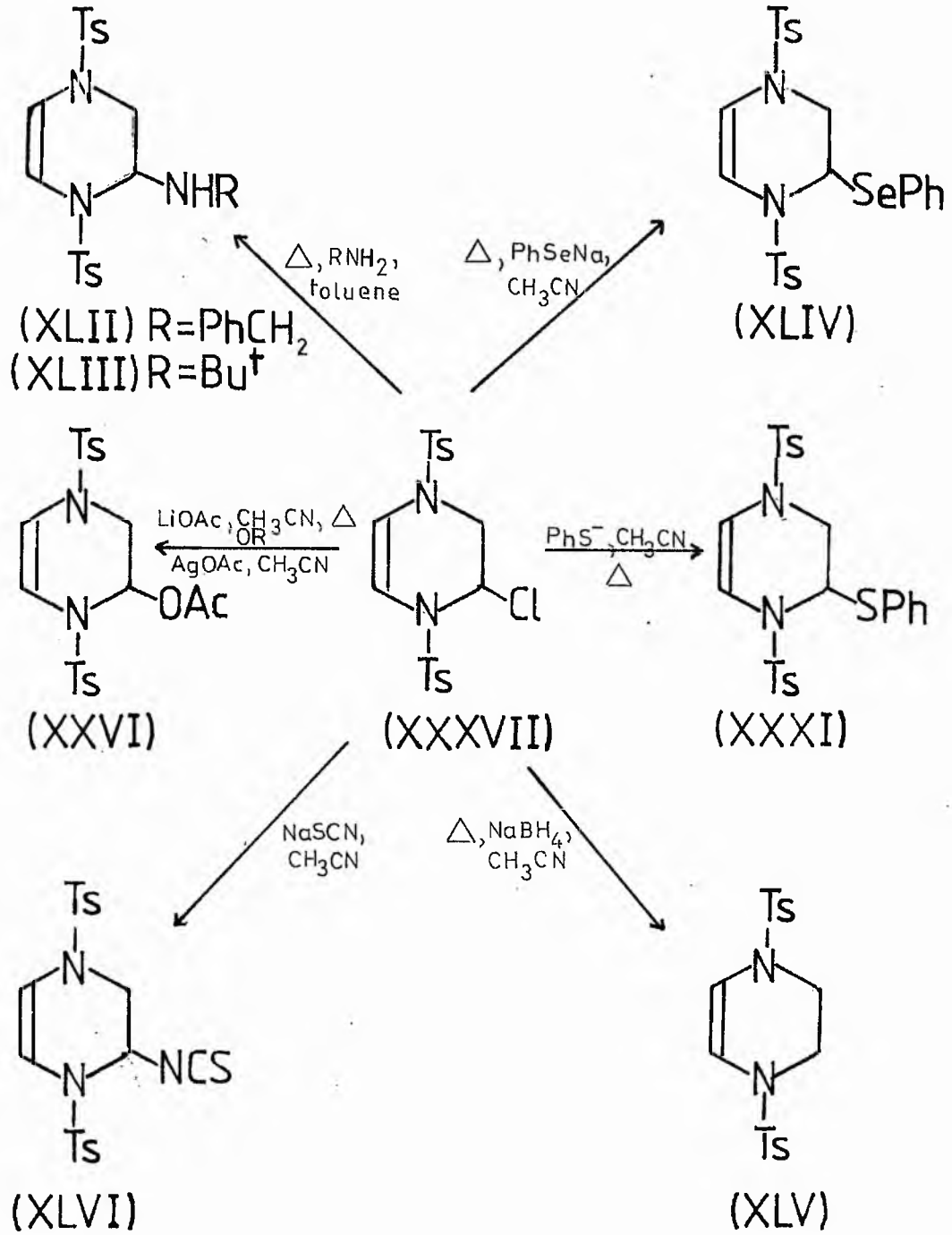
Compound (XXXVII) is very sensitive towards water and alcohols. The solid hydrolysed on prolonged standing in a stoppered vial and reacted with even traces of water or alcohol in solution. This necessitated the use of scrupulously dried aprotic solvents for all the substitution reactions described below. Dimethylformamide and dimethyl sulphoxide have been extensively used as solvents for nucleophilic substitution, but the difficulty of obtaining them totally anhydrous ruled out their use here.

The reaction of (XXXVII) and benzylamine in toluene gave the 2-benzylamino derivative (XLII), identified by its elemental analysis and spectral properties. It possessed a sharp NH stretch at 3310cm^{-1} in the infra-red. Its n.m.r. spectrum showed two separate tolyl methyl peaks like the 2-phenylthio compound (XXXI) (p.54) and presumably for the same reason. Attempted methylation of (XLII) with methyl iodide either neat or in various solvents was unsuccessful, starting material always being recovered. This also happened when (XLII) was heated in toluene with methyl p-toluenesulphonate; on heating (XLII) alone with the latter reagent tars were obtained.

A similar nucleophilic substitution occurred when the 2-chloro compound (XXXVII) was treated with tert.-butylamine; the product (XLIII) was unstable in air and it was not possible

*These reactions are summarised on the flow sheet overleaf.

Nucleophilic substitution reactions of 1,4-bis-(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine.



to obtain correct analytical figures for it. However, it had essentially the expected spectroscopic properties.

The preparation of phenylselenides by nucleophilic substitution of alkyl halides with the selenophenyl anion generated by reduction of diphenyl diselenide with sodium borohydride in ethanol is a well documented procedure[89]. This method was modified by substituting acetonitrile for ethanol as the solvent and the 2-phenylseleno compound (XLIV) was successfully prepared from (XXXVII). It was identified by its elemental analysis and infra-red and n.m.r. spectra; the latter were very similar to those of the 2-phenylthio compound (XXXI).

The 2-phenylthio-1,2,3,4-tetrahydropyrazine (XXXI) was prepared in a similar reaction by treating (XXXVII) with sodium thiophenoxide in acetonitrile; the product was identical with that synthesised by an alternative route (see p. 54).

The 2-acetoxy compound (XXVI) (p.51) was obtained by treatment of (XXXVII) with lithium acetate in acetonitrile; sodium acetate did not react owing to its insolubility. Compound (XXXVI) was also formed when the 2-chloro compound (XXXVII) reacted with silver acetate in acetonitrile.

An example of nucleophilic substitution of (XXXVII) which indicates the lability of its chlorine atom was its reduction by sodium borohydride in acetonitrile to give 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine (XLV), a reaction only given by very reactive alkyl halides.

Attempts to convert the 2-chloro compound (XXXVII) into the 2-iodo-1,2,3,4-tetrahydropyrazine (XLI) by the standard method of refluxing in acetone with sodium iodide were unsuccessful, the only isolable product being the 2-hydroxy compound (XVII). When (XXXVII)

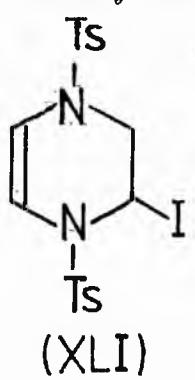
was treated with sodium iodide in acetonitrile mixtures were obtained. In view of the ready hydrolysis of the 2-chloro compound (XXXVII) it is likely that (XLI) would be even more susceptible to such a reaction and attempts to prepare it were abandoned. It is possible that the synthesis of (XLI) might be achieved by working under totally anhydrous conditions using special techniques.

Reaction of the 2-chloro compound (XXXVII) with sodium, potassium or ammonium thiocyanate in acetonitrile resulted in a rapid reaction at room temperature with the precipitation of sodium chloride. The n.m.r. spectrum of the product was consistent with either the isothiocyanate (XLVI) or the thiocyanate (XLVIa) structure, thiocyanate ion being an ambident nucleophile which is known to attack in either of two ways. Confirmation of the isothiocyanate structure (XLVI) was provided by the infra-red spectrum which had an intense, broad absorption at 2000cm^{-1}. This is characteristic of isothiocyanates; thiocyanates possess a sharp peak in this region[90]. The product was unstable to light, moisture and bases and correct analytical figures could not be obtained for it. When treated with DBN in $CDCl_3$ (XLVI) gave a product with a very similar n.m.r. spectrum to that obtained from the 2-chloro compound (XXXVII) under the same conditions (p.71). Attempts to reduce the compound with sodium borohydride gave foul smelling mixtures while reaction with water gave the 2-hydroxy compound (XVII). Attempts to prepare a cyclised derivative by reaction with mercaptoacetic acid led to the isolation of a very insoluble product the structure of which has not been determined.

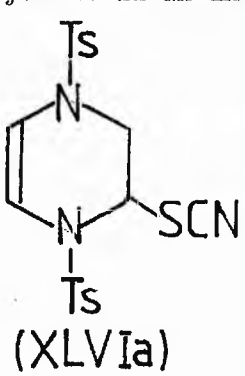
The reaction of the 2-chloro compound (XXXVII) with cyanide ion was attempted but despite a great deal of effort it was not possible to synthesise the cyanide (XLVIII). Early experiments

using potassium cyanide in dimethylformamide were unsuccessful and only the 2-hydroxy compound (XVII) was isolated even when the solvent was carefully dried[91]. Although totally dry dimethylformamide is probably impossible to obtain[91], a blank experiment heating the 2-chloro compound at 100° in dimethylformamide alone did not lead to the formation of (XVII). On refluxing (XXXVII) with potassium cyanide in acetone (XVII) was again produced. Attempts to solubilise potassium cyanide in acetonitrile or methylene chloride with the crown ether dibenzo-18-crown-6 were unsuccessful suggesting that this latter reagent is not as suitable for this purpose as 18-crown-6 which has been used successfully for the preparation of cyanides. When this last named crown ether was complexed with potassium cyanide and refluxed with (XXXVII) in dry acetonitrile, however, the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) was again obtained. No reaction occurred when a solution of (XXXVII) was stirred with solid silver cyanide in acetonitrile.

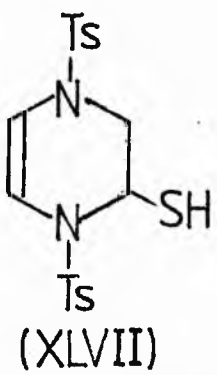
The reason for the isolation of the hydrolysis product (XVII) rather than (XLVIII) may possibly be attributed to the presence of potassium carbonate in the potassium cyanide used, the former reacting preferentially with the chloride (XXXVII). A suitable method for the synthesis of (XLVIII) would perhaps be reaction of (XXXVII) with tetrabutylammonium cyanide in an inert solvent.



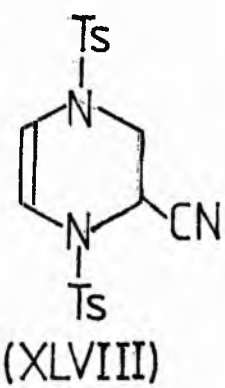
(XLI)



(XLVIa)



(XLVII)



(XLVIII)

(XLVII)

It was not possible to prepare a sulphide/by the reaction of the 2-chloro compound with sodium sulphide ($Na_2S.9H_2O$) in acetone

or acetonitrile, the 2-hydroxy compound (XVII) being produced. This may be attributed to the fact that the reagent is a hydrated salt; it is also only sparingly soluble in the solvents used. A totally dry solution of lithium sulphide was prepared by passing dry hydrogen sulphide into a solution of phenyl lithium in dry tetrahydrofuran. Refluxing this solution with (XXXVII), however, led to mixtures.

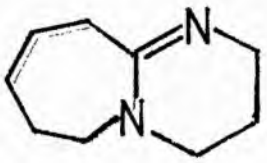
All the nucleophilic substitution reactions mentioned in this section are summarised on the flow diagram. It was found that the 2-chloro compound (XXXVII) reacted faster with sodium methoxide in methanol than with the latter alone. This indicates an S_N2 substitution, as for S_N1 substitution the reaction rate is independent of the nucleophile. It is likely that most of the reactions discussed in this section proceed by S_N2 mechanisms, the exception being the reaction of (XXXVII) with silver acetate which is almost certainly S_N1.

b) Attempted elimination reactions.

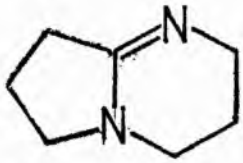
Many bases have been used to effect elimination of hydrogen halide but clearly many (for example sodium ethoxide) are not suitable for use with (XXXVII) due to their high nucleophilicity and hence the likelihood of competing substitution reactions. Tertiary organic bases, on the other hand, do not present this problem. When (XXXVII) was refluxed in triethylamine intractable tars were produced; a similar but slower reaction was observed when (XXXVII) was treated with triethylamine at room temperature in methylene chloride.

Two non-nucleophilic bases which have been widely used in recent years for the elimination of hydrogen chloride are diazabicyclo[5.4.0]undec-5-ene[92] (DBU) (L) and diazabicyclo[4.3.0]non-

5-ene[93] (DBN) (LI). Treatment of (XXXVII) with DBU led to the



(L)



(LI)

formation of intractable mixtures under all conditions tried. Attempts to follow the reaction by n.m.r. in deuterochloroform showed no sign of the required product (XXI). With DBN in dry toluene at room temperature (XXXVII) gave an oily mixture the components of which could not be separated by chromatography; the n.m.r. of this mixture showed a broad peak in the olefinic region (6.08) but the spectrum was not changed by shaking the solution with water. The desired product (XXI) might be expected to undergo rapid addition of water to give 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) recognisable by its characteristic spectrum.

Another highly non-nucleophilic base used for elimination is 1,8-bis-(dimethylamino) naphthalene ('proton sponge')[94]. However, the 2-chloro compound (XXXVII) did not react with this reagent, starting material being recovered even on heating in toluene at 100°.

The lack of success with organic bases led to attempts to achieve the required elimination by means of inorganic bases. No reaction was observed when (XXXVII) was stirred with either sodium hydride or sodamide in tetrahydrofuran; with phenyl lithium it was rapidly converted into tars.

A possible explanation for the lack of success in the above

experiments may be that (XXXVII) readily eliminates HCl but that the resulting 1,4-dihydropyrazine (XXI) is so reactive that it undergoes a variety of reactions (e.g. polymerisation, isomerisation, oxidation, etc.) to give mixtures.

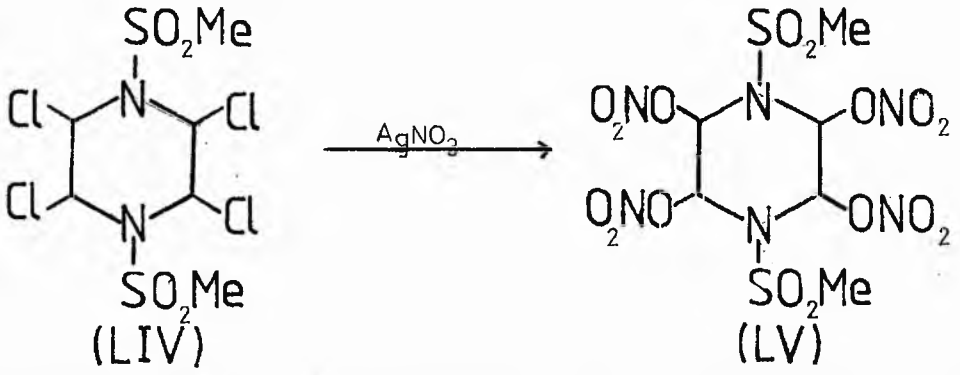
Silver salts have been used[95] to synthesise olefins from halides. On treatment of (XXXVII) with a solution of silver tetrafluoroborate in dry acetonitrile, acetone, or benzene, silver chloride was precipitated in quantitative yield and a product which appeared homogeneous by t.l.c. was isolated from the solution. This compound (LII) was an amorphous white solid which could not be obtained crystalline; it had a very broad n.m.r. spectrum which showed signals for the tolyl methyl group and aromatic protons. In view of the reported[52] tendency of 1,4-dihydropyrazines to oxidise to stable paramagnetic radical species (which give broad n.m.r. spectra) this would appear to be evidence for the presence of the required compound (XXI). Further evidence was provided by the fact that on shaking a solution of (LII) in deuterochloroform with water or ethanol a sharp spectrum of the respective 2-substituted 1,4-bis-(p-toluene-sulphonyl)-1,2,3,4-tetrahydropyrazine (XVII) or (XV) was obtained. When (LII) was treated with these reagents in preparative experiments (XVII) and (XV) were isolated in good yield. However, the reproducible elemental analysis of (LII) was not in accordance with the proposed structure nor with that of a tetrafluoroborate (see experimental) and the molecular weight (580) suggests the presence of some polymeric material in the product. This latter observation was supported by the mass spectrum of (LII).

A similar product (LIII) was obtained when (XXXVII) was treated with silver nitrate in acetonitrile. This compound had the same

properties as that obtained from silver tetrafluoroborate but it had a slightly different elemental analysis.

Attempts were made to trap any 1,4-dihydropyrazine formed in this reaction both with bromine and by means of a [4 + 2]cycloaddition with furan, cyclopentadiene and 2,3-dimethylbutadiene. With bromine mixtures were obtained, while the dienes did not react, the same product being obtained as in their absence. When the isolated product (LIII) was warmed with cyclopentadiene a vigorous exothermic reaction occurred with tars being produced.

Currie et al.[83] have prepared the tetranitrato compound (LV) by reaction of the tetrachloro compound (LIV) with silver nitrate and during the present investigation the 2-acetoxy compound (XXVI) was

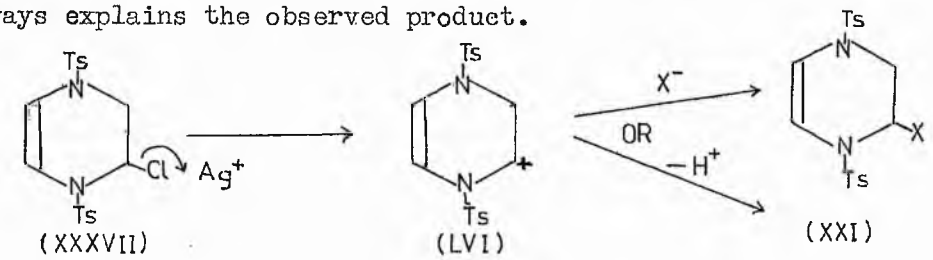


(LIV) (LV)

prepared by reaction of (XXXVII) with silver acetate (p.67). These facts would indicate that (LII) might be a nitrate; however elemental analysis did not support this theory (see experimental).

The first step in the formation of (LII) and (LIII) is presumably loss of chloride to give the carbonium ion (LVI).

This may then lose a proton to give the 1,4-dihydropyrazine or undergo attack by a nucleophile. However, neither of these pathways explains the observed product.

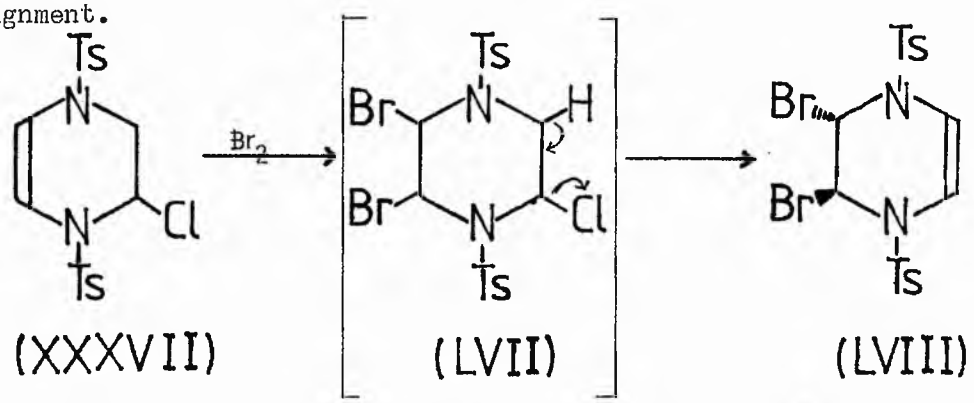


(XXXVII) (LVI) (XXI)

Preparation and reactions of trans-1,4-bis-(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4 -tetrahydropyrazine.

The ready electrophilic addition reactions of the double bond in 2-substituted-1,4,-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines led to an investigation of their reaction with bromine.

On treating the 2-chloro compound (XXXVII) with bromine in acetonitrile or methylene chloride an instantaneous reaction occurred, the bromine being decolourised and white fumes being evolved. Evaporation of the solvent yielded a solid which was shown by elemental analysis to have the molecular formula $C_{18}H_{18}N_2S_2O_4Br_2$ and which possessed the absorption at ~1650cm^{-1} in the infra-red characteristic of the 1,2,3,4 -tetrahydropyrazine double bond. The n.m.r. spectrum, which showed singlets at 6.30 δ and 6.80 δ, corresponding to the olefinic protons and those in the 2- and 3- positions, was consistent with the 2,3-dibromo-1,2,3,4-tetrahydropyrazine structure (LVIII). The ^{13}C n.m.r. spectrum was also in agreement with this assignment.



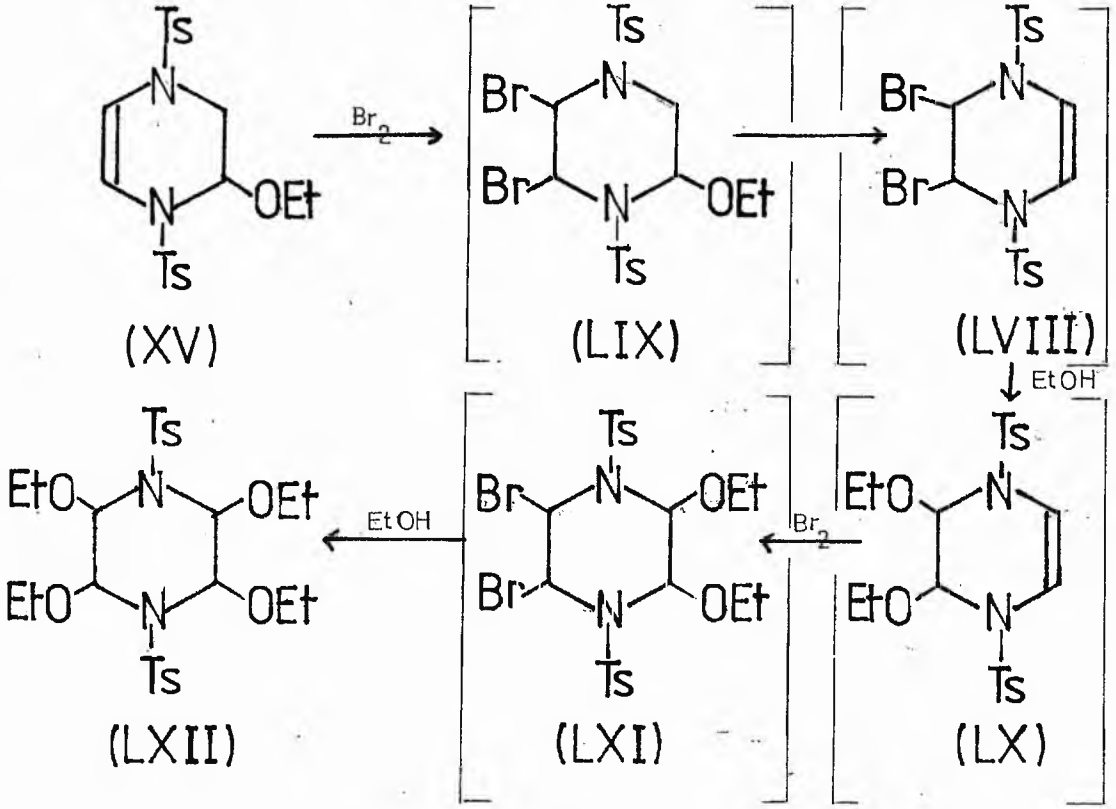
(XXXVII) (LVII) (LVIII)

The initial addition product, the 2-chloro-5,6-dibromopiperazine (LVII) is presumably not isolated because steric crowding makes it very unstable. Because the bromine atoms in this molecule may reasonably be assumed to be trans - diaxial, elimination of hydrogen bromide is not possible. Strain is therefore relieved by elimination of HCl, even though chloride is a poorer leaving group than bromide.

The same compound (LVIII) was also formed when the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) was treated with bromine in methylene chloride, presumably via an intermediate analogous to (LVII) followed by elimination of water.

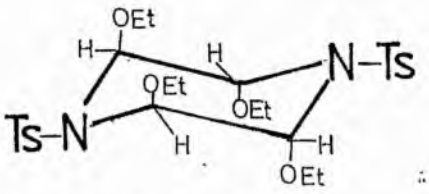
When bromine was added to the 2-ethoxy compound (XV) in acetonitrile a mixture was obtained. The reaction was followed by n.m.r.; when one mole of bromine was added the presence of the 2-ethoxy compound (XV), ethanol, and the 2,3-diethoxy compound (LX) was indicated (by their ethyl $\underline{CH_3}$ signals). The addition of further bromine led only to intractable mixtures. When bromination of (XV) was carried out in the presence of ethanol a compound was isolated which was identified by its elemental analysis and spectral properties as the tetraethoxypiperazine (LXII).

These results are probably due to the fact that the ethoxy group is a much poorer leaving group than either hydroxy or chloro. Presumably a sequence of reactions occurs like that shown below which can only go to completion in the presence of excess ethanol.

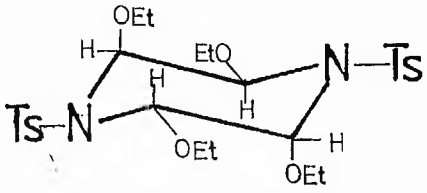


Because this compound (LXII) is prepared by nucleophilic substitution of trans - bromine atoms only two of the possible stereoisomers can occur; (LXIIa) and (LXIIb).

The sharp melting point and simple n.m.r. spectrum of



(LXIIa)



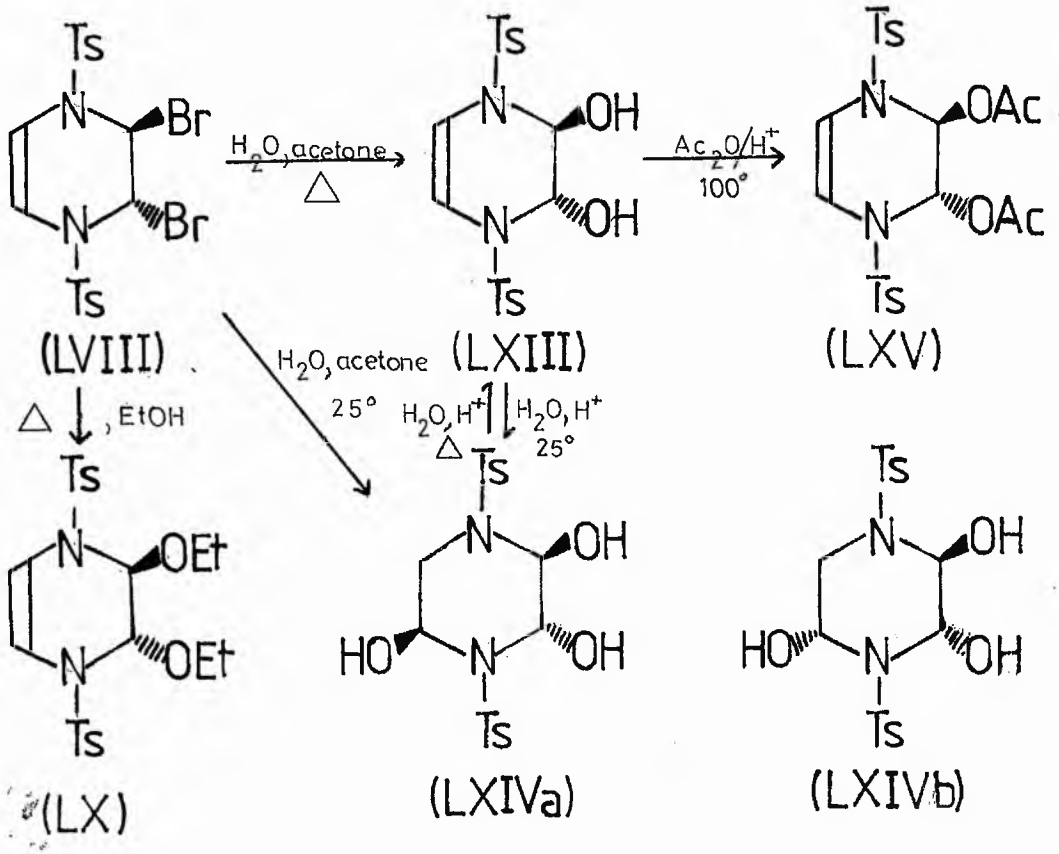
(LXIIb)

(LXII) indicate that only one of these is likely to be present. It can be seen that in (LXIIa) all the ring hydrogens are equatorial and would be expected to give a single peak in the n.m.r., while in (LXIIb) two are axial and two equatorial indicating a more complex spectrum. As the observed resonance for (LXII) is a sharp singlet (LXIIa) would appear the more likely configuration.

The 2,3-dibromo compound (LVIII) is extremely reactive towards water and ethanol; in refluxing ethanol it afforded the trans -2,3-diethoxy-1,2,3,4-tetrahydropyrazine (LX). In aqueous acetone the 2,3-dihydroxy compound (LXIII) was obtained.

The 2,3-dihydroxy compound (LXIII) added water under acid conditions in the cold to give the 2,35-trihydroxypiperazine (LXIV) identified by elemental analysis; it was too insoluble for determination of its n.m.r. spectrum.

Because of this it was not possible to say whether the stereochemistry of the compound was as in (LXIVa) or (LXIVb). This reaction was readily reversed on warming : it is similar to the interconversion described earlier (p. 44) for the



2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) and 2,5-dihydroxypiperazine (VIII). The 2,3,5-trihydroxypiperazine (LXIV) was also formed directly from the 2,3-dibromo compound (LVIII) on treatment with aqueous acetone at room temperature.

When the 2,3-dihydroxy-1,2,3,4-tetrahydropyrazine (LXIII) was heated in acetic anhydride containing conc. hydrochloric acid the diacetate (LXV) was formed in quantitative yield, the product being identified by elemental analysis and spectral characteristics.

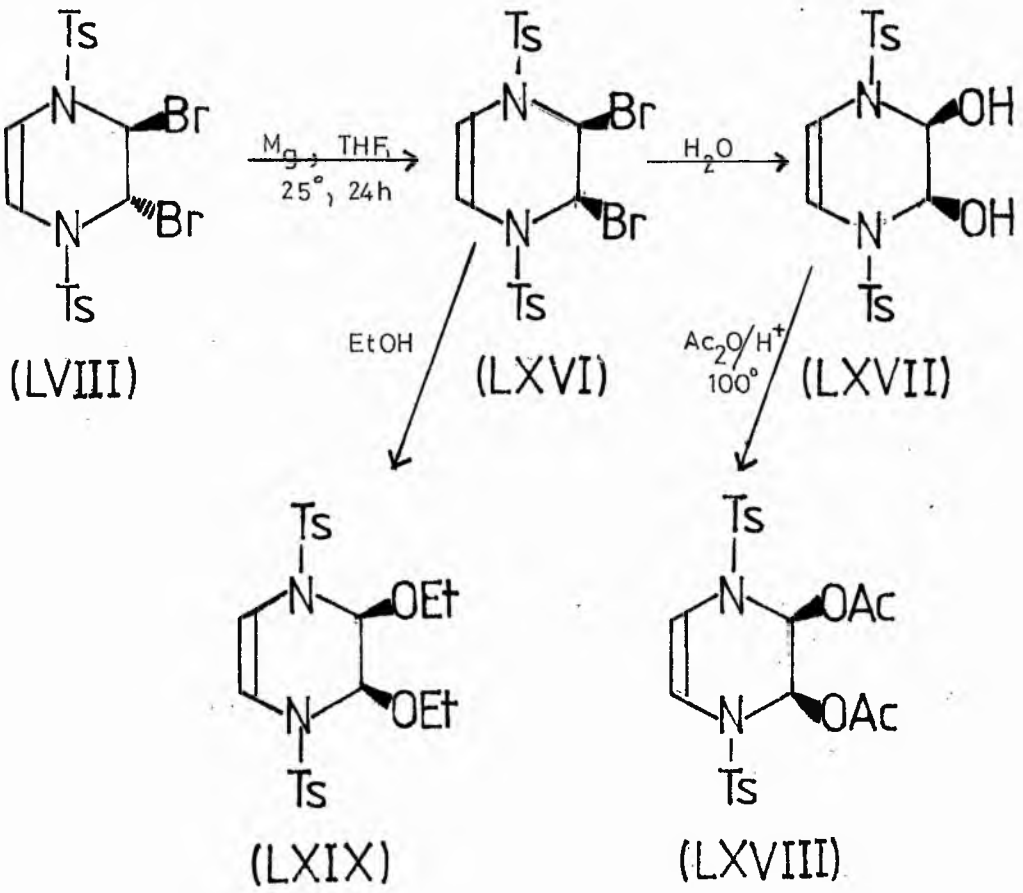
Attempts to tosylate the 2,3-diol (LXIII) both under standard conditions and with p-toluenesulphonyl chloride/4-dimethylaminopyridine in acetonitrile were unsuccessful.

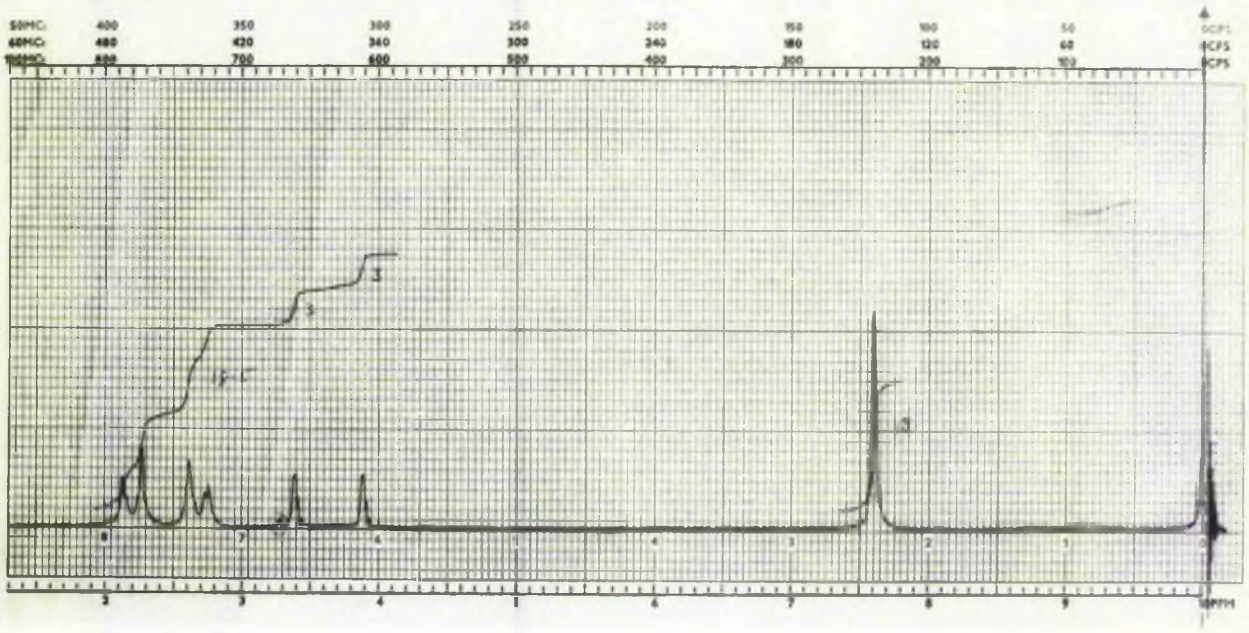
When the 2,3-dibromo compound (LVIII) was heated in methylene

chloride a reaction occurred to give a product which did not contain bromine. It was not possible to identify this compound from spectral data which indicated it to be a mixture even after prolonged refluxing in CH_2Cl_2.

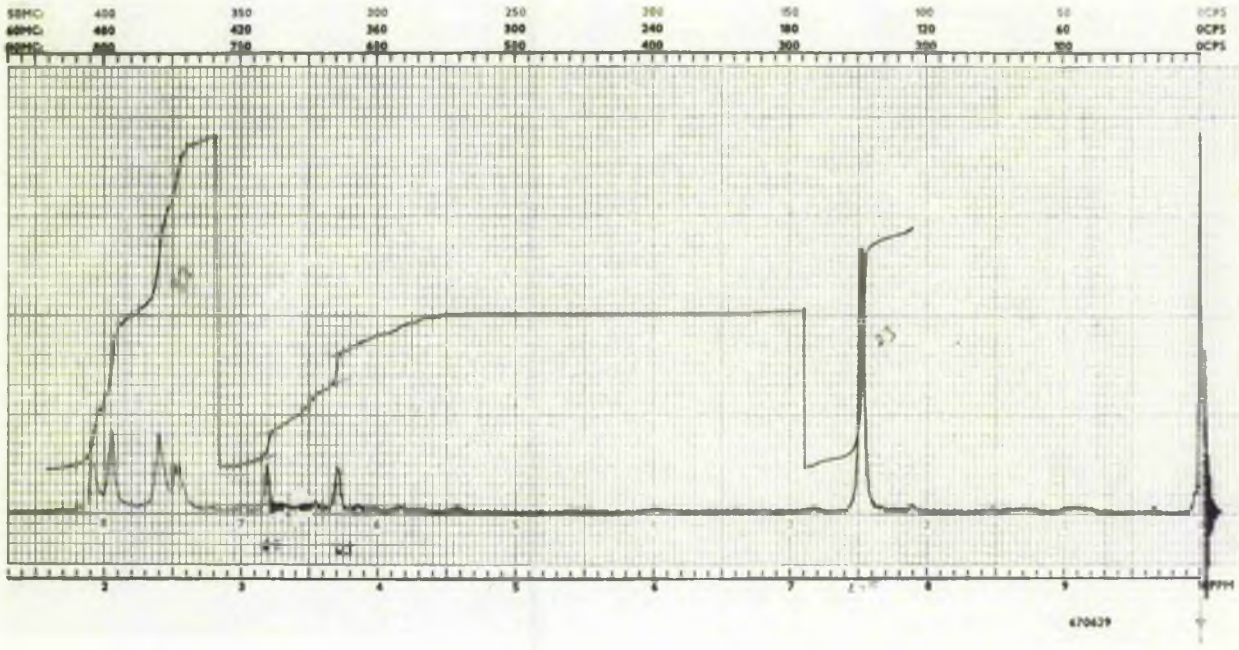
A wide variety of reagents has been used for the elimination of bromine from vicinal dibromides to give olefins, and it was therefore decided to apply this method to the synthesis of the 1,4-dihydropyrazine (XXI) from (LVIII).

In an attempt to eliminate bromine from (LVIII) it was treated with a large excess of magnesium powder in dry tetrahydrofuran. The resulting unstable product was surprisingly found to be the cis-isomer (LXVI). This assignment was confirmed by its infra-red and n.m.r. spectra which resembled those of starting material; the product had resonances at 6.30 δ and 6.80 δ in the n.m.r. as opposed to 6.10 δ and 6.60 δ for the trans-isomer.





Trans 1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine

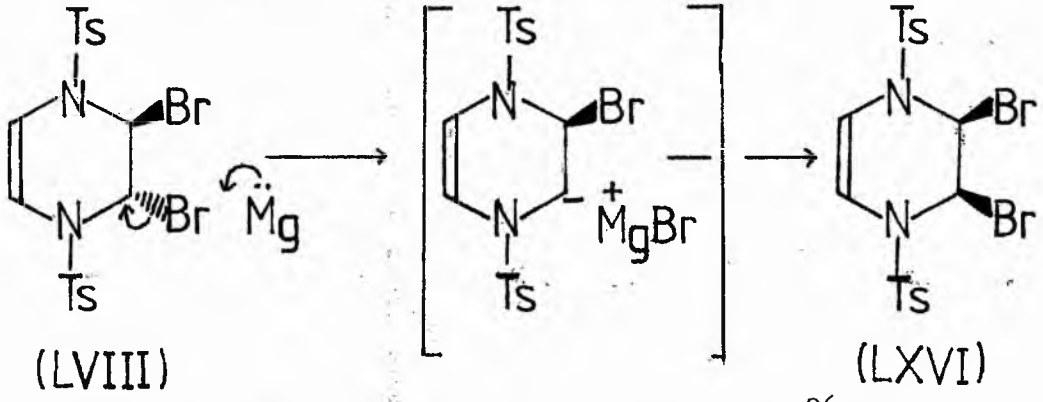


Cis-1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine

60 MHz N.M.R. Spectra of isomeric dibromo compounds (LVIII) and (LXVI)

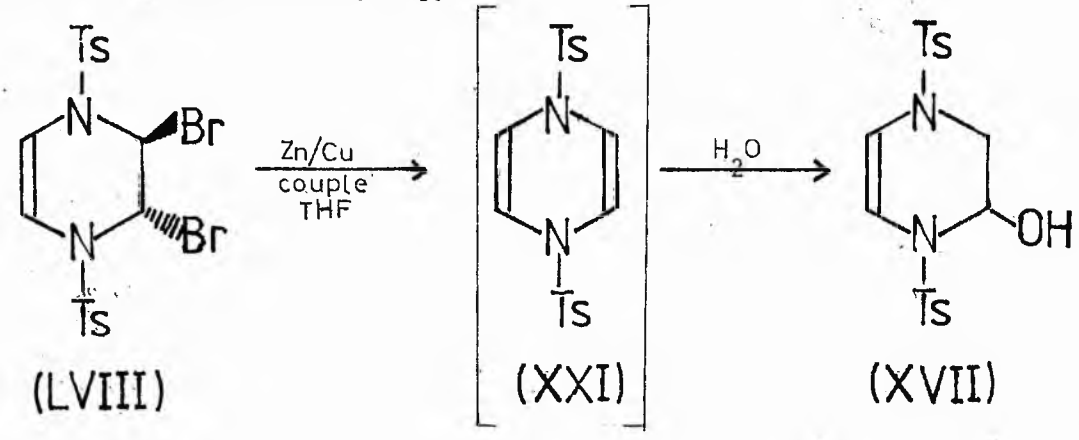
The dibromide (LXVI) hydrolyses even more readily than the trans-isomer (LVIII) and satisfactory analytical figures could not be obtained. It was converted into the cis - 2,3-dihydroxy, - diacetoxy and -diethoxy derivatives (LXVII), (LXVIII) and (LXIX), respectively, by the methods used for the trans-isomer. Elemental analysis and spectral properties of (LXVII - LXIX) fully supported the proposed structures.

The mechanism of the isomerisation of (LVIII) to (LXVI) presumably involves a close ion pair as shown below with the bromine becoming reattached with inversion of configuration.



(LVIII) (LXVI)

The reaction of (LVIII) with zinc/copper couple[96] was investigated. In an early experiment the sole isolated product was the 2-hydroxy-1,2,3,4-tetrahydropyrazine which was obtained in good yield. This strongly suggested the addition of traces of water to an initially formed 1,4-dihydropyrazine.

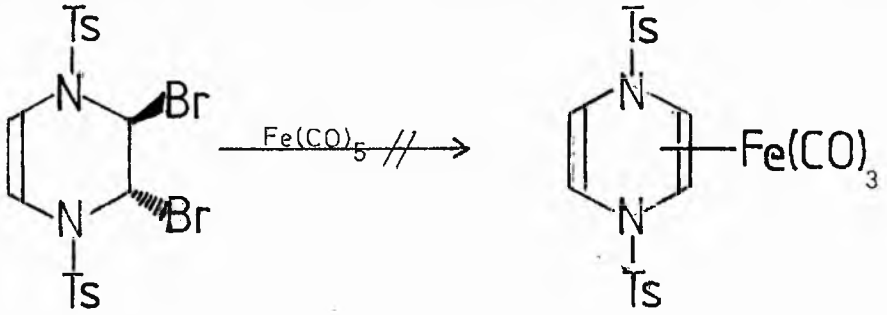


(LVIII) (XXI) (XVII)

Under more rigorously anhydrous conditions the reaction gave a single product which was less polar than starting material on t.l.c.. However, it was not possible to isolate this material even under dry nitrogen as on removal of the solvent it was rapidly transformed into an intractable oily mixture. The addition of water to a solution of the above product led to the formation of the 2-hydroxy compound (XVII) in good yield. Attempts to follow the course of the reaction between (LVIII) and zinc-copper couple were unsuccessful; it was not possible to observe the olefinic region due to the extreme intensity of the tetrahydrofuran peaks and broadening by suspended particles of metal.

When (LVIII) was stirred with silver powder in dry tetrahydrofuran intractables were formed.

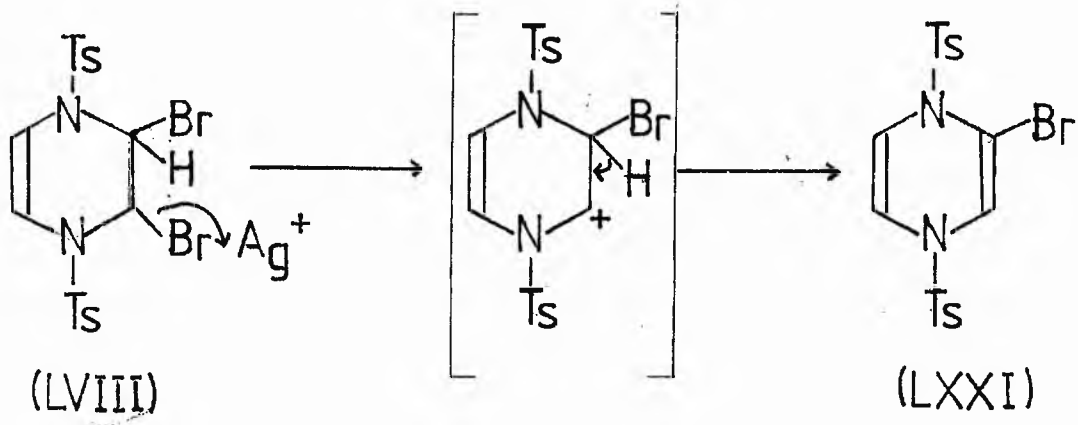
Treatment of (LVIII) with iron pentacarbonyl[97] gave a compound the structure of which has not been determined. Elemental analysis did not correspond either to (XXI) or to the complex(LXX); the compound



(LVIII) (LXX)

contained neither bromine or iron. For details of its spectroscopic properties see experimental.

An attempt was made to obtain the substituted 1,4-dihydropyrazine (LXXI) by reaction of (LVIII) with one mole of silver nitrate. However, this reaction did not proceed as shown; an insoluble substance of unassigned structure being obtained. This did not contain bromine



(LVIII) (LXXI)

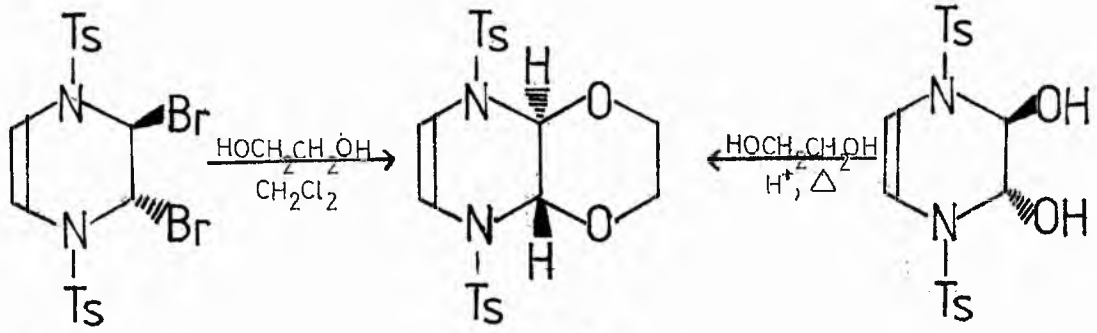
and its n.m.r. spectrum could not be interpreted.

Iodide ion has been frequently used[98] for elimination of bromine from vicinal dibromides. Treatment of (LVIII) with sodium iodide in acetonitrile yielded only intractable mixtures. A similar result was obtained with thiourea[99].

Triphenylphosphine[100] and trimethyl phosphite[101] have been used in the preparation of olefins from dibromides, but no reaction occurred when (LVIII) was refluxed with either of these reagents in dry toluene.

Preparation of fused heterocycles from 2,3-disubstituted-1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines.

When the trans-dibromide (LVIII) was treated with one equivalent of ethylene glycol in methylene chloride a compound was formed, the spectral data and elemental anaylsis of which indicated it to be the bicyclic molecule (LXXII) which is a new ring system. An alternative and better synthesis of (LXXII) consisted of refluxing the 2,3-dihydroxy-1,2,3,4-tetrahydropyrazine(LXIII) with one equivalent of ethylene glycol in acetone containing HCl. Attempts to prepare

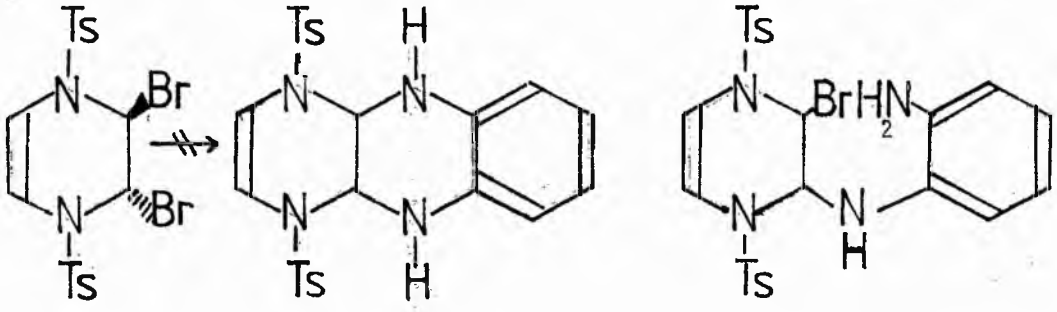


(LVIII) (LXXII) (LXIII)

the sulphur analogue of (LXXII) using ethanedithiol failed. When (LVIII) was treated with this reagent a product of unknown structure was obtained; the infra-red and n.m.r. spectra indicated the presence of at least one NH group, which suggests that ring opening had occurred. When the diol (LXIII) was refluxed with ethanedithiol under the conditions used for ethylene glycol no reaction took place.

Treatment of (LVIII) with ethylenediamine in methylene chloride gave an unidentified product which possessed only tolyl methyl and aromatic protons in the n.m.r. (for details see experimental).

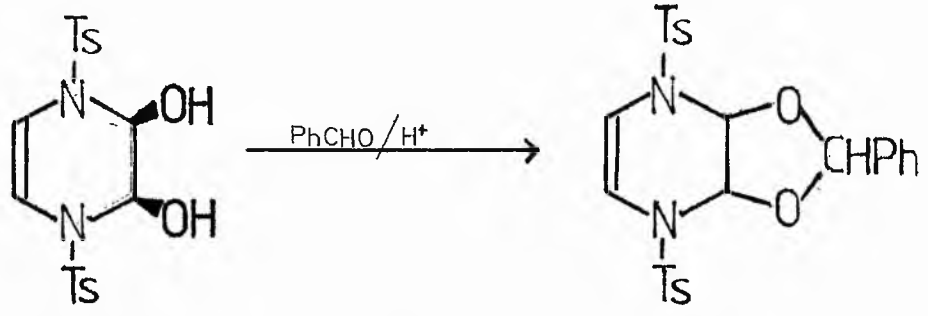
When the 2,3-dibromo compound (LVIII) was treated with two equivalents of o-phenylenediamine an immediate precipitate of the base hydrobromide was produced; the filtrate contained an unstable product which decomposed on attempted isolation. Since o-phenylene-



(LXXIII) (LXXIV)

diamine is a planar molecule it is unlikely that formation of (LXXIII) is sterically possible. Accordingly alternative reactions are likely to occur, e.g. the formation of (LXXIV) which would not be expected to be very stable.

Fused heterocycles such as (LXXV) may be prepared from cis-diols and aldehydes or ketones, whereas trans-diols do not react[102]. Such a reaction would therefore provide further evidence for the stereochemistry of the cis-diol (LXVII).



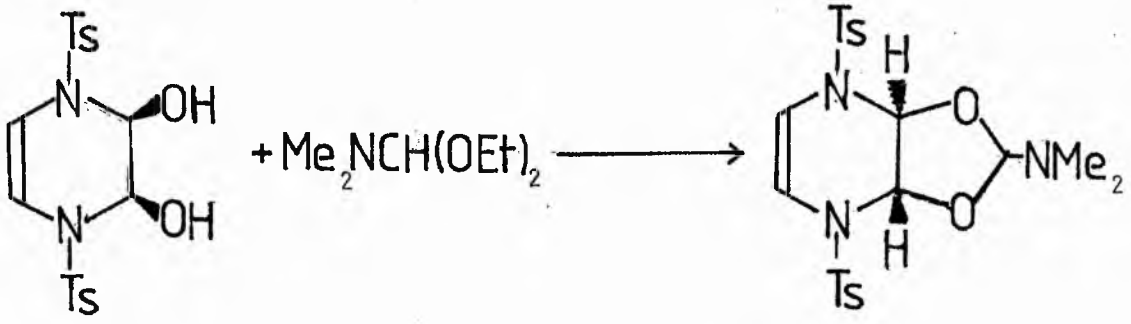
(LXVII) (LXXV)

Accordingly the cis- and trans-diols (LXVII) and (LXIII) were treated with a variety of reagents and catalysts. No reaction was observed with acetone in the presence of HCl, acid ion exchange resin, p-toluenesulphonic acid or anhydrous copper sulphate. With benzaldehyde in boiling toluene or benzene containing p-toluenesulphonic acid both diols (LXVII) and (LXIII) gave intractable mixtures. No reaction was observed between either diol and catechol with various catalysts in tetrahydrofuran.

It is surprising that a cis-diol such as (LXVII) does not react readily with acetone. A possible explanation for this is that just as the 2-hydroxy compound (XVII) does not form esters due to the lack of nucleophilicity of the hydroxy group (see p. 52) the oxygen atoms of the diol (LXVII) are insufficiently nucleophilic for cyclisation to occur.

Dimethylformamide diethyl acetal has been used to prepare heterocycles from diols[102]. On treatment with this reagent in methylene chloride the two isomeric diols behaved differently. The trans-isomer did not react but the cis-diol underwent an immediate

reaction. The product was too unstable to be obtained pure and its

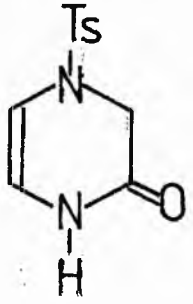


(LXVII) (LXXVI)

structure could therefore not be confirmed. The fact that (LXVII) did react whereas(LXIII) did not is additional evidence for the assignment of configuration (see also ^{13}C n.m.r. evidence in Appendix).

Cycloaddition reactions

The possibility of trapping as a Diels-Alder adduct (p.73) a 1,4-dihydropyrazine produced in some of the reactions already described led to an investigation of the reaction of the tetrahydropyrazine (XLV) with dienes in an attempt to probe the reactivity of the double bond as a dienophile. Molecular orbital calculations kindly carried out for the system (LXXVII) by Dr. M. Tute of Pfizer Ltd., showed that the



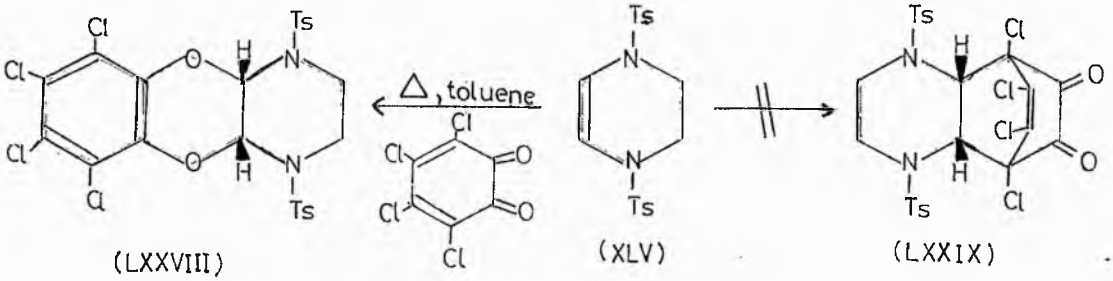
(LXXVII)

double bond of 1,2,3,4-tetrahydropyrazines may be expected to be electron rich, a result which is in accordance with experimental observations. Accordingly it was decided to attempt [4+2] cycloaddition reactions of this double bond with electron poor dienes. The 2-unsubstituted 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine (XLV) was

chosen as the substrate as here there is no possibility of stereochemical complications or unwanted side reactions of substituents.

When (XLV) was refluxed with tetraphenylcyclopentadienone in toluene or xylene no reaction occurred even after prolonged periods. With tetrachloro-o-benzoquinone under these conditions, however, a reaction took place and the colour of the quinone was discharged after 3h.

The product had an elemental analysis consistent with structure (LXXVIII); the absence of a carbonyl group in its infra-red spectrum excluded the alternative structure (LXXIX).



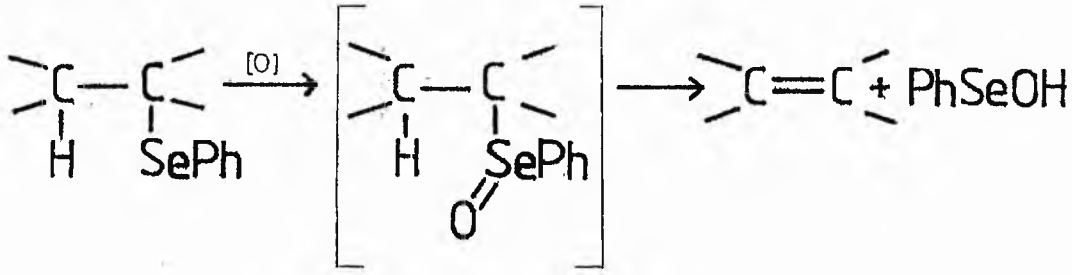
(LXXVIII) (XLV) (LXXIX)

Compound (LXXVIII) was too insoluble for an n.m.r spectrum to be obtained. There is ample precedent[104] for this mode of cycloaddition with tetrachloro-o-benzoquinone and olefins bearing bulky substituent groups.

Oxidation of 2-substituted 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines.

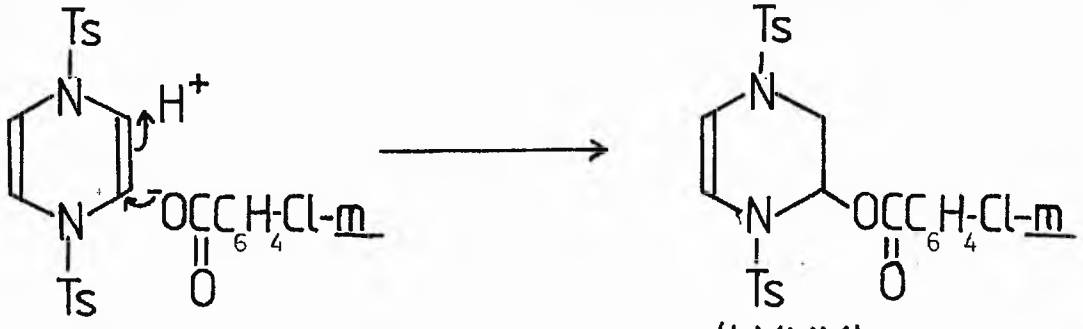
(a) 1,4-bis-(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine.

Selenoxides possessing a β-hydrogen are known[105] to decompose spontaneously to olefins and phenylseleninic acid.



This represents a possible approach to the synthesis of the 1,4-dihydropyrazine (XXI). Since evidence had already been obtained (p. 80) that (XXI) very readily undergoes electrophilic addition reactions, it was thought that the protic solvents normally used for the oxidation of selenides would not be suitable in this case. Nevertheless, to test this assumption the selenide (XLIV) was oxidised with hydrogen peroxide in acetone which afforded the 2-hydroxy compound (XVII) indicating that (XXI) had been formed transiently and had immediately reacted with water. In a control experiment the selenide was treated with aqueous acetone without added peroxide under the same conditions; no reaction occurred which further supports the above hypothesis.

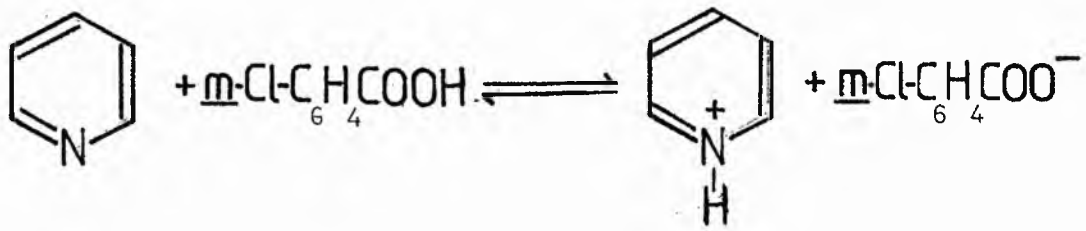
m-Chloroperbenzoic acid is an oxidising agent which can be used in inert solvents. When (XLIV) was treated with this reagent in methylene chloride an immediate reaction occurred. The resulting product, however, was not the desired 1,4-dihydropyrazine (XXI) but the m-chlorobenzoate (LXXX), identified by elemental analysis and spectral properties. The n.m.r. spectrum of (LXXX) showed the two



(LXXX)

p-tolyl methyl peaks characteristic of other compounds having an aryl substituent in the 2-position. The isolation of (LXXX) implies that the m-chlorobenzoic acid formed in the course of the oxidation adds to an initially formed 1,4-dihydropyrazine, which is most unusual for

such a weak nucleophile as m-chlorobenzoate ion. In order to avoid this electrophilic addition the reaction was repeated in the presence of pyridine; however, the same product (LXXX) was obtained although the reaction was slower. This is probably because the equilibrium shown below is set up; sufficient acid will still be present for the



addition product (LXXX) to be formed.

Another oxidising agent which may be used in an inert solvent is iodosobenzene[106]; on stirring the selenide (XLIV) with this reagent at room temperature in methylene chloride or on refluxing in benzene the iodosobenzene was converted into iodobenzene but only starting material could be recovered from the solution. Control experiments were performed with iodosobenzene in the absence of (XLIV); in methylene chloride at room temperature the oxidant did not dissolve, while in refluxing benzene it dissolved at the same rate as in the presence of (XLIV). The 2-phenylthio derivative (XXXI) was successfully oxidised to the sulphoxide (XXXIII) using iodosobenzene in refluxing benzene.

When the selenide (XLIV) was reacted with a complex of the crown ether 18-crown-6 and potassium periodate in methanol the 2-methoxy compound (XIV) was formed in good yield. A control experiment showed that no reaction took place between the selenide (XLIV) and methanol in the absence of the complex. These experiments would again seem to indicate the transient formation of (XXI).

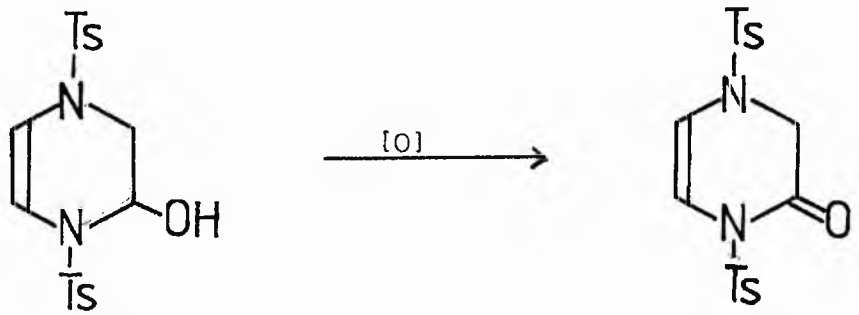
Unfortunately the crown ether complex was insoluble in acetonitrile or other suitable aprotic solvents and this approach had to be abandoned.

No apparent reaction occurred when the selenide (XLIV) was treated with periodic acid in methylene chloride.

The reaction of tetrabutylammonium hydroxide and periodic acid gave a compound which analysed correctly for tetrabutylammonium periodate. However this material did not oxidise either the selenide (XLIV) or sulphide (XXXI) and further experiments to confirm its structure are needed.

(b) Oxidation of 1,4 -bis-(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine.

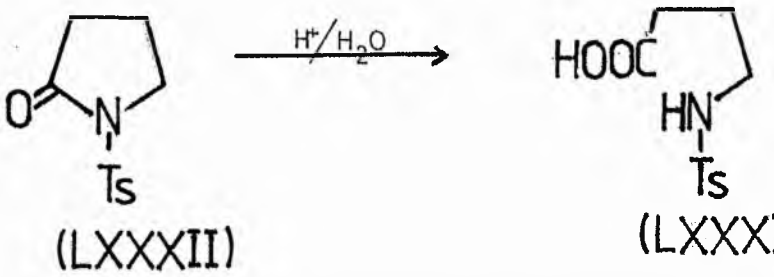
Many ketopiperazines have been found to be biologically active and it was of interest to attempt the oxidation of the 2-hydroxy compound (XVII) to (LXXXI) as shown.



(XVII) (LXXXI)

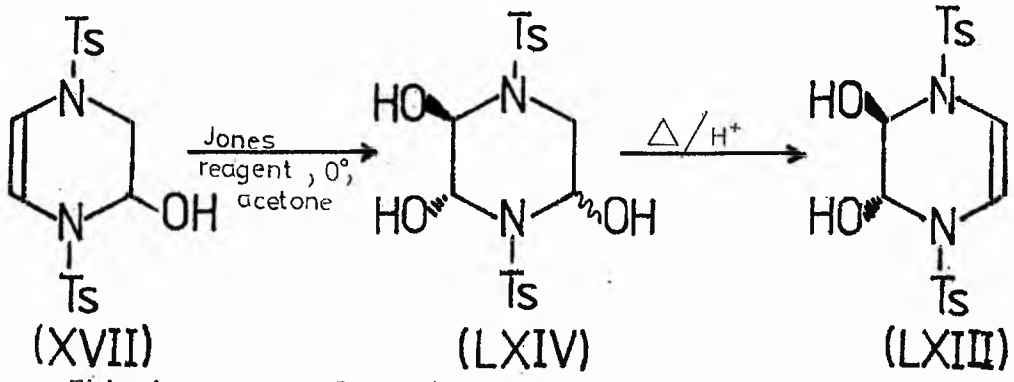
No reaction occurred when (XVII) was treated with chromic oxide in pyridine at room temperature; on heating at 100° mixtures were obtained. Manganese dioxide in boiling toluene also failed to effect a reaction.

Rudinger[107] has shown that N-p-toluenesulphonyl lactams such as (LXXXII) under aqueous acidic conditions readily undergo fission of the CO-N bond to give (LXXXIII).



(LXXXII) (LXXXIII)

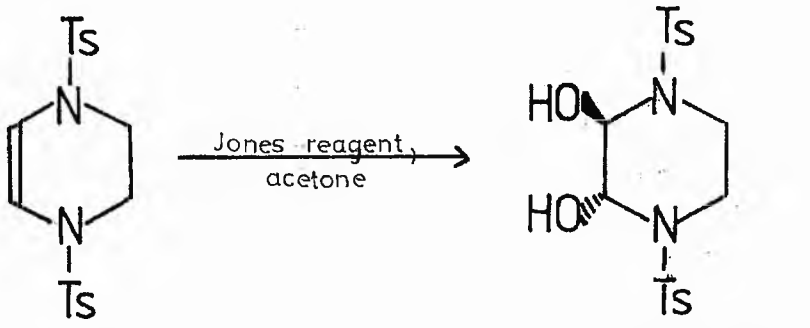
The same grouping CONTs being present it might be expected that a ring opened product analagous to (LXXXIII) might be obtained on oxidation of (XVII) under aqueous acidic conditions. On treatment of (XVII) with Jones reagent in acetone, however, an insoluble product was precipitated. This was identified as the 2,3,5-trihydroxypiperazine (LXIV) previously prepared by a totally different method (see p.76).



(XVII) (LXIV) (LXIII)

This is an unusual reaction as Jones reagent, which does not normally attack double bonds[108], has reacted at this site in preference to oxidising the hydroxyl group.

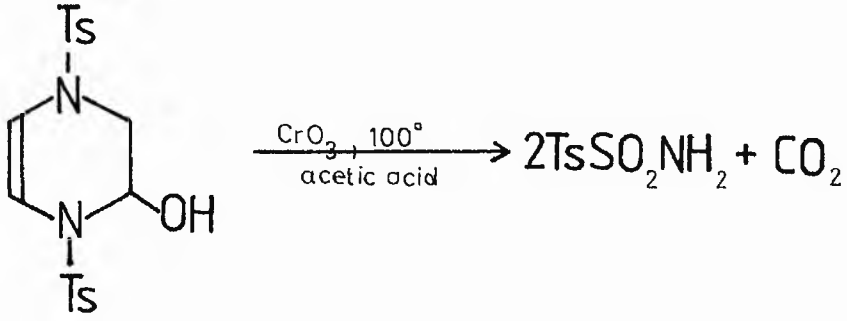
In order to confirm the generality of this reaction the 2-unsubstituted 1,4-bis-(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine (XLV) was treated with Jones reagent under similar conditions. An analogous reaction gave (LXXXIV) in good yield. It was identified by elemental analysis and its infra-red spectrum.



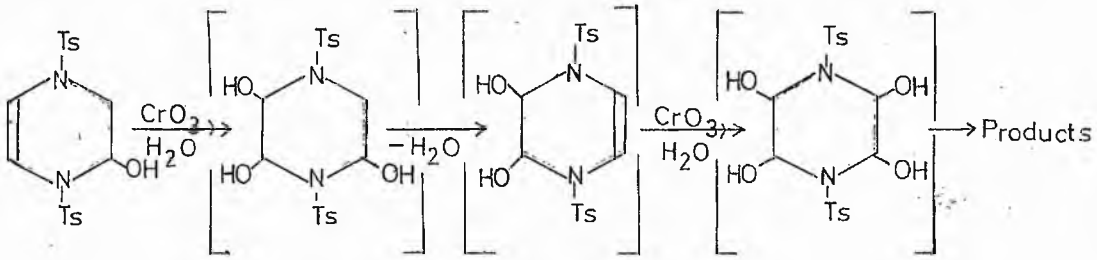
(XLV) (LXXXIV)

The mechanism of this reaction probably involves the initial formation of a chromate ester as chromic oxidation gives trans-diols. The reaction is another example of the electron rich nature of the double bond in 1,2,3,4-tetrahydropyrazines. Further oxidation of the hydroxyl groups in (LXIV) and (LXXXIV) is presumably prevented by their insolubility which removes them from the solution as soon as they are formed.

When the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) was heated with chromic oxide in acetic acid at 100°, carbon dioxide was evolved and p-toluenesulphonamide was isolated from the solution.



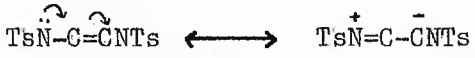
It may be speculated that the reaction proceeds via the tetrahydroxy compound (LXXXV) followed by cleavage and decarboxylation as shown.



SUMMARY AND GENERAL CONCLUSIONS

The results of the present work lead to certain general observations about the chemistry of the systems studied.

The double bond in 1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines has been shown to be electron rich by the facile electrophilic addition of water and alcohols, its hydroxylation with Jones reagent, and its [4+2] cycloaddition with an electron-deficient diene. This property may be attributed to the mesomeric effect of the two adjacent nitrogen lone pairs as shown.



Further evidence in support of this point is that some reactions of the 1,2,3,4-tetrahydropyrazines appear to proceed via carbonium ion intermediates stabilised by the adjacent nitrogen lone pair (p. 45).

However, the fact that esters could not be prepared from the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) under basic conditions, nor ketals from the cis diol (LXVII), indicates that the sulphonylamino groups exert a powerful electron-withdrawing inductive effect. Further evidence for this is provided by the extreme reactivity of the 2-chloro-1,2,3,4-tetrahydropyrazine (XXXVII) towards nucleophiles (p. 65).

During the course of this work attempts were made to synthesise 1,4-bis(p-toluenesulphonyl)-1,4-dihydropyrazine (XXI) by a wide variety of routes. Although definitive evidence has been obtained (see text) for the transient formation of (XXI) it was not possible either to isolate it or to obtain conclusive spectral evidence for its presence. Accordingly it must be concluded that (XXI) is highly reactive, undergoing electrophilic addition to revert to a stable tetrahydropyrazine. It was originally thought that the electron withdrawing p-toluenesulphonyl

groups would reduce the electron density on the nitrogen atoms to such an extent that they would not be able to conjugate with the electrons of the 1,4-dihydropyrazine double bonds. The basis for this assumption was the successful isolation of 1,4-diacyl-1,4-dihydropyrazines[47] (p. 11) which also possess electron withdrawing groups on the nitrogen atoms. However, the acyl groups in such compounds would be expected to remove the lone pairs on the nitrogen atoms by conjugative interaction; since the sulphonyl group does not contain genuine double bonds[109] the p-toluenesulphonyl substituents are probably unable to exert a substantial -M affect and the electron withdrawing inductive effect seems to be insufficient to reduce the electron density of the nitrogen atoms in the 1,4-dihydropyrazine.

With the exception of 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine[45] all the authenticated 1,4-dihydropyrazines reported in the literature[24,46,53,55] have aryl substituents on the carbons of the heterocyclic ring. The presence of these groups means that an alternative mode of conjugation is possible which does not result in a delocalised 8π system. Another contributing factor to the stability of such systems may be the steric effect of the bulky aryl groups which forces the molecule into a non-planar conformation and hence prevents delocalisation. In the absence of aryl substituents a compound such as (XXI) might perhaps possess a fully conjugated 8π electron system which would explain its extraordinary reactivity.

EXPERIMENTAL SECTION

General

Infra-red spectra were recorded using KBr discs and a Perkin Elmer 137G spectrophotometer calibrated with polystyrene film.

Proton magnetic resonance spectra were recorded (in $CDCl_3$ solution unless otherwise stated) on a JEOL JNM C-60 HL 60MHz spectrophotometer with tetramethylsilane as the internal standard. Melting points were determined using open capillary tubes in an electrically heated Gallenkamp melting point apparatus and are corrected.

Microanalyses were determined by the microanalysis unit, University of Nottingham, and by the analytical section of Imperial Chemical Industries Ltd., Alderley Edge, Macclesfield.

Thin-layer chromatography was carried out using pre-spread plates (5 x 20cm; Polygram SIL G/UV_{254} and Polygram ALOX N/UV_{254} from Camlab, Cambridge), eluted with ethyl acetate/light petroleum 3:2 unless otherwise state

Column chromatography was carried out using Fison silica-gel MFC (80-200 mesh) and Fison alumina (100-250 mesh).

Ether, benzene and toluene were dried over freshly cut sodium wire, tetrahydrofuran by distillation from lithium aluminium hydride and acetonitrile over grade 3A molecular sieves. Other solvents were dried over type 5A molecular sieves unless otherwise stated.

Benzenesulphonylaminoacetaldehyde dimethyl acetal (I).[58]

Aminoacetaldehyde dimethyl acetal (10g, 0.095mol) in water (75ml) containing potassium carbonate (15g) was treated with a solution of benzenesulphonyl chloride (16.8g, 0.095mol) in toluene (150ml) and the mixture was stirred for 24h.. The organic phase was separated and washed with water (3 x 100ml), dried over $MgSO_4$ for 6h and the toluene evaporated under reduced pressure to afford (I) as an oil (22.0g, 98%) which could not be further purified; $\nu_{max.}$ 3280 (NH), 2960, 1600, 1445, 1328, 1165, 1092, 756, 718 and 689cm^{-1}; δ 3.08(2H,d, J 5.5Hz, CH_2), 3.26(6H,s,$2OCH_3$), 4.34(1H,t,J 5.5Hz,CH), 5.52(1H,s,NH), 7.35-8.15(8H,m,ArH).

p-Toluenesulphonylaminoacetaldehyde dimethyl acetal (II).

(a) This compound was obtained by the method above; crystallisation of the initially formed oil from ether/light petroleum yielded pure (II) as white needles (22.14g, 90%) m.p. 44-46° [Found : C, 51.05; H,6.5; N, 5.3; $C_{11}H_{17}NO_4S$ requires C, 50.9; H, 6.55; N, 5.4%]; $\nu_{max.}$ 3280 (NH), 2980, 1600, 1328, 1230, 1170, 1130, 1077, 1025, 940, 903, 875, 820, 710, 700 and 665cm^{-1}; δ 2.37(3H,s,CH_3), 2.88(2H,d,J 5.5Hz, CH_2), 3.30(6H,s, $2OCH_3$), 4.20(1H,t,J 5.5Hz,CH), 5.12(1H,s,broad, NH), 7.10(4H,q,J 7.5Hz, ArH).

(b) Aminoacetaldehyde dimethyl acetal (2.5g, 0.023mols)in water (20ml) containing potassium carbonate (3.8g) and benzyltriethylammonium chloride (0.1g) was treated with a solution of p-toluenesulphonyl chloride (4.5g, 0.13mols)in toluene (50ml). After 1h the reaction was shown to be complete by T.L.C.. The organic phase was separated and washed with water (3 x 50ml), dried over $MgSO_4$ overnight and the toluene evaporated under reduced pressure to afford (II) as an oil. Crystallisation from ether/light petroleum gave pure (II) (6.5g, 95%) identified by its

m.p., infra-red spectrum and a mixed melting point determination.

p-Bromobenzenesulphonylaminoacetaldehyde dimethyl acetal (III).

This compound was obtained as under (a) above. On removal of the toluene under reduced pressure a white solid was obtained. Crystallisation from ether/light petroleum yielded pure (III) (29.1g, 95%) m.p. 64-66° (lit[58] m.p. 64-66°); $\nu_{max.}$ 3200 (NH), 2975, 2905, 1580, 1565, 1333, 1047, 892, 817, 750, 649cm^{-1}; δ 2.90(2H,m, broad, sharpened after treatment with D_2O, CH_2), 3.25(6H,s,$2OCH_3$), 4.20(1H,t J 5.5Hz,CH), 5.10(1H,s, broad, NH), 7.25(4H,s,ArH).

p-Nitrobenzenesulphonylaminoacetaldehyde dimethyl acetal (IV).

This compound was obtained by method (a) above as a yellow solid. Several crystallisations from ether/light petroleum yielded pure (IV) (22.04g, 80%), m.p. 114-115° (lit[58] m.p. 114-115°); $\nu_{max.}$ 3230 (NH), 2960, 2840, 1765, 1600, 1525, 1345, 1165, 978, 857, 732, 682cm^{-1}; δ 3.25(2H,d, J 5.0Hz,CH_2), 3.44(6H,s,$2OCH_3$), 4.50(1H,t, J 5.0Hz,CH), 5.00(1H,s,broad,NH), 8.44(8H,q,J 5.0Hz, ArH).

p-Toluenesulphonylaminoacetaldehyde diethyl acetal (V).

Aminoacetaldehyde diethyl acetal (100g, 0.74mols) was dissolved in water (1l) containing potassium carbonate (150g) and benzyltriethylammonium chloride (1g). The solution was treated with p-toluenesulphonyl chloride (141g, 0.74mols) in toluene (800ml) and the mixture was stirred for 3h., at the end of which time T.L.C. showed the reaction to be complete. The organic layer was separated, washed with water (3 x 500ml), dried overnight over $MgSO_4$, and the toluene removed under reduced pressure to yield (V) as an oil. Crystallisation of this from ether/

light petroleum yielded pure (V) as white needles (207g, 97%) m.p. 62-63° [Found: C, 54.2; H, 7.3; N, 4.9; $C_{13}H_{21}NO_4S$ requires C, 54.4; H, 7.3; N,4.8%]; $\nu_{max.}$ 3280 (NH); 2980, 2920, 2880, 1600, 1328, 1230, 1175, 1130, 1090, 1025, 940, 900, 875, 820, 710, 700, 665cm^{-1}; δ 1.15(6H,t J 6.75Hz, $CH_2\underline{CH_3}$), 2.40(6H,s,$ArCH_3$), 3.05(2H,d,broad, sharpened after treatment with D_2O, J 6.0Hz, CH_2), 3.3-3.8(4H,m,$\underline{CH_2}CH_3$),

p-Bromobenzenesulphonylaminoacetaldehyde diethyl acetal (VI)

This was obtained by the method usedfor (V) above, but on one tenth the scale. After a similar work up (VI) was obtained as a white solid; crystallisation from ether/light petroleum yielded pure (VI) (10.2g, 95%), m.p. 68-70° [Found: C,50.0; H, 5.2; N, 7.4; $C_{12}H_{18}NO_4SBr$ requires C,50.0; H,5.1; N,7.5%]; $\nu_{max.}$ 3200 (NH), 2980, 2905, 1600, 1570, 1335, 1050, 892, 820, 750, 650cm^{-1}; δ 1.15(6H,t, J 6.75Hz, $CH_2\underline{CH_3}$), 3.05(2H,t J 6.0Hz,CH_2), 3.3-3.8(4H,m,$\underline{CH_2}CH_3$), 4.50(1H,t,J 6.0Hz, CH), 5.25(1H,t, broad J 6.0Hz,NH), 7.75(4H,s,ArH).

Trans-1,4-bis(benzenesulphonyl)-2,5-dihydroxypiperazine (VII)

Benzenesulphonylaminoacetaldehyde dimethyl acetal (I) (24g) was dissolved on acetic acid (200ml) containing conc. HCl (20ml) and water (20ml) and the solution was allowed to stand for 30h. at room temperature. The white crystalline product (12.7g, 65%) was collected by filtration, washed with water and aqueous acetone and sucked dry in air. It had m.p. 174-175° (lit[58] m.p. 175°); $\nu_{max.}$ 3464(OH), 3040, 1600, 1495, 1450, 1420, 1350, 1333, 1260, 1178, 1030, 969, 909, 757, 722, 656, 643cm^{-1}.

Trans-1,4-bis(p-toluenesulphonyl)-2,5-dihydroxypiperazine (VIII).

(a) p-Toluenesulphonylaminoacetaldehyde dimethyl acetal (II) (1.85g) in acetic acid (10ml) containing water (4ml) and conc. HCl (4ml) was allowed to stand for 30h at room temperature. The white crystalline product (1.37g, 90%) was filtered, washed with water (300ml) and aqueous acetone (30%, 50ml) and dried at 56°/1mmHg for 12 h. The product could not be crystallised as it is very insoluble. It had m.p. 158-160° [Found: C, 50.4; H, 5.4; N, 6.4; $C_{18}H_{22}N_2S_2O_6$ requires C,50.7; H, 5.2; N, 6.6%]; $\nu_{max.}$ 3460 (OH), 3060, 3000, 2920, 2880, 1600, 1495, 1450, 1420, 1350, 1330, 1300, 1258, 1165, 1125, 1050, 985, 950, 925, 880, 815, 755, 680, 650cm^{-1}.

(b) (VIII) was also obtained from the diethyl acetal (127.5g), using the above procedure (yield: 95.0g, 88%). The product was identified by mixed melting point and its infra-red spectrum.

Trans-1,4-bis(p-bromobenzenesulphonyl)-2,5-dihydroxypiperazine (IX).

p-Bromobenzenesulphonylaminoacetaldehyde dimethyl acetal (III) (3.2g) in acetic acid (20ml) containing conc. HCl (2ml) and water (2ml) was allowed to stand for 30h at room temperature. The white crystalline product (2.1g, 78%) was filtered, washed with water (300ml) and aqueous acetone (30%, 50ml) and crystallised from dimethylformamide/water to give analytically pure (IX), m.p. 178-180° [Found: C, 34.6; H,3.0; N,5.2: $C_{16}H_{16}N_2O_6S_2Br_2$ requires C, 34.5; H, 2.5; N, 5.0%]; $\nu_{max.}$ 3420 (OH), 2980, 2910, 1580, 1450, 1410, 1330, 1050, 980, 890, 820, 750, 650cm^{-1}.

Trans-1,4-bis(p-toluenesulphonyl)-2,5-dimethoxypiperazine (X).

p-Toluenesulphonylaminoacetaldehyde dimethyl acetal (II) (1g) was dissolved in methanol (20ml) containing conc. HCl (2ml) and the solution

was allowed to stand for 30h at room temperature. White crystals separated out; these were filtered and dried in air to give (X) (0.54g, 61%) m.p. 163-165° [Found: C, 52.9; H, 5.8; N, 6.3: $C_{20}H_{26}N_2S_2O_6$ requires C, 52.9; H, 5.7; N, 6.2%]; $\nu_{max.}$ 3110, 3040, 3000, 2960, 2940, 1600, 1500, 1450, 1350, 1305, 1280, 1110, 1120, 1080, 1060, 1015, 970, 950, 920, 820, 800, 750, 725, 705, 680cm^{-1}; δ 2.40(6H,s,CH_3), 3.10(6H,s,OCH_3), 3.15(2H, dd, J_{DE} 13.0Hz, further split J_{CE} 2.0Hz, H_E), 3.70(2H,d,broad, H_D), 5.0(2H,s,H_C), 7.75(8H,q,J 9.0Hz, ArH).

Trans-1,4-bis(p-toluenesulphonyl)-2,5-diethoxypiperazine (XI).

This was prepared in analogous fashion to (X) substituting the diethyl acetal (V) for (II) and ethanol for methanol. Yield: 0.6g (71%), m.p. 165-167° (lit[62] m.p. 170.7°); $\nu_{max.}$ 3060, 2980, 2880, 1600, 1500, 1450, 1400, 1350, 1305, 1280, 1110, 1120, 1070, 1050, 1015, 970, 950, 920, 820, 800, 750, 725, 705, 670cm^{-1}; δ 0.88(6H,t, J 7.0Hz, $CH_2\underline{CH_3}$), 2.40(6H,s,CH_3), 3.15(2H,dd, J_{DE} 13.0Hz, further split J_{CE} 2.0Hz, H_E), 3.40(4H,m,$\underline{CH_2}CH_3$), 3.70(2H,d, broad, H_D), 5.0(2H,s,H_C), 7.75(8H,q,J 9.0Hz, ArH).

1,4-Bis(benzenesulphonyl)2-methoxy-1,2,3,4-tetrahydropyrazine (XII).

(a) From (I). The aminoacetal (I) (3.0g) in methanol (5ml) containing water (5ml) and sulphuric acid (1.5ml) was refluxed for 30min. On cooling a white precipitate was obtained; this was filtered and crystallised from methanol to give pure (XII) (1.87g, 80%) m.p. 158-60° (lit[61] m.p. 159-61°); $\nu_{max.}$ 3100, 2940, 1640, 1600, 1450, 1350, 1280, 1170, 955, 725, 690, 630cm^{-1}; δ 2.0(1H,dd, J_{DE} 13.0Hz, J_{CE} 2.5, H_E), 3.1(3H,s,OCH_3), 4.0(1H,dd, J 13.0Hz, J_{CD} 2.5Hz, H_D), 5.05(1H,m,H_C), 6.30(2H,q,J_{AB} 7.5Hz further split J 2.5Hz, H_A,H_B), 7.3-8.0(10H,m,ArH).

(b) From (VII). The dihydroxypiperazine (VII) was heated with methanol (50ml) and conc. HCl (1ml). The mixture was refluxed until all the solid had dissolved (4h). On cooling the 2-methoxy compound (XII) (0.43,90%) crystallised out; its identity was confirmed by its melting point, infra-red and n.m.r. spectra.

1,4-Bis(benzenesulphonyl)-2-ethoxy-1,2,3,4-tetrahydropyrazine (XIII) was prepared as in (b) above, yield 0.45g (98%). It had m.p. 155-7° (lit m.p.[58] 155-7°); $\nu_{max.}$ 3095, 2915, 1635, 1600, 1438, 1345, 1170, 960, 720, 685, 630cm^{-1}; δ 0.8(3H,t, J 7.5Hz, ethyl CH_3), 2.15(1H,dd, J_{DE} 13.0Hz, J_{CE} 1.7Hz, H_E), 3.4(2H,m, ethyl CH_2), 4.0(1H,d, broad, J 13.0Hz, H_D), 5.1(1H,m, broad, H_C), 6.25(2H,q,J 7.0Hz, further split J 2.0Hz, H_A,H_B), 7.40-7.80(10H,m,ArH).

1,4-Bis(p-toluenesulphonyl)-2-methoxy-1,2,3,4-tetrahydropyrazine (XIV)

(a) was prepared by method (a) used for (XII) above. Yield, 2.1g (79%) m.p. 175° (lit[58] m.p. 175°); $\nu_{max.}$ 3115, 3040, 3000, 2960, 2940, 1650, 1600, 1495, 1450, 1400, 1350, 1280, 1190, 1170, 1120, 1080, 1045, 1005, 960, 940, 820, 730, 710, 675cm^{-1}; δ 2.10(1H,dd, J_{DE} 13.2Hz, J_{CE} 1.7Hz, H_E), 2.41(6H,s,CH_3), 3.07(6H,s,OCH_3), 3.92(1H,d, broad, J 13.2Hz, H_D), 4.98(1H,s,H_C), 6.17(2H,q, J_{AB} 7.0Hz, further split J 1.5Hz, H_A,H_B), 7.43(8H,q,J 8.5Hz, further split J 2.5Hz, ArH).

(b) From (XVII). The 2-hydroxy compound (XVII) (1g) was suspended in methanol (50ml) and HCl (1ml) added. The mixture was refluxed for 3h, the solid dissolving in the process. On cooling a white solid crystallised out; this was filtered and recrystallised from methylene chloride/light petroleum to give (XIV), (0.97g, 94%), m.p. 173-175°, identified with the material prepared under (a) above by mixed melting point and infra-red and n.m.r. spectra.

1,4-Bis(p-toluenesulphonyl)-2-ethoxy-1,2,3,4-tetrahydropyrazine (XV).

(a) This was prepared as for (XIV) above but substituting ethanol for methanol. Yield, 0.98g, (92%) m.p. 167-169° (lit[62] m.p. 172°); $\nu_{max.}$ 3120, 3040, 2985, 2920, 2880, 1650, 1595, 1490, 1450, 1400, 1350, 1280, 1190, 1170, 1120, 1070, 1050, 970, 940, 920, 820, 800, 750, 725, 705, 670cm^{-1}; δ 0.75(3H,t,J 6.1Hz, $CH_2\underline{CH_3}$), 2.12(1H,dd, J_{DE} 13.0Hz, J_{CE}, 2.0Hz, H_E), 2.40(6H,s,CH_3), 3.3(2H,m,$\underline{CH_2}CH_3$), 3.90(1H,d, broad, J 13.0Hz, H_D), 5.05(1H,m,H_C), 6.15(2H,q, J_{AB} 7.0Hz, further split J 1.5Hz, H_A,H_B), 7.40(8H,q, J 8.5Hz, further split J 2.5Hz, ArH).

(b) From (VIII). The 2,5-dihydroxypiperazine (0.5g) was treated with ethanol (50ml) and conc. HCl (1ml). The mixture was refluxed until all the solid had dissolved (4h). On cooling (XV) (0.41g, 80%) crystallised out; its identity was confirmed by its melting point, infra-red and n.m.r. spectra.

1,4-Bis(p-benzenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine (XVI).

The dihydroxypiperazine (VII) (1.0g) in acetic acid (20ml) containing water (2ml) and conc. HCl (2ml) was heated on a steam bath until the solution was homogeneous (15min). The solution was cooled in ice and poured into water (300ml); the resultant white precipitate was filtered and washed with water (400ml), dissolved in methylene chloride (50ml) and dried over $MgSO_4$ (24h). The solution was filtered and the methylene chloride evaporated under reduced pressure to give a white solid. Crystallisation from methylene chloride/light petroleum gave pure (XVI), (0.8g, 80%), m.p. 153-154° (lit[58] m.p. 152-153°); $\nu_{max.}$ 3510 (OH), 3125, 1651, 1600, 1495, 1445, 1400, 1352, 1310, 1280, 1173, 1120, 1080, 1020, 965, 880, 800, 724, 687, 633cm^{-1}; δ 2.59(1H,dd, J_{DE} 12.5Hz, J_{CE} 2.0Hz, H_E), 2.72(s, broad, OH), 4.08(d, broad, J 12.5Hz, H_D),

5.72(s,broad, H_C), 6.32(q,J_{AB} 7.0Hz, further split J 2.0Hz, H_A,H_B), 7.40-8.12(m,ArH).

1,4-Bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) was prepared as for (XVI) above, yield 0.84g, (88%), m.p. 162-164° [Found: C,52.9; H,4.9; N,6.9. $C_{18}H_{20}N_2O_5S_2$ requires C,52.8; H,5.1; N, 6.7%;] $\nu_{max.}$ 3520 (OH), 3115, 2820, 1650, 1600, 1495, 1450, 1400, 1340, 1310, 1285, 1170, 1120, 1080, 1020, 960, 920, 880, 815, 800, 753, 745, 705, 675cm^{-1}; δ 2.39(3H,s,CH_3), 2.48(1H,dd, J_{DE} 10Hz, J_{CE} 2.0Hz, H_E), 2.6(1H,s,OH), 3.84(1H,d, broad, J 10Hz, H_D), 5.50(1H,m, broad, H_C), 6.05(2H,q, J_{AB} 7.0Hz, further split J 2.0Hz, H_A,H_B), 7.34(8H,q, J 9.0Hz, ArH).

1,4-Bis(p-bromobenzenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine (XVIII)

The dihydroxypiperazine (IX) (0.2g) was suspended in acetic acid (20ml) containing water (2ml) and conc. HCl (2ml). The suspension was stirred at 100° for 30min. to give a homogeneous solution. This was cooled and poured into water to give a white solid. Filtration followed by crystallisation from acetone gave pure (XVIII), (0.15g, 70%), m.p. 164-166° [Found : C,35.9; H,2.4; N,5.5. $C_{16}H_{15}N_2O_5S_2Br$ requires C,35.7; H,2.6; N,5.2%]; $\nu_{max.}$ 3460 (OH), 2980, 2910, 1640, 1580, 1450, 1405, 1330, 1050, 980, 890, 820, 750, 650cm^{-1}; δ (DMF) 2.35(2H,dd, J_{DE} 10Hz, J_{CE} 2.0Hz, H_E), 3.95(1H,d, broad, J 10Hz, H_D), 5.70(1H,m,broad H_C), 6.15(2H,q, J_{AB} 7.0Hz, further split J 1.5Hz, H_A,H_B), 7.8(4H,s,ArH).

Addition of water to 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine at different pH's.

(a) The 2-hydroxy compound (XVII) (0.2g) was dissolved in acetone (10ml)

containing water (1ml) and conc. HCl (1ml). The solution was allowed to stand for 24h after which time a white solid had crystallised. This was collected by filtration, washed well with water, acetone and ether and dried to give the 2,5-dihydroxypiperazine (VIII) identified by its infra-red spectrum and mixed melting point.

(b) The 2-hydroxy compound (XVII), (0.2g) was dissolved in acetone (10ml) containing water (1ml). After 24h, no reaction had occurred as shown by T.L.C.; the addition of water (10ml) caused the precipitation of a white solid, which was filtered and dried. Crystallisation from methylene chloride/light petroleum gave back pure (XVII) (0.2g) identified by its infra-red spectrum and mixed melting point.

(c) The 2-hydroxy compound (XVII) (0.2g) was dissolved in acetone (10ml) containing water (1ml) and 4M sodium hydroxide solution (1ml). The solution went yellow; on standing for 24h it turned brown. T.L.C. showed a mixture of products to be present including starting material; there was no sign of the 2,5-dihydroxypiperazine (VIII).

Addition of ethanol to 1,4-bis(p-toluenesulphonyl)-2-ethoxy-1,2,3,4-tetrahydropyrazine.

The 2-ethoxy compound (XV) (0.4g) was dissolved in ethanol (50ml) containing conc. HCl (1ml) and the solution allowed to stand at room temperature for 24h. A white solid crystallised. This was collected by filtration, washed with ethanol and dried to give the diethoxypiperazine (XI) identified by its infra-red and n.m.r. spectra.

Conversion of 1,4-bis(p-toluenesulphonyl)-2-methoxy-1,2,3,4-tetrahydropyrazine into the 2-hydroxy derivative (XVII).

The 2-methoxy compound (XIV) (0.3g) was dissolved in acetone

(50ml) containing water (5ml) and conc. HCl (1ml). The solution was refluxed for 6h after which time T.L.C. showed the reaction had gone to completion. The solvent was evaporated under reduced pressure and the resultant white solid crystallised from methylene chloride/light petroleum to give the 2-hydroxy compound (XVII) (0.24g, 83%) identified by its infra-red spectrum and mixed melting point.

Conversion of trans-1,4-bis(p-toluenesulphonyl)-2,5-dihydroxypiperazine into the 2,5-dimethoxy derivative (X).

The 2,5-dihydroxypiperazine (VII) (0.2g) was stirred with methanol (50ml) containing conc. HCl (2ml) at room temperature. After 5min all the solid had dissolved; after a further 20min a solid crystallised from the solution. This was filtered, washed with methanol and ether and dried. An n.m.r. spectrum confirmed its identity as the 2,5-dimethoxypiperazine (X) (yield, 0.2g).

Conversion of 1,4-bis(p-toluenesulphonyl)-2,5-dimethoxypiperazine into the 2,5-dihydroxy derivative (VIII).

The 2,5-dimethoxypiperazine (X) (0.2g) was dissolved in CD_3COCD_3 (3ml) containing 4M hydrochloric acid (0.5ml) and the reaction was followed by n.m.r. After 30min the n.m.r. spectrum of the solution showed an olefinic quartet at 6.30 δ to be present; there was no sign of an aldehyde proton. After 2h a white solid began to crystallise from the solution; after 24h this was filtered and washed with acetone and ether. It was identified as the 2,5-dihydroxypiperazine (VIII) by its infra-red spectrum and mixed melting point.

Deuterium exchange experiments with 1,4-bis(benzenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine.

(a) The 2-hydroxy compound (XVI) (0.2g) was dissolved in tetrahydrofuran (15ml) containing D_2O (0.5ml) and the solution refluxed for 1h. The solvent was removed under reduced pressure and $CDCl_3$ (1ml) was added. An n.m.r. spectrum showed the peaks at 2.59 δ and 2.72 δ to be decreased by 75% indicating exchange of the protons H_D and H_E (p. 36).

(b) This was carried out as under (a) above but conc. DCl/D_2O, 1:1 (0.5ml) was substituted for D_2O. No sign of deuteration could be detected by n.m.r.

(c) This was carried out as under (a) above but $4MNaOD/D_2O$, 1:1 (0.5ml) was substituted for D_2O. A mixture was obtained and the n.m.r. spectrum was uninformative.

Action of heat on 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine.

In these experiments (XVII) (0.3g) was placed in a sample tube and heated at 10^{-1} torr in a sample drier.

(a) At 111°. The sample appeared unchanged for 15min; after this it yellowed in colour, the change becoming more pronounced until after 1h the solid melted and bubbled. At this stage the reaction was terminated and the oil cooled. T.L.C. showed a complex mixture containing some starting material.

(b) At 100°. Results were as under (a) above but a longer time (5h) was required to reach the melting stage.

(c) At 56°. No reaction was observed even after 8h.

Action of heat on 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine in various solvents.

(a) The 2-hydroxy compound (XVII) (0.3g) in toluene (25ml) was refluxed in a Dean and Stark apparatus for 8h. No reaction had occurred after this time and iodine (0.1g, large excess) was added and the solution refluxed for a further 8h. No reaction appeared to have occurred as shown by T.L.C. The toluene was removed under reduced pressure to yield a dark oil; crystallisation of this from methylene chloride/ether gave (XVII), (0.27g, 90%) identified by its infra-red spectrum and a mixed melting point.

(b) The experiment was repeated as under (a) above substituting xylene for toluene. Again, no reaction appeared to have occurred after 8h as shown by T.L.C. On addition of iodine and refluxing further all the starting material disappeared; evaporation of the solvent under reduced pressure yielded a black tar.

(c) The 2-hydroxy compound (XVII) (0.3g) was dissolved in cyclohexanone (100ml) and refluxed. After 9h no reaction appeared to have occurred by T.L.C. The solvent was distilled off under reduced pressure to yield unchanged 2-hydroxy compound (0.3g, 100%), identified by its infra-red spectrum and mixed melting point.

(d) (i) The 2-hydroxy compound (XVII) (0.3g) was suspended in decalin (100ml) and refluxed for 5min. A black, intractable tar was produced.

(ii) The experiment was repeated but the solution was heated at 170° ; again only tar was produced.

(iii) The experiment was repeated at 160°with the same result.

Attempted dehydration of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with phosphorus pentoxide.

(a) The 2-hydroxy compound (XVII) (0.3g) was dissolved in toluene (50ml) and refluxed in a Dean and Stark apparatus for 30min. The

solution was then cooled to 100° and excess phosphorus pentoxide (0.3g) was added. A black tar was immediately deposited. The colourless solution was decanted and the toluene evaporated under reduced pressure. There was no residue indicating that all the starting material had been converted into the intractable tar.

(b) The 2-hydroxy compound (XVII) (0.3g) was dissolved in sodium dried toluene (50ml) and the solution was cooled to 0°. Phosphorus pentoxide (0.3g) was added and the reaction mixture allowed to stand at 0° for 24h. T.L.C. showed that no apparent reaction had occurred. The reaction mixture was warmed to 70° when T.L.C. showed the presence of seven spots, the most intense having R_F=0.

Attempted elimination of ethanol from 1,4-bis(p-toluenesulphonyl)-2-ethoxy-1,2,3,4-tetrahydropyrazine

The 2-ethoxy compound (XV) (1g) was mixed with ammonium bromide (1g) and placed in a tube which was connected to a vacuum pump via a U shaped trap, cooled in an ice-salt bath. The mixture was heated at $200°/10^{-1}$ torr. Fumes were evolved as the mixture rapidly turned black; some of these condensed as a brown oil. Both this oil and the residual black tar consisted of complex mixtures as shown by T.L.C.

Attempted dehydration of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with phosphorus oxychloride/pyridine.

The 2-hydroxy compound (XVII) (0.5g) was dissolved in pyridine (1.3g) and cooled to -5°. Phorphorus oxychloride (0.3g, 1.5eq) was added dropwise with vigorous stirring at this temperature; white crystals of pyridine hydrochloride were formed and the solution turned very dark. It was decanted into a separating funnel containing crushed ice

and water, extracted with chloroform, washed with 2M HCl (25ml) and water (25ml) and dried ower magnesium sulphate. Evaporation of the solvent under reduced pressure yielded a complex mixture as shown by T.L.C.

Attempted dehydration of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with thionyl chloride/pyridine.

(a) The 2-hydroxy compound (XVII) (0.3g) was dissolved in pyridine (3ml) and cooled to 0°. Thionyl chloride (0.12g) was added dropwise. After 24h starting material was still present as shown by T.L.C.; this had disappeared after 2 days. The solution was poured into 2M HCl (50ml) and extracted with chloroform. The organic phase was dried overnight over $MgSO_4$ and the solvent evaporated under reduced pressure to yield a brown tar (0.28g) which was shown to be a complex mixture by T.L.C.

(b) The experiment was repeated as under (a) above but the reaction mixture was heated for 30min at 100°. After this time T.L.C. showed that no starting material remained. The reaction mixture was cooled and worked up as under (a); again a tarry mixture (0.24g) was isolated.

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-p-toluenesulphonyloxy-1,2,3,4-tetrahydropyrazine.

(a) The 2-hydroxy compound (XVII) (0.3g) was dissolved in pyridine (20ml) and p-toluenesulphonyl chloride (0.16g, 1 equivalent) was added. The solution was allowed to stand at 25° for 9h, while monitored by T.L.C. every hour. No apparent reaction occurred during this period. The reaction mixture was warmed to 50° and maintained at this temperature for 3h; there was no apparent reaction and the temperature was increased to 100°. After 6h at this temperature no reaction appeared to have

occurred. The solution was split into two portions A and B.

Portion A was cooled and poured into 2M HCl to give a white precipitate which was filtered and dissolved in methylene chloride. The solution was washed with water, dried over $MgSO_4$ for 6h and the solvent evaporated under reduced pressure to yield a white solid. Recrystallisation of this from methylene chloride/light petroleum gave pure (XVII) (0.12g) which was identified by its infra-red spectrum and by a mixed melting point.

Portion B was heated to reflux temperature at which point it rapidly turned black and deposited a black tar. When the pyridine solution was worked up as for portion A only a tar insoluble in organic solvents was obtained.

(b) The 2-hydroxy compound (XVII) (0.41g) was dissolved in chloroform (10ml) and p-toluenesulphonyl chloride (0.38g, 2 equivalents) and benzyltriethylammonium chloride (0.05g) were added. The solution was divided into two equal portions.

Portion A was treated with a solution of potassium hydroxide (0.114g) in water (5ml). After 24h T.L.C. showed no apparent reaction; the temperature was raised to 60°, when a yellow colour was produced in both layers and T.L.C. showed that a reaction was occurring. After 6h no starting material remained; the organic phase was separated, washed with water (20ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil which on trituration with ether gave a yellow floccular solid. This was filtered and examined by n.m.r. spectroscopy which indicated the 2-ethoxy compound (XV) (0.17g) had been formed, presumably from reaction of (XVII) with the stabilising ethanol in the chloroform.

Portion B was treated with a solution of potassium carbonate (0.28g) in water (5ml). No reaction was observed by T.L.C. after 24h at

room temperature or on heating at 60° for 6h.

(c) The 2-hydroxy compound (XVII) (0.4g) was dissolved in acetonitrile (100ml) and 4- dimethylaminopyridine (0.11g) and p-toluenesulphonyl chloride (0.38g, 2 equivalents) were added. The reaction was refluxed for 6h.; no reaction was apparent by T.L.C. (The reaction was initially tried in toluene but this solvent proved unsatisfactory as the base did not dissolve).

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-methanesulphonyloxy-1,2,3,4-tetrahydropyrazine.

(a) The 2-hydroxy compound (XVII) (0.41g) was dissolved in pyridine (10ml) and treated with methanesulphonyl chloride under various conditions summarised in the table below. The course of reaction was followed by T.L.C. of aliquots which had been treated with 2M HCl and extracted with methylene chloride.

Temperature	Molar equivalents of CH_3SO_2Cl	TLC after 10min	TLC after 1h
25°	1.5	No apparent reaction	Slight reaction
50°	1.0	Starting material + two other spots	
	1.5		
75°	1.0	Starting material + two other spots	Tar deposited
100°	1.0	Tar deposited	Tar deposited

Examination of the tars deposited at the higher temperatures showed them to be mixtures of polar materials.

(b) The 2-hydroxy compound (XVII) (0.41g) was dissolved in methylene chloride (20ml) and methanesulphonyl chloride (0.11g, 1 equivalent) and triethylamine (0.1g) were added. The reaction mixture was allowed

to stand at 25° for 24h when T.L.C. showed no apparent reaction. The solution was refluxed for 3h but still no reaction occurred; it was evaporated to dryness under reduced pressure to yield a white solid which was recrystallised from methylene chloride/light petroleum to give pure starting material (XVII) (0.35g) identified by its infra-red spectrum.

The experiment was repeated as above but using refluxing tetrahydrofuran or acetonitrile as solvent. In both cases T.L.C. indicated that no reaction had occurred.

(c) The 2-hydroxy compound (XVII) (0.41g) was dissolved in chloroform (10ml) and methanesulphonyl chloride (0.22g, 2 equivalents) and benzyltriethylammonium chloride (0.05g) were added. The solution was divided into two equal parts.

Portion A was treated with a solution of potassium hydroxide (0.11g) in water (5ml) at room temperature. The organic phase immediately turned dark red and T.L.C. showed a large number of products to be present; the reaction was abandoned.

Portion B was treated with a solution of potassium carbonate (0.28g) in water (5ml) and stirred for 24h. No apparent reaction had occurred as shown by T.L.C.; the mixture warmed at 60° for 6h, again no reaction was observed.

(d) The 2-hydroxy compound (XVII) (0.2g) was mixed with methanesulphonic anhydride (0.5g) and heated under dry nitrogen at 111°. An intractable black tar formed immediately which was insoluble in the common organic solvents.

(e) The 2-hydroxy compound (XVII) (0.2g) was mixed with methanesulphonic anhydride (0.5g) and heated under dry nitrogen at 100° until the reactants had melted (2min). The resultant oil was cooled to yield

a hard plastic material from which methanesulphonic anhydride was removed by trituration with ether. The residual brown oil was examined by T.L.C. and found to contain many components.

Reaction of trans-1,4-bis(p-toluenesulphonyl)-2,5-dihydroxypiperazine with methanesulphonyl chloride.

The 2,5-dihydroxypiperazine (VIII) (0.3g) was dissolved in pyridine (20ml) and methanesulphonyl chloride (0.16g) was added. The results are tabulated below.

Temperature	Time	Observations
25°	5min 1h	No apparent reaction. Starting material, 2-hydroxy compound (XVII) and traces of other products.
50°	5min	"
	1h	All starting material gone, (XVII) and 5 other products present
100°	5min	Intractable tar.

All observations were made by T.L.C. of aliquots treated with aqueous acid followed by extraction into methylene chloride.

Reaction of 1,4-bis-(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with p-tolyl chlorothionoformate[80]

(a) The 2-hydroxy compound (XVII) (0.3g) was dissolved in pyridine (20ml) and p-tolyl chlorothionoformate (0.22g) was added; the solution was allowed to stand for 24h at room temperature. It was then poured

into 2M HCl and extracted with methylene chloride; the organic phase was washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to yield a brown oil (0.4g) which proved to be a complex mixture by T.L.C.

(b) The 2-hydroxy compound (XVII) (0.3g) was dissolved in methylene chloride (25ml) containing triethylamine (1ml) and p-tolyl chlorothionoformate (0.22g) was added. After 6h T.L.C. showed a similar mixture as that obtained in (a) above; evaporation of solvent gave a similar oil (0.37g). Attempts to separate the components of this oil were unsuccessful.

1,4-bis(p-toluenesulphonyl)-2-acetoxy-1,2,3,4-tetrahydropyrazine (XXVI)

(a) The 2,5-dihydroxypiperazine (VIII) (1g) was suspended in acetic anhydride (10ml) containing conc. HCl (0.5ml) and heated at 100° until the solution was homogeneous (20min); it was cooled in ice and poured into cold water (200ml) with stirring. A white precipitate was formed which was filtered and crystallised three times from ethyl acetate to give pure (XXVI) (0.94g, 72%), m.p. 152-153° [Found: C,53.5; H,5.05; N,6.0; $C_{20}H_{22}N_2O_6S_2$ requires C,53.2; H,4.9; N,6.2%]; $\nu_{max.}$ 3140, 3080, 2960, 1780, 1660, 1600, 1500, 1458, 1405, 1350, 1280, 1205, 1180, 1120, 1080, 1040, 980, 820, 730, 710, 675cm^{-1}; δ 1.48(3H,s, CH_3), 2.40(s,6H, Ar CH_3), 2.25(1H,dd, J_{DE} 13.5Hz, J_{CE} 2.0Hz, H_E), 4.25(1H,d,broad, H_AH_B), 6.55(1H,s,broad,H_C), 7.43(8H,q,J 8.5Hz, further split J 2.0Hz, ArH).

(b) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry acetonitrile (50ml) and a solution of silver acetate (0.17g) in the same solvent (10ml) was added. An immediate precipitate of silver chloride was formed and removed by filtration through celite. The solvent was evaporated under reduced pressure to yield a viscous oil

which solidified after much trituration with dry ether and was collected by filtration. Several recrystallisations from dry benzene gave the pure 2-acetoxy compound (XXVI) (0.26g) identified by its infra-red and n.m.r. spectra.

(c) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry acetonitrile (100ml) and lithium acetate (0.1g) was added. The solution was refluxed for 3h, when the reaction was complete as shown by T.L.C. The acetonitrile was evaporated under reduced pressure to give a pale oil which was taken up in methylene chloride, washed with water, and the organic phase separated and dried over $MgSO_4$. The methylene chloride was evaporated under reduced pressure to give a white solid which on crystallisation from dry benzene gave (XXVI) (0.34g) identified by its n.m.r. spectrum.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with acetic anhydride in pyridine.

The 2-hydroxy compound (XVII) (0.3g) was dissolved in pyridine (25ml) and acetic anhydride (1ml) was added; the solution was allowed to stand in the cold until all the starting material had disappeared by T.L.C. (24h). It was poured into 2M HCl and extracted with methylene chloride. The organic phase was separated and dried over $MgSO_4$; the solvent was evaporated under reduced pressure to yield an oil, trituration of which with dry ether dissolved some of it. A solid crystallised from the ethereal solution; this was collected by filtration and identified as starting material (0.1g) by its infra-red spectrum and mixed melting point. The remaining oil was a complex mixture which did not appear to contain any of the 2-acetoxy compound (XXVI).

Reaction of trans-1,4-bis(p-toluenesulphonyl)-2,5-dihydroxypiperazine with refluxing acetic anhydride.

The 2,5-dihydroxypiperazine (VIII) (0.3g) was dissolved in acetic anhydride (5ml) and the solution was heated to reflux. After 1min. the contents of the flask had solidified yielding a black tarry material. Acetone (25ml) was added and the resulting black solution was treated with decolourising charcoal when it turned straw yellow. The acetone was evaporated under reduced pressure to yield a dark yellow oil (0.2g) which had R_F=0 on T.L.C. in ethyl acetate. Redevelopment of the plate with acetone showed the product to be a complex mixture.

Reaction of trans-1,4-bis(p-toluenesulphonyl)-2,5-dihydroxypiperazine with trifluoroacetic anhydride.

The 2,5-dihydroxypiperazine (VIII) (0.3g) was suspended in trifluoroacetic anhydride (20ml) and allowed to stand for 24h, when all the solid had dissolved to form a deep yellow solution. The trifluoroacetic anhydride was evaporated under reduced pressure to yield a yellow oil (0.28g) which on trituration with dry ether gave a pale yellow solid. Recrystallisation of this from methylene chloride/light petroleum gave the 2-hydroxy compound (XVII) (0.26g) m.p. 163-164°, identified by mixed melting point and its infra-red spectrum.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with trifluoroacetic anhydride.

The 2-hydroxy compound (XVII) (0.3g) was dissolved in trifluoroacetic anhydride (10ml) to give a yellow solution which was allowed to stand for 24h. The reaction was followed by T.L.C. in various solvent systems (ethyl acetate/light petroleum mixtures, chloroform,

methylene chloride and benzene). No apparent reaction had occurred even after 24h. The trifluoroacetic anhydride was evaporated under reduced pressure to yield a yellow oil (0.29g) which on trituration with dry ether gave a white solid, recrystallisation of which from methylene chloride/light petroleum yielded pure (XVII) (0.25g) identified by mixed melting point and its infra-red spectrum.

1,4-bis(p-toluenesulphonyl)-2-phenylthio-1,2,3,4-tetrahydropyrazine (XXXI).

(a) The 2-hydroxy compound (XVII) (0.5g) was dissolved in dry acetone (50ml) and conc. HCl (1ml) was added together with excess thiophenol (0.5g). The solution was refluxed for 8h after which time the reaction was complete as shown by T.L.C. The acetone was evaporated under reduced pressure to give a brown oil. Addition of ether resulted in rapid crystallisation of a white solid; this was filtered and recrystallised from methylene chloride/light petroleum to give pure (XXXI) (0.52g, 80%), m.p. 170-172° [Found: C,57.7; H,5.0; N,5.3; $C_{24}H_{24}N_2O_4S_3$ requires C,57.6; H,4.8; N,5.6%]; $\nu_{max.}$ 3110, 3030, 3000, 2990, 2920, 2870, 1650, 1600, 1580, 1480, 1455, 1440, 1370, 1350, 1305, 1270, 1170, 1110, 1090, 1010, 1000, 940, 900, 820, 810, 780, 740, 700, 690, 670, 650cm^{-1}; δ 2.35(3H,s,$ArCH_3$), 2.37(1H, dd, J 12.0Hz, J_{CE} 3.0Hz, H_E), 2.39(3H,s,$ArCH_3$), 3.3(1H,d,broad, J 12.0Hz, H_D), 5.25(1H,m,broad, H_C), 6.12(2H,q,J_{AB} 13.5Hz, further split J 3.0Hz, H_AH_B), 7.05-7.7(13H,m,ArH).

(b) From (XXXVII). The 2-chloro compound (XXXVII) (0.42g) was dissolved in acetonitrile (100ml), and a solution of sodium thiophenoxide (0.14g) in the same solvent (50ml) was added. The reaction mixture was refluxed under dry N_2 for 6h, cooled, filtered through celite to remove NaCl and the acetonitrile evaporated under reduced

pressure to yield a white solid. Crystallisation from methylene chloride/light petroleum gave pure (XXXI) (0.47g, 94%) identified by its infra-red and n.m.r. spectra and mixed melting point.

1,4-Bis(p-toluenesulphonyl)-2-phenylsulphinyl-1,2,3,4-tetrahydropyrazine (XXXIII).

(a) The thioether (XXXI) (0.5g) was dissolved in acetic acid (100ml) and excess 30% hydrogen peroxide (10ml) was added. The solution turned cloudy but on stirring this cloudiness disappeared. After 3h T.L.C. of a sample obtained by pouring a portion into water and extracting with chloroform showed the reaction to be complete. The solution was poured into water (500ml) to give a white precipitate; this was filtered and washed with water (200ml), dissolved in methylene chloride and dried over $MgSO_4$ (12h). The solution was filtered and the methylene chloride evaporated from the filtrate under reduced pressure to give a white solid; crystallisation from methylene chloride/ether gave pure (XXXIII) (0.31g, 60%) m.p. 124-126° (dec.) [Found: C,55.9; H,4.9; N,5.5; $C_{24}H_{24}N_2O_5S_3$ requires C,55.8; H,4.65; N,5.4%]; $\nu_{max.}$ 3100, 3000, 2930, 2870, 1650, 1600, 1480, 1440, 1390, 1370, 1305, 1280, 1160, 1115, 1090, 1040 (S=O), 1010, 980, 950, 910, 810, 750, 730, 700, 690, 670, 660 cm^{-1}; δ 2.25(1H,dd, J_{DE} 12.0Hz, further split J_{CE} 3.0Hz, H_E), 2.40(6H,s,CH_3) 4.50(1H,d,broad, J_{DE} 12.0Hz, H_D), 4.50(1H,m,broad, H_C), 6.25(2H,q,J_{AB} 15.0Hz, further split J 3.0Hz, H_AH_B), 7.1-7.8(13H,m,ArH).

(b) The thioether (XXXI) (0.5g) was dissolved in methylene chloride (100ml) and a solution of m-chloroperbenzoic acid (0.18g) in the same solvent (10ml) was added. The solution was allowed to stand overnight when the reaction was complete as shown by TL.C. The solution was washed with sodium bicarbonate solution (3 x 25ml) and water (2 x 25ml)

dried overnight over $MgSO_4$ and the solvent evaporated under reduced pressure to yield a viscous oil which solidified after trituration with ether. The white solid thus obtained was crystallised from methylene chloride/ether to give pure (XXXIII) (0.42g, 80%) which was identified by its infra-red spectrum and by mixed melting point.

(c) The thioether (XXXI) (0.5g) was dissolved in dry toluene (100ml) and iodosobenzene (0.5g) was added; the suspension was heated at 100° for 3h when all the iodosobenzene had dissolved. The solvent was evaporated under reduced pressure to give an oil which solidified on trituration with ether. This was filtered and crystallised from benzene to give the sulphoxide (XXXIII) (0.42g, 81%) identified by its n.m.r. spectrum.

(d) The sulphide (XXXI) (0.5g) was dissolved in acetonitrile (200ml) containing lithium periodate (0.2g) and the solution refluxed (6h) until no starting material remained. The solution was filtered and the solvent evaporated under reduced pressure to give an oil which on trituration with dry ether gave a floccular white solid. This was filtered and crystallised from benzene to give the sulphoxide (XXXIII) (0.4g,80%) identified by a mixed melting point with an authentic sample.

Attempted pyrolysis of 1,4-bis(p-toluenesulphonyl)-2-phenylsulphinyl-1,2,3,4-tetrahydropyrazine

Samples (0.2g) of the sulphoxide (XXXIII) were treated as described below.

(a) The sulphoxide was refluxed in dry toluene (5min); bubbles were observed and the solution turned brown. T.L.C. (chloroform) showed a mixture.

(b) The sulphoxide was heated in dry toluene at 100°; bubbles of gas

were evolved. After 5min T.L.C. (chloroform) showed the presence of three components including starting material. After 20min a more complex mixture had been produced.

(c) Sodium dried benzene was added and the solution refluxed. Results as for (b).

(d) Dry acetonitrile was added and the solution was refluxed. Results as for (b).

(e) At 50° in dry toluene there was no apparent reaction after 6h.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylsulphinyl-1,2,3,4-tetrahydropyrazine.

(a) The sulphoxide (XXXIII) (0.3g) was dissolved in acetone (25ml) and excess 30% hydrogen peroxide (3ml) was added. The solution was allowed to stand for 24h when no apparent reaction had occurred as shown by T.L.C.. More 30% hydrogen peroxide (8ml) was added and the solution left for a further 24h; again no reaction had taken place. The solution was refluxed for 8h, poured into water (500ml) and extracted with methylene chloride (50ml). The organic phase was dried over $MgSO_4$ (12h), filtered and the methylene chloride evaporated under reduced pressure to give a white solid which was crystallised from methylene chloride/ether. It was identified as unchanged (XXXIII) (0.29g, ~100%) by its infra-red and n.m.r. spectra and mixed melting point determination with an authentic sample.

(b) The sulphoxide (XXXIII) (0.3g) was dissolved in glacial acetic acid (25ml) and 30% hydrogen peroxide (5ml) was added. The solution was allowed to stand at room temperature (24h). No reaction was observed on T.L.C. The solution was heated at 100° for 1h; only an intractable mixture was obtained after work-up as in (a) above.

Attempted reaction of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with hydrogen sulphide.

The 2-hydroxy compound (XVII) (0.3g) was dissolved in acetone (50ml) and conc. HCl (1ml) was added. Hydrogen sulphide was passed into / the solution for 5min, the flask stoppered and allowed to stand for 24h. No reaction was apparent by T.L.C.; the solution was then refluxed for 10h, being resaturated with hydrogen sulphide every hour, but no reaction appeared to have taken place as shown by T.L.C. Evaporation of the acetone under reduced pressure gave back unchanged (XVII) (0.3g) identified by its infra-red spectrum and mixed melting point.

1,4-Bis(p-toluenesulphonyl)-2,5-dichloropiperazine (XXXVI).

(a) The 2-hydroxy compound (XVII) (0.3g) was dissolved in methylene chloride (25ml) and the solution cooled to 0°. Thionyl chloride (5ml, large excess) was added, and the solution kept at 0° for 24h. Colourless, cubic crystals separated from the solution; these were collected by filtration. The crystalline product (0.33g, 94%) proved extremely insoluble and could not be crystallised, nor could an n.m.r. spectrum be obtained. It had m.p. 154-6° [Found: C,46.7; H,4.3; N,5.9. $C_{18}H_{20}N_2S_2O_4Cl_2$ requires C,46.65; H,4.3; N,6.0%]; $\nu_{max.}$ 3060, 3035, 2920, 1600, 1500, 1475, 1390, 1355, 1340, 1320, 1270, 1180, 1170, 1110, 1095, 1040, 980, 950, 815, 800, 705, 680, 635cm^{-1}.

(b) The 2-hydroxy compound (XVII) (0.5g) was treated dropwise with thionyl chloride (10ml, large excess). A vigorous, endothermic reaction occurred with evolution of sulphur dioxide and HCl. The solid dissolved, but after 20min a white solid had precipitated and the evolution of gases had stopped. The solid was filtered, washed with

dry ether (20ml) and dried to yield (XXXVI) (0.51g, 91%) identified by its infra-red spectrum and mixed melting point with the sample prepared under (a). [Found: C,46.8; H,4.2; N,5.9; Cl,15.2; $C_{18}H_{20}N_2S_2O_4Cl_2$ requires C,46.65; H,4.3; N,6.0; Cl,15.3%].

(c) The 2,5-dihydroxypiperazine (VIII) (1g) was treated dropwise with thionyl chloride (20ml, large excess). A vigorous endothermic reaction occurred with evolution of gases. When evolution of gas had ceased (30min) the residual solid was filtered and washed with dry ether (50ml) to give (XXXVI) (0.92g,83%) identified by its infra-red spectrum and mixed melting point with the sample prepared under (a).

(d) The 2-hydroxy compound (XVII) (0.3g) was dissolved in dry toluene (25ml). Hydrogen chloride was bubbled into the solution; this process was repeated hourly for 5h to ensure that the solution remained saturated with the gas. At the end of this period T.L.C. showed some reaction and a small amount of material had crystallised out. After a further 24h more material had come out of solution; this was filtered and washed with dry ether (3 x 25ml) to give a pale brown solid (0.18 g) which was identified as (XXXVI) by its infra-red spectrum and mixed melting point.

1,4-bis(benzenesulphonyl)-2,5-dichloropiperazine

This compound was prepared in analogous fashion to (XXXVI) by method (c) above, using the 2,5-dihydroxypiperazine (VII) (12 g). Yield 11.68g, 89%, m.p. 146-148° [Found: C,44.3; H,3.6; N,6.5; $C_{16}H_{16}N_2O_4S_2Cl_2$ requires C,44.1; H,3.7; N,6.4%] $\nu_{max.}$ 3100, 2940, 1600, 1490, 1470, 1390, 1350, 1305, 1290, 1110, 1040, 1020, 980, 950, 815, 800, 710, 680, 635cm^{-1}.

1,4-Bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine (XXXVII)

The 2,5-dichloropiperazine (XXXVI) (0.3g) was suspended in sodium dried toluene (50ml) and heated with stirring at 100°. HCl gas was evolved and the solid dissolved within 1h. The toluene was evaporated under reduced pressure to yield a pale yellow oil. On cooling and trituration with ether a white solid was obtained which on crystallisation from methylene chloride/light petroleum gave the pure 2-chloro compound (XXXVII) (0.27g, 98%) m.p. 134-136° [Found: C,50.4; H,4.2; N,6.8; Cl,8.1, $C_{18}H_{19}N_2O_4S_2Cl$ requires C,50.4; H,4.46; N,6.7; Cl,8.3%]; $\nu_{max.}$ 3110, 3040, 2960, 2920, 2860, 1658, 1600, 1490, 1450, 1400, 1360, 1350, 1310, 1280, 1210, 1180, 1110, 1035, 1020, 1000, 950, 930, 900, 810, 745, 720, 710, 675, 660, 630cm^{-1}; δ 2.40(6H,s,CH_3), 3.25(1H,dd,J_{DE} 12.0Hz, further split J_{CE} 2.0Hz, H_E), 4.15(1H,d,broad, J 12.0Hz, H_D), 6.12(2H,q,J_{AB} 9.0Hz, further split J 3.0Hz, H_AH_B), 6.20(1H,m,H_C), 7.40(8H,q,ArH).

1,4-Bis(p-benzenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine

This compound was prepared in an analogous fashion to (XXXVII) above from 1,4-bis(benzenesulphonyl)-2,5-dichloropiperazine (10g). Yield, 9.2g (90%), m.p. 135-137° [Found: C,48.4; H,3.9; N,7.0; Cl,8.7; $C_{16}H_{15}O_4N_2S_2Cl$ requires: C,48.2; H, 3.8; N,7.0; Cl,8.9%]; $\nu_{max.}$ 3100, 2940, 1658, 1600, 1490, 1450, 1390, 1370, 1350, 1290, 1210, 1110, 1040, 1020, 1000, 950, 930, 900, 750, 710, 680, 625cm^{-1}. δ 3.25(1H, dd, J_{DE} 12.0Hz, further split J_{CE} 2.0Hz, H_E), 4.15(1H,d,broad, J 12.0Hz, H_D), 6.15(2H,q,J_{AB} 9.0Hz, further split J 3.0Hz, H_AH_B), 6.20(1H, m,H_C), 7.3-7.9(10H,m,ArH).

Reaction of 1,4-bis(p-toluenesulphonyl-2,5-dichloropiperazine with water

(a) At room temperature.

The 2,5-dichloropiperazine (XXXVI) (0.3g) was dissolved in dimethylformamide (25ml) and water (2ml) was added. The reaction mixture was allowed to stand for 18h and poured into water to give a white precipitate (0.24g, 95%) which was filtered, washed with water (2 x 25ml), acetone (2 x 25ml) and ether (25ml) and dried under reduced pressure. An infra-red spectrum of the product indicated it to be the 2,5-dihydroxypiperazine (VIII); this was confirmed by its m.p. and mixed melting point with an authentic sample.

(b) On warming.

The 2,5-dichloropiperazine (XXXVI) (0.2g) was suspended in acetone (50ml) containing water (1ml) and refluxed until all the solid had dissolved; HCl was evolved in the process. The solvent was evaporated under reduced pressure and the resultant white solid crystallised from methylene chloride/light petroleum to give the pure 2-hydroxy compound (XVII) (0.16g, 92%) identified by its infra-red and n.m.r. spectra.

Reaction of 1,4-bis(p-toluenesulphonyl)-2,5-dichloropiperazine with ethanol.

The 2,5-dichloropiperazine (XXXVI) (0.3g) was suspended in chloroform (50ml) containing ethanol (2ml) and refluxed until all the solid had dissolved. The solvent was evaporated under reduced pressure and the resultant white solid crystallised from methylene chloride/light petroleum to yield a pure product (0.22g, 77%) which was identified as the 2-ethoxy compound (XV) by its n.m.r. spectrum and mixed melting point.

Action of heat on 1,4-bis(p-toluenesulphonyl)-2,5-dichloropiperazine

The 2,5-dichloropiperazine (XXXVI) (0.5g) in a tube fitted

with a side arm and attached to a vacuum pump was heated at 100° and 10^{-1} torr and the following observations noted. After 2-3mins the solid melted and bubbled vigorously, this continued for 10min during which time a white solid was deposited in the upper cool. portion of the tube. At the end of this time the reaction was terminated by removing the heat; a dark oil remained at the bottom of the tube which solidified on cooling. The sublimate (0.24g) was removed; it had m.p. 62-63° and was identified as p-toluenesulphonyl chloride by its infra-red and n.m.r. spectra and mixed melting point.

The dark residue was triturated with ether, which dissolved the bulk of it, leaving a black oil which appeared a complex mixture by T.L.C. Addition of light petroleum to the ethereal solution resulted in crystallisation of more p-toluenesulphonyl chloride (0.17g) identified as above. The combined yield was 79% theoretical (calculated for 2 moles).

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with triphenylphosphine in carbon tetrachloride[84]

Triphenylphosphine (0.26g) was dissolved in carbon tetrachloride (50ml). The 2-hydroxy compound (XVII) (0.41g) was added and the reaction mixture refluxed for 24h. No reaction was apparent by T.L.C.; on cooling in ice unchanged starting material crystallised. This was filtered and identified by its infra-red spectrum.

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine using a Vilsmeier reagent[85].

Phosphorus pentachloride (1g) was added to dimethylformamide (25ml) at 0°. The mixture turned dark and then almost solid; much heat

was evolved. After 15min the reaction had subsided and excess dimethylformamide was decanted, the solid product was washed with clean dimethylformamide (3 x 10ml) and ether (20ml). Fresh dimethylformamide (25ml) and the 2-hydroxy compound (XVII) (0.42g) were now added and the reaction mixture heated at 100° for 8h. The solution was cooled and poured into water; the floccular white precipitate was filtered and dried in air. Crystallisation from methylene chloride/ light petroleum gave starting material identified by its infra-red spectrum and melting point.

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-iodo-1,2,3,4-tetrahydropyrazine[86].

Triphenylphosphine (0.26g) was dissolved in dimethylformamide (25ml) and iodine was added until a faint colouration occurred. The 2-hydroxy compound (XVII) (0.41g) was added and the solution refluxed for 24h. At the end of this time T.L.C. showed a mixture of starting material and several other products.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with methyltriphenoxyphosphonium iodide in hexamethylphosphoramide[88]

The 2-hydroxy compound (0.5g) was dissolved in hexamethylphosphoramide which had been freshly distilled from calcium hydride and methyltriphenoxyphosphonium iodide (0.7g) was added. The solution was allowed to stand for a total of 48h at room temperature after which time T.L.C. (benzene) showed that no reaction had taken place. The reaction was heated at 100° for 8h; again no reaction was apparent and the temperature was raised to 120°, when the solution rapidly darkened. After 5min the solution was cooled and poured into water to give an oil. This

was extracted with chloroform, washed with water and the organic phase dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave an oil which T.L.C. (benzene) showed to be a very complex mixture.

1,4-bis(p-toluenesulphonyl)-2-benzylamino-1,2,3,4-tetrahydropyrazine (XLII).

The 2-chloro compound (XXXVII) (0.42g) was dissolved in dry toluene (50ml). Benzylamine (0.21g, 2 moles) was added and a dense white precipitate was formed. The reaction mixture was heated at 100° for 5min to complete the reaction and then cooled to 0°. The precipitate was filtered and its identity was established as benzylamine hydrochloride by comparison of its infra-red spectrum with that of an authentic sample. The toluene was evaporated from the filtrate under reduced pressure to give a pale brown solid. Crystallisation from methylene chloride/ether gave pure (XLII) (0.44g, 89%) m.p. 150-152° [Found : C,59.6; H,5.3; N,8.4; $C_{24}H_{25}N_3S_2O_4$ requires C,59.6; H,5.2; N,8.7%]; $\nu_{max.}$ 3310 (NH), 3110, 3020, 2920, 2860, 1650, 1600, 1495, 1475, 1450, 1395, 1350, 1280, 1170, 1120, 985, 965, 940, 810, 775, 730, 705, 675cm^{-1}; δ 1.90(1H,dd, J_{DE} 12.0Hz, further split J_{CE} 2.0Hz, H_E), 2.25(3H,s,CH_3), 2.32(3H,s,CH_3), 3.70(2H,s,$\underline{CH_2}$Ph), 3.75(1H,dd, broad J 12.0Hz, H_D), 4.68(1H,s,broad, H_C), 6.1(2H,q, J 10.5Hz, further split J 3.0Hz, H_AH_B), 6.95-7.55(13H,m,ArH).

Attempted methylation of 1,4-bis(p-toluenesulphonyl)-2-benzylamino-1,2,3,4-tetrahydropyrazine.

(a) The amine (XLII) (0.3g) was dissolved in ether (200ml) and methyl iodide (2ml) was added. The reaction vessel was tightly stoppered and allowed to stand for 24h; no reaction was apparent by T.L.C. nor on standing for longer periods. No solid precipitated from the solution.

(b) The amine (XLII) (0.2g) was stirred with methyl iodide (10ml)

for 5h; the methylating agent was then distilled off and the residual solid identified as starting material by its infra-red spectrum.

(c) The amine (XLII) (0.43g) was dissolved in dry toluene (100ml) and methyl p-toluenesulphonate (0.34g) was added. The solution was heated at 100° for 8h; no reaction was apparent by T.L.C.

(d) The amine (XLII) (0.3g) was treated with methyl p-toluenesulphonate (2g) and the mixture was gradually heated to 100°, the amine dissolving in the molten methylating agent. After 3h the reaction mixture was cooled and the excess methyl p-toluenesulphonate removed by trituration with ether. The residue proved to be an intractable tar.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with t-butylamine.

The 2-chloro compound (XXXVII) (0.3g) was dissolved in dry toluene (100ml) and excess t-butylamine (1ml) was added. After 30h at room temperature, extremely fine white crystals had come out of solution and T.L.C. showed no starting material left. The crystals were removed by filtration. The solvent was evaporated from the yellow filtrate under reduced pressure to give an oil which solidified on cooling. This was crystallised from methylene chloride/dry ether to give a white crystalline solid (0.27g) which rapidly turned brown on exposure to air and was therefore handled under nitrogen. It had m.p. 98 - 100° [Found: C,58.4; H,7.0; N,8.1; $C_{22}H_{29}N_3O_4S_2$ requires C,57.0; H,6.3; N,9.1%]; $\nu_{max.}$ 3340 (NH), 3100, 3080, 2960, 2920, 2860, 1640, 1600, 1490, 1450, 1390, 1350, 1270, 1230, 1170, 1110, 1080, 990, 950, 930, 860, 810, 805, 780, 745, 705, 680, 660cm^{-1}; δ 1.00(9H,s, t-but CH_3), 1.72(1H,dd, J 12.0Hz, further split J_{CE} 3.0Hz, H_E), 2.28(3H, s, $ArCH_3$), 2.32(3H,s,$ArCH_3$), 3.50(1H,d,broad, J 12.0Hz, H_D), 4.82(1H,

broad, H_C), 6.0(2H,q, J_{AB} 15.0Hz, further split J 1.5Hz, H_AH_B), 6.9-7.6(8H,m,ArH).

1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine (XLIV).

Diphenyl diselenide (0.16g) was dissolved in acetonitrile (100ml) in a flask equipped with a nitrogen inlet and a reflux condenser. Dry nitrogen was passed over this solution and sodium borohydride was added until the yellow colour was discharged. A solution of the 2-chloro compound (XXXVII) (0.43g) in acetonitrile (20ml) was added and the reaction mixture refluxed for 3h. It was cooled in ice and precipitated salts removed by filtration through celite. The acetonitrile was evaporated under reduced pressure to give a grey solid which was extracted with methylene chloride. The solvent was removed under reduced pressure and the resultant white solid crystallised from methylene chloride/light petroleum to yield pure (XLIV) (0.33g, 60%) m.p. 170-172° [Found C,52.6; H,4.3; N,4.8; $C_{24}H_{24}N_2O_4S_2Se$ requires C,52.6; H,4.4; N,5.1%]; $\nu_{max.}$ 3100, 3030, 2995, 2950, 2920, 2880, 1645, 1595, 1580, 1480, 1440, 1350, 1305, 1265, 1170, 1120, 990, 935, 890, 805, 775, 735, 705, 670, 655cm^{-1}; δ 2.32(3H,s,CH_3), 2.40(3H,s,CH_3), 2.45(1H,dd, J 12.0Hz, further split J 3.0Hz,H_E), 3.8(1H,d,broad, J 12.0Hz, H_D), 5.45(1H,s, broad, H_C), 6.15(2H,q,J_{AB} 15.0Hz, further split J 3.0Hz, H_AH_B), 7.0-7.7(13H, m,ArH).

1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine (XLV).

The 2-chloro compound (XXXVII) (2.1g) was dissolved in acetonitrile (50ml) and sodium borohydride (1g) was added. The reaction mixture was refluxed under dry nitrogen (3h), allowed to cool and filtered. The solvent was evaporated under reduced pressure and the

resulting grey solid crystallised from methylene chloride/ether to give pure (XLV) (1.8g, 91%) m.p. 188-190° [Found: C,54.9; H,5.2; N,7.2; $C_{18}H_{20}N_2O_4S_2$ requires C,55.1; H,5.1; N, 7.1%]; $\nu_{max.}$ 3100, 2920, 2870, 1650, 1600, 1490, 1460, 1445, 1390, 1350, 1290, 1265, 1250, 1205, 1170, 1110, 1015, 950, 805, 800, 730, 705, 670cm^{-1}; δ 2.35(6H, s,CH_3), 3.0(4H,s, ring CH_2), 6.1(2H,s,olefinic CH), 7.30(8H,q,J 6.0Hz, ArH).

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-iodo-1,2,3,4-tetrahydropyrazine (XLI).

(a) The 2-chloro compound (XXXVII) (0.45g) was dissolved in acetone (50ml) and sodium iodide (0.18g) was added. The solution was refluxed for 3h after which time it had gone brown and cloudy. On cooling a white precipitate of sodium chloride was obtained which was filtered; acetone was evaporated from the filtrate under reduced pressure to give a brown oil. This was taken up in methylene chloride and washed with 2M sodium thiosulphate solution (50ml) and then with water. The colourless organic phase was separated and dried over $MgSO_4$; evaporation of the solvent under reduced pressure gave a white solid (0.38g) identified as the 2-hydroxy compound (XVII) by its infra-red spectrum and mixed melting point.

(b) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry acetonitrile (100ml) and a solution of sodium iodide (0.5g) in the same solvent (25ml) was added. A reaction occurred at room temperature with the solution turning red-brown and a precipitate being formed; T.L.C. showed the absence of starting material after 10min. The precipitated sodium chloride was removed by filtration and the acetonitrile evaporated under reduced pressure to give an intractable mixture.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with sodium thiocyanate.

The 2-chloro compound (XXXVII) (0.42g) was dissolved in dry acetonitrile (50ml) and a solution of sodium thiocyanate (0.082g) in the same solvent (10ml) was added. The solution turned pink and over 5min a precipitate of sodium chloride was formed; this was removed by filtration through celite when the solution turned yellow. Solvent was evaporated under reduced pressure to give a yellow solid; crystallisation from methylene chloride/ether and then benzene gave a white crystalline material (0.36g), m.p. 143-5° [Found: C,50.1; H,4.2; N,9.3; S,19.1; $C_{19}H_{19}N_3S_3O_4$ requires C,50.8; H,4.2; N,9.3; S,21.3%]; $\nu_{max.}$ 3100, 3060, 3000, 2970, 2920, 2860, 2020, 1650, 1600, 1490, 1450, 1400, 1350, 1305, 1270, 1210, 1170, 1125, 1080, 1070, 970, 920, 810, 740, 710, 700, 670cm^{-1}; δ 2.40(6H,s,CH_3), 2.75(1H,dd,J_{DE} 12.0Hz, further split, J_{CE} 1.5Hz, H_E), 4.05(1H,d,broad, J 12.0Hz, H_D), 5.65(1H,m,H_C), 6.15(2H,q,J_{AB} 7.0Hz, further split J 1.5Hz, H_AH_B), 7.45(8H,q,J 8.5Hz, ArH).

Attempted preparation of 1,4-bis(p-toluenesulphonyl)-2-cyano-1,2,3,4-tetrahydropyrazine (XLVIII).

(a) The 2-chloro compound (XXXVII) (0.4g) was dissolved in dry dimethylformamide (50ml) and potassium cyanide (0.1g) was added. The flask was equipped with a calcium chloride tube and heated at 100° for 3h when T.L.C. showed only a more polar material to be present. The solution was cooled, poured into water and the resultant white precipitate filtered. The solid obtained was taken up in methylene chloride, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the 2-hydroxy compound (XVII) identified by its

infra-red spreetrum and mixed melting point determination.

(b) Dimethylformamide was dried by the method of Thomas and Rochow[91].

The 2-chloro compound (XXXVII) (0.3g) was dissolved in the above solvent (50ml) and potassium cyanide (0.1g) was added. The flask was fitted with a calcium chloride drying tube and heated at 100° for 1h; it was then worked up as in (a) above but again only the 2-hydroxy compound (XVII) identified as above could be isolated.

(c) The 2-chloro compound (XXXVII) (0.2g) was dissolved in acetone (50ml) which had been dried over $MgSO_4$ and then molecular sieves. Potassium cyanide (0.1g) was added and the solution refluxed for 8h; at the end of this period only a mixture of starting material and the 2-hydroxy compound (XVII) could be detected by T.L.C. The acetone was evaporated under reduced pressure and the resultant oil taken up in methylene chloride and washed with water. The organic phase was dried over $MgSO_4$ and the solvent removed to give a pale oil which solidified on trituration with ether to give a white solid. This appeared to be a mixture of the 2-chloro and 2-hydroxy compounds (XXXVII) and (XVII) as shown by T.L.C. An infra-red spectrum showed no sign of a CN peak.

(d) The 2-chloro compound (XXXVII) (0.43g) was dissolved in methylene chloride (50ml). This solution was added slowly to a stirred suspension of potassium cyanide (0.2g) in methylene chloride containing dibenzo-18-crown-6 (0.1g). The reaction mixture was refluxed for 6h but no reaction was apparent by T.L.C. and the potassium cyanide did not seem to dissolve.

(e) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry acetonitrile (50ml) and potassium cyanide (0.1g) and dibenzo-18-crown-6 (0.36g) were added with stirring. The reaction mixture was refluxed for 6h (after 3h the cyanide had largely dissolved) when T.L.C. showed

a mixture. The solvent was evaporated under reduced pressure to yield an oil (0.87g) which did not give clear spots on T.L.C. Separation of this mixture on a silica column gave dibenzo-18-crown-6 (0.34g), the 2-chloro compound (XXXVII) (0.31g) and the 2-hydroxy compound (XVII) (0.1g) eluted off with benzene, methylene chloride and ethyl acetate, respectively. The remaining material was eluted with acetone and shown to be a mixture by T.L.C. in acetone.

(f) 18-crown-6 (2.6g) was dissolved in methanol (50ml) and potassium cyanide (0.65g) was added with stirring; when it had all dissolved the methanol was evaporated under reduced pressure and the resulting white complex azeotroped with benzene to remove water and alcohol. The complex (0.35g) was dissolved in dry acetonitrile (100ml) and the 2-chloro compound (XXXVII) (0.43g) in the same solvent (25ml) was added. The solution was refluxed for 8h after which time there was no sign of any reaction by T.L.C. The solvent was removed under reduced pressure to give an oil which partly dissolved on trituration with methylene chloride. The addition of ether to the solution brought about the crystallisation of the 2-chloro compound (XXXVII) (0.36g) identified by its infra-red and n.m.r. spectra.

(g) The 2-chloro compound (XXXVII) (0.43g) was dissolved in hexamethylphosphoramide (25ml), freshly distilled from calcium hydride, and potassium cyanide (0.1g) was added. The suspension was stirred for 24h after which time the solution was poured into water and the resultant precipitate filtered, taken up in methylene chloride and washed with water. The organic phase was separated, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give an oil which solidified on trituration with ether. N.M.R. indicated that this was a mixture of starting material and the 2-hydroxy compound (XVII). Five spots could be distinguished on T.L.C. An infra-red spectrum showed a small peak at 2200cm^{-1} which might be assigned to cyanide.

Attempted reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with sodium sulphide.

The 2-chloro compound (XXXVII) (0.3g) was dissolved in acetone (50ml) and sodium sulphide nonahydrate (0.1g) was added. The solution was refluxed for 3h; T.L.C. indicated gradual formation of the 2-hydroxy compound (XVII). The reaction was not pursued.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with lithium sulphide.

A solution of n-butyl lithium (1.15M) in tetrahydrofuran (25ml) was treated with hydrogen sulphide (dried by passing through anhydrous aluminium sulphide) for 10min. The solution was flushed with dry nitrogen and a solution of the 2-chloro compound (XXXVII) (0.43g) in the same solvent (50ml) was added by means of a syringe. The solution was refluxed until no starting material could be detected by T.L.C. (3h), cooled and treated with carbon dioxide to remove excess n-butyl lithium. The precipitated salts were removed by filtration through celite and the solvent evaporated under reduced pressure to give an oil (0.49g); attempts to purify this on a silica column gave small quantities of the 2-hydroxy compound (XVII) and a mixture of more polar compounds.

Comparison of the rate of reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with methanol and sodium methoxide.

(a) The 2-chloro compound (XXXVII) (0.3g) was dissolved in methanol (100ml) at 25° and the reaction monitored by T.L.C. After 24h some reaction had occurred but some starting material was still present as shown by T.L.C.

(b) The reaction mixture was prepared as above and the solution was

refluxed for 2h when T.L.C. showed the reaction to be complete. Solvent was evaporated under reduced pressure to give the 2-methoxy compound (XIV) (0.27g, 90%) identified by its infra-red spectrum and mixed melting point.

(c) The 2-chloro compound (XXXVII) (0.3g) was dissolved in methanol (100ml) containing sodium (0.2g) and the solution allowed to stand at 25°. Conversion to the 2-methoxy compound (XIV) was complete in 1h as shown by T.L.C. Evaporation of the solvent under reduced pressure gave pure (XIV) (0.29g, 98%) identified by its infra-red and n.m.r. spectrum.

Attempted dehydrohalogenation of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with triethylamine.

(a) The 2-chloro compound (XXXVII) (0.3g) was placed in a flask equipped with a condenser and a calcium chloride drying tube and triethylamine (25ml) was added. The mixture was refluxed for 20min but rapidly turned brown and little solid dissolved. The triethylamine was decanted and evaporated under reduced pressure but no residue was obtained. The tar left in the flask was insoluble in organic solvents and in water; it was not investigated further.

(b) The 2-chloro compound (XXXVII) (0.3g) was dissolved in methylene chloride (25ml) and triethylamine (1ml) was added. The solution gradually turned brown and deposited a tar. T.L.C. showed a complex mixture in the solution.

Attempted dehydrohalogenation of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with diazabicyclo [5,4,0] undec-5-ene (DBU).

(a) This method was tried several times using different work-up

procedures. The 2-chloro compound (XXXVII) (0.3g) was dissolved in dry tetrahydrofuran (25ml) and DBU (0.11g) was added. The solution rapidly changed from colourless to a deep yellow. T.L.C. showed five spots, two of them bright yellow. The best separation was achieved using ethyl acetate/light petroleum (3:2). The solvent was evaporated under reduced pressure to yield an orange oil; trituration of this with dry ether did not yield a solid. Various work-up procedures were tried to separate the products; these are summarised below.

Experiment A.

The oil (0.38g) was placed on a silica column and eluted first with toluene and then with methylene chloride; these did not move the products. The column was then eluted with ethyl acetate/light petroleum (3:2) which removed a yellow band. The solvent was evaporated from this fraction under reduced pressure to give a white solid (0.24g) which was recrystallised from methylene chloride/light petroleum and shown to be the 2-ethoxy compound (X V) by its n.m.r. spectrum. It was presumably formed by reaction of the product with ethanol in the ethyl acetate.

Experiment B.

The oil (0.34g) was chromatographed on a silica column but eluted with distilled ethyl acetate/light petroleum (3:2). A brown band was eluted which was shown to be a mixture of the three least polar products by T.L.C.

Experiment C.

The oil (0.39g) was chromatographed on alumina, eluting with distilled ethyl acetate/light petroluem (3:2); the eluted band showed four spots by T.L.C.

Experiment D.

The oil (200mg) was placed on a thick layer plate and eluted with distilled ethyl acetate/light petroleum (3:2) followed by ethyl acetate/light petroleum (4:1). After 2h the plate was dried; the four least polar bands were each removed and extracted by boiling with dry acetone. The extracts yielded only very small quantities of oil for each band (total, 60mg). The most polar bands were removed and treated in the same way. T.L.C. using acetone as elutant showed each of these to be a mixture. (Total yield 0.23g).

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with diazabicyclo [3,4,0] non-5-ene (DBN).

(a) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry toluene (100ml) and DBN (0.12g) was added. The solution immediately turned yellow; after 1h white crystals of the base hydrochloride separated; T.L.C. showed the presence of only one product. Evaporation of the toluene under reduced pressure gave an oil; T.L.C. showed this to be a mixture of several components.

(b) The 2-chloro compound (XXXVII) (0.43g) was dissolved in methylene chloride (50ml) under dry nitrogen and DBN (0.12g) was added. The same observations were made as in (a) above; after 1h the solution was decanted from the crystals and the solvent evaporated with a current of dry nitrogen. T.L.C. of the resultant oil showed it to be a mixture; $CDCl_3$ was added and the n.m.r. spectrum determined. This showed a broad singlet at δ 6.2 which integrated to less than two protons, broad aromatic and tolyl methyl peaks, and DBN impurity.

(c) The 2-chloro compound (XXXVII) (0.1g) was dissolved in $CDCl_3$ (1.5ml) and a drop of DBN was added. An n.m.r. spectrum run immediately was identical with that obtained under (b) above; the addition of water did not cause any change in the spectrum.

Attempted dehydrohalogenation of 1,4-bis(p-toluenesulphonyl)-2-chloro - 1,2,3,4-tetrahydropyrazine with proton sponge (1,8-bis (dimethylamino)-naphthalene).

The 2-chloro compound (XXXVII) (0.42g) was dissolved im dry toluene (80ml) and a solution of 'proton sponge' (0.25g) in the same solvent was added. The flask was equipped with a calcium chloride drying tube and heated at 100° for 3h. No reaction was apparent by T.L.C.; the solvent was evaporated under reduced pressure and the resultant oil (0.6g) placed on a short silica column. Elution with methylene chloride afforded the unchanged 2-chloro compound (XXXVII) identified by infra-red and n.m.r. spectra.

Attempted reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with sodium hydride.

The 2-chloro compound (XXXVII) (0.3g) was dissolved in tetrahydrofuran (50ml) (freshly distilled from lithium aluminium hydride) under dry nitrogen and excess sodium hydride (1g) was added. The suspension was stirred for 3h when it had developed a yellow colour; however, T.L.C. showed no apparent reaction. The sodium hydride was filtered through celite (dried at 100°) and solvent evaporated under reduced pressure to give a white solid; recrystallisation from methylene chloride/ether gave back starting material (0.28g) identified by its infra-red and n.m.r. spectra.

Attempted reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with sodamide.

The 2-chloro compound (XXXVII) (0.5g) was dissolved in tetrahydrofuran (200ml) (freshly distilled from lithium aluminium hydride)

under dry nitrogen and excess sodamide (2g) was added with stirring. The mixture was stirred for 8h when it became yellow; T.L.C. showed no sign of reaction. The sodamide was removed by filtration through celite and the solvent evaporated under reduced pressure to give a yellow oil. Addition of dry ether afforded a white crystalline solid (0.47g) which was identified as unchanged starting material by means of its infra-red and n.m.r. spectra.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with n-butyl lithium.

The 2-chloro compound (XXXVII) (0.4g) was dissolved in tetrahydrofuran (50ml) (freshly distilled from lithium aluminium hydride) under dry nitrogen and a solution of n-butyl lithium in the same solvent was added by means of a syringe through a rubber septum cap. The solution immediately turned brown; the reaction could not be followed by T.L.C. due to streaking. After 3h carbon dioxide was passed through the solution
and the reaction mixture filtered through celite (dried at 100°) to remove the precipitated lithium salts. The tetrahydrofuran was evaporated under reduced pressure to give a brown oil; trituration of this with dry ether dissolved some material. This crystallised on standing to give the 2-hydroxy compound (XVII) (0.14g) identified by its infra-red spectrum. The residual brown tar consisted of a mixture of polar materials.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with silver tetrafluoroborate.

(a) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry tetrahydrofuran (25ml) and silver tetrafluoroborate (0.15g) in the same

solvent (10ml) was added. An instant white precipitate was formed and T.L.C. showed that no starting material remained. On standing for 15min polymerisation appeared to occur, the whole contents of the flask solidifying into a plastic material.

(b) The 2-chloro compound (XXXVII) (0.43g) was dissolved in dry acetonitrile (50ml) and a solution of silver tetrafluoroborate (0.19g) in the same solvent was added. The precipitated silver chloride (0.21g) was filtered and the colourless filtrate was evaporated to dryness under reduced pressure to yield a viscous white oil. After much trituration with dry ether a white solid (LII) (0.31g) was obtained; on standing in light it turned brown indicating the presence of silver. T.L.C. was not satisfactory, only streaks being obtained. The compound had m.p. 118-123° [Found: C,48.9; H,5.1; N,7.7; $C_{18}H_{18}N_2S_2O_4$ requires C,55.4; H,4.65; N,7.2%]; δ 2.39(6H,s), 7.5(9H,m).

(c) The experiment was repeated using the same quantities as under (b) but using benzene (25ml) as the solvent. Analogous results were obtained, the compound (0.34g) having m.p. 118-123°.

(d) The 2-chloro compound (0.21g) was dissolved in $CDCl_3$ (2ml) and silver tetrafluoroborate (0.1g) in the same solvent (0.2ml) was added. The precipitated silver chloride (0.1g) was filtered and an n.m.r. spectrum run on the filtrate. This showed the same features as that described under (b) above.

Reaction of the product of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine and silver tetrafluoroborate with water and alcohols.

Two solutions of the 2-chloro compound (XXXVII) (0.21g) in $CDCl_3$ (2ml) were treated with silver tetrafluoroborate as in (d) above and their n.m.r. spectra obtained; these were consistent with those of previous samples. A drop of water was added to one tube and a drop of

ethanol to the other. N.m.r. spectra recorded immediately after the addition showed little change, but after 5min the first showed the spectrum of the 2-hydroxy-1,2,3,4-tetrahydropyrazine (XVII) and the latter that of the 2-ethoxy compound (XV).

Attempted purification of (LII).

(a) The unknown (0.5g) was placed on a silica column and eluted with toluene followed by methylene chloride which removed the product from the column leaving behind a black band, presumably due to silver. However, the product (0.46g) m.p. 119-122° had the same n.m.r. spectrum as before [Found: C,48.8; H,4.7; N,7.7%].

(b) The unknown (0.5g) was placed on a column of deactivated alumina and eluted with methylene chloride, with similar results to the above; yield of product 0.43g, m.p. 118-122°.

(c) The product (0.3g) was dissolved in acetonitrile (25ml) and anhydrous potassium carbonate (2g) was added in order to remove traces of HBF_4. This caused the solution to turn yellow; the potassium carbonate was filtered and the solvent evaporated under reduced pressure to give a yellow oil which appeared to be a complex mixture as shown by T.L.C.

(d) The 2-chloro compound (XXXVII) (0.21g) was dissolved in acetonitrile (25ml) in the presence of triethylamine (0.1g) and silver tetrafluoroborate (0.1g) was added as before. The presence of the triethylamine appeared to have no effect upon the course of the reaction; standard work-up gave (LII) (0.18g) m.p. 118-121° as before.

(e) To remove any residual silver from the product the unknown (0.2g) was dissolved in methylene chloride (20ml) and quickly washed with ice-cold saturated sodium chloride solution (25ml) and then ice-water (50ml) (T.L.C. confirmed that this rapid washing did not affect the product).

The solution was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give a white solid (0.2g), m.p. 118-123°, which had the same n.m.r. spectrum as before the treatment. [Found: C,48.5; H,5.0; N, 7.6; S,13.1; molecular weight 580; $C_{18}H_{18}N_2S_2O_4$ requires C,55.4; H,4.65; N,7.2; S,16.4% ; molecular weight 398].

Attempted Diels-Alder reactions of (LII)

(a) The 2-chloro compound (0.6g) was dissolved in dry acetonitrile (25ml) containing furan (1ml) and silver tetrafluoroborate (0.3g) in acetonitrile (10ml) was added. An immediate white precipitate was produced which was filtered off and the solvent was evaporated from the filtrate under reduced pressure. The resultant oil was repeatedly triturated with dry ether when it solidified to give compound (LII) (0.48g), m.p. 116-122°.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-chloro-1,2,3,4-tetrahydropyrazine with silver nitrate.

The 2-chloro compound (XXXVII) (0.43g) in acetonitrile (25ml) was treated with a solution of silver nitrate (0.17g) in the same solvent (10ml). An instant white precipitate was formed which was removed by filtering through celite. The solvent was removed under reduced pressure to yield a dark oil (0.36g) which solidified on trituration with light petroleum to give a white solid (0.29g). This was crystallised from methylene chloride/light petroleum to give a product (LIII) with m.p. 116-121°. The n.m.r. spectrum and T.L.C. were similar to those of the product obtained with silver tetrafluoroborate. [Found: C,46.6; H,5.35, N,6.7; $C_{18}H_{18}N_2S_2O_4$ requires C,55.4; H,4.65; N,7.2% ; $C_{18}H_{19}N_3S_2O_7$ requires C,47.4, H,4.2, N,9.3%].

Attempts to trap (LIII)

(a) The 2-chloro compound (XXXVII) (0.43g) was dissolved in acetonitrile (25ml) containing cyclopentadiene (0.13g) and a solution of silver nitrate (0.17g) in the same solvent (10ml) was added. An immediate white precipitate was formed. The mixture was allowed to stand for 24h when it was worked up in the usual manner to give an oil (0.36g) which solidified on trituration with ether to give (LIII) (0.28g) identified by its melting point and n.m.r. spectrum.

(b) A sample of (LIII)(0.2g) was treated with excess cyclopentadiene (5ml). No apparent reaction took place in the cold but on gentle warming a vigorous reaction occurred to give a polymeric material which was insoluble in organic solvents and in water.

(c) The 2-chloro compound (XXXVII) (0.3g) was dissolved in acetonitrile (25ml) containing excess 2,3-dimethylbutadiene (1ml) and a solution of silver nitrate (0.12g) in the same solvent was added. An instant precipitate was obtained and the reaction was worked up as under (a) above. Product (LIII) was again obtained; it was dissolved in dry tetrahydrofuran (50ml) containing 2,3-dimethylbutadiene and the solution refluxed for 6h. No apparent reaction occurred as shown by T.L.C. The tetrahydrofuran was evaporated under reduced pressure and the resultant oil triturated with ether to give starting material (0.23g), m.p. 118-122°, identified by its n.m.r. spectrum.

(d) The 2-chloro compound (XXXVII) (0.3g) was dissolved in acetonitrile (50ml) and a solution of silver nitrate (0.12g) in the same solvent was added. The precipitated silver chloride was filtered and the solvent was evaporated under reduced pressure to give an oil which solidified on trituration with ether (yield 0.27g). It was taken

up in methylene chloride (25ml) and bromine (0.06g) was added. This was decolourised immediately; T.L.C. showed a mixture which included starting material and more bromine was added until the colour persisted for 1h. T.L.C. showed a complex mixture; evaporation of the solvent under reduced pressure gave a red oil (0.48g). Attempts to separate the components of this by column chromatography were unsuccessful.

Trans-1,4-bis(p-toluenesulphonyl)2,3-dibromo-1,2,3,4-tetrahydropyrazine(LVIII)

(a) The 2-chloro compound (XXXVII) (0.5g) was dissolved in methylene chloride (50ml) and bromine added dropwise until it was no longer decolourised even on standing for 15min; white fumes were evolved in the course of the reaction. The solvent was evaporated under reduced pressure to yield an orange solid; this was triturated with dry ether and filtered. Crystallisation from methylene chloride/ether gave (LVIII) as a pale orange solid (0.5g, 77%), m.p. 140° [Found: C,39.1; H,3.3; N, 5.1; Br,28.4; $C_{18}H_{16}N_2Br_2S_2O_4$ requires C,39.1; H,3.6; N,5.1; Br,29.0%]; $\nu_{max.}$ 3100, 3030, 2920, 1655, 1595, 1490, 1400, 1370, 1330, 1300, 1190, 1175, 1090, 1080, 950, 820, 735, 700, 680cm^{-1}; δ 2.40(6H,s,CH_3), 6.10(2H, s,2-H,3-H), 6.60(2H,s,5-H,6-H), 7.65(8H,q, J 8.5Hz, ArH).

(b) The 2-hydroxy compound (XVII) (0.5g) was dissolved in acetonitrile (50ml). Bromine was added and the reaction was worked up as for (a) above to yield (LVIII) (0.57g, 80%) identified by its infra-red and n.m.r. spectra and mixed melting point with a sample prepared as under (a).

1,4-bis(p-toluenesulphonyl)-2,3,5,6-tetraethoxypiperazine (LXII)

The 2-ethoxy compound (XV) (0.3g) was dissolved in acetonitrile (25ml) containing ethanol (5ml) and bromine was added until a permanent

colouration was obtained. On standing a white crystalline material separated from the solution; this was filtered and crystallised from acetonitrile to yield pure (LXII) (0.31g, 92%), m.p. 218-220° [Found: C,54.4; H,6.9; N,4.9; $C_{26}H_{38}N_2S_2O_8$ requires C,54.7; H,6.7; N,4.9%]; $\nu_{max.}$ 3065, 3020, 2980, 2920, 2880, 1600, 1500, 1480, 1440, 1390, 1350, 1330, 1320, 1300, 1170, 1130, 1065, 1040, 1000, 900, 820, 730, 700 655cm^{-1}; δ 0.9(12H, t, J 8.0Hz, $CH_2\underline{CH_3}$), 2.35(6H,s,$ArCH_3$), 3.5(8H,m, $\underline{CH_2}CH_3$), 5.0(4H,s,ring protons), 7.55(8H,q, J 15.0Hz, ArH).

Trans-1,4-bis(p-toluenesulphonyl)-2,3-diethoxy-1,2,3,4-tetrahydropyrazine (LX).

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in ethanol (100ml) and the solution refluxed for 1h. On cooling the trans-2,3-diethoxy compound crystallised; it was filtered and recrystallised from ethanol to give pure (LX) as white needles (0.46g, 96%), m.p. 157-159° [Found: C,54.7; H,6.1; N,5.8; $C_{22}H_{28}N_2O_6S_2$ requires C,55.0; H,5.8; N,5.8%]; $\nu_{max.}$ 3110, 3060, 2950, 2925, 2900, 1650, 1600, 1495, 1450, 1425, 1350, 1275, 1160, 1140, 1100, 940, 810, 735, 705, 675cm^{-1}; δ 0.65(6H,t, J 7.5Hz, $CH_2\underline{CH_3}$), 2.35(6H,s,$ArCH_3$), 3.35(4H,q, J 3.0Hz, $\underline{CH_2}CH_3$), 5.18(2H,s,2-H, 3-H), 5.95(2H,s, 5-H,6-H), 7.42(8H,q, J 9.0Hz, ArH).

Trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine (LXIII).

The 2,3-dibromo compound (LVIII) (1g) was dissolved in acetone (100ml) containing water (10ml) and the solution was refluxed for 1h. The solvent was evaporated under reduced pressure to yield a cream solid; crystallisation from ether/light petroleum gave pure (LXIII) as white needles (0.74g, 97%) m.p. 160-161° [Found: C,50.9; H,4.7; N,6.6;

$C_{18}H_{20}N_2S_2O_6$ requires C,50.9; H,4.7; N,6.6%]; $\nu_{max.}$ 3480 (OH), 3120, 3040, 2980, 2930, 2860, 1660, 1600, 1595, 1440, 1380, 1280, 1160, 1140, 1080, 960, 810, 770, 705, 740cm^{-1}; δ2.40(6H,s,CH_3), 5.50(2H,s, 2-H, 3-H), 6.05(2H,s, 5-H,6-H), 7.45(8H,q, J 8.5Hz, ArH).

1,4-bis(p-toluenesulphonyl)-2,3,5-trihydroxypiperazine (LXIV)

The 2,3-dibromo compound (LVIII) (0.8g) was dissolved in acetone (20ml) containing water (10ml). The solution was allowed to stand overnight when a white crystalline product had separated. It was filtered and washed with acetone (20ml) and ether (20ml) to give analytically pure (LXIV), (0.62g, 96%) which was extremely insoluble in organic solvents and could not be recrystallised. It had m.p. 181-183° [Found: C,49.1; H,4.9; N,6.1; $C_{18}H_{22}N_2S_2O_7$ requires C,48.9; H,5.0; N,6.3%]; $\nu_{max.}$ 3480 (OH), 3100, 3030, 2960, 2920, 2880, 1600, 1490, 1440, 1400, 1370, 1300, 1240, 1180, 1090, 1060, 1030, 1015, 980, 950, 915, 870, 810, 705, 670 cm^{-1}.

Action of heat on 1,4-bis(p-toluenesulphonyl)-2,3,5-trihydroxypiperazine (LXIV).

(a) The piperazine (LXIV) (0.2g) was suspended in acetone (50ml) and the mixture was refluxed for 1h, when all the solid had dissolved. Evaporation of the solvent under reduced pressure gave the 2,3-dihydroxy compound (LXIII) (0.17g) which was crystallised from ether/light petroleum and identified by infra-red and n.m.r. spectra and mixed melting point with an authentic sample.

(b) The piperazine (LXIV) (0.2g) was suspended in acetic acid (10ml) containing conc. HCl (1ml) and the suspension was heated at 100° until all the solid had dissolved (10min). The solution was cooled,

poured into water and the resulting white precipitate filtered and allowed to dry in air. Crystallisation from ether/light petroleum gave (LXIII) (0.16g) identified as under (a).

Trans-1,4-bis(p-toluenesulphonyl)-2,3-diacetoxy-1,2,3,4-tetrahydropyrazine (LXV)

The 2,3-dihydroxy compound (LXIII) (0.5g) was dissolved in acetic anhydride (20ml) and conc. HCl (1ml) was added. The solution was heated at 100° for 15min, cooled in ice and poured into water with vigorous stirring. The resulting floccular white precipitate was filtered, dissolved in ether and dried over $MgSO_4$. The solution was filtered, concentrated and cooled in ice to produce crystalline (LXV) (0.52g, 87%), m.p. 186-188° [Found: C,52.3; H,4.8; N,5.4; $C_{22}H_{24}N_2O_8S_2$ requires C,52.0; H,4.7; N,5.5%]; $\nu_{max.}$ 3120, 3030, 3000, 2960, 2920, 1750 (C=O), 1650, 1595, 1490, 1450, 1400, 1365, 1300, 1220, 1190, 1160, 1125, 1080, 1010, 980, 960, 930, 890, 820, 800, 770, 700, 670cm^{-1}; δ 1.6(6H,s,$COCH_3$), 2.42(6H,s,$ArCH_3$), 6.28(2H,s, 2-H, 3-H), 6.54(2H,s, 5-H, 6-H), 7.50(8H,q, J 8.5Hz, ArH).

Cis-1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine (LXVI).

The trans-2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry tetrahydrofuran (50ml); excess magnesium powder (1g) was added and the mixture stirred for 24h. The magnesium was filtered through celite and the solvent removed under reduced pressure to give a yellow solid. Dry ether was added and the solid filtered under nitrogen to give (LXVI) (0.53g), m.p. 124-127°, mixed melting point with starting material 109-112°. The product hydrolysed rapidly in air; on keeping

over phosphorus pentoxide in a vacuum desiccator it slowly decomposed to a tar. Gravimetric analysis was carried out on a freshly prepared sample [Found: C,36.6; H, 3.2; N,4.5; Br,26.7; $C_{18}H_{16}N_2Br_2S_2O_4$ requires C,39.1; H,3.6; N,5.1; Br,29%]; $\nu_{max.}$ 3100, 3030, 2920, 1655, 1595, 1490, 1400, 1370, 1330, 1190, 1175, 1090, 1080, 950, 820, 735, 700, 680cm^{-1}; δ 2.40(6H,s,CH_3), 6.30(2H,s,2H,3-H), 6.80(2H,s,5H,6-H), 7.75(8H,q,J 8.5Hz,ArH).

Cis-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine (LXVII).

This compound was prepared analogously to the trans isomer (LXIII). The cis-2,3-dibromide (LXVI) (0.55g) gave the cis-2,3-dihydroxy compound (0.4g) on hydrolysis (yield 0.35g, 86%), m.p. 135-137° [Found: C,51.1; H,4.9; N,6.3; $C_{18}H_{20}N_2S_2O_6$ requires C,50.9, H,4.7; N,6.6%]; $\nu_{max.}$ 3480 (OH), 3120, 3040, 2980, 2925, 2860, 1660, 1600, 1440, 1380, 1275, 1155, 1140, 1080, 960, 770, 710, 735cm^{-1}; δ 2.40(6H,s,CH_3), 5.65(2H,s,2-H,3-H), 6.23(2H,s,5-H, 6-H), 7.20(8H,q, J 8.5Hz, ArH).

Cis-1,4-bis(p-toluenesulphonyl)-2,3-diethoxy-1,2,3,4-tetrahydropyrazine (LXIX)

This compound was prepared in an analogous fashion to the trans isomer (LX). Under these conditions the cis dibromide (LXVI) gave the cis-2,3-diethoxy compound (0.47g, 97%) m.p. 152-154°[Found: C,54.6; H,5.8; N,5.5; $C_{22}H_{28}N_2O_6S_2$ requires C,55.0; H,5.8; N,5.8%] ; $\nu_{max.}$ 3100, 3060, 2980, 2925, 2895, 1660, 1600, 1495, 1450, 1425, 1395, 1350, 1280, 1160, 1120, 1100, 940, 900, 810, 730, 705, 675cm^{-1}; δ 0.65(6H,t,J 7.5Hz, $CH_2\underline{CH_3}$), 2.35(6H,s,ArCH_3), 3.35(4H,q, J 3.0Hz, $\underline{CH_2}CH_3$), 5.2(2H,s,2-H,3-H), 6.05(2H,s,5-H,6-H), 7.45(8H,q, J 9.0Hz, ArH).

Attempted elimination of bromine from trans-1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine.

(a) With zinc-copper couple[96].

(i) The 2,3-dibromo compound (LVIII) (0.5g) was dissolved in dry tetrahydrofuran (50ml), zinc-copper couple[96] (previously dried in vacuo over phosphorus pentoxide) (1g) was added and the suspension stirred under dry nitrogen for 3h. At the end of this time the couple was removed by filtration through prebaked celite; on cooling of the filtrate a white solid separated and was collected by filtration; it appeared to be inorganic by its infra-red spectrum. The tetrahydrofuran was evaporated from the filtrate under reduced pressure to give a white solid which was crystallised from methylene chloride/ether to give the 2-hydroxy compound (XVII) (0.37g) identified by its infra-red spectrum and mixed melting point.

(ii) Freshly prepared 2,3-dibromo compound (LVIII) (0.3g) was placed in a prebaked two-necked flask equipped with stirrer, condenser and calcium chloride tube, and tetrahydrofuran (50ml) was distilled from lithium aluminium hydride directly into the flask. Zinc-copper couple (1g) (dried as under (i) above) was added and the mixture stirred under dry nitrogen for 1h when T.L.C. showed the formation of a single less polar product. The couple was removed by filtration through celite; on cooling of the filtrate some inorganic material was precipitated and was filtered to give a clear solution. T.L.C. of this still showed a single product; the solvent was evaporated under reduced pressure to yield an oil which solidified on addition of dry ether. However, on filtration it was transformed into an intractable mixture in the air.

(iii) The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry tetrahydrofuran (50ml) and dry zinc-copper couple (1g) was added. The reaction was carried out as under (ii) above, but the solution was decanted from the couple and divided into two equal portions. The tetrahydrofuran was evaporated from one portion by a stream of dry nitrogen to give an intractable brown oil. The other portion was treated with water; an instantaneous reaction was observed by T.L.C. with a single more polar product being formed. On evaporation of the solvent under reduced pressure a white solid was obtained which was crystallised from methylene chloride/ether to give the 2-hydroxy compound (XVII)(0·1g) identified by its infra-red spectrum and a mixed melting point determination.

(b) With thiourea[99].

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry acetonitrile (50ml) and a solution of thiourea (0.08g) in the same solvent (100ml) was added. An immediate white precipitate was obtained; this was filtered, a T.L.C. of the filtrate showed a single product which was less polar than the starting material. Solvent was evaporated under reduced pressure to give an oil which solidified on trituration with ether. When it was attempted to filter this in air it collapsed to an intractable oil.

(c) With iodide ion.

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry acetonitrile (100ml) and sodium iodide (0.15g) in the same solvent (25ml) was added. The solution immediately went very dark and a precipitate was produced; T.L.C. showed the presence of several components and the reaction was not worked up.

(d) With triphenylphosphine[100].

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry toluene (50ml) and a solution of triphenylphosphine (0.35g) in the same solvent (10ml) was added. The temperature was kept at 60° for 3h when T.L.C. showed that no reaction had occurred. The solvent was evaporated under reduced pressure to leave an oil which solidified on trituration with dry ether; this was filtered and identified as the 2,3-dibromo compound (LVIII) by its n.m.r. and infra-red spectra.

(e) With silver powder.

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry tetrahydrofuran (50ml) and silver powder (0.2g, excess) was added. The suspension was stirred under nitrogen for 1h, silver bromide was precipitated and the solution turned brown. Only intractable tar could be isolated on evaporation of the solvent in a dry-box.

(f) With iron pentacarbonyl[97].

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in dry acetonitrile (50ml) and iron pentacarbonyl (0.4g) was added under dry nitrogen. A red-brown precipitate was formed; the mixture was refluxed for 1h when no starting material could be detected by T.L.C. The precipitate was filtered and solvent evaporated from the filtrate to give a white amorphous solid which could not be got crystalline. [Found: C,47.5; H,5.3; N,5.6; $C_{18}H_{18}N_2S_2O_4$ requires C,55.4; H,4.65; N,6.7%; $C_{21}H_{18}N_2S_2O_7Fe$ requires C,47.5; H,3.4; N,5.3%]; δ 2.40(s,broad), 7.5(m,broad).

Reaction of trans-1,4-bis(p-toluenesulphonyl)2,3-dibromo-1,2,3,4-tetrahydropyrazine with silver nitrate.

(a) The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in acetonitrile (50ml) and silver nitrate (0.34g, 2mol) in the same solvent (25ml) was added. An instantaneous reaction occurred with a white precipitate being formed and the solution turning yellow. The silver bromide was filtered through celite and the solvent removed under reduced pressure to yield an oil which appeared to be a complex mixture by T.L.C.

(b) The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in acetonitrile (50ml) and silver nitrate (0.77g) in the same solvent (25ml) was added. An instantaneous reaction occurred and silver bromide was precipitated; this was filtered through celite and the solvent evaporated under reduced pressure to give a white solid (0.34g) which was crystallised from acetonitrile to give a crystalline product shown to be pure by T.L.C. It had m.p. 177-179° [Found: C,53.0; H, 4.9; N, 5.8%]; δ (DMSO) 2.35(s), 3.25(m), 5.1(m), 7.4(m,ArH).

Preparation of 7,10-bis(p-toluenesulphonyl)-2,5-dioxa-7,10-diazabicyclo [4,4,0] dec-8-ene

(a) The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in methylene chloride (50ml) and dry ethylene glycol (0.08g) was added. After 3h the solvent was removed under reduced pressure to give a pale oil. Addition of light petroleum resulted in crystallisation of (LXXII) (0.41g, 91%) which was purified by three recrystallisations from ether/light petroleum when it had m.p. 118-120° [Found: C,52.9; H,5.2; N,5.9; $C_{20}H_{22}N_2S_2O_6$ requires C, 53.3; H,4.9; N,6.2%]; $\nu_{max.}$ 3120, 3100, 3050, 2950, 2920, 2860, 1670, 1595, 1490, 1450, 1400, 1350, 1330, 1295, 1270, 1210, 1170, 1090, 1065, 1040, 990, 960, 940, 920, 885, 850, 825, 805, 720, 700, 680, 660cm^{-1}; δ 2.35(6H,s,CH_3), 3.60(4H,m,CH_2-CH_2), 4.75(2H,s,2-H,3-H), 5.95(2H,s,5-H,6-H), 7.35(8H,q, J 8.5Hz, ArH).

(b) The 2,3-dihydroxy compound (LXIII) (0.42g) was dissolved in dry acetone (50ml) and ethylene glycol (0.08g) and conc. HCl (0.5ml) were added. The reaction mixture was refluxed for 6h when the reaction appeared complete by T.L.C.. The solvent was removed under reduced pressure and the resulting white solid crystallised from ether/light petroleum to give (LXXII) (0.38g,88%) identified by its infra-red and n.m.r. spectra.

Reaction of trans-1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine with ethanedithiol.

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in methylene chloride (50ml) and excess (0.1g) of ethanedithiol was added. The solution was allowed to stand for 24h; after only 3h no starting material remained but two products were observed by T.L.C.. After 24h one of these had disappeared and the solution appeared to contain a single product. It was decanted from a brown oil which had separated and the solvent evaporated under reduced pressure to give a white solid (0.38g) which was crystallised from ether/light petroleum. It had m.p. 84-86° [Found: C,47.2; H,5.2; N,6.7; S,23.9; $C_{20}H_{22}N_2S_4O_4$ requires C,49.4; H,4.8; N,5.7; S,26.5%]; $\nu_{max.}$ 3360 3250, 3040, 2920, 1650, 1600, 1540, 1500, 1380, 1300, 1150, 1090, 1015, 900, 810, 700cm^{-1}; δ 2.45(6H,s), 3.2(4H,s), 5.1(4H,s,broad), 7.75(8H,q,ArH).

Attempted reaction of trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with ethanedithiol.

The 2,3-diol (LXIII) (0.5g) was dissolved in acetone (50ml) and ethanedithiol (0.11g) and conc. HCl (0.5ml) were added. The solution was refluxed for 8h; T.L.C. showed no sign of reaction. The solvent was evaporated under reduced pressure to give an oil, trituration of

which with dry ether gave a white solid (0.47g) identified as starting material by its infra-red spectrum and melting point.

Reaction of trans-1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine with ethylenediamine.

The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in methylene chloride (25ml) and ethylenediamine (0.06g) in the same solvent (10ml) was added. An instantaneous reaction occurred as seen by T.L.C. The solvent was evaporated under reduced pressure to yield a pale oil; trituration with petrol gave a white solid (0.34g). The product proved extremely soluble in other organic solvents and therefore difficult to crystallise. It had m.p. 110-112° [Found C,48.6; H,5.2; N,8.1%]; 2.35(s,sharp) 7.4(m,sharp).

Reaction of trans-1,4-bis(p-toluenesulphonyl)-2,3-dibromo-1,2,3,4-tetrahydropyrazine with o-phenylenediamine.

(a) The 2,3-dibromo compound (LVIII) (0.55g) was dissolved in methylene chloride (50ml) and a solution of o-phenylenediamine (0.11g) in the same solvent (10ml) was added. An immediate precipitate was produced; this was filtered off to give a colourless solution which T.L.C. showed to contain a single product. On evaporation of the solvent under reduced pressure an oil was formed which appeared a mixture by T.L.C.

(b) The above reaction was repeated but instead of evaporating the solvent to dryness ether was added which brought about crystallisation of a white solid. All attempts to isolate this were unsuccessful; it turned to a dark oil even when the solvent was evaporated with a stream of dry nitrogen.

Attempted cyclisation of trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with benzaldehyde.

(a) The 2,3-diol (LXIII) (0.42g) was dissolved in toluene (50ml) and benzaldehyde (0.23g) and conc. sulphuric acid (1 drop) were added, when the solution turned brown. It was refluxed in a Dean and Stark apparatus until T.L.C. showed that no starting material remained (15min). A black tar had separated from the solution; the latter was decanted and the tar discarded. Evaporation of the toluene under reduced pressure gave a brown oil, some of which dissolved in ether the remainder being an intractable mixture. The ethereal solution yielded a white solid (0.23g) which could not be identified. It had m.p. 123-5°, δ 2.30 (s), 2.35 (s), 2.40 (s, ArMe), 5.5 (s, br), 7.2-7.9 (m, ArH).

(b) The 2,3-diol (LXIII) (0.43g) was dissolved in benzene (50ml) containing benzaldehyde (0.12g) and p-toluenesulphonic acid (0.2g); the solution turned brown at this point. The reaction mixture was refluxed using a Dean and Stark apparatus; it rapidly darkened and black tar was deposited. Work-up as under (a) above gave similar intractables and a small amount (0.1g) of the same product obtained under (a) above, identified by mixed melting point.

Attempted cyclisation of cis-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with benzaldehyde.

This reaction was performed as in (b) above; only intractable tars were obtained.

Attempted cyclisation of cis and trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with acetone.

Samples (0.2g) of each diol were dissolved in dry acetone (25ml) with each of the following catalysts:HCl (saturated solution),

p-toluenesulphonic acid (0.1g), ion exchange resin (0.1g), and anhydrous copper sulphate (0.1g). No reaction was observed by T.L.C. either in the cold or on refluxing. Starting material was recovered quantitatively in each case.

Attempted cyclisation of cis and trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with catechol.

Samples (0.21g) of each diol were dissolved in dry tetrahydrofuran (20ml) and catechol (0.11g) was added, together with one of the following: HCl, p-toluenesulphonic acid (0.1g), ion exchange resin (0.1g). No reaction was observed by T.L.C. either at room temperature or on refluxing.

Attempted reaction of trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with dimethylformamide diethyl acetal.

The trans-2,3-diol (LXIII) (0.42g) was dissolved in methylene chloride (25ml) and the acetal (0.16g) in the same solvent was added. The solution was allowed to stand for 24h; no apparent reaction was observed by T.L.C.. Refluxing for 6h also appeared to have no effect.

Reaction of cis-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxy-1,2,3,4-tetrahydropyrazine with dimethylformamide diethyl acetal.

The cis-2,3-diol (LXVII) (0.42g) was treated as above. An immediate reaction occurred, the solution turning yellow and no starting material being observed by T.L.C. after 15min. The solvent was evaporated under reduced pressure to yield a yellow oil which consisted of at least two components having similar R_F values. Addition of ether gave a floccular white solid having a similar T.L.C.. Attempts to purify by column chromatography were unsuccessful. The crude product

had δ 1.3(t), 2.35(s), 3.2(q), 4.1(s), 5.1(s), 6.0(s), 7.4(m), all very broad.

Attempted reaction of 1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine with tetraphenylcyclopentadienone.

(a) The 1,2,3,4-tetrahydropyrazine (XLV) (0.39g) was dissolved in toluene (100ml) and tetracyclopentadienone (0.38g) was added; the solution was refluxed for 12h but T.L.C. showed that no reaction had taken place.

(b) The reaction was repeated as for (a) above but refluxing in xylene (100ml) as the solvent. Again, no reaction had occurred after 12h.

Reaction of 1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine with tetrachloro-o-benzoquinone.

The tetrahydropyrazine (XLV) (0.39g) was dissolved in dry toluene (50ml) and tetrachloro-o-benzoquinone (0.25g) was added. The mixture was refluxed for 3h, when the red colour was discharged and a small quantity of brown tar had been deposited. The colourless solution was decanted and the toluene evaporated under reduced pressure to give a pale pink solid; it was recrystallised from acetonitrile to give pure (LXXVIII) (0.5g, 78%) m.p. 228-30° [Found: C,45.0; H,3.2; N,4.0; Cl,21.8; $C_{24}H_{20}N_2O_6S_2Cl_4$ requires C,45.1; H,3.1; N,4.4; Cl,22.2%]; $\nu_{max.}$ 3060, 3040, 2970, 2920, 2880, 1600, 1570, 1490, 1430, 1370, 1350, 1285, 1260, 1165, 1115, 1110, 1090, 1040, 1025, 940, 895, 815, 805, 720, 700, 660cm^{-1}.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine with hydrogen peroxide.

The selenide (XLIV) (0.3g) was dissolved in acetone (25ml) and

excess 30% hydrogen peroxide (2ml) was added. The solution was allowed to stand for 1h when T.L.C. showed reaction to be complete. The reaction mixture was poured into water and the resultant cloudy suspension extracted with methylene chloride. The organic phase was dried overnight($MgSO_4$) and the solvent evaporated under reduced pressure to give a white solid. This was crystallised from methylene chloride/light petroleum to yield the 2-hydroxy derivative (XVII) (0.21g) identified by its infra-red spectrum and mixed melting point.

In a control experiment the reaction was carried out in the same way but without the addition of the hydrogen peroxide. No reaction was apparent by T.L.C. after 1h. Evaporation of the acetone under reduced pressure gave back starting material (identified by its infra-red spectrum) in quantitative yield.

Reaction of 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine with m-chloroperbenzoic acid.

(a) The selenide (XLIV) (0.55g) was dissolved in methylene chloride (25ml) and a solution of m-chloroperbenzoic acid (0.16g) in the same solvent (10ml) was added. The solution gradually turned yellow and the reaction was shown to be complete in 10min by T.L.C. A portion of this solution was washed with saturated sodium bicarbonate solution and water and the organic phase dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield a yellow oil. This was taken up in ether and the ethereal solution allowed to stand in an ice/salt bath for 5h when colourless crystals had separated. These were filtered and recrystallised from ether to yield 1,4-bis(p-toluenesulphonyl)-2-m-chlorobenzoyloxy-1,2,3,4-tetrahydropyrazine (LXXX) (0.23g) m.p. 136-138° [Found C,55.0; H,4.4; N,5.4; $C_{25}H_{23}N_2O_6S_2Cl$ requires

C,54.9; H,4.2; N,5.1%]; $\nu_{max.}$ 3120, 3080, 3030, 2990, 2920, 2885, 1720 (C=O) 1650, 1595, 1570, 1490, 1470, 1450, 1425, 1390, 1355, 1280, 1250, 1220, 1170, 1119, 1070, 1050, 1010, 975, 805, 745, 725, 700, 670cm^{-1}; δ 2.14(3H,s,ArCH_3), 2.14(3H,s,ArCH_3), 3.34(1H,dd, J_{DE} 15.0Hz, further split J 1.5Hz, H_E), 4.42(1H,d,broad, J 15.0Hz, H_D), 6.55(2H,q, J 7.5Hz, H_AH_B), 6.95-8.0(9H,m,H_C and ArH).

(b) In the presence of pyridine.

(i) The 2-phenylselenide (XLIV) (0.27g) was dissolved in methylene chloride (25ml) and a solution of m-chloroperbenzoic acid (0.1g) in the same solvent was added together with pyridine (0.045g). T.L.C. indicated the formation of the 2-chlorobenzoate ester (LXXX) after 15min; this was isolated by washing with water, drying the organic phase over $MgSO_4$ and evaporation of the solvent under reduced pressure to give a yellow oil. Addition of ether resulted in a white solid crystallising from the solution; this was filtered and recrystallised from ether/light petroleum to give the ester (LXXX) identified by its n.m.r. spectrum.

(ii) The selenide (XLIV) (0.27g) was dissolved in methylene chloride (25ml) and a solution of m-chloroperbenzoic acid (0.1g) in the same solvent containing pyridine (1ml) was added. T.L.C. showed the same reaction as in (a) above.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine with iodosobenzene.

(a) The selenide (XLIV) (0.55g) was dissolved in methylene chloride (50ml) and iodosobenzene (0.25g) was added. A control experiment without the selenide was set up and the two suspensions were stirred; after 3h all the iodosobenzene had dissolved in the flask containing the selenide but not in the control. The solvent was removed

from the former by evaporation under reduced pressure, the resultant oil was triturated with dry ether to give a white solid which was crystallised from methylene chloride/ether to give back starting material, identified by its infra-red and n.m.r. spectra and a mixed melting point.

(b) The selenide (XLIV) (0.55g) was dissolved in dry benzene (50ml) and iodosobenzene (0.25g) was added. The suspension was refluxed until all the iodosobenzene had dissolved. The solvent was evaporated under reduced pressure to yield an oil which was worked up as in (a) above to give starting material as in (a).

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine with potassium periodate-18-crown-6.

Potassium periodate (0.2g) and 18-crown-6 were stirred in refluxing aqueous methanol (50ml). When all the solids had dissolved the solvent was evaporated under reduced pressure and the product azeotroped with benzene to remove water and alcohol.

The selenide (XLIV) (0.25g) was stirred with excess of the above complex (0.2g) in methanol (25ml) for 15min, when T.L.C. showed that a single new product had been formed. The solvent was evaporated under reduced pressure, and the resultant solid extracted with methylene chloride; addition of ether to this extract resulted in the crystallisation of a white solid, which was filtered and identified by its n.m.r. spectrum as the 2-methoxy compound (XIV) (0.15g)

Control experiment with 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine and methanol.

The selenide (XLIV) (0.25g) was dissolved in methanol (25ml).

No reaction had occurred by T.L.C. after 15min and the starting material was recovered quantitatively on evaporation of the solvent.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine with periodic acid.

The selenide (XLIV) (0.55g) was dissolved in methylene chloride (25ml) and a solution of periodic acid (0.17g) in the same solvent (10ml) was added. The solution turned yellow and a solid was precipitated; however, T.L.C. showed no apparent reaction. The precipitate was removed by filtration and solvent blown off with dry nitrogen; the resultant solid was extracted with $CDCl_3$ and an n.m.r. spectrum obtained. This appeared to show starting material. Addition of ether to the chloroform solution led to the crystallisation of a white solid (0.41g) which was identified as starting material by a mixed melting point.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylseleno-1,2,3,4-tetrahydropyrazine with tetrabutylammonium periodate.

Periodic acid (1.9g) in water (25ml) was added to a solution of tetrabutylammonium hydroxide in water (23ml, 0.4mol). A white solid precipitated from the solution; it was filtered, dried and crystallised from methylene chloride/ether to give the product (4.1g) m.p. 182-3° [Found: C,44.2; H,8.4; N,3.0; $C_{16}H_{36}NO_4I$ requires C,44.3; H,8.3; N,3.2%].

The selenide (XLIV) (0.55g) was dissolved in methylene chloride (25ml) and a solution of the supposed tetrabutylammonium periodate prepared above (0.43g) in the same solvent (10ml) was added. The solution immediately went yellow and a small quantity of solid came out of solution; T.L.C. showed only starting material to be present. The solution was decanted from the solid and ether was added; this

caused precipitation of the tetrabutylammonium periodate. The solution was filtered; evaporation of the solvent from the filtrate under reduced pressure gave back starting material identified by infra-red and n.m.r. spectra and mixed melting point.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-phenylthio-1,2,3,4-tetrahydropyrazine with tetrabutylammonium periodate.

This reaction was carried out as above using the 2-phenylthio derivative (XXXI) (0.5g). No reaction was apparent by T.L.C. and the reaction was not worked up.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with chromic oxide in pyridine.

(a) Chromic oxide (0.1g) was cautiously added to pyridine (10ml) at 0° with stirring. The 2-hydroxy compound (XVII) (0.4g) in the same solvent (20ml) was added and the solution was allowed to stand at room temperature for 30h. No reaction was apparent by T.L.C. and the reaction was not pursued further.

(b) Pyridine (0.95g) was dissolved in methylene chloride (25ml) at 5° and chromic oxide (0.6g) was added. The solution was stirred for 5min at 5°, then warmed to room temperature and the 2-hydroxy compound (XVII) (2.4g) in the same solvent (50ml) added. No reaction was apparent by T.L.C. after 24h and the reaction was not investigated further.

Attempted oxidation of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with manganese dioxide.

The 2-hydroxy compound (XVII) (0.5g) was dissolved in toluene

(200ml) and active manganese dioxide (1g) was added. The suspension was refluxed in a Dean and Stark apparatus for 6h. There was no sign of reaction by T.L.C.; the solution was cooled, the manganese dioxide filtered through celite and the toluene evaporated under reduced pressure to give a pale brown oil which solidified on addition of ether. The product was filtered and identified as starting material by its infra-red spectrum and mixed melting point.

Oxidation of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with Jones reagent.

The 2-hydroxy compound (XVII) (1g) was dissolved in acetone (100ml) and Jones reagent (1.3ml) added dropwise from a burette until the first slight orange colour persisted. A green precipitate was formed and the solution became warm. The reaction mixture was poured into water and the resultant white precipitate filtered, washed with water (50ml) and acetone (20ml) and dried in air to yield an extremely insoluble white solid (0.9g, 83%) m.p. 181-183°. This was identified as the 2,3,5-trihydroxypiperazine (LXIV) by infra-red spectrum, mixed melting point and analysis [Found: C,48.6; H,5.0; N,6.4%]. Its identity was confirmed by conversion into the trans-2,3-diol (LXIII) identified by n.m.r. and infra-red spectra and a mixed melting point with an authentic sample.

Oxidation of 1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazine (XLV) with Jones reagent.

Compound (XLV) (0.39g) was dissolved in acetone (50ml) and Jones reagent was added from a burette until the first permanent yellow colour appeared; a precipitate was formed during the addition. The reaction

mixture was poured into water and the resultant white precipitate was filtered, washed with water (50ml) and acetone (20ml) and dried in air to give trans-1,4-bis(p-toluenesulphonyl)-2,3-dihydroxypiperazine (LXXXIV) (0.41g, 96%), an insoluble material, m.p. 183-185° [Found: C,50.4; H,5.1; N,6.3; $C_{18}H_{22}N_2S_2O_6$ requires C,50.7; H,5.2; N,6.6%]; $\nu_{max.}$ 3490 (OH), 3060, 2970, 2880, 1600, 1480, 1450, 1420, 1360, 1335, 1300, 1280, 1230, 1160, 1100, 1050, 1015, 1000, 930, 815, 800, 720, 710, 680cm^{-1}.

Oxidation of 1,4-bis(p-toluenesulphonyl)-2-hydroxy-1,2,3,4-tetrahydropyrazine with chromic oxide in acetic acid.

The 2-hydroxy compound (XVII) (1g) was dissolved in glacial acetic acid (100ml) and chromic oxide (0.2g) in the same solvent (50ml) was added. The solution was heated at 100° for 1h; it turned deep green and a gas was evolved which turned lime - water milky, identifying it as carbon dioxide. The solution was cooled in ice and poured into water to give a white precipitate which was filtered and dried. Crystallisation from ether/light petroleum gave a white solid (0.54g, 79%), m.p. 137-139°. It was identified as p-toluenesulphonamide by analysis [Found: C,49.3; H,5.5; N,8.0; $C_7H_9NSO_2$ requires C,49.1; H,5.3; N,8.2%], n.m.r. and infra-red spectra and a mixed melting point with an authentic sample.

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APPENDIX

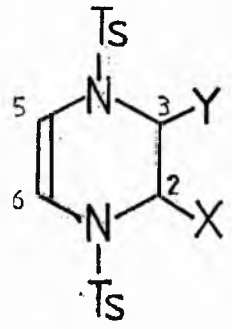
Carbon^{13} n.m.r. data for some tetrahydropyrazines

The ^{13}C n.m.r. spectra of compounds (I) and (II) are listed in the following table.

$TsNHCH_2CH(OEt)_2$

(I)

Ts = Me-C$_6$H$_4$-SO$_2$- (1′, 2′, 3′, 4′)



(II)

Table.

Compound	Chemical Shifts in ppm (multiplicity)							
	C-4′ C-1′	C-2′ C-3′	C-5†	C-6†	C-3	C-2	$ArCH_3$	Others
								100.7(d) $\underline{CH}(OEt)_2$
(I)	137.0(s)	129.7(d)						63.0(t) $O\underline{CH_2}CH_3$
	143.4(s)	127.1(d)			45.5(t)	NCH_2		14.2(q) $CH_2\underline{CH_3}$
(II;X=OMe	135.4(s)	129.9(d)	111.9(d)	106.2(d)	45.6(t)	80.2(d)	21.6(q)	54.7(q) OCH_3
Y=H)	134.4(s)	129.2(d)						
	144.3(s)	127.5(d)						
	143.6(s)	126.9(d)						
(II;X=OEt,	134.2(s)	129.8(d)	111.7(d)	105(d)	45.7(t)	78.7(d)	21.5(q)	62.8(t) $O\underline{CH_2}CH_3$
Y=H)	134.4(s)	129.1(d)						14.3(q) $CH_2\underline{CH_3}$
	143.5(s)	127.3(d)						
	144.1(s)	126.7(d)						

Compound	Chemical Shifts in ppm (multiplicity)							
	C-4' C-1'	C-2' C-3'	C-5†	C-6†	C-3	C-2	$ArCH_3$	Others
(II;X=OH, Y=H)	135.2(s) 134.7(s) 144.3(s)	129.9 * (s) 129.8 127.4 * (s) 127.2	109.6(d)	107.4(d)	47.5(t)	74.1(d)	21.6(q)	
(II;X=OAc, Y=H)	135.7(s) 144.1(s)	129.9(d) 129.1(d) 127.4(d) 127.1(d)	109.7(d)	106.8(d)	45.7(t)	73.6(d)	21.5(q)	168.9 C=O 20.1 $\underset{O}{C}-CH_3$
(II;X=Cl, Y=H)	134.4(s) 130.6(s) 145.1(s) 144.3(s)	129.8(d) 127.4(d)	110.4(d)	104.9(d)	50.7(t)	64.3(d)	21.6(q)	
(II;X=NCS, Y=H)	134.5(s) 134.1(s) 144.9(s) 144.4(s)	130.1(d) 129.9(d) 126.9(d)	110.2(d)	105.6(d)	47.6(t)	62.1(d)	21.51(q)	129.5(s) $N=\underline{C}=S$
(II;X=Y =Br) (trans)	134.7(s) 146.1(s)	130.4(d) 128.7(d)	106.6(d)		59.6(d)		21.7(q)	
(II;X=Y =OEt) (trans)	136.5(s) 143.5(s)	129.0(d) 127.4(d)	106.6(d)		81.8(d)		21.4(q)	62.4 (t) $O\underline{CH_2}CH_3$ 14.3 (q) $CH_2\underline{CH_3}$

* Very broad.

Compound	Chemical Shifts in ppm (Multiplicity)							
	C-4' C-1'	C-2' C-3'	C-5†	C-6†	C-3	C-2	$ArCH_3$	Others
(II;X=Y	136.5(s)	128.9(d)	106.6(d)		80.9(d)		21.3(q)	62.4 OCH_2CH_3(t)
=OEt)	143.5(s)	127.4(d)						14.3 CH_2CH_3(q)
(Cis)								

† These assignments may be reversed.

All spectra were measured in $CDCl_3$. We are grateful to PCMU for measurement of the spectra of compounds (I) and (II;OMe,OH,OAc,Cl,; to Pfizer Ltd., for measurement of the spectra of (II; X=OEt,NCS,Y=H and X=Y=OEt) and to Fisons Ltd., for measurement of the spectrum of (II; X=Y=Br).

Assignments were made on the basis of the multiplicities of the undecoupled spectra and by comparison of the shifts with those of the model compound (I) (p.32).

Discussion

Compound (I) shows four singlets for the different types of aromatic carbon C-1', C-2', C-3' and C-4' in the p-toluenesulphonyl group. The methyl substituted carbon resonates at 143.4 ppm from TMS and that bearing the sulphonyl substituent at 137.0 ppm. These figures are as expected; for comparison/the values for similarly substituted positions in p-$Me_6H_4SO_2NHBu$ are 143.1 and 137.6 ppm, respectively.[1] The values for the unsubstituted aryl carbons 2' and 3' are within the normal range for p-substituted toluenes. The other two types of carbon which this compound has in common with all the tetrahydropyrazines studied are the tolyl methyl group and the aminomethylene group. The former resonates

at 21.5 ppm (very close to the value for toluene) and the latter at 45.5, well within the expected range. The spectrum of (I) also shows the expected two signals for the ethoxy group and one for the acetal carbon.

The unsymmetrical structures of the 2-substituted 1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines (II; Y=H) result in the aryl carbons of the two p-toluenesulphonyl substituents being non-equivalent (as also shown by their p.m.r. spectra, p. 37). Thus in the 2-methoxy compound (II; X=OMe, Y=H) (p. 36) there are eight lines for the aromatic carbons instead of the four in compound (I).

The two sp^2 hybridised carbons (C_5 and C_6) appear as a pair of doublets in the undecoupled spectrum; one between 109.7 and 111.7, and the other at 104.9 - 107.4 according to the nature of X. These peaks are in the characteristic region for enamines.

The most variable feature of the spectra of compounds (II) is the shift of C-2 which varies quite widely with the nature of the substituent. Little data is available for N-CH-X groups, but the general trend follows that for compounds of the type R_2CHX. Thus in the 2-methoxy compound (II; X=OMe, Y=H) this carbon resonates at 80.2 ppm, in the 2-hydroxy compound (II; X=OH, Y=H) at 74.1 ppm and in the 2-chloro compound (II; X=Cl, Y=H) at 64.3 ppm. For comparison the equivalent carbons in 2-propyl methyl ether[2a], 2-propanol[2b] and 2-chloropropane[2c] resonate at 72.6 ppm, 63.4 ppm and 53.7 ppm, respectively.

The methylene group (C-3) resonates as a triplet, the shift of which varies from 45.7 ppm in the 2-alkoxy compounds (II; X=OMe and OEt, Y=H) to 50.7 in the 2-chloro compound (II; X=Cl, Y=H). It is to be expected that a strongly polar substituent such as Cl will affect

electron distribution through two σ bonds.

Using the same 2-substituted propanes CH_3CHXCH_3 to illustrate the trend, 1-C in 2-propyl methyl ether resonates at 21.4 ppm[2a], but at 26.8 ppm in 2-chloropfopane[2c].

The 2-acetoxy compound (II, X=OAc, Y=H) (p. 51) in addition gives the expected signals for the acetate group, i.e. a methyl quartet at 20.1 ppm and carbonyl singlet at 168.9 ppm (the comparative figures for ethyl acetate are 20.0 and 170.0)[2d].

Although the isothiocyanate (II, X=NCS, Y=H) is an unstable compound (p. 68) as is reflected in its complex spectrum which contains peaks due to impurities, it was nevertheless possible, by analogy with the related compounds (II), to make assignments for all the carbons. The signal at 129.5 ppm was assigned to the carbon of the N=C=S group; the figure for the corresponding signal in cyclohexylisothiocyanate is 132.0 ppm[2e]. Thiocyanates resonate at higher field; for example the isothiocyano group in ethyl isothiocyanate appears at 130.6 ppm[2e] and the thiocyano group in ethyl thiocyanate at 111.9 ppm[3].

The 2,3-disubstituted 1,4-bis(p-toluenesulphonyl)-1,2,3,4-tetrahydropyrazines, being symmetrical molecules, have a simpler spectrum than the compounds discussed so far. Thus the two sets of aryl carbons are equivalent and give only four lines in the decoupled spectrum, while there is only one line for the two sp^2 and sp^3 hybridised carbons, respectively. The latter have similar shifts to those in the molecules already discussed, depending on the nature of X.

The carbon[13] n.m.r. spectra of the cis and trans diethoxy compounds (II, X=Y=OEt) (p.77 and p. 78) provide a means of assigning the configurations to the two isomers. The signal for C-2

and C-3 appears at 81.8 ppm in the trans-isomer but at 80.9 in the cis-isomer. This difference is comparable with, e.g., that between the cis- and trans-1,2-dichlorocyclohexanes, where the CHCl carbons resonate at 64.6 and 65.2 ppm, respectively.[4]

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