2,3 - DIHYDRO - 1,4 - DIAZEPINES.

being a Thesis

presented by

ANITA MICHAELLE GORRINGE

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition and has not previously been presented for a Higher Degree.

The work was carried out in the Department of Chemistry of the United College in the University of St. Andrews, under the direction of Mr. D. M. G. Lloyd, B.Sc., F.R.I.C.

CERTIFICATE

I hereby certify that Miss Anita Michaelle Gorringe, A.R.I.C., has spent twelve terms at research work under my supervision, has fulfilled the conditions of ordinance No. 16 (St. Andrews), and is qualified to submit the accompanying thesis in application for the degree of Ph.D.

Director of Research

CAREER

From October 1949 to May 1959 I was variously employed doing laboratory work. During this time I attended part-time courses at Rutherford College of Technology, Newcastle upon Tyne, and obtained an Ordinary National Certificate (Chemistry) in 1953, a Higher National Certificate in 1955, and passed the examination for Graduate Membership of the Royal Institute of Chemistry in 1958. I was elected to Associateship of the Royal Institute in the following year.

I entered the University of St. Andrews in January 1965 as a post-graduate Student. The research described in this thesis was carried out between January 1965 and December 1967, during which time I received research grant from the Wellcome Foundation Ltd.

PUBLICATIONS (to February 1968)

(1) Diazepines Part VI. Condensation Products from Benzoylacetone and Ethylenediamine.

A. M. Gorringe, D. Lloyd and D. R. Marshall.,

J.Chem.Soc.(C), 1967, 2340.

(2) Diazepines Part VII. Electrophilic substitution of Dihydrodiazepinium Salts.

A. M. Gorringe, D. Lloyd, D. R. Marshall and L.A. Mulligan

Chem. and Ind., 1968, 130.

also

(3) Structure of a Diacetylnitrocyclopentadiene.
A.N. Campbell-Crawford, A.M. Gorringe and D. Lloyd.
Chem. and Ind., 1966, 1961.

ACKNOWLEDGEMENTS

I would like to thank Mr. Douglas Lloyd for his many helpful suggestions and constant encouragement during the last three years.

I am grateful to Mr. Andrew Watson for assistance in determining spectra and to other members of the Technical Staff in the St. Andrews University Chemistry Department.

My thanks are also due to the Wellcome Foundation Ltd. for a research grant which enabled me to carry out this research.

SUMMARY

A number of previously unknown 2,3-dihydro-1,4-diazepines have been prepared. These include dihydrodiazepines produced by condensation reactions between ethylenediamine and benzoylacetone or dibenzoylmethane, and those obtained by the reaction of N-methylethylenediamine with acetylacetone, benzoylacetone or dibenzoylmethane. All the preparations were carried out in acetic acid and low yields in the case of 2,3-dihydro-5,7-diphenyl-1,4-diazepine were shown to be due to competitive acetylation of the diamine. Condensations between ethylenediamine and benzoylacetone using equimolar amounts of acetic acid and the diamine yielded the alternative condensation product 1,2-bis (2-benzoyl-1-methylvinylamino) ethane after a short reaction time. Longer reaction times gave low yields of diazepine and other products derived from the alkaline hydrolysis of the diketone.

Isomeric diazepines were formed in the reaction of N-methylethylenediamine with benzoylacetone. These isomers were separated and structures assigned to them on the basis of their U.V. and N.M.R. Spectra.

The reaction of trans 1,2-diaminocyclohexane with acetylacetone in buffered aqueous solution at room temperature was studied in some detail and it was shown that the formation of the alternative condensation product trans 1,2-bis(2-acetyl-1- methylvinylamino) cyclohexane was favoured at pH 8-9 and dihydrodiazepine formation

favoured at pHs approx. 4·5 and approx.11. Attempts to prepare a diazepine by the reaction of trans 1,2-diaminocyclohexane with malondialdehyde were unsuccessful.

Bromination of dihydrodiazepinium salts generally took place in the 6 position. In general 5,(7)-phenyl substituents were not brominated when an excess of bromine was used, but in the case of 2,3-dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate bromination of the phenyl groups did occur.

Bromination of the methyl group took place when 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine in methanol was treated with bromine. Bromination of the diazepinium perchlorate in the same solvent gave the 6-bromo compound.

6,6-Dihalo-2,3-dihydro-1,4-diazepines were obtained by treating a solution of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine or 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine in benzene with bromine. Treatment of 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with dilute hydrobromic acid gave the monobrominated dihydrodiazepinium bromide and bromine.

The electrophilic substitution of dihydrodiazepinium salts has been extended to include nitration. 6-Nitro compounds were readily obtained by the use of a suitable nitrating mixture. 2,3-Dihydro-6-nitro-5,7-dimethyl-1,4-diazepinium salts are unstable in aqueous alkaline solution, and bis(2-acetyl-2-nitro-1-methylvinylamino) ethane was obtained when the nitro dihydrodiazepine was treated with alkali and then the pH of the solution

adjusted to 8-9.

2,3-Dihydro-1,4-diazepines have been shown to exist as dications in concentrated sulphuric acid solution by examination of the U.V. spectra and N.M.R. spectra of these solutions. The second protonation takes place on the 6 carbon atom; similar species are assumed to be the intermediates in electrophilic substitution reactions and the debromination reactions of bromo diazepinium bromides, which are observed in acidic media. The latter reaction is an example of a reversible electrophilic substitution.

Some 6-bromo-2,3-dihydro-1,4-diazepines gave normal substitution products when treated with nucleophiles, but the replacement of bromine by hydrogen occurred in other instances. Kinetic studies showed that the reactions of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine and 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine with methoxide to yield the 6-methoxy compound, were bimolecular with second order rate constants of $8{\cdot}0 \times 10^{-5}$ litre moles^{-1} sec^{-1} and $8{\cdot}5 \times 10^{-5}$ litre moles^{-1} secs^{-1} respectively. Attempts were made to elucidate the mechanism of the "abnormal" substitution reaction (i.e. replacement of bromine by hydrogen), but no entirely satisfactory answer was found.

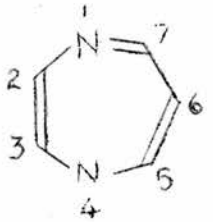
6-Amino-2,3-dihydro-1,4-diazepinium salts were obtained by the reduction 2,3-dihydro-6-nitro-5,7-dimethyl-1,4-diazepinium perchlorate and its 5,7-diphenyl analogue, by means of cyclohexene and palladium/charcoal catalyst. These amino dihydrodiazepines readily condensed

with aromatic aldehydes, and the benzylidene-imino dihydrodiazepines obtained in this way were reduced to benzylamino dihydrodiazepines by means of sodium borohydride. 6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate gave diazonium salts when treated with nitrous acid in acidic solution. A Sandmeyer reaction with cuprous chloride converted the diazonium chloride into a 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepinium salt.

CONTENTS

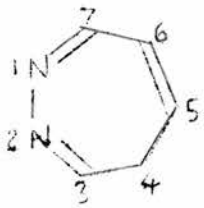
PART I - INTRODUCTORY REVIEW

Diazepines are compounds having seven-membered rings, two of the ring atoms being nitrogen and the remainder carbon. The term diazepine strictly refers to diazacycloheptatrienes; three isomers are possible, viz.



(and tautomers)
1,4-diazepine
(IA)

(and tautomers)
1,3-diazepine
(IB)



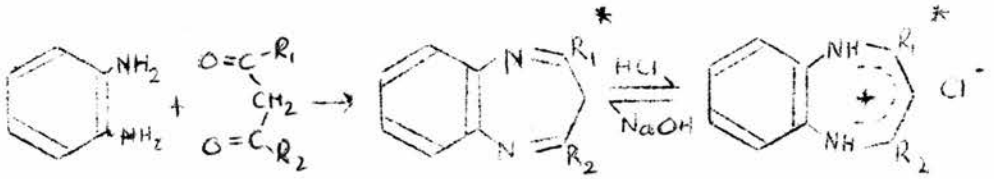
(and tautomers)
1,2-diazepine
(IC)

The present review deals with derivatives of 1,4-diazepines(IA). The parent compound of this series is not known, but a number of 2,3-dihydro and 2,3-benzo-1,4-diazepines have been described, and in this review the term "diazepine" is used to refer to compounds of these types. The remaining chapters of the thesis are concerned with studies of 2,3-dihydro-1,4-diazepines.

(A) PREPARATION OF 2,3-DIHYDRO- AND 2,3-BENZO-1,4-DIAZEPINES.

The most common route to these diazepines is by the reaction (condensation and/or addition) between a 1,2 diamine and a suitable substrate, which may be a β-diketone, β-dialdehyde, β-ketoester, β-chlorovinylaldehyde or 2,3-unsaturated acid or ester. These reactions are usually carried out under neutral or weakly acidic conditions.

Thiele and Steinmig[1] reported the first 2,3-benzo-1,4-diazepines, which were prepared by the condensation of o-phenylenediamine with β-diketones in ethanolic acetic acid, and isolated as their highly coloured hydrochlorides by the addition of hydrochloric acid to the reaction mixture.



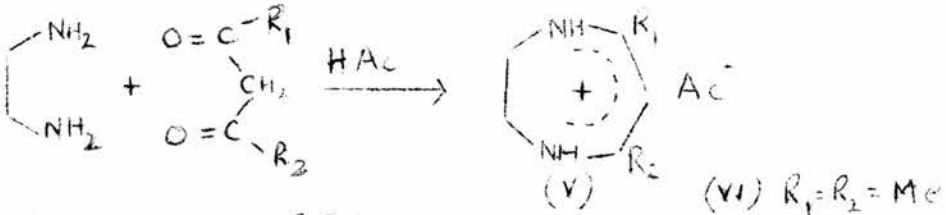
(II) $R_1 = R_2 = Me$. (III) $R_1 = Me$, $R_2 = C_6H_5$. (IV) $R_1 = R_2 = C_6H_5$.

The free bases of these compounds can be obtained by treatment of the salts with alkali.

1,2- and 2,3-Naphthalenediamines have been reacted with β-diketones similarly[2,3,4]. Reactions between β-diketones and aromatic diamines have also been carried out in ether[3] and in benzene[5] using dry hydrogen chloride as a catalyst, improved yields being claimed in the latter case. Lloyd et al[3], in preparations of diazepines derived from substituted o-phenylene-diamines, found that in cases where the diamine was difficult to obtain pure, it was advantageous to prepare the diamine just prior to its use by the reduction of the o-nitro amine, using hydrazine and Raney nickel.

* Evidence for the validity of such structures is given on pages 9, 10 & 11.

Schwarzenbach and Lutz[6] reported the preparation of the dihydrodiazepine (VI) from ethylenediamine and acetylacetone. An earlier claim of its preparation by Rosanova[7] has been shown to be incorrect as the physical constants given are those of an alternative product of condensation, 1,2-bis-(2-acetyl-1-methyl vinylamino) ethane, though the analytical figures given, apparently correspond to those expected for the diazepine.



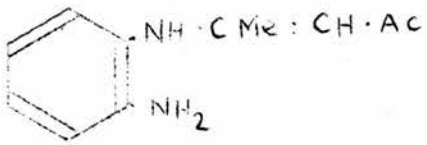
(V) (VI) $R_1 = R_2 = Me$

It had been noted[6,8] that the yield of diazepine produced by condensation of diamines and diketones was dependent upon the reaction conditions and the formation of the alternative open chain product (VII) by the condensation of two molecules of acetylacetone and one of ethylenediamine had been mentioned[6]

$$Me{\cdot}CO{\cdot}CH : CMe{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CMe : CH{\cdot}CO{\cdot}Me.$$
(VII)

Lloyd and Marshall[9] studied the reaction of 1,2-diaminocyclopentane and acetylacetone in a graded series of buffered aqueous solutions and showed that at room temperature the open chain compound analogous to (VII), isolated by its precipitation, was preferentially formed at a pH of approx. 8, and that the diazepine analogous to (V) was preferentially

formed at pH approx. 4·5 and 11. At higher temperatures diazepine was formed exclusively. Lloyd et al[3] showed that in the reaction between o-phenylenediamine and acetylacetone an alternative mono condensation product (VIII) is probably formed at pH approx. 6.



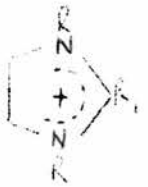
(VIII)

That these open chain compounds possess the enamine structure rather than the ketimine has been shown by several workers.[24,25]

The preparation of an N-methyl substituted benzodiazepine was carried out by Halford and Fitch by cyclisation of the mono condensation product analogous to (VIII) in dry benzene with hydrogen chloride as catalyst, and the simultaneous removal of water at reduced pressure.

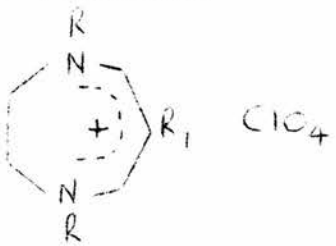
Several N,N[1] disubstituted ethylenediamines have been made to react with β-diketones and β-dialdehydes[10,11] to give diazepinium salts, the condensations having been effected in the presence of perchloric acid. It is interesting to note that under these conditions N,N[1]-dibenzylethylenediamine gave 1,3-dibenzylimidazolinium perchlorate (IX) when treated with malondialdehyde, and that reaction with acetylacetone in alkali gave 1,3-dibenzyl-2-methylimidazolinium perchlorate (X) after

the addition of perchloric acid.



(IX) R=$PhCH_2$, R_1=H. (X) R=$PhCH_2$, R_1=Me.

The use of malondialdehyde and 2-substituted malondialdehydes provided a route to the diazepines (XI a-g), which do not possess substituents in the 5 and 7 positions.

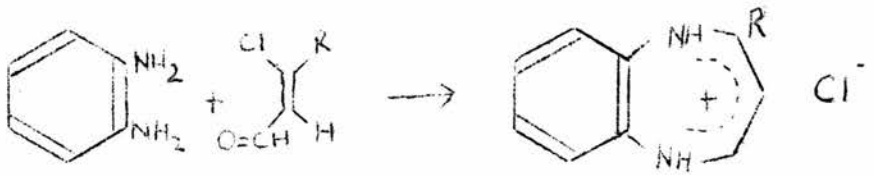


(XIa) R=R_1=Me (11) (XIb) R=Ph, R_1=NO_2 (11)
(XIc) R=Ph, R_1=OH (10) (XId) R=Ph, R_1=OMe (10)
(XIe) R=Ph, R_1=OAc (10) (XIf) R=Ph, R_1=Br (10)
(XIg) R=Ph, R_1=H (10).

The use of 2-nitromalondialdehyde with o-phenylenediamine gives a benzodiazepine[12] and the unsubstituted benzodiazepine has been prepared[3] using the diacetal of malondialdehyde and o-phenylenediamine in acetic acid solution, the addition of hydrochloric acid to the reaction mixture precipitating the hydrochloride. The unsubstituted dihydrodiazepine has been prepared[11], but no details are given.

Weissenfels et al[13] have made a number of 5-substituted benzodiazepines by reacting β-chlorovinylaldehydes with

o-phenylenediamine in methanolic hydrochloric acid:



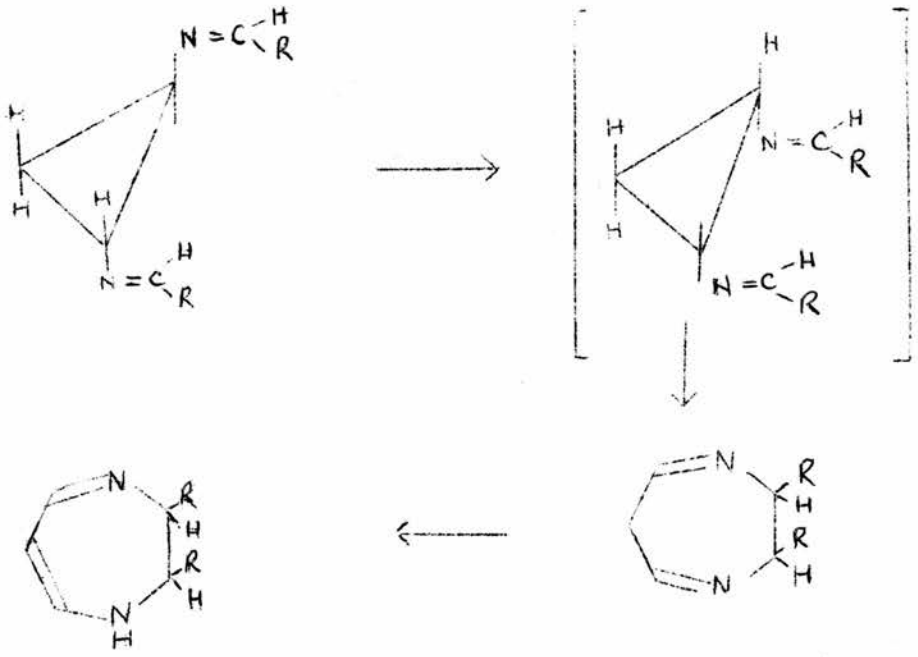
(XIIa) R = Ph, (XIIb) R = p-$(Me)_2$NHPh, (XIIc) R = p-ClPh,
(XIId) R = p-BrPh, (XIIe) R = p-NO_2Ph, (XIIf) R = p-CH_3OPh

These workers consider that the first step in this reaction is the condensation of the carbonyl group with the primary amino group, as they were able to prepare these intermediates by carrying out the reaction in neutral solution; treatment of these intermediates with hydrochloric acid gave the diazepinium hydrochlorides. Benzodiazepinium salts with fused 5,6-cycloalkene substituents and fused 5,6-heterocyclic substituents were also obtained[13] from β-chlorovinylaldehydes and o-phenylenediamine.

Similar reactions using ethylenediamine instead of o-phenylenediamine have been carried out recently by Gagan[14], who has prepared the diazepines with fused 5,6-cyclopenteno, cyclohexeno and cycloheptено substituents. The first two compounds were isolated by distillation of the free bases and the last as a perchlorate.

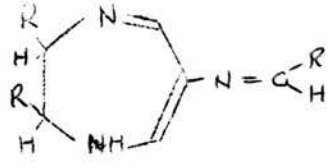
A novel means of access to 5,6,7-unsubstituted diazepines is the bond isomerism which takes place on heating the double Schiff's bases of 1,2-diaminocyclopropane[15]. This is analogous to the

Cope rearrangement.



(XIIIa) R=Ph. (XIIIb) R=p-MePh. (XIIIc) R=p-$N(Me)_2$Ph.
(XIIId) R= ∝ napthyl.

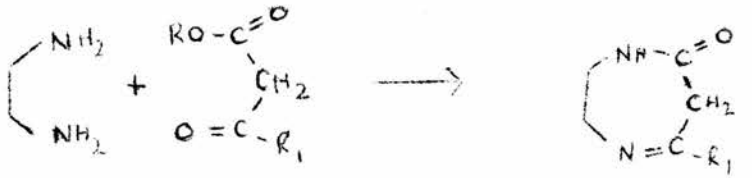
It was shown that the transition of the diamine from the trans to the cis form was the slowest step in this reaction by preparation of the treble Schiff's base of triaminocyclopropane and benzaldehyde. The diazepine (XIV) was produced almost immediately at a much lower temperature than required in the preparation of (XIIIa). Two of the aldimino groups in the treble Schiff's base are necessarily in the cis conformation.



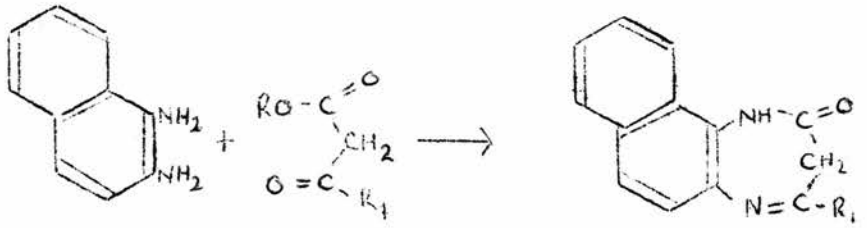
(XIV)

R = Ph

The condensation of β-ketoesters with ethylenediamine[16] and with 1,2-naphthalenediamine[2] produces tetrahydro-diazepinones and naphtho-dihydro-diazepinones resp.

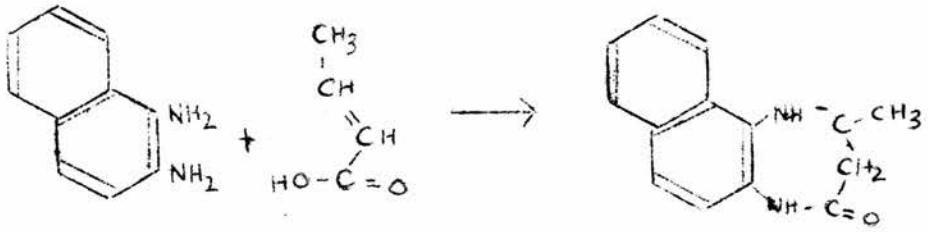


(XV) R_1 = Me, R = Et (16) (XVI) R_1 = Ph R = Et (16)



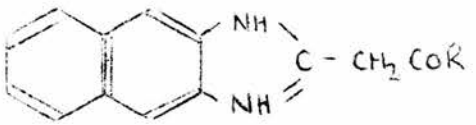
(XVII) R = Et, R_1 = Me

The structure assigned to compound (XVII) was based on the assumption that the more active ∝ -amino group had condensed with the ester, followed by cyclisation via the enol form of the ketone. The compound given on reduction of (XVII) was isomeric with the reduced diazepinone (XVIII) produced by the reaction of crotonic acid and 1,2-naphthalenediamine.



(XVIII)

Condensations of acetoacetic ester or benzoylacetic ester with 2,3-naphthalenediamine are said to produce the 2 substituted naphthimidazoles[4] below.

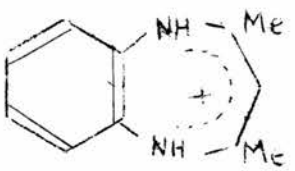


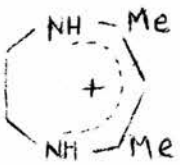
(XIX) R=Me. (XX) R=Ph.

Reactions between aromatic aldehydes and o-phenylenediamine are said[46] to give 1,5,7 triaryl-2,3-benzodiazepines, but attempts by Nielsen[47] to repeat such preparations were unsuccessful.

(B) STRUCTURE AND PHYSICAL PROPERTIES OF 1,4-DIAZEPINES

The 1,4-diazepines are basic substances, readily forming monoacid salts. Schwarzenbach and Lutz[38,18] measured the pKa of 2,3 dihydro-5,7-dimethyl-1,4-diazepine and its 2,3-benzo analogue and found the former to be a much stronger base (pKa 13·4) than the latter (pKa 9·0). The diazepinium monocations of compounds can be represented thus:

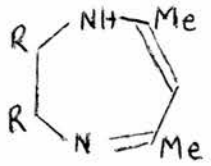




Where  indicates the delocalised electron system that accounts for the stability of these salts. The monocations of the benzodiazepines are highly coloured and those of the dihydrodiazepines colourless, though a high intensity absorption is shown in

their U.V. spectra above 300mμ.

The stable structures of the free bases of benzodiazepinium and of dihydrodiazepinium salts have been shown to be different. 2,3-Dihydro-5,7-dimethyl-1,4-diazepine and 2,3-dihydro-5,7-dimethyl-2,3-diphenyl-1,4-diazepine have the unsymmetrical structure shown below[15].



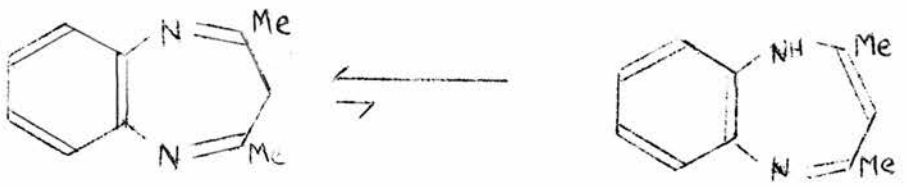
(XXI) R = H

(XXII) R = Ph

The N.M.R. spectrum of compound (XXI) showed two single proton signals at τ 2·24 and 5·6. I.R. spectroscopy revealed an abnormal C = N absorption between 1500 and 1600cm^{-1}. Its U.V. spectrum in tetrahydrofuran (λmax 288mμ, ε =8,690) was not in accordance with the alternative diimine structure. Similarly U.V. and I.R. data are in accord with the congugated structure for compound (XXII).

Schwarzenbach and Lutz[38] recognised the existence of two structures for 2,3-benzo-5,7-dimethyl-1,4-diazepine base, the one which was first formed on the treatment of a salt with alkali giving rise to a momentary yellow coloration, and the stable colourless form which was precipitated. The pKa of 9·0 quoted above is that of the yellow unstable form and was measured using a complicated flow device. An equilibrium mixture of the two forms was found to have a pKa of approx. 4·5. Veibel and Nielsen[19]

have measured the pKa (equil.) of other benzodiazepines. The following structures were assigned[38] to the two forms of 2,3-benzo-5,7-dimethyl-1,4-diazepine.

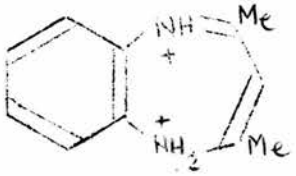


Colourless - stable Yellow - unstable.

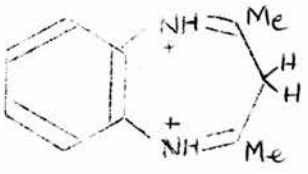
The validity of the structure assigned to the stable form has received additional support[20] in that its I.R. spectrum showed no NH absorption and its U.V. spectrum is similar to that of benzylideneaniline. N.M.R. spectrum in deuterated chloroform shows methylene protons at τ 7·3[15].

A colourless diacid salt of 2,3-benzo-5,7-dimethyl-1,4-diazepine was produced by treatment of a suspension of the monohydrochloride in conc. hydrochloric acid with dry hydrogen chloride[1]. Other diacid salts of benzodiazepines have been reported[3].

The structure (XXIII) was previously assigned to the dication by Lloyd et al[3], but its N.M.R. spectrum in conc. sulphuric acid[15] showed methylene protons at τ 5·3 and NH protons at τ -3·4, which favoured the structure (XXIV) for the dication.



(XXIII)

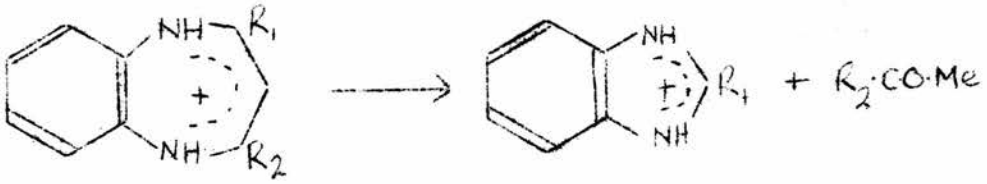


(XXIV)

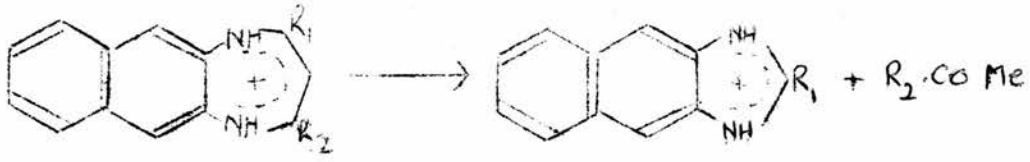
(C) CHEMICAL PROPERTIES OF 1,4-DIAZEPINES

(1) Hydrolysis

Benzodiazepines readily undergo changes in which the first step is necessarily hydrolysis. Neutral aqueous solutions of such diazepines and their salts decompose on heating or standing at room temperature into substituted benzimidazoles and ketones [1,2,3,4].



(XXV) $R_1=R_2=Me$ (1)
(XXVI) $R_1=Me$, $R_2=Ph$ (1)



(XXVII) $R_1=Ph$, $R_2=Me$ (4)
(XXVIII) $R_1=R_2=Ph$ (4)

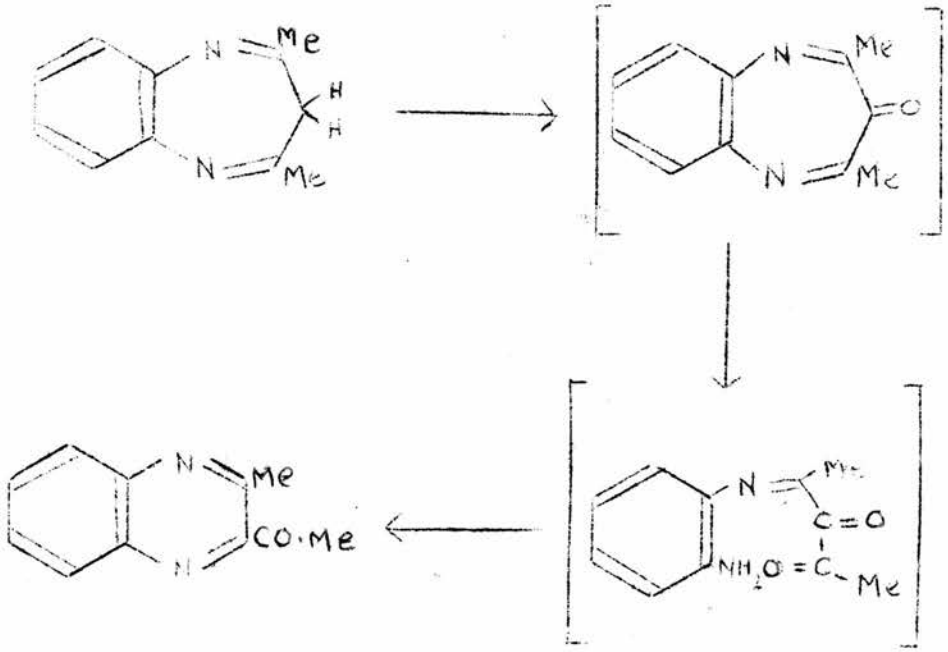
The first step in these decompositions is considered to be the formation of an anil which tautonerises to an oxoenamine. 1,4 Addition to the double bond produces a compound which is stabilised by decomposition to a ketone and imidazole. By such a mechanism diazepines with different substituents at C5 and C7 would be expected to give two benzimidazoles and two ketones. This is found to be so in the case of (XXVI)[1]. As the addition of mineral acid greatly retards the reaction it is suggested[3] that the initial hydrolysis involves the free base, and also that dihydrodiazepines do not undergo this reaction because of their higher basicity. Similar transformations are observed in the dry distillation of benzodiazepinium salts[3].

Further evidence of the existence of hydrolytic equilibria between benzodiazepinium salts and their components is the formation from compound (XXV) and phenylhydrazine of dimethyl phenyl pyrazole[1] and the formation of 2,3-dimethylquinoxaline[21] from compound (XXV) and diacetyl[21]. Under alkaline conditions 2,3-dihydro-5,7-dimethyl-1,4-diazepine is cleaved by the action of benzoyl chloride, dibenzoylethylenediamine being obtained[24].

(2) OXIDATION AND DEHYDROGENATION.

Oxidation of 2,3-benzo-5,7-dimethyl-1,4-diazepine with peracids gave the substituted quinoxaline[20] (XXIX) identical to that prepared from pentane-2,3,4-trione and o-phenylenediamine. It was considered that a preliminary oxidation at C6 occurred

followed by hydrolysis of the diazatropone and recondensation to give the quinoxaline (XXIX).

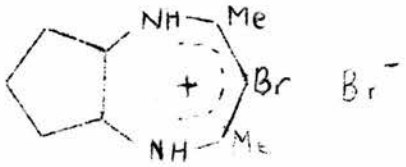


(XXIX)

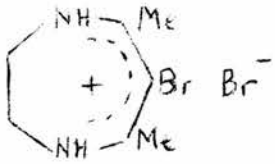
Lloyd et al[3] tried to dehydrogenate 2,3-cyclohexano-2,3-dihydro-5,7-dimethyl-1,4-diazepine in order to obtain a 2,3-benzo-1,4-diazepine, but were not successful. They also attempted to dehydrogenate 2,3-benzo-4,5,6,7 tetra hydro-1,4-diazepine, but no product corresponding to 2,3-benzo-1,4-diazepine was obtained.

(3) SUBSTITUTION REACTIONS.

Bromination of 2,3-dihydro-5,7-dimethyl-1,4-diazepine and of 2,3-cyclopentano-2,3-dihydro-5,7-dimethyl-1,4 diazepine with an equimolar quantity of bromine yielded the following brominated compounds.



(XXX)



(XXXI)

The bases were formed from these salts by treatment with alkali. Exclusive C6 bromination also occurred when N-bromosuccinimide was used as brominating agent.

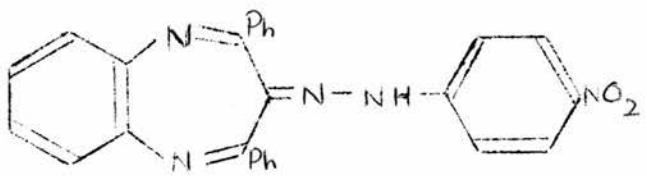
Treatment of (XXXI) with sodium ethoxide or methoxide gave the 6-ethoxy and 6-methoxy derivatives, respectively.

Bell and Marshall[23] studied the kinetics of halogenation of 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate and concluded that in aqueous perchloric acid a simple bimolecular reaction between bromine and diazepine takes place. They found that a secondary bromination took place at C6 to give an unstable 6,6-dibromo derivative which was hydrolysed rapidly. The kinetics of iodination in buffered acetate solution were more complex. The rate was found to be proportional to the acetate ion concentration and inversly proportional to a function of the iodide concentration. It was concluded that the transition state contained a diazepinium cation, iodine cation and acetate ion, the acetate ion acting as a base. An isotope effect $\frac{kH}{kD} > 2$ was observed.

Bromination of 2,3-benzo-5,7-dimethyl-1,4-diazepine with an equimolar amount of bromine gave unreproducable results[3] as did bromination with N-bromo succinimide. However the use of a 6-molar equivalent of bromine gave 2,3-(tetrabromobenzo)-5,7-dimethyl-1,4-diazepinium bromide.

The same workers tried to nitrate 2,3-benzo-5,7-dimethyl-1,4-diazepine using copper nitrate or urea nitrate, but only tars were produced. There is a recent report[48] of the nitration of 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate and 2,3-dihydro-1,4,5,7-tetramethyl-1,4-diazepinium perchlorate using nitric and sulphuric acid mixtures at 70°. The 6-nitro derivatives were obtained.

Barltrop et al[20] coupled 2,3-benzo-5,7-diphenyl-1,4-diazepine with a p-nitro benzene diazonium salt. Coupling took place in the 6 position to give compound (XXXII).



(XXXII)

(D) PRESENT WORK

The work reported in Parts II and III of this thesis deals with further experimental work which has been carried out on the preparation and properties of various 2,3-dihydro-1,4-diazepines.

PART II DISCUSSION

CHAPTER I

PREPARATION OF 2,3-DIHYDRO-1,4-DIAZEPINES

In the present work several hitherto unknown 2,3-dihydro-1,4-diazepines have been prepared. In general the method employed has been the condensation of 1,2-diamines with β-diketones in acetic acid.

In some cases advantages in yield and in purity of product were gained by using mono-oxoenamine perchlorates, e.g. (I) and (II) as starting materials from which to prepare the diazepines, though as is shown later (II) or its free base are not necessarily the true intermediate in diazepine formation from the diamine and diketone.

(I) $R=R_1=Me$.

$ClO_4^- H_2\overset{+}{N}R \cdot CH_2 \cdot CH_2 \cdot NH \cdot CR:CH \cdot COR_1$

(II) $R=Me$, $R_1=Ph$.

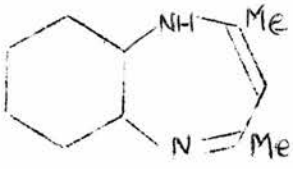
Compounds (I) and (II) were obtained by the ready condensation of N-methylethylenediamine with acetylacetone or benzoylacetone in methanol containing an equimolar quantity of perchloric acid. Dibenzoylmethane did not give an analogous product.

Each diazepine preparation will be discussed separately, since the information acquired and subsequent related investigations are individual to each diazepine.

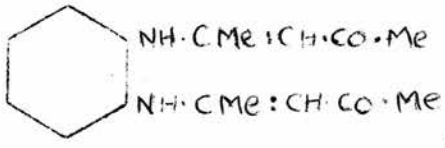
A. Preparation of 2,3-cyclohexano-2,3-dihydro-5,7-dimethyl-1,4-diazepine.

This compound had been reported previously[3,24], but no details were given. The prior preparation of 1,2-trans-diaminocyclohexane was necessary as this starting material was not available commercially at the time of the present work. This involved the preparation of cyclohexane-1,2-dione dioxime and its reduction using sodium in alcohol. The diamine was finally isolated as its dihydrochloride.

The work of Lloyd et al [9] on the condensation of 1,2 diamines with acetylacetone, indicated that the formation of diazepine (III) in aqueous solution at room temperature would be preferred at pH 4-5 and pH 10-11, and that at pH 7-9 the open chain di-(oxoenamine) (IV) would be produced.



(III)



(IV)

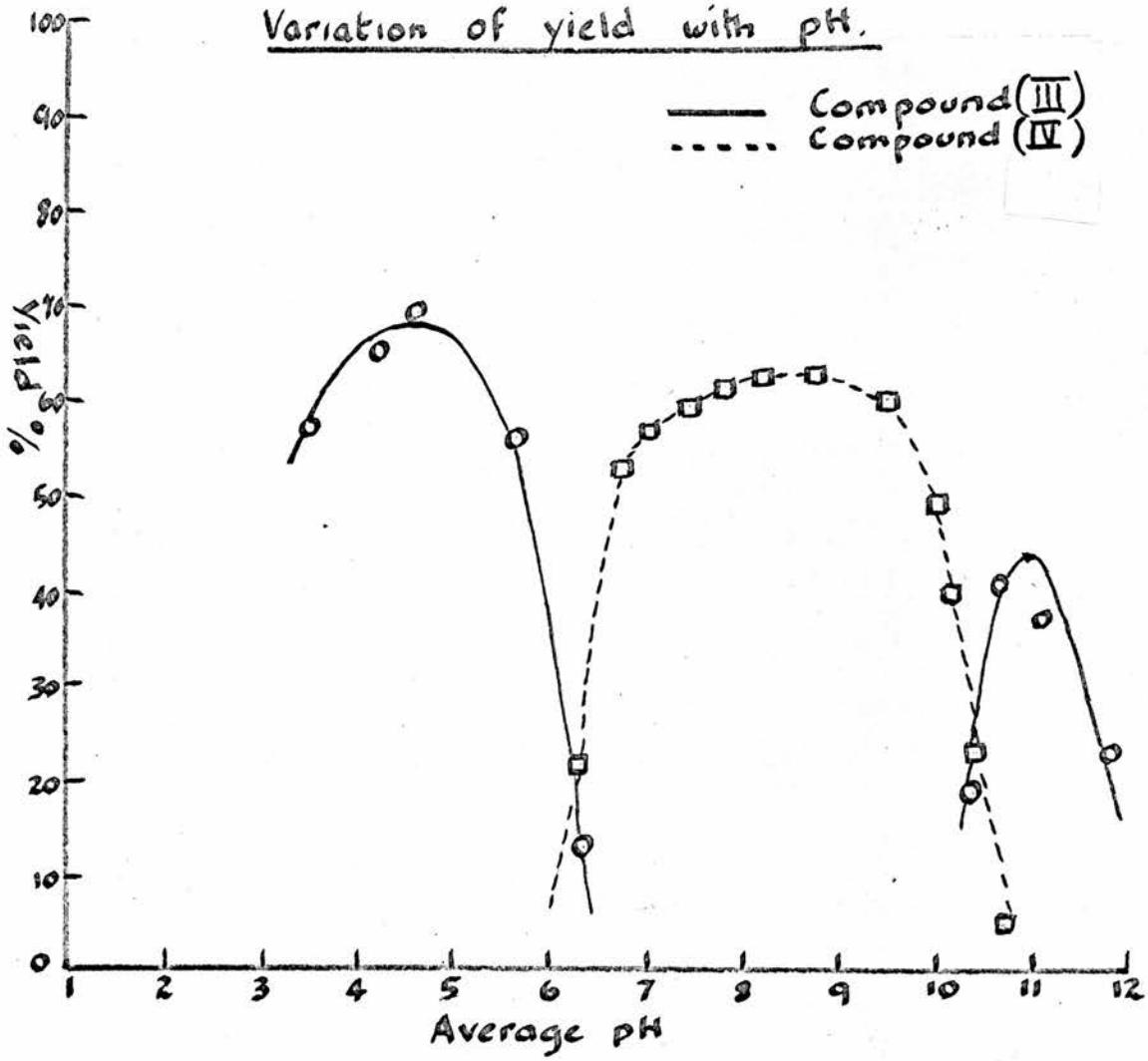
Preliminary attempts at condensing 1,2-diamino-cyclohexane with acetylacetone were carried out in buffered aqueous solutions at pH approx. 4 and at pH approx 8·5. At the former pH treatment of the reaction mixture with alkali yielded a compound whose elemental analysis and U.V. spectrum confirmed its identity

as 2,3-cyclohexano -2,3-dihydro-5,7-dimethyl-1,4-diazepine (III) This compound on treatment with perchloric acid gave a perchlorate whose U.V. spectrum was the same as the free base in aqueous solution. When the condensation was carried out at pH approx.8·5 another compound readily precipitated. Analysis confirmed that this was 1,2-bis(2 -acetyl-1-methylvinylamino) cyclohexane (IV). Treatment of this compound with perchloric acid resulted in its rapid hydrolysis, as indicated by the change in U.V. spectrum in acidified aqueous medium. The final spectrum was that of acetylacetone.

The variation of yield of these products with pH was studied in a manner similar to that of Lloyd et al[9]. Constant amounts of acetylacetone and 1,2-diaminocyclohexane in a 2·5:1 molar ratio were allowed to react in a constant volume of graded buffer solutions at 20°. The open chain compound (IV) which precipitated was removed by filtration and the diazepine (III) was isolated by treating the filtrate with potassium hydroxide solution. The results so obtained are represented graphically in Fig. I.

Clearly the formation of di-(oxoenamine) is preferred at pH 8-9. Its formation is aided by a favourable hydrolytic equilibrium at these pHs and by its precipitation from solution. The formation of diazepine or diazepinium salts at the lower and higher pHs would be a consequence of reduced competition from the alternative reaction.

Fig. I


Variation of yield with pH.
Compound (III)
Compound (IV)
% Yield
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
Average pH

The lower yields of diazepine at very high and very low pHs is probably due to unfavourable hydrolytic equilibria of the diazepine or diazepinium salts.

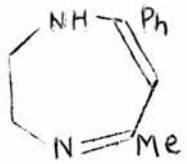
B. Attempted condensations between trans 1,2-diaminocyclohexane and malondialdehyde.

It was hoped to prepare a 2,3- dihydro-1,4-diazepine which was unsubstituted in positions 1,4,5,6, and 7, by the reaction of malondialdehyde and trans 1,2-diaminocyclohexane. A benzodiazepine of this type has been prepared[3] by the reaction of o-phenylenediamine and 1-ethoxy-1,3,3-trimethoxy propane in glacial acetic acid. U.V. data has been reported for the analogous dihydrodiazepine and details of its preparation are in press[49].

Many attempts were made to condense malondialdehyde with trans 1,2-diaminocyclohexane under acidic conditions and in all cases no diazepine was isolated, resinous intractable materials being obtained. U.V. studies of these materials suggested that diazepine formation had not taken place. An absorption at approx. 330mμ would have been expected for such a compound. This is based on that quoted for 2,3-dihydro-1,4-diazepine and on the similarity of the U.V. spectrum of the 2,3-dihydro-5,7-dimethyl-1,4-diazepinium cation and 2,3-cyclohexano-2,3-dihydro-5,7-dimethyl-1,4-diazepinium cation (methanolic solution λmax 325mμ). One typical attempted reaction is described in the experimental section.

(C) Preparation of 2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine.

Interest in this compound arose in part from an earlier claim to its preparation by Ried and Höhne[16]. The product described as the diazepine (V), although prepared from ethylenediamine and benzoylacetone under conditions normally producing diazepines[24] had a m.pt. of 183° which is that of the open chain compound (VI). The structure of (VI) has been verified by N.M.R.[25] and mass spectroscopy[26]. Although structure (V) is shown for the 5-methyl-7-phenyl compound it might of course exist as the alternative tautomer with an -NH-group adjacent to the C-methyl group, or as an equilibrium mixture of the two tautomers



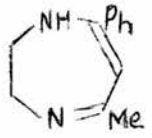
Ph·CO·CH:CMe·NH·CH_2CH_2·NH·CMe:CH·COPh.

(V) (VI)

When Ried and Höhne's method was repeated, by reacting benzoylacetone with ethylenediamine at 120° in acetic acid so that the ethylenediamine to acetic acid molar ratio was 1:0·625, it was found that (VI) formed initially, but on further heating of the reaction mixture (1 hr. at 120°) none of this compound could be isolated. When the reaction mixture was poured into water a small amount of solid, and a larger amount of oil separated. The solid was identified as 1,2-bis(1-phenylethylidene-amino)

ethane (VII), by its N.M.R. spectrum and elemental analysis. No depression in m.pt. was observed on mixing with the authentic compound prepared from acetophenone and ethylenediamine[27]. The oil which separated was characterised as acetophenone by preparation of its semicarbazide. On the addition of concentrated alkali to the remaining aqueous liquor a further solid separated. This was shown to be the desired diazepine by its N.M.R. spectrum and analysis of its perchlorate. The melting point of the diazepine base was 146–147° and of its perchlorate 123–124°.

The isolation of these products from the reaction mixture can be explained if the following reactions are taking place under the experimental conditions.

(1) $NH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2 + Me \cdot CO \cdot CH_2 \cdot CO \cdot Ph \longrightarrow$  $+ H_2O$

(V)

(2) $NH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2 \rightleftarrows Ph \cdot CO \cdot CH{:}CMe \cdot NH \cdot CH_2 \cdot CH_2 \cdot NH \cdot CMe{:}CH \cdot CO \cdot Ph + 2H_2O.$
$+$
$2\ Me \cdot CO \cdot CH_2 \cdot CO \cdot Ph$

(VI)

(3) $Me \cdot CO \cdot CH_2 \cdot CO \cdot Ph + H_2O \longrightarrow Me \cdot COOH + Me \cdot CO \cdot Ph.$

(4) $NH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2 + 2Me \cdot CO \cdot Ph \rightleftarrows C(Me)Ph{:}N \cdot CH_2 \cdot CH_2 \cdot N{:}C(Me) \cdot Ph + 2H_2O$

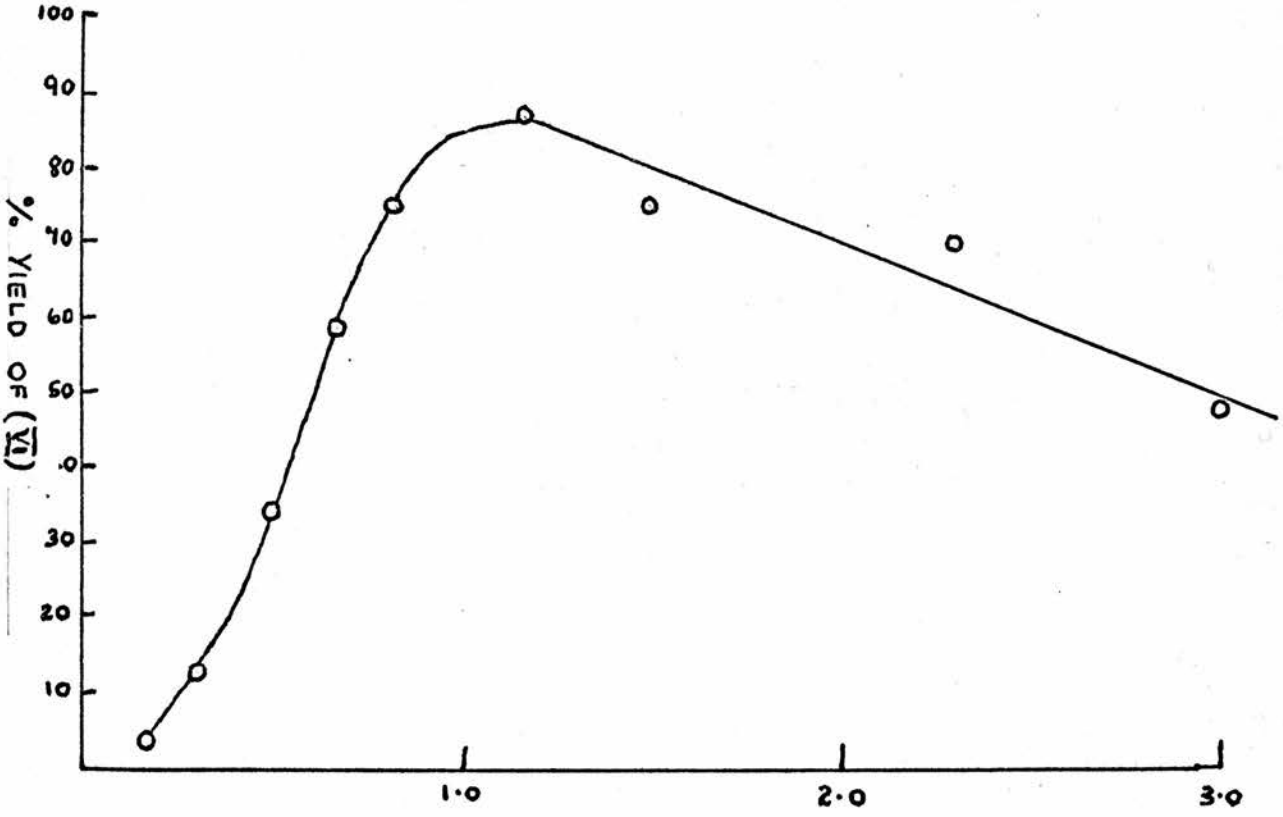
(VII)

Initially compound (VI) is formed and may be precipitated, but as heating is continued the comparatively irreversible reactions (1) and (3) take over and displace the equilibrium (2) until no (VI) remains.

The low yields of (V) and the production of (VII) are accounted for by the ready alkaline hydrolysis of benzoylacetone.

Conditions which would reduce the formation of (VI) and prevent the hydrolysis of benzoylacetone were then sought, as being those most likely to favour the production of diazepine. Compounds of type (VI) are known to be hydrolysed by acid or alkali. An investigation of the yield of this compound in relation to pH could not be carried out in aqueous solution because of the low solubility of benzoylacetone. However some idea of the dependence of its formation on the acidity of the reaction medium was gained by reactions carried out in aqueous 80% ethanol using different ratios of ethylenediamine to acetic acid, the amounts of ethylenediamine and benzoylacetone being held constant. The results of these experiments are depicted graphically in Fig. II and clearly indicate optimum ethylenediamine to acetic acid ratio of 1:1·1. This suggested that the use of a large excess of acetic acid should increase the yields of diazepine and yields of 50-60% were obtained by using a 1:17 molar ratio of ethylenediamine to acetic acid.

FIG II


% YIELD OF (XI)
100
90
80
70
60
50
40
30
20
10
1·0
2·0
3·0
MOLS ACETIC ACID.
MOLS ETHYLENEDIAMINE.

D. Preparation of 2,3-dihydro-5,7-diphenyl-1,4-diazepine.

Preliminary attempts to prepare this compound were based on the method used in the previous diazepine preparation, i.e. by heating equimolar amounts of dibenzoylmethane and ethylenediamine in an excess of acetic acid and with final isolation of the diazepine as is perchlorate. The yields (24-25%) were lower than expected and increased reaction time from 1½ to 19 hours made no difference to the yield. Unreacted dibenzoylmethane could be recovered in good yield by pouring the reaction mixture into water and extracting with ether. The acetic acid which had passed into the ether layer was neutralised with sodium bicarbonate solution, and after drying the ether layer dibenzoylmethane was obtained by removal of the solvent.

During one of these recovery procedures the appearance of some crystalline material was observed when the acetic acid was almost neutralised. Its N.M.R. spectrum in trifluoroacetic acid (signals at τ 2·2, 4·7, 5·9 and 7·6 in ratio 10:1:4:3) suggested that this compound might be 1-(2-benzoyl-1-phenylvinylamino) -2-acetylamino ethane, (VIII)

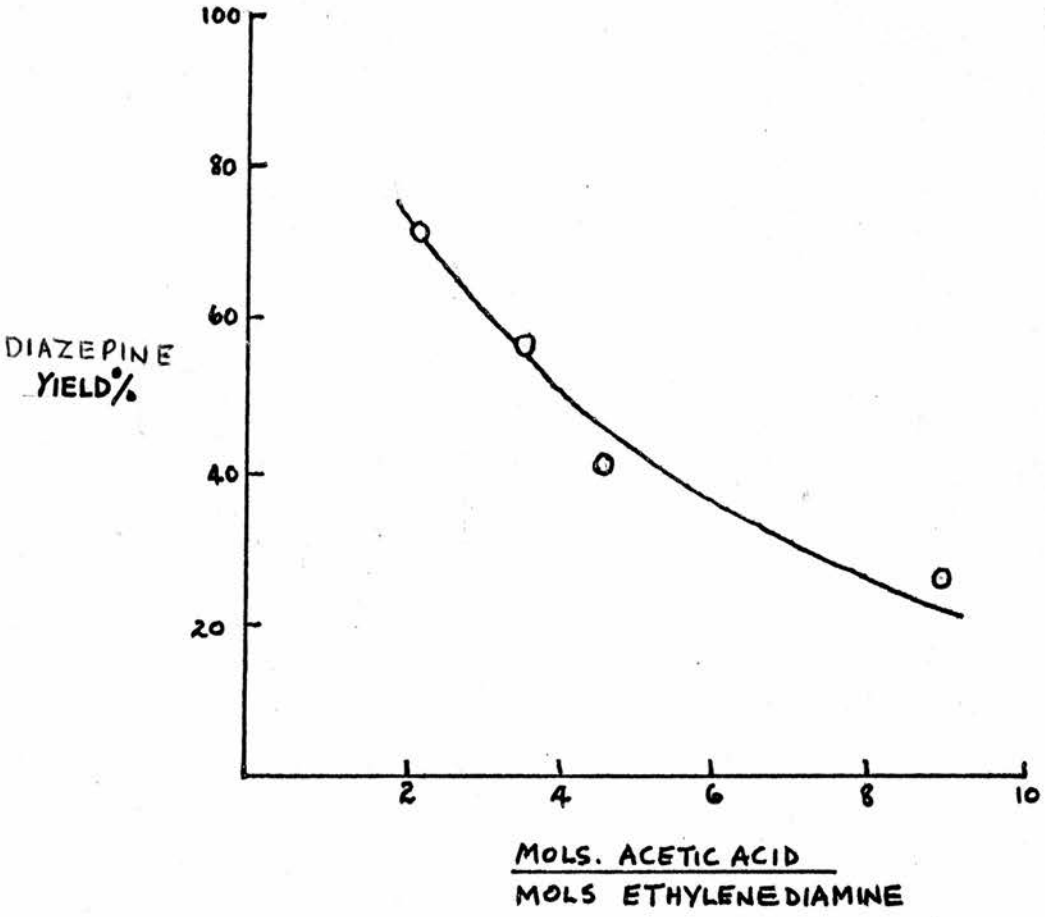
$$Me \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot NH \cdot CPh{:}CH \cdot CO \cdot Ph$$

(VIII)

and elemental analysis was in agreement with this structure.

It seemed therefore that the acetylation reaction might be competing with diazepine formation. This was confirmed by using

FIG. III


100
80
60
40
20
DIAZEPINE YIELD%
2
4
6
8
10
MOLS. ACETIC ACID
MOLS ETHYLENEDIAMINE

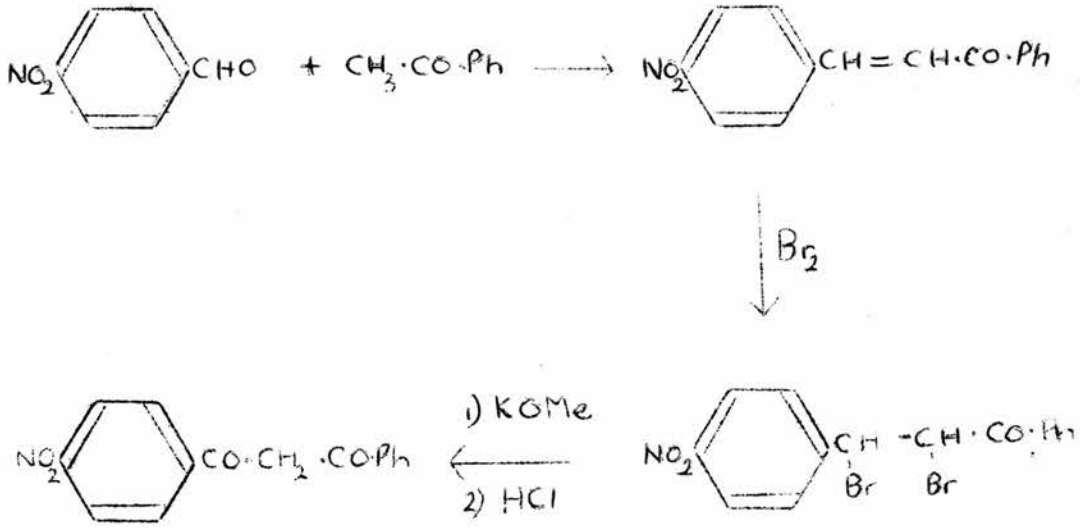
the same proportions of reactants, but heating the ethylenediamine and acetic acid and distilling off one fifth of the acetic acid prior to the addition of dibenzoylmethane. When the reaction mixture was worked up the yield of diazepine was reduced to 1·2% and the yield of (VIII) increased to 64%.

On the assumption that the acetylation proceeds via the amine acetate and that diazepine formation involves nucleophilic attack at a carbonyl group, it was thought that diazepine formation should be favoured by increasing the proportion of ethylenediamine to acetic acid. This was done by using different excess quantities of ethylenediamine and constant amounts of acetic acid and dibenzoylmethane. As can be seen from Fig. III the expected increase in diazepine yields were observed. The yield could also be increased by using 2:1 molar proportions of ethylenediamine and dibenzoylmethane, but a reduced amount of acetic acid. This is given as the final method for preparation of this diazepine in the experimental section.

E. Preparation of 2,3-dihydro-5-p nitrophenyl-7-phenyl-1,4-diazepine

This diazepine was easily prepared in a way similar to that used for 2,3-dihydro-5,7-diphenyl-1,4-diazepine. However, the preparation of the starting diketone presented some difficulties. The first attempt involved the reaction of acetophenone with p-nitro benzoylchloride in the presence of sodium amide[28]. Low yields of the diketone were obtained after column chromatography.

The method finally used[29] in this preparation, (outlined below) although involving more steps, produced the diketone in good yield.



F. Preparation of 2,3-dihydro-1,5,7-trimethyl-1,4-diazepine.

Attempts to prepare this compound were made by refluxing equimolar quantities of N-methylethylenediamine and acetylacetone, in acetic acid. Examination of the reaction mixture by U.V. spectroscopy suggested the formation of diazepine by a characteristic absorption at 329mμ. However the diazepinium perchlorate could not be isolated from the reaction mixture by treatment with perchloric acid and water, presumably because of its high solubility in aqueous medium. The free base was liberated from the reaction mixture by treatment with concentrated sodium hydroxide and extraction with ether. The N.M.R. spectrum of the brown liquid remaining after drying the extract and removing the ether, indicated

that the diazepine base was impure.

It was found that N-methyl ethylene diamine readily condenses with acetylacetone in methanol containing an equimolar quantity of perchloric acid to give the mono condensation product (I). This precipitates from solution

$$ClO_4^- H_2N^+Me \cdot CH_2 \cdot CH_2 \cdot NH \cdot CMe:CH \cdot CO \cdot CH_3$$
(I)

The N.M.R. spectrum of (I) in trifluoroacetic acid showed the N-methyl group protons as a 1:2:1 triplet at τ 6·9. This suggested that condensation had taken place at the primary amino group. When (I) was heated with acetic acid at reflux temperature the diazepinium perchlorate was obtained, and the reaction mixture was much lighter in colour than in the direct preparation. Removal of most of the acetic acid left a viscous golden residue which slowly crystalised. It proved impossible to free these crystals from acetic acid. The N.M.R. spectrum of the residue showed that it contained diazepinium salts and acetic acid only. The free base was obtained as a pale yellow oil by the process described earlier and its N.M.R. spectrum was that expected for this diazepine.

G. Preparation of 2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine

This compound was prepared in a manner similar to the preliminary preparation of 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate. The low yield (27%) is now thought to be due to the competitive acetylation reaction as discussed in Chapt. 1(D). The yield could

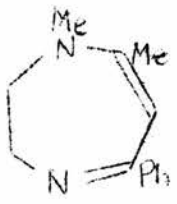
probably be improved by the use of less acetic acid in the preparation. As the diamine is expensive, the use of an excess of this material to improve the yield is not envisaged.

The diazepinium perchlorate obtained from an aqueous solution of the reaction mixture was slow in crystallising and somewhat impure, and it could not be satisfactorily purified by recrystallisation from methanol as expected. The most effective purification technique was found to be reprecipitation from acetonitrile by addition of ether, after thoroughly washing the solution with water.

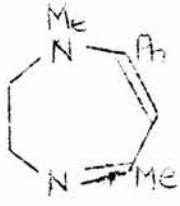
The base could be obtained as an almost colourless oil by treatment of the salt with sodium hydroxide solution and extraction with benzene.

H. Preparation of 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine and 2,3-dihydro-1,5-dimethyl-7-phenyl-1,4-diazepine.

The condensation of N-methyl ethylenediamine with benzoylacetone to form diazepine might be expected to give rise to the two isomers (IX A) and (X A).



(IX A)



(X A)

Examination of the N. M.R. spectrum in trifluoroacetic acid of the diazepinium perchlorate obtained from this condensation indicated the presence of two isomeric diazepinium salts (IX) and (X) in an approx 3:1 molar ratio. They were isolated by a lengthy fractional crystallisation from methanol. (IX) had a m.pt. of 124•5–126° and (X) a m.pt. of 167–170°.

Assignment of structure to (IX) and (X).

The U.V. spectra in methanol of the diazepinium perchlorates (IX) and (X) were different. In common with other 5 and/or 7 phenyl substituted diazepines they showed two absorptions, that associated with the phenyl group λ max 250–260mμ and that associated with the diazepine system, found at higher wavelength. The latter absorption of (IX) was found to be at longer wavelength than that of (X) by 5mμ.

Using a basic value of 339mμ for the unsubstituted diazepine substituent increments were calculated (Table V) from the U.V. data of diazepines of known structure (Table IV) (cf [49]). Only the position of the diazepine type absorption has been considered.

TABLE IV

SUBSTITUENT			λ max mμ
1	5	7	
-	-	-	339 (1)
-	Me	Me	325 (2)
-	Me	Ph	341•5(3)
-	Ph	Ph	358 (4)
Me	Me	Me	329 (5)

TABLE V

Substituent	Calculation	Increment mμ
5 or 7 Me	(2)-(1)÷2	-7
5 or 7 Ph	(3)+7-(1)	+9·5
5and 7 Ph	(4)-(1)	+19
1 Me	(5)+14-(1)	+4

On the above basis the calculated position of absorption for (IXA) and (XA) would be

$$(339-7 + 9{\cdot}5 + 4) = 345{\cdot}5 m\mu$$

and that of 2,3-dihydro-1-methyl-5,7 diphenyl-1,4-diazepine

$$(339 + 19 + 4) = 362 m\mu$$

The position of absorption for (IX) λmax 346mμ was very near to that calculated, but that of (X) was less by 4·5mμ. Similarly the position of absorption for 2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine λ max 356mμ was less than calculated λ max 362mμ.

The common feature which could be present in the structures of the two last mentioned diazepines is a phenyl group adjacent to an N-methyl group. Should there be steric interaction between these groups the co-planarity of the phenyl and diazepine systems might be reduced, thereby decreasing the amount of conjugation. A phenyl group of this kind might have a lower increment value than one which is sterically unhindered. This is in accordance with the calculated and observed spectra and

and suggests that isomer (IX) corresponds to structure (IXA) and isomer (X) to the structure (XA).

From N.M.R. data.

The N.M.R. spectra in trifluoroacetic acid of the diazepinium perchlorates (IX) and (X) were compared with those of the 5,7-dimethyl and 5,7-diphenyl analogues. It was hoped that the position of the signal given by the N-methyl protons would indicate the correct assignment of structure to (IX) and (X). As can be seen from Table VI the evidence is inconclusive.

TABLE VI

N.M.R. spectra of 2,3-dihydro-1,4-diazepinium salts in trifluoroacetic acid. τ values given.

2,3-dihydro-1,4-diazepinium salt	4NH	2,3CH_2	6H	1NCH_3	5,7CH_3	5,7C_6H_5
1,5,7-trimethyl	2·3(b)	6·23	4·87	6·67	7·72 7·76	-
1-methyl 5,7diphenyl	2·0(b)	5·99	4·43	6·68	-	2·47
IX	2·4(b)	6·01	4·47	6·49	7·52	2·40
X	2·4(b)	6·09	4·70	6·87	7·60	2·47

(b) = broad. All signals are singlets unless otherwise indicated.

Since these N.M.R. spectra are those of salts which have a delocalised electron system it was thought that the N.M.R. spectra of the free bases in deuteriochloroform might provide more conclusive as to the structure of (III) and (IV), as any "equalising" effect of delocalisation would be absent. Table VII shows the N.M.R. spectra of the free bases.

TABLE VII

N.M.R. spectra of 2,3-dihydro-1,4-diazepines in deuterio chloroform. τ values given

2,3-dihydro-1,4-diazepine	2,3CH_2	6H	1NCH_3	5,7·CH_3	5,7C_6H_5
1,5,7-trimethyl	6·3(m) 6·75(m)	5·29	7·09	7·96 8·04	-
1-methyl-5,7-diphenyl	5·97(m) 6·70(m)	4·51	7·30	-	2·35(cx) *2·64(cx)
Diazepine base from Compound (IX)	6·05(m) 6·7(m)	4·83	7·11	8·0	2·3(cx) 2·65(cx)
Diazepine base from Compound (X)	6·15(m) 6·75(m)	4·95	7·33	7·8	2·6

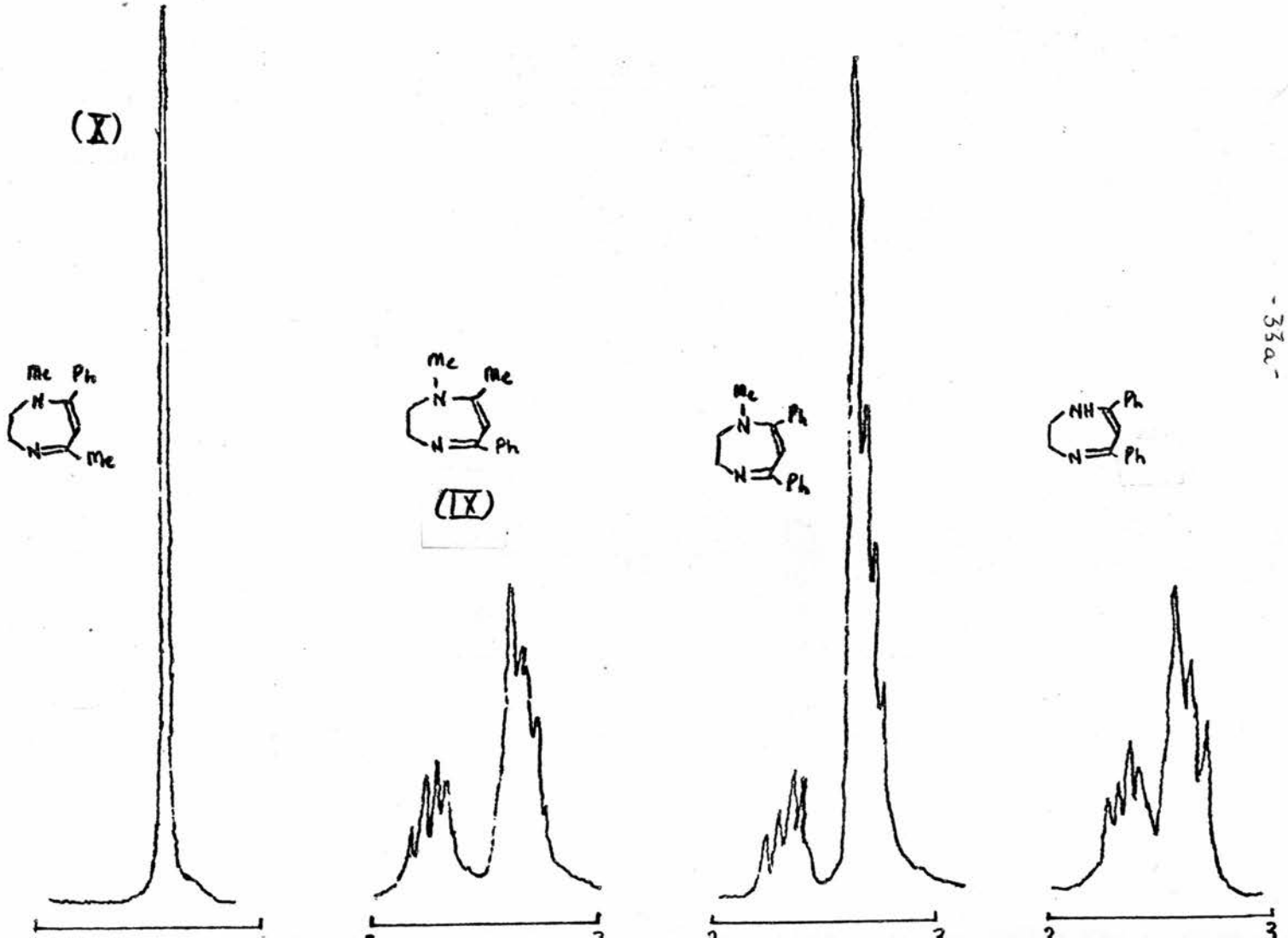
(m) = multiplet. (cx) = aromatic complex

*Appears to have a singlet superimposed on an aromatic complex

A study of the positions of the signals given by the N-methyl protons, suggests that (IX) has a N-methyl group with a similar environment to 2,3-dihydro-1,5,7-trimethyl-1,4-diazepine and (X) has a N-methyl group with a similar environment to 2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine. This is in agreement with the assigned structures (IX)=(IXA), (X)=(XA) from U.V. data. The phenyl signals (Fig. IV) also indicate the correctness of such assignments. Compound (X) gives a singlet signal and 2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine appears to have a singlet superimposed on a complex signal. (IX) has a complex signal which is similar to that of 2,3-dihydro-5,7-diphenyl-1,4-diazepine. The singlet phenyl signal can therefore be assigned to a phenyl group adjacent to a N-methyl.

FIG. IV

Phenyl signals in N.M.R spectra of diazepines - solvent $CDCl_3$



Further comments on methods of preparation of 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine and 2,3 dihydro-1,5-dimethyl-7-phenyl-1,4-diazepine.

These compounds could be obtained by heating the diketone and diamine in acetic acid at reflux temperature and isolation of the diazepines as perchlorates. The yield however was low. (approx.20%)

As with N-methyl ethylenediamine and acetylacetone an open chain mono condensation product (II) was readily obtained by the reaction of the diamine and benzoylacetone in methanol containing perchloric acid.

$$ClO_4^- \quad H_2\overset{+}{N}\ Me\cdot CH_2\cdot CH_2\cdot NH\cdot CMe{:}CH\cdot CO\cdot Ph$$

(II)

The N.M.R. spectrum of (II) in trifluoroacetic acid suggested that condensation had taken place between the primary amino group and the acetyl carbonyl group, as the N-methyl protons signal appeared as a 1:2:1 triplet at τ 6·87 and the remaining methyl group protons gave a signal at τ 7·19, very near to that given by the methyl protons of the di-condensation product of benzoylacetone and ethylenediamine τ 7·23. The structure of the latter compound has been proven (see Chap. 1(C)).

Cyclisation of (II) in acetic acid gave much higher yields of the diazepinium perchlorates. N.M.R studies of the diazepinium perchlorates produced by both methods showed almost the same proportions of the isomers. It was thought that if (II) were the true intermediate the production of diazepine (X) would be favoured.

The cyclesation of (II) to diazepine was studied in trifluoroacetic acid at room temperature by N.M.R. and again a similar proportion of isomers was obtained, whilst the hydrolysis of (II) was not observable. Compound (II) is therefore not necessarily the true intermediate of diazepine formation.

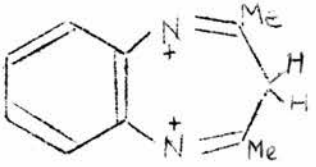
CHAPTER 2

DISSOCIATION CONSTANTS OF 2,3-DIHYDRO-1,4-DIAZEPINES

In hydrolytic solvents the 2,3-dihydro-1,4-diazepines exist mainly as the monocation unless the medium is very acidic or very alkaline. Solutions of the free bases in water, methanol or ethanol show the same U.V. spectrum as solutions of the monoacid salts. 6-Bromo-diazepines are less basic than their unsubstituted analogues; cf pKa 13·4[18] for 2,3-dihydro-5,7-dimethyl-1,4-diazepinium cation and pKa 11·8[23] for 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium cation. This decrease in basicity is reflected in the U.V. spectrum in methanol of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine. A bathochromic shift and an increase in intensity are observed on acidification, though similar changes are not observed with the 5,7-dimethyl analogue.

The formation of 1,4-diazepinium dications has long been known in the 2,3-benzo series, in that a colourless salt is produced in a very acidic medium[1], whereas the monoacid salt is highly coloured.

The N.M.R. spectrum in conc. sulphuric acid has been recorded[15] for 2,3-benzo-5,7-dimethyl-1,4-diazepine and is consistent with the dication structure shown below.



The same workers examined the N.M.R. spectrum in conc. sulphuric acid of 2,3-dihydro-5,7-dimethyl-1,4-diazepine and recorded signals 1:4:6 at τ 5·3,5·6,7·2. These they attributed to the monocation. Repetition of this work showed the signals to be in a ratio of 2:4:6, which suggests that the diazepine exists as the dication in conc. sulphuric acid and that the second protonation takes place in the 6 position. A similar dication is given by 2,3-dihydro-5,7-dimethyl-1,4-diphenyl diazepinium perchlorate in conc. sulphuric acid.

Changes in the U.V. spectrum of 2,3-dihydro-5,7-dimethyl-1,4 diazepine have been observed[24] in conc. sulphuric acid and are consistent with the non-conjugated diazepinium dication structure. The monocations show an intense absorption in the region 320-380mμ, the exact value depending upon substituents, which is associated with the conjugated diazepinium structure. The absence of such absorptions in conc. sulphuric acid was shown for 2,3-dihydro-5,7-dimethyl-1,4-diazepine[24] and has also been shown for its 6-bromo analogue.

The U.V. spectra of 2,3-dihydro-5,7-diphenyl-1,4-diazepinium monocation and its 6-bromo analogue show an absorption at high wavelength associated with the conjugated dihydrodiazepinium structure, and although conjugation with the phenyl groups will also affect this absorption it will be referred to as the "diazepine" absorption. Similarly the absorption found at lower wavelength will be referred to as the "phenyl" absorption.

In conc. sulphuric acid these phenyl diazepines show loss of "diazepine" absorption. The "phenyl" absorption moves to a higher wavelength and is more intense. This is particularly noticeable in the 6-bromo-compound.

The pKa_1 for 2,3-benzo-5,7-dimethyl-1,4-diazepinium dication has been estimated[3] to be approx. -1 and that of the dihydro analogue to be approx. -3.

It was now hoped to make accurate determinations of the dissociation constants of the dications listed below.

2,3-dihydro-5,7-dimethyl-1,4-diazepinium dication (a)

6 bromo- " " " " (b)

" 5,7-diphenyl " " (c)

6 bromo- " " " " (d)

by quantitative examination of the U.V. spectra of the monocations in sulphuric acid of different strengths. The ratio of monocation concentration (BH^+) to dication concentration (BH_2^{++}) was readily found in cases (a)(b) and (c) by measurement of the intensity of the "diazepine" absorption, but in the case of (d) an overlap of absorptions of the mono and dications involved the solving of simultaneous equations in order to find these ratios.

Using the relationship

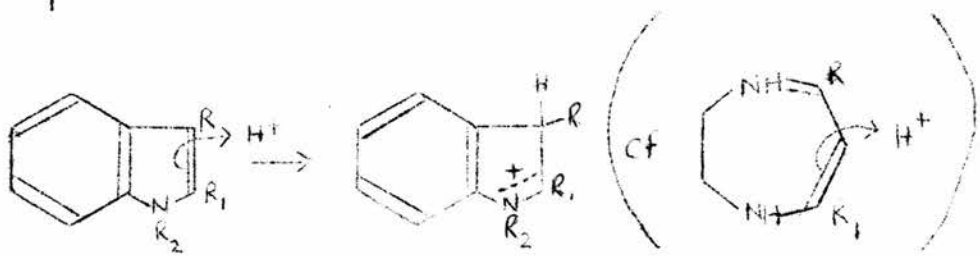
$$H = pKa_1 + \log \frac{(BH^+)}{(BH_2^{++})} \quad (1)$$

and an appropriate acidity function H, the determination of pKa_1 was attempted.

Choice of acidity function.

The acidity function Ho is said to measure the tendency of a solution to transfer a proton to a neutral base[34] and the acidity function H+ measures the tendency of a solution to transfer a proton to a univalent cation. The difference between H+ and Ho for pure sulphuric acid has been calculated[36] as 0·28 log unit and Bonner and Lockhart[37] have shown H+ and Ho to differ by a constant amount in 30-35% and 75-95% sulphuric acid. Therefore a plot of $\log(BH^+)/BH_2^{++}$ against Ho was first made, in order to find the applicability of Ho or H+ in the determination of these pka_1 values. Such a plot should have unit slope (equation(1)).

Another acidity function H_I[40] has been devised to compare the basicities of a large number of substituted indoles and as this involves protonation on a carbon atom as shown below, it was thought that it might be an applicable acidity function for determining the pKa_1 values of diazepinium dications.



Although the protonation of indoles is not strictly comparable with the protonation of diazepinium monocations, because the latter are charged species and the former neutral molecules, perhaps the acidity function which should be used for protonation of diazepinium

monocations, might differ from H_I by a constant amount in a similar way to Ho and H+.

Results.

The plot of log $(BH^+)/(BH_2^{++})$ against Ho (original Hammett[34] and revised[41]) gave slopes that were well below unity for all the diazepines examined.

However, in cases (a) and (b) by plotting the H_I function against log $(BH^+)/(BH_2^{++})$ slopes of 1·06 and 1·00 respectively were obtained (Fig. V). In cases (c) and (d) slopes of 0·87 and 0·83 were obtained (Fig. VI). The calculation of log $(BH^+)/(BH_2^{++})$ from U.V. data was more involved in case (d) and may have been a source of error. In case (c) it was necessary to extrapolate from given H_I values in 8 to 12 molar sulphuric acid up to 13·3 molar sulphuric acid. This could also provide a source of error.

The "pKa_1" values which have been obtained, although they cannot be considered as valid thermodynamic constants, serve to compare the basicities of these diazepinium mono cations as they represent the concentration of sulphuric acid to bring about 50% protonation. The results are shown below.

"pKa_1"					
-6·72	2,3-dihydro-	5,7-dimethyl-	1,4-diazepinium	dication	(a)
-7·51	6-bromo-	"	"	"	(b)
-8·68		5,7-diphenyl	"	"	(c)
-7·48	6-bromo-	"	"	"	(d)

FIG. V.

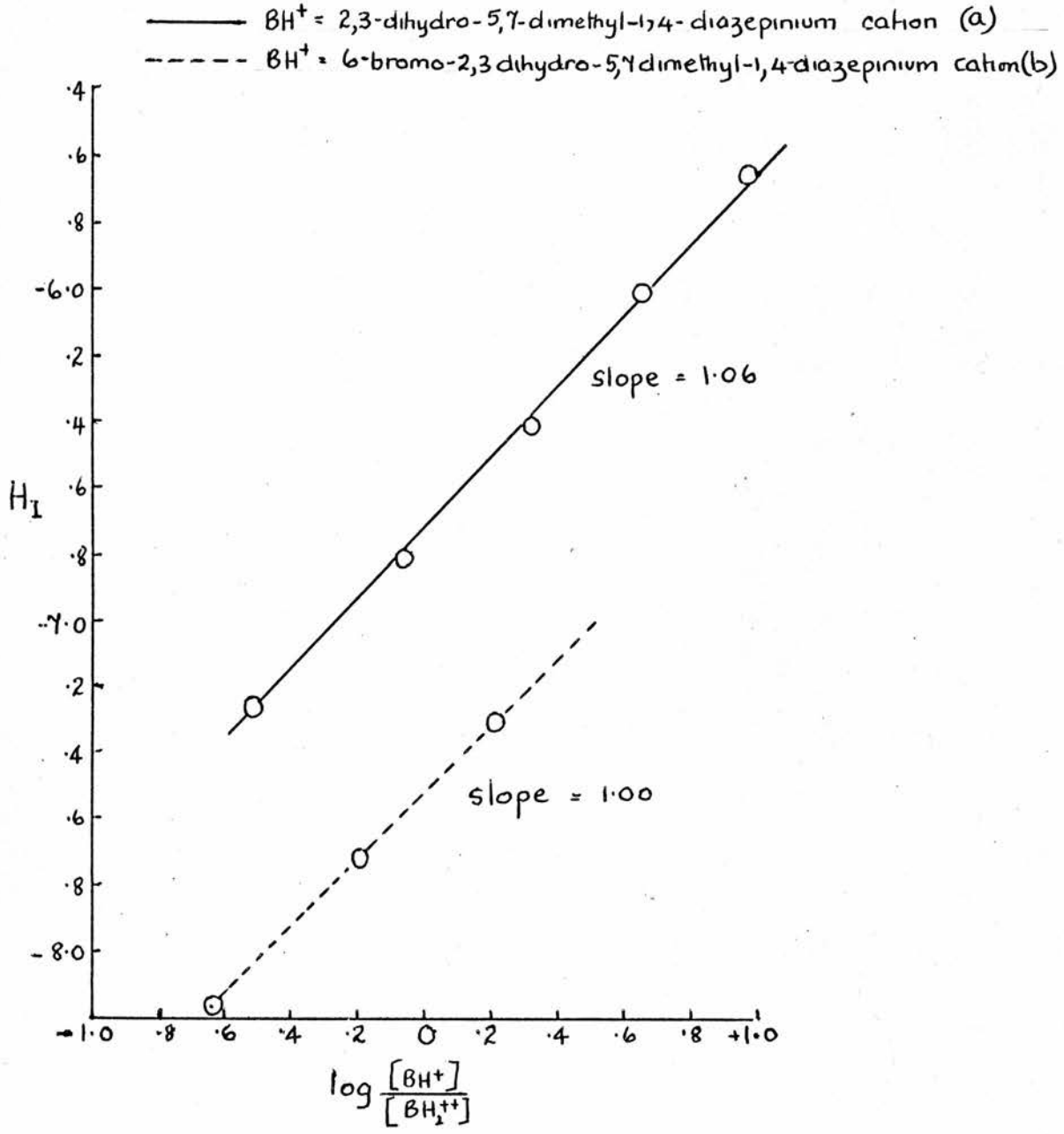
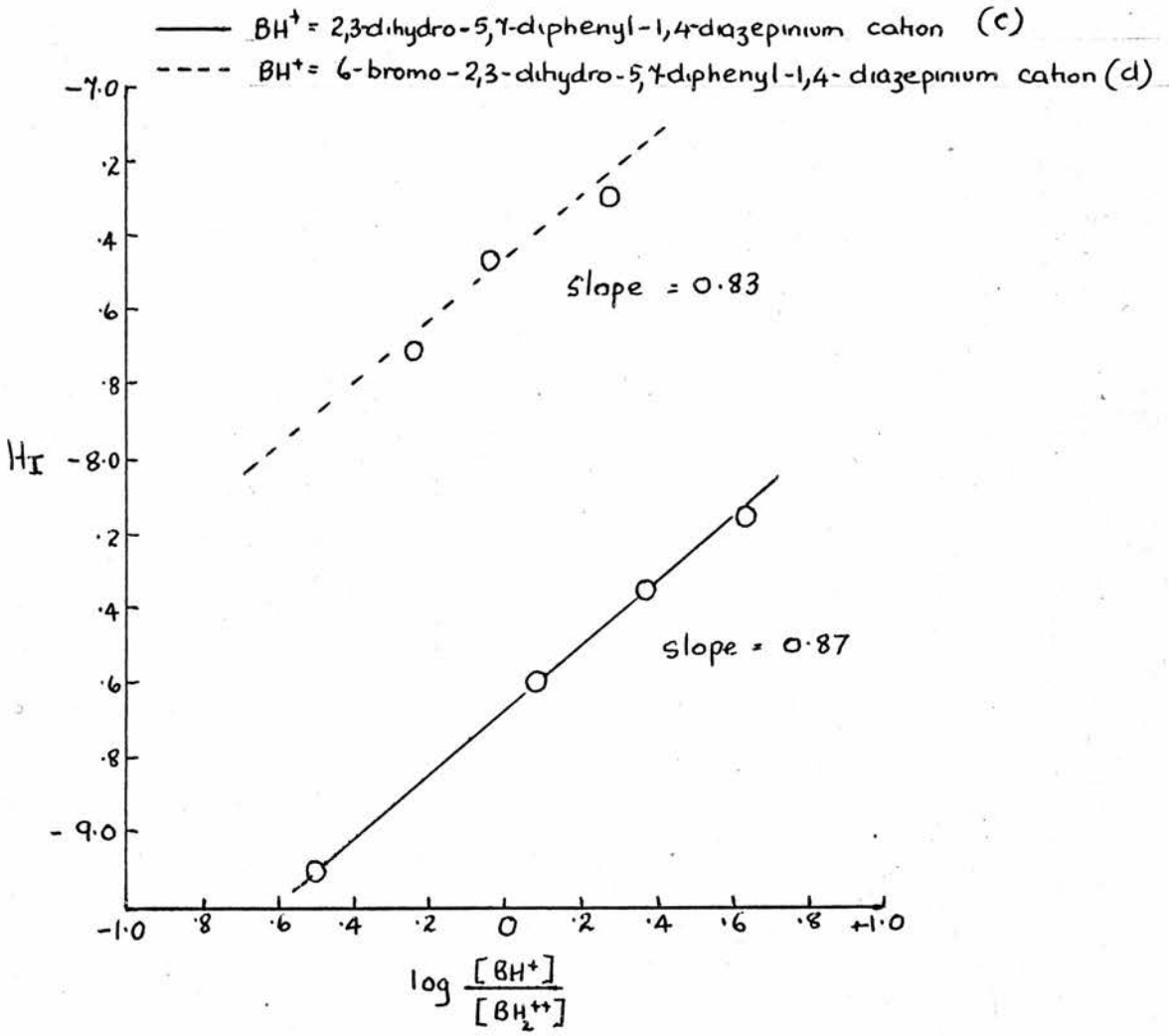

BH+ = 2,3-dihydro-5,7-dimethyl-1,4-diazepinium cation (a)
BH+ = 6-bromo-2,3 dihydro-5,7 dimethyl-1,4-diazepinium cation(b)
slope = 1·06
slope = 1·00
H_I
·4
·6
·8
-6·0
·2
·4
·6
·8
-7·0
·2
·4
·6
·8
-8·0
-1·0
·8
·6
·4
·2
0
·2
·4
·6
·8
+1·0
log [BH+] / [BH2++]

FIG. VI


—— BH⁺ = 2,3-dihydro-5,7-diphenyl-1,4-diazepinium cation (c)
---- BH⁺ = 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium cation (d)
-7.0
·2
·4
·6
·8
H_I -8.0
·2
·4
·6
·8
-9.0
slope = 0.83
slope = 0.87
-1.0 ·8 ·6 ·4 ·2 0 ·2 ·4 ·6 ·8 +1.0
log [BH⁺] / [BH₂⁺⁺]

The notable feature in these results is the greater basicity of the 6-bromo-5,7-diphenyl monocation compared to its unbrominated analogue. The reverse is true in the 5,7 dimethyl series and would be expected on the grounds of the electron withdrawing nature of the bromine atom.

It is possible that this unexpectedly reversed order of basicity may be due to steric interaction between the phenyl groups and the bromine atom in the monocation. This would decrease the coplanarity of the diazepine system and the phenyl groups and thus reduce the stabilising effects of the phenyl group on the monocation. The "pKa_1" values obtained for both brominated compounds are similar, which might suggest that the phenyl groups are less effective than might be expected in stabilising the monocation.

The N.M.R. spectra of 6 brominated and unbrominated 2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium cations are consistent with such steric interaction, in that the signal given by the methyl protons is shifted downfield by 0·3 ppm. in the brominated compound whereas the signal given by the phenyl group protons is shifted upfield by 0·1 ppm. This unexpected upfield shift is interpreted as being due to reduction of electron withdrawal from the phenyl groups by the positively charged diazepinium system, because of the lack of co-planarity caused by steric interaction.

CHAPTER 3

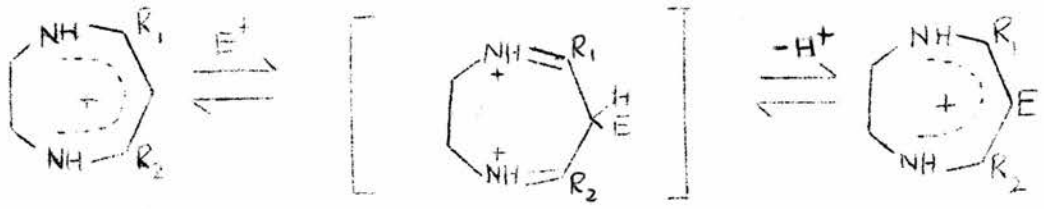
ELECTROPHILIC SUBSTITUTION IN 2,3-DIHYDRO-1,4-DIAZEPINES

(A) Deuteration.

It was reported[23] that when 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate was recrystallised from deuterium oxide, the hydrogen atoms attached to both nitrogen atoms and the 6-carbon atom were exchanged for deuterium. Kinetic studies[39] of the relative rates of exchange in deuterium oxide have shown that exchange is slower at the 6-carbon atom. The N.M.R. spectrum of this compound in deuterio-sulphuric acid indicates a very rapid exchange at this carbon atom.

Examination of solutions of 2,3-dihydro-5,7-dimethyl-1,4-diazepine and the 5,7-diphenyl analogue in deuterio-trifluoroacetic acid showed that the calculated amount of exchange had taken place too quickly for any comparison of the relative rates of NH and CH exchange.

Exchange of hydrogen for deuterium on carbon 6 essentially involves electrophilic attack by D^+, producing the 2,3-dihydro-1,4-diazepinium dications as intermediates.



(E+ = electrophile)

Since such stabilised intermediate structures cannot be drawn for substitution at the 5 and 7 positions those positions are less likely to be attacked by electrophiles. It is noteworthy that the 2-position of 2-imidazolinium salts is essentially similar to the 5- and 7-positions of the vinylogous dihydro diazepinium salts, and substitution by bromine at this 2-position was not observed. Molecular orbital calculations[50] also indicate a greater reactivity of the 6-position of dihydrodiazepines, as compared to the 5-and 7-positions, towards electrophilic reagents.

(B) Halogenation

Halogenation takes place at the 6-position when 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate is treated with bromine or iodine[23]. N-bromo succinimide will also effect bromination in this position[22].

It was possible that 5(7)-phenyl substituents would be attacked by bromine; though it was thought that the supposed unreactivity of the 5,7 positions would affect the attached phenyl groups. It was found that treatment of 2,3-dihydro-5,7-diphenyl 1,4-diazepine with bromine in chloroform solution produced the same brominated dihydro diazepinium bromide whether equimolar or 2-molar quantities of bromine were used. Substitution in the phenyl groups had not taken place.

The 6-bromo derivatives of all the diazepines described in Chapter 1 have been obtained with the exception of 2,3-cyclohexano-

2,3-dihydro-5,7-dimethyl-1,4-diazepine; bromination of the latter compound was not investigated.

The usual method of preparation was by treatment of a solution of the diazepinium perchlorate or the free diazepine base in methanol or ethanol with an equimolar quantity of bromine. The precipitation of the bromo diazepinium salt was aided by the addition of ether. To ensure uniformity of anion in cases when the diazepinium perchlorate had been used as the starting material, the bromo diazepine base was liberated and treated with a suitable acid.

Bromination of 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine.

Usually the 6-bromo-2,3-dihydro-1,4-diazepinium salt is obtained when the starting material has been in the form of the diazepine base or salt. A curious exception to this was found in the bromination of 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine. When the perchlorate of this diazepine in methanol was treated with bromine the expected 6-bromo derivative was obtained in good yield. Its perchlorate (XII) had a m.pt. of 145-146°. However, when a solution of the diazepine base in methanol was treated with bromine a compound (XIII) was obtained in 40-45% yield. Compound (XIII) did not show the properties of the expected 6-bromo-2,3-dihydro-1,4-diazepinium bromide corresponding to (XII), although elemental analysis indicated that (XIII) was isomeric with this bromide. The U.V. spectra of (XII) and (XIII) differed, though both were typical of 5-phenyl-2,3-dihydro-1,4-diazepinium salts.

(XII) λ max 266mμ (ε = 3,030) 368mμ (ε = 15,020)

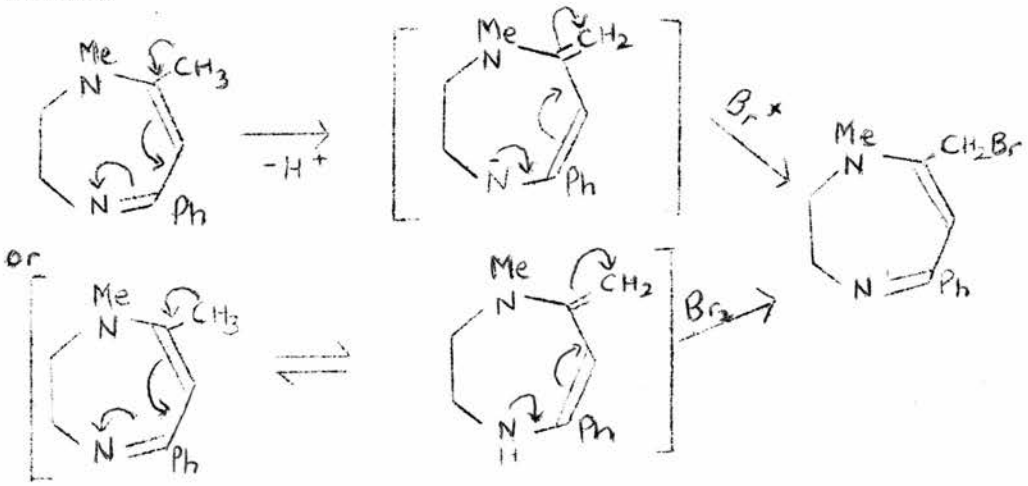
(XIII) λ max 268mμ (ε = 7,605) 364mμ (ε = 21,050)

The diazepine base corresponding to (XII) could be isolated without decomposition by treatment with conc. alkali and extraction with benzene. Attempts to isolate the base from (XIII) produced purple/brown decomposition products. Compound (XIII) could be converted into its perchlorate by treatment of its bromide with perchloric acid in methanol. This perchlorate melted at 157-159° and a mixed melting point with (XII) showed a depression. The quantitative U.V. spectrum of this perchlorate was the same as that of compound (XIII).

The N.M.R. spectrum of (XIII) in trifluoroacetic acid indicated that bromination had taken place in the 7-methyl group. A signal for a methine proton was observed at τ4·32 and there was no signal due to methyl protons above τ6·5. The usual signal for the 5-or(7)-methyl group of a bromo diazepinium salt is at τ 7·2. The signals in the region τ 5·7 and τ 6·03 were difficult to assign with certainty, but the total integrated to six protons, presumably all methylene, two of which could be assigned to the 7-CH_2Br group. Reexamination of the N.M.R. spectrum after 24 hrs. showed that (XIII) was stable in trifluoroacetic acid solution. The N.M.R. spectrum of (XII) in trifluoroacetic acid showed the presence of methyl protons at τ7·21 and the absence of any signal between τ4 and τ5 corresponding to a methine proton. Compound (XII) was

unstable in trifluoroacetic acid and a little decomposition had already taken place before the spectrum could be examined, and within an hour the spectrum had changed completely. However, the N.M.R. spectrum of the base from (XII) in deuteriochloroform showed that (XII) was undoubtedly 6-bromo-2,3 dihydro-1,7-dimethyl-1,4-diazepinium perchlorate. (Signals at τ 2·2-2·8(complex), 5·95(m), 6·4(m), 7·2(s) and 7·68(s) in ratio of 5:2:2:3:3).

The preferred methyl bromination would seem to depend on the particular structure of this diazepine and upon the basicity of the medium in which the bromination is carried out. The basic strength of the 2,3-dihydro-1,4-diazepines is such that in methanolic solution there would be both diazepine base and monocation present. It seems likely that it is the base which is the reactive species in this bromination, as the base must have a fixed bond structure. This has an active methyl group, since it incorporates the structure $CH_3-\underset{|}{\overset{|}{C}}=\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}=X$. Bromination of the diazepine could take the following course.



Bromination of 2,3-dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate.

The bromination of this compound is said[11] to give the 6-bromo derivative. The present work shows that bromination also takes place in the phenyl groups and suggests that competition between the phenyl groups and the 6-position of the diazepinium ring is such that a 6-bromo-2,3-dihydro-1,4-diazepinium salt would normally be accompanied by substitution in a phenyl group.

The first indication that phenyl bromination had taken place was given by the U.V. spectrum of the product obtained when a solution of 2,3-dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate in methanol was treated with an equimolar quantity of bromine. The brominated diazepinium salts were precipitated by the addition of ether in two portions. The first crop showed a "diazepine" absorption at λ max 349m and the second crop an absorption at 347mμ. A large bathochromic shift is usually associated with the bromination of the diazepine ring yet neither of these products showed this; the latter product absorbed at the same wavelength as the starting material. A similar preparation was carried out using a 2·5 molar quantity of bromine, and crystals which separated from solution were examined. They showed a U.V. absorption at 376mμ, but the N.M.R. spectrum indicated that only partial bromination had taken place in the 6 position. The integration of the phenyl signal suggested that substitution had taken place in the benzene rings. The bromination was then carried

out using a 7-molar quantity of bromine and the product (XXX) was analysed. The figures obtained were consistent with partial bromination in the benzene rings.

Attempts to hydrolyse the latter product (XXX) with aqueous alkali to a bromine substituted dianilinoethane, produced only dark coloured resinous materials, whose composition was unknown. It had been shown that the unbrominated diazepinium salt could be partially hydrolysed with alkali to give a compound (XIV) whose analysis and N.M.R. spectrum in deuterio chloroform indicated the following structure.

$$HNPh \cdot CH_2 \cdot CH_2 \cdot NPh \cdot CMe{:}CH \cdot COCH_3$$
(XIV)

From the U.V. spectrum of the resulting solution compound (XIV) appeared to be further hydrolysed by aqueous acetic acid to dianilinoethane and acetylacetone.

Treatment of product (XXX) with mineral acid in aqueous methanol precipitated a mixture of compounds whose high melting point range and U.V. spectrum suggested dianilinoethane derivatives in the form of their salts. Treatment of this mixture with alkali liberated the free bases. Thin layer chromatography showed the presence of at least five compounds, one of which appeared to be present in a major amount. Recrystallisation from ethanol produced this compound (XV) in a pure state. Analysis of (XV) was consistent with a tetra brominated dianilino ethane. Attempts to prepare a bis-(2,6-dibromoanilino) ethane and bis (2,4-dibromoanilino) ethane from

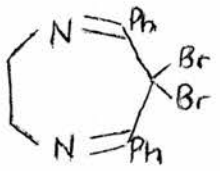
ethylene dibromide and the appropriate dibromoanilines were unsuccessful since no reaction appeared to take place.

Compound (XV) was, however, thought to be bis (2,4-dibromoanilino) ethane because the complex phenyl proton signal of its N.M.R. spectrum in trifluoroacetic acid was very similar to that of 2,4-dibromoaniline and unlike that of 2,6 dibromoaniline.

Bromination of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine.

Kinetic studies[23] of the halogenation of 2,3-dihydro-5,7-dimethyl-1,4-diazepine, have shown that 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine will react with more bromine to give the 6,6-dibromo derivative, the base being more reactive than the monocation in this bromination by a factor of 10^9. The 6,6-dibromo derivative had not been isolated, but its hydrolysis product 3,3-dibromoacetyl acetone had been obtained in an impure state.

In the present work the 6,6-dibromo derivative produced by the bromination of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine was isolated. Treatment of a solution of the monobrominated diazepinium base in benzene with slightly more than an equimolar quantity of bromine gave an immediate precipitate of 6-bromo-2,3-dihydro-5,7-diphenyl diazepinium bromide in approx. 50% yields. This was identified by its I.R. spectrum and a mixed m.pt. with authentic material. This salt was filtered off, and the resultant benzene solution evaporated in a rotary film vacuum evaporator, when a compound was obtained whose properties indicated that it was 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine(XVI).



(XVI)

Its I.R. spectrum (hexachlorobutadiene mull) did not show a characteristic diazepine NH stretching absorption at 3,200-3,300cm^{-1} and its N.M.R. spectrum in deuteriochloroform (signals at τ 2·3-2·6 (complex) and 5·72(S) in ratio 10:4) are in accord with the structure (XVI) shown.

Treatment of 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine, prepared by the action of N-chloro succinimide on the unchlorinated diazepine base, with bromine gave 6-bromo-6-chloro-2,3-dihydro-5,7-diphenyl 1,4-diazepine. The identity of this compound was deduced from the similarity of its N.M.R. spectrum and I.R. spectrum to those of (XVI).

(C) Nitration of 2,3-dihydro-1,4-diazepinium salts.

2,3-Dihydro-1,4-diazepinium salts are readily nitrated in the 6-position at room temperature or below by treatment with a suitable nitrating mixture. 2,3-Dihydro-5,7-dimethyl-1,4-diazepinium perchlorate was treated with a sulphuric acid/f.nitric acid mixture and high yields (77%) of the 2,3-dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate were obtained by pouring the mixture on to ice. Somewhat lower yields of the 6-nitro compound were obtained

when fuming nitric acid alone was used, but this may be due to the higher solubility of the diazepinium salts in this medium.

Sulphuric acid/nitric acid mixtures were found unsuitable for nitrating 5,7-phenyl substituted diazepines. Sticky materials which were very reluctant to crystallise were obtained and examination of their N.M.R. spectrum in trifluoroacetic acid suggested that nitration had also taken place in the phenyl groups. The normal singlet signal observed for phenyl protons of 5,7-phenyl substituted diazepines was replaced by a complex aromatic signal. The use of mixtures containing an equal volume of fuming nitric acid and concentrated nitric acid (83% HNO_3), at 0° was found to be a suitable nitrating agent for 2,3-dihydro-5,7-diphenyl-1,4-diazepinium salts and their 5-methyl-7-phenyl analogues. In practice the free bases were dissolved in the nitrating mixture and the 6-nitro compounds isolated as their nitrates. Treatment of 2,3-dihydro- 6-nitro- 5,7-diphenyl-1,4-diazepinium nitrate with perchloric acid in methanol gave the perchlorate salt, but this was not so with 2,3-dihydro-5-methyl- 6-nitro- 7-phenyl-1,4-diazepinium nitrate, perhaps due to higher solubility of this perchlorate.

The N.M.R. spectra in trifluoroacetic acid of these nitrated diazepinium salts were in accord with nitration at the 6 position, as no methine proton signals were observed. The signals assigned to the NH protons were found at lower field than the signals of the NH protons of their unsubstituted analogues. This is presumably due to the introduction of an electron withdrawing substituent.

Attempts to nitrate 2,3-dihydro-5,7-dimethyl-1,4 diphenyl-1,4-diazepinium perchlorate using 83% nitric acid failed. Dark coloured intractable materials were obtained. In view of the results obtained in the bromination of this compound it is reasonable to assume that nitration in the phenyl groups would readily take place also.

Hydrolysis of 2,3-dihydro-5,7-dimethyl-6-nitro-1,4-diazepine.

In preliminary nitration experiments attempts were made to isolate the free nitro-diazepine base by treating the diluted nitration reaction mixture with alkali (pH >11) and extracting the product with ether. Only a small amount of unnitrated diazepine base was obtained, but when the pH of the aqueous layer was adjusted to pH 8-9 by the addition of a little acid and further extracted with ether some yellow material passed into the ether layer. Extraction was continued using toluene as this appeared to be more efficient. Removal of the solvent from the extracts gave a small amount of a yellow crystalline compound (XXXI). The N.M.R. spectrum in deuteriochloroform of (XXXI) gave two singlet methyl proton signals at τ 7·61 and 7·68 and a singlet methylene proton signal at τ 6·25, in a ratio of 6:2. No other signals were observed. When a solution of (XXXI) in methanol was treated with a little perchloric acid the solution changed from yellow to colourless and the addition of a little ether gave a precipitate of ethylenediamine perchlorate. Compound (XXXI) was considered to be 1,2-bis(2-acetyl-1-methylvinylamino-2-nitro) ethane. The nitrogen analysis (found 17·05; required 17·84%) was not conclusive, but suggested this was a reasonable structure.

The formation of this compound was considered to be due to hydrolysis of the nitro diazepine at very high pHs into 3-nitro-acetylacetone and ethylenediamine and recombination of these compounds at pH 8-9 to give the oxoenamine. This latter pH range is known to be favourable to the formation of this type of compound (see Chap. 1 part (A)). Further confirmation was obtained by treatment of a solution of the nitrated diazepinium perchlorate with aqueous alkali. At first the solution becomes colourless, its U.V. spectrum showing an absorption at 312mμ which is probably due to the nitro diazepinium base. Gradually the solution becomes yellow and its U.V. spectrum shows an absorption at 326mμ. Changes in the U.V. spectrum of (XXXI) were also observed in aqueous alkali. The initial absorptions at 305 and 307mμ were replaced by one at 326mμ. This final absorption is probably due to 3-nitro-acetylacetone.

2,3-Dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate was shown to be stable in strongly acid solution.

The U.V. spectrum of a solution of this compound in 20% sulphuric acid was unchanged after a week.

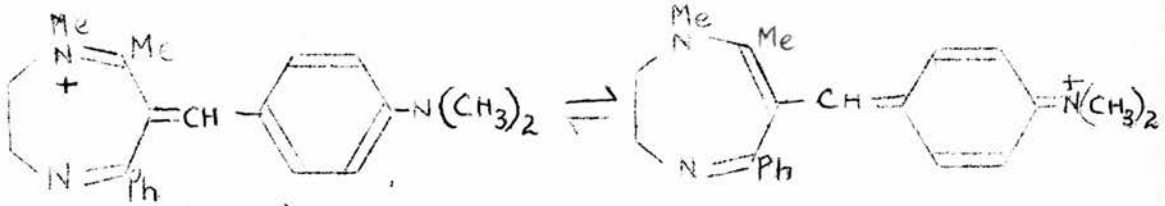
(D) Reaction of 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepinium perchlorate with p-dimethylaminobenzaldehyde.

The unusual behaviour of this diazepine in bromination reactions, i.e. the bromination of the 7-methyl group under basic conditions, led to further experiments which might have detected nucleophilic reactivity of this methyl group. On heating the diazepinium perchlorate with p-dimethylaminobenzaldehyde in acetic anhydride

an intense red/violet coloration was observed. Treatment of the reaction mixture with ether gave a mixture of the diazepinium perchlorate and a purple compound (XXXII). The diazepinium perchlorate was removed by crystallisation from methanol in which compound (XXXII) was less soluble.

The N.M.R. spectrum of (XXXII) in trifluoroacetic acid solution (signals at τ 1·8-2·9 (complex), 5·2(m), 5·5(m), 6·02(s), 6·44(s) and 8·00(s) in the ratio of 10:2:2:3:6:3) indicated that condensation with the aldehyde had in fact taken place at the 6 position of the diazepinium salt producing 2,3-dihydro-1,7-dimethyl-6- p- dimethylamino benzylidene -5-phenyl-1,4-diazepinium perchlorate.

The trifluoroacetic acid solution of compound (XXXII) was pale yellow and the addition of methanol readily precipitated purple crystals of (XXXII). Solutions of (XXXII) in non acidic solvents were purple; methanolic solution showed an absorption at λ max 520mμ. The colour of these solutions is probably due to the contribution of the cation structures shown below.



(XXXII)

The loss of colour in acidic solvents will then be associated with a second protonation, probably at the dimethylamino group, and localisation of the positive charges.

A similar condensation reaction was attempted with p-dimethylaminobenzaldehyde and 2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium perchlorate. Thin layer chromatography showed that several coloured materials had formed and the reaction was not further investigated.

CHAPTER 4

REACTIONS OF SUBSTITUTED -2,3-DIHYDRO-1,4-DIAZEPINES

(A) (1) Reactions of 6-bromo-2,3-dihydro-1,4-diazepinium salts with acids.

Examination of the N.M.R. spectra in trifluoracetic acid of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide and 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium bromide showed that bromine had been replaced by hydrogen in observable amounts within a few minutes. The presence of the 6H-compounds was indicated by the appearance of signals characteristic of the phenyl, methyl and methine protons of these compounds.

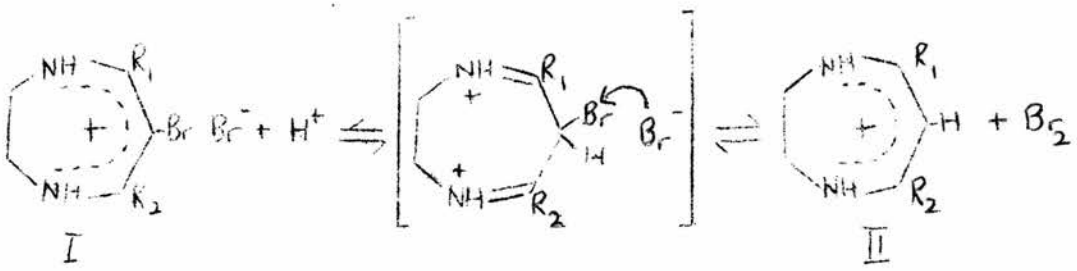
Solutions of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine and its perchlorate were stable in trifluoroacetic acid for at least one week, but the addition of potassium chloride or sodium bromide to these solutions brought about debromination. The presence of halide ion would therefore seem necessary for this reaction to take place.

6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide did not undergo debromination in trifluoroacetic acid solution. After three days a methyl proton signal appeared in the same position as that of the 6H-compound (τ7·65) but it was not accompanied by the presence of a methine proton at τ4·9. Similar changes were observed in the N.M.R. spectra in trifluoracetic acid of the base and the perchlorate of this compound, and since these changes were retarded by the presence of a little trifluoroacetic anhydride and accelerated

by the presence of a little water, they are probably associated with the hydrolytic cleavage of the bromo diazepine which is known to take place in the presence of acid[22].

U.V. spectra show that debromination of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide and its 5,7-diphenyl analogue occurs in conc. sulphuric acid. Dilution of such solutions with water gave U.V. spectra characteristic of the bromo compounds, but dilution with dilute sodium thiosulphate solution gave U.V. spectra characteristic of the 6H-compounds, the ionic reaction of bromine with thiosulphate ion presumably having taken place more quickly than rebromination.

This acidic debromination reaction would appear to be general for 6-bromo-2,3-dihydro-1,4-diazepines in highly acidic media in the presence of bromide ion and seems to be a reversible electrophilic substitution as shown below.



I II

In conc. sulphuric acid the equilibrium is in favour of II whilst in dilute sulphuric acid it is in favour of I.

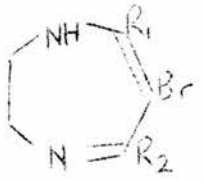
The presence of a larger brominating species in trifluoroacetic acid was proposed to explain the increased amount of para and decreased amount of ortho substitution in the bromination[42] and

chlorination[43] of toluene in this medium, as compared to the halogenations carried out in acetic acid. A possible explanation for the debromination of phenyl substituted diazepines in trifluoroacetic acid may be the presence of this larger brominating species in this medium, which may affect the position of equilibrium with the more sterically hindered phenyl substituted diazepinium salts. This larger brominating species may be as effective a brominating agent towards 2,3-dihydro-5,7-dimethyl-1,4-diazepinium salts as molecular bromine and the equilibrium in this case will favour the brominated compound.

(2) Reactions of 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with acid.

The treatment of a solution of the above compound in benzene with dilute aqueous hydrobromic acid gave an immediate precipitate of the mono halogenated diazepinium salt and a solution of bromine in the benzene layer. The second bromination of this diazepine would appear to be reversed readily by dilute aqueous acid.

(B) Reactions of 6-bromo-2,3-dihydro-1,4-diazepines with bases.



(I) $R_1=R_2=Ph$.

(II) $R_1=R_2=Me$.

(III) $R_1=Me$, $R_2=Ph$.

The diazepines (I), (II) and (III) reacted with molar methoxide solution at reflux temperature to give 6-methoxy compounds. Diazepines (II) and (III) reacted with piperidine and pyrrolidine to yield the expected substitution product.

"Abnormal" substitution, that is the replacement of bromine by hydrogen occurred on treating a 0·1M solution of diazepine (I) with molar ethoxide solution at reflux temperature. The yields of the 6H-compound were from 35-45% and the 6-ethoxy compound was not found in these cases. When a similar reaction was carried out with the diazepine concentration reduced to 0·01M, mixtures corresponding to an approximately 35% yield each of normal and "abnormal" substitution products were obtained. Further treatment of this mixture at 0·1M concentration in molar ethoxide solution produced a similar mixture, which suggests that the 6-ethoxy compound is not an intermediate in the abnormal substitution reaction.

Diazepines (II)[22] and (III) gave the 6-ethoxy compounds and no abnormal substitution products were detected in the case of (III). Compound (II), however, gave only the 6H-compound when treated with isopropoxide and t. butoxide solutions. There is thus some suggestion of steric influence in the "abnormal" reaction path.

Attempts to prepare the 6-N-piperidinyl derivative of diazepine (I) gave a mixture corresponding to 80% normal and 20% abnormal substitution products. Attempts to separate these products by recrystallisation were unsuccessful.

High yields (90%) of the 6H-product were obtained when (I) was treated with benzylamine at 100°, and a correspondingly high yield of benzaldehyde was obtained on acidification of an ether extract of the reaction mixture. The benzaldehyde was isolated as its 2,4-

dinitrophenylhydrazone. Attempts to carry out the same reaction on (II) and (III) resulted in no isolable products from (II) and a low yield of the ring contracted product 2-phenyl imidazolinium bromide from (III). In both cases the yield of the 2,4-dinitro phenyhydrazone of benzaldehyde was low (10-15%) and its purity suspect. Again it was shown that the normal substitution product, i.e. the 6-benzylamino-2,3-dihydro-1,4-diazepine, was not the precursor of the 6H-compound, since treatment of this benzylamino derivative as its perchlorate with an excess of benzylamine at 100° resulted in its recovery unchanged after dilution of the reaction mixture with ether.

The "abnormal" substitution product was obtained in yields of 20-40% when (I) was heated in refluxing toluene, benzene and ethanol. In the case of benzene, it was necessary to heat the reaction mixture for three hours before there were indications that some reaction had occurred from the formation of a precipitate of diazepinium salts. After twenty four hours of heating in ethanol starting material was recovered in 48% yield. This would suggest that added base accelerates this reaction.

Substitution reactions were attempted on the N-methyl diazepines analogous to (I), (II) and (III), designated hereafter (Ia), (IIa) and (IIIa). Low yields of the 6-N-piperidinyl derivative of (IIa) were obtained and after a prolonged reaction time of (IIa) with methoxide solution an N.M.R. spectrum revealed the presence of starting material, 6-methoxy- and 6H-diazepine. Compound (IIIa) did not appear to react

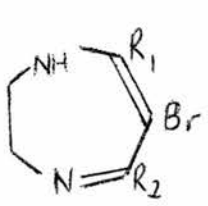
with molar methoxide solution or piperidine when the same conditions required to produce the methoxy and 6-N-piperidinyl derivatives of (III) were used, since starting material was recovered in good yield (60% - 80%). When (Ia) was treated with molar ethoxide and molar methoxide solutions for prolonged reaction periods starting materials were recovered in good yield. However, a low yield of the 6H-compound was obtained when (Ia) was treated with piperidine at reflux temperature for twenty four hours. A shorter reaction time (4hrs. at 60°) gave only starting material recovered in approx. 60% yield.

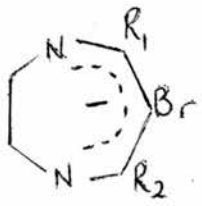
The reactivity of the N-methyl diazepines appears to be much less towards both normal and abnormal substitution reactions.

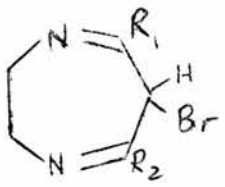
Kinetic measurements were made on the normal substitution reaction of (I) and (III) with methoxide ion, which showed the rate determining step to be bimolecular between diazepine and methoxide ion.

Comparison of the rate constant of the reaction of (I) with methoxide at 25°, with the lack of reactivity of (Ia) with methoxide at elevated temperatures suggests a difference of reactivity of greater than 140.

The ready nucleophilic substitution of the 6-bromo atom of these dihydro diazepines is in itself unexpected, since in its normal tautomeric form (A) this position should be deactivated towards nucleophilic attack. It is, however, possible that under the influence of base, prototropic rearrangement *via* the delocalised diazepinide anion (B) to tautomer (C) might occur.





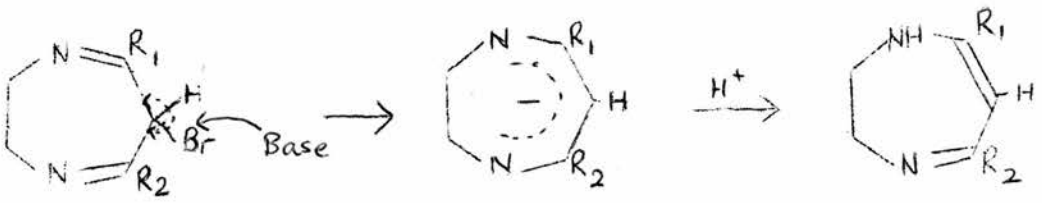


(A) (B) (C)

Although the equilibrium concentration of tautomer (C) is likely to be very small, the 6-position would be strongly electrophilic owing to the bromine atom and the two adjacent azomethene groups, and may account for the facile nucleophilic substitution at this position.

The mechanism of the "abnormal" substitution of the bromine atom (i.e. by hydrogen) is obscure, but could also involve tautomer (C) or the anion (B). Possible mechanisms are now briefly mentioned, though none of them is entirely satisfactory.

Perhaps the closest analogies are the ready replacement of bromine by hydrogen in N-bromosuccinimide and some β-dicarbonyl compounds, reactions which are themselves not completely understood. Nucleophilic attack at the bromine atom by base, which can be added reagent or another diazepine molecule (as it must be when the bromo diazepine is heated alone in neutral solvent) may lead to an anion which in turn extracts a proton either from solvent or from another diazepine molecule.



In support of this mechanism are the notably higher yields of the 6H product when the added base is benzylamine which is likely to be an effective agent in this type of reaction.

The involvement of a species such as (B) or (C) is strongly suggested by the fact that under identical conditions N-methyldihydrodiazepines do not undergo this reaction. Only under more vigorous conditions and with longer reaction times have small amounts of the debrominated product been observed in two instances, so that it is not unreasonable to assume that a more complex reaction scheme is then involved.

An alternative mechanism may involve the loss of bromide ion from anion (B) to produce a delocalised electron deficient species, a process which may be similar to the production of dichloro carbene from the (CCl_3) anion or the production of a nitrene in the Hofmann and related rearrangements. However, the formation of the 6H product involves the addition of the equivalent of a hydride ion and a proton, and a suitable source for the latter is difficult to envisage.

In general hydride ion abstraction at any stage seems unlikely, for although isopropoxide in isopropanol and α-phenylethoxide in

α-phenyl ethanol brought about "abnormal" substitution, neither acetone or acetophenone could be detected in the reaction mixture.

Homolysis of the C-Br bond to give a diazepine radical also seems unlikely, since added base accelerates the reaction, and also from the observation that if the debromination was carried out by heating the base in toluene, no trace of dibenzyl could be detected by gas-liquid chromatography of the products.

(C) Reduction of 2,3-dihydro-6-nitro-1,4-diazepinium salts.

The reductions of 2,3-dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate and of 2,3-dihydro-6-nitro-5,7-diphenyl-1,4-diazepinium perchlorate were conveniently effected by the use of cyclohexene and a palladium/charcoal catalyst in methanol or ethanol at reflux temperature.

The U.V. spectra of the amino compounds showed "diazepine" absorptions at higher wavelength than the corresponding nitro compounds e.g. λ max 323mμ for 2,3-dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate compared with λ max 352mμ for its 6-amino analogue, and λ max 338mμ(ε = 14,900) for 2,3-dihydro-6-nitro-5,7-diphenyl-1,4-diazepinium perchlorate compared with λ max 406 (ε = 8,100) for its 6-amino analogue. This provided a suitable means of following the progress of the reduction by sampling at intervals and after appropriate dilution of the sample, examination of the U.V. spectrum.

The reduction of the methyl substituted diazepinium salt in methanol was complete within twenty four hours. Its diphenyl

analogue required a longer reaction time and the addition of more catalyst after twenty four hours. Ethanol was finally used as solvent in this reduction.

6-Amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate was soluble in water. The analogous diphenyl compound was less soluble, but the addition of acid readily brought the compound into solution. This increased solubility in acid is presumably due to protonation of the amino group, as indicated by changes in the U.V. spectra on acidification. The "diazepine" absorption of the dimethyl amino diazepinium salt is at λ max 352mμ in methanol solution, but changes to λ max 328mμ upon acidification. Similarly the diphenyl amino diazepinium salt shows an absorption at λ max 406mμ, but on the addition of acid changes to λ max 348mμ. It may be noted that replacement of the 6-hydrogen atom by the amino group shifts the "diazepine" absorption to longer wavelength, presumably because of interaction of the amino nitrogen lone pair. As might be expected, protonation of this nitrogen atom shifts the "diazepine" absorption to a shorter wavelength.

Attempts to obtain the free bases of these amino diazepinium salts failed. Examination of the N.M.R. spectrum in trifluoroacetic acid of an impure material obtained by treatment of the diphenyl amino diazepinium salt with alkali and extraction of the resultant solution with benzene, suggested that some decomposition had taken place under the alkaline conditions. The amino diazepinium salts

themselves are stable in trifluoroacetic acid solution.

(D) Reactions of 6-amino-2,3-dihydro-1,4-diazepinium salts.

(1) With aromatic aldehydes.

When benzaldehyde was added to 6-amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate the mixture became very warm as rapid condensation took place with the formation of the benzylidene-imino diazepinium salt. Similar condensations were effected between this amino diazepinium salt and thienyl-2-aldehyde and between two molecules of diazepinium salt and one molecule of terephthaldehyde.

6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate was also condensed with benzaldehyde, but the product was not obtained in a crystalline form. However, it was readily reduced by sodium borohydride in methanol, to give the benzylamino diazepinium perchlorate. Sodium borohydride was also used to reduce the benzylidine-imino group of the 5,7-dimethyl analogue.

(2) Diazotisation.

The addition of sodium nitrite solution to a solution of 6-amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate in perchloric acid at -5° produced a yellow solid, which decomposed with violence at $230-231^{\circ}$. At room temperature this compound was stable for several days, although after longer periods gradual discoloration was observed.

As its I.R. spectrum showed an absorption at 2,200cm^{-1} characteristic of diazonium salts, this compound was assumed to be

2,3-dihydro-5,7-diphenyl-1,4-diazepinium-6-diazonium diperchlorate.

Attempts were made to change the anions of this diazonium diazepinium salt to borofluoride by carrying out the diazotisation in hydrogen borofluoride solution. The product obtained melted at 180°, but its I.R. spectrum was very similar to the corresponding diperchlorate, showing a characteristic perchlorate absorption. As it ignited on a spatula to give a green flame, it is likely that this salt contained both perchlorate and borofluoride ions. Attempts were made to decompose this compound by heating it in order to obtain the fluoro diazepine, but when decomposition commenced it proceeded very rapidly leaving a black tarry residue from which no products could be isolated. As the free amino diazepine cannot be isolated (see p. 65), it was not possible to remove perchlorate ion prior to diazotisation in hydrogen borofluoride solution and possibly the presence of the perchlorate ion caused the rapid and unfruitful decomposition of the diazonium salt.

Diazotisation of a solution of the amino diazepinium perchlorate in hydrochloric acid gave a good yield of the diazonium salt with mixed chloride and perchlorate anions. The presence of perchlorate was shown by its I.R. spectrum and the presence of chloride was required since the amount of perchlorate ion present in the original mixture was insufficient to account for the total anion concentration present in the yield of the diazepinium-diazonium di salt obtained. This diazonium salt was converted into the chloro diazepine by a

Sandmeyer reaction. The yield was low, but attempts to increase it by changing the conditions of reaction were not investigated.

No solid diazonium salt was produced by diazotisation of 6-amino-2,3-dihydro-5,7-dimethyl-1,4-diazepine in perchloric acid or in hydrogen borofluoride solution. Treatment of the diazotised mixture with aqueous alkali gave an ether soluble precipitate. Addition of perchloric acid to the ethereal extract gave a white precipitate, which showed an absorption at 2200 cm^{-1} in its I.R. spectrum. It is possible that the diazonium salt may be converted into the 6-N-nitrosamino derivative which may be ether soluble. Treatment of the ethereal solution with acid would convert this into the diazonium perchlorate.

Analysis of these diazonium salts were not attempted because of their rapid decomposition at high temperature.

PART II - EXPERIMENTAL

U.V. spectra were recorded using a Unicam S.P. 800 spectrophotometer. N.M.R. data were obtained using a Perkin-Elmer R.10 N.M.R. spectrophotometer operating at 60 Mc/s. I.R. spectra were recorded using a Perkin-Elmer 137 sodium chloride spectrophotometer.

RELATED TO CHAPTER I

(A) Preliminary examination of condensation reactions between trans-1,2-diaminocyclohexane and acetylacetone.

(1) A solution of trans-1,2-diaminocyclohexane dihydrochloride (1·0g) and acetylacetone (0·5g) in water (10 mls), was buffered to a pH of 4-5 (indicator paper) by the addition of sodium acetate solution and hydrochloric acid. After warming at 80-90° for 10 mins. the mixture was kept overnight. A concentrated solution of sodium hydroxide was added until precipitation appeared complete. The precipitate (0·57g) was removed by filtration and had a m.pt. 210-220° (d); after recrystallisation from benzene 218-222° (d).

Elemental analysis showed this compound to be 2,3-cyclohexano-2,3-dihydro-5,7-dimethyl-1,4-diazepine (III)

(Found; C,73·4; H,10·1; N,16·0 $C_{11}H_{18}N_2$ requires C,74·1; H,10·1; N,15·7%)

Treatment of (III) with 60% perchloric acid gave a perchlorate which when recrystallised from water had a m.pt. 188-189°.

(2) A solution of trans-1,2-diaminocyclohexane dihydrochloride (0·5g) and acetylacetone (0·75g) was buffered to a pH of 8-9 (indicator paper)

by the addition of potassium dihydrogen phosphate and concentrated sodium hydroxide solutions. A precipitate formed quickly and after the reaction mixture had stood for half an hour this was removed by filtration. It had a m.pt. 128°, recrystallised from water m.pt. 136·5°.

Elemental analysis showed this compound to be 1,2-bis-(2-acetyl-1-methylvinylamino) cyclohexane (IV)

(Found C,68·9; H,9·3; N,10·0 $C_{16}H_{22}N_2O_2$ requires C,69·0; H,9·0; N,10·1%).

Condensations between trans-1,2-diaminocyclohexane and acetyl acetone in a graded series of buffer solutions.

Each reaction mixture was prepared and treated as follows:- Potassium dihydrogen phosphate solution (10mls.; 1·5M) was added to trans-1,2-diaminocyclohexane dihydrochloride solution (4mls.; 1M). x mls. (shown in Table I) of 4N sodium hydroxide solution were then added and the volume made up to 50 mls. After noting the pH, (pH meter) the solution was transferred to a stoppered conical flask and placed in a water bath thermostated at 20° for 48 hrs.

At the end of the reaction time the pH was again noted. Any precipitate which had formed was removed by filtration, dried, weighed and its m.pt. noted. The precipitate was the oxoenamine (IV).

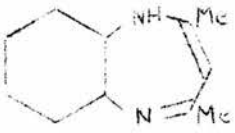
The filtrate was treated with 100 mls. of 5N potassium hydroxide solution and the precipitated diazepine filtered off. After drying the diazepine (III), it was weighed and its m.pt. noted.

The results so obtained are shown in Table I. The graphical representation Chap 1, Fig. I makes use of yields only where a

reasonable purity of the product is indicated from melting point determinations.

TABLE I

Mls. 4N.NaOH	pH			Yield of diazepine III			Yield of oxoenamine IV		
	Initial	Final	Average	mg.	%	m.pt.°	Mg.	%	m.pt.°
0·25	3·9	3·1	3·5	409	57·4	218–23	0	0	–
0·5	4·8	3·6	4·2	436	65·0	218–23	0	0	–
0·75	5·0	4·2	4·6	494	69·4	218–23	0	0	–
1·0	5·8	5·4	5·6	398	55·9	218–23	0	0	–
2·0	6·4	6·2	6·3	94	13·2	180–85	242	21·8	130–35
3·0	6·9	6·5	6·7	*37		160–65	588	52·9	136–137
3·5	7·2	6·8	7·0	*37		135–38	630	56·7	137–8
4·0	7·6	7·2	7·4	*20		130–35	663	59·6	137–8
4·5	8·1	7·5	7·8	* –			685	61·6	134–7
5·0	8·5	7·9	8·2	*20			703	63·2	134–7
5·5	9·0	8·4	8·7	*19			720	64·7	134–7
6·0	9·3	9·7	9·5	* –			665	59·8	134–7
6·5	9·7	10·3	10·0	* –			526	47·3	134–7
7·0	10·1	10·7	10·4	137	19·2	195–200	258	23·2	136–37
7·5	10·5	10·9	10·7	287	40·3	185–90	47	4·3	136–38
8·5	11·0	11·2	11·1	265	37·2	190–206	0	0	–
10	11·6	12·0	11·8	162	22·7	210–14	0	0	–



(III)

(IV)

*In these instances the product showed obvious signs of impurity either by m.pt. or its sticky nature.

(B) An attempted condensation between trans-1,2-diamino-cyclohexane and malondialdehyde.

trans-1,2-Diaminocyclohexane dihydrochloride (1·9g) and 1-ethoxy-1,3,3-trimethoxy propane (1·9g) were dissolved in acetic acid (5mls.) and heated at reflux temperature for ten minutes. Perchloric acid (3mls.; 60%) was added and the mixture left overnight. Excess solvent was removed under vacuum leaving a gum which did not crystallise. The gum was shaken with ether several times and then treated with concentrated sodium hydroxide solution. The mixture was further shaken with ether in order to extract the diazepine if present. Much of the gum remained after extraction. The ether extract was dried and the ether removed. A small amount of pale yellow non-crystalline material remained. A qualitative U.V. spectrum showed an absorption maximum at λ 285mμ. This was not the absorption expected for the diazepine (λmax 330mμ).

Preparation of trans-1,2-diaminocyclohexane dihydrochloride.

The method used was basically that of Jaeger et al[31], by nitrosation of ethyl 2-oxocyclohexanecarboxylate. Other workers[32,33] had reported difficulty in isolating isonitrosocyclohexanone when using this method. In the preparation below this step is eliminated by direct treatment of the reaction mixture with hydroxylamine hydrochloride. The amine was isolated by extraction with chloroform instead of by steam distillation. Similar variations in the preparation of trans-1,2-diaminocyclopentane have been applied to the method of Cope et al[30] by other workers[9].

Cyclohexane-1,2-dione-dioxime.

Ethyl 2-oxocyclohexanecarboxylate (17g.) was added to a stirred solution of sodium hydroxide (4·4g.) in water (100mls.). A solution of sodium nitrite (6·9g.) dissolved in water (20mls.) was then added. The mixture was stirred for 48 hrs. under a flow of nitrogen. Conc. hydrochloric acid (20mls.) was added and the mixture stirred until all the carbon dioxide had been evolved. After neutralisation with sodium hydroxide solution the reaction mixture, which contained the monoxime, was treated with hydroxylamine hydrochloride (6·9g.) in water (20mls.) containing sodium hydroxide(4g.) The mixture was stirred for 1½hrs., and then the precipitated dioxime was filtered off Yield 9·46g (67%). Recrystallised from water m.pt. 187-190°. (Lit 190-195°).

trans-1,2-Diaminocyclohexane.

Cyclohexane-1,2-dione-dioxime (5g.) was dissolved in ethanol (250 mls.). Sodium (50g.) was added gradually over ½ hr. The mixture was heated at reflux temperature until all the sodium had reacted. Water (100 mls.) was added and the mixture steam distilled until all the ethanol was removed. The distillate was made acidic and again distilled. The aqueous residue was added to the major portion of reaction mixture which was then extracted with chloroform (8x15mls.). The extract was dried over anhydrous potassium carbonate and dry hydrogen chloride passed into it in order to precipitate the trans-1,2-diaminocyclohexane dihydrochloride. Yield 4·5g.(68%) m.pt. 310-312°.

(C) (1) Reaction of ethylenediamine and benzoylacetone in acetic acid using a 1:0·625 molar ratio of ethylenediamine to acetic acid.

Acetic acid (6·25g.) was added to a mixture of benzoylacetone (10g.) and ethylenediamine (10g.) at 120°; after the mixture had been heated for a further hour at 120° it was poured into water (300mls). The solid which separated was filtered off and washed with a little ether. Yield 1·2g.; recrystallised from methanol m.pt. 108-110°. This substance was shown to be 1,2-bis-(1-phenylethylideneamino) ethane by its N.M.R. spectrum in deuteriochloroform (signals at τ 2·45, 6·1 and 7·7 in ratio of 5:2:3). A mixed m.pt. with an authentic sample showed no depression.

The aqueous filtrate was extracted with ether (4x50mls.) After drying this extract the ether was removed leaving a liquid (4·1g.) which was characterised as acetophenone by preparation of its semicarbazide m.pt. 198°.

The remaining aqueous layer was treated with sodium hydroxide (100g.) and crystals separated overnight. These were filtered off and washed with a little water followed by ether. Yield 1·36g.; recrystallised from benzene, m.pt. 146-147°. The compound was shown to be 2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine (V) by its N.M.R. spectrum (Table VIII) and by elemental analysis.

(Found: C,76·92; H,7·65; N,14·78 $C_{12}H_{14}N_2$ requires C,77·38; H7·58; N,15·04%).

This base could be converted into its perchlorate m.pt. 123·5-124° by treatment with perchloric acid.

(2) 1,2-Bis-(2-benzoyl-1-methylvinylamino) ethane (VI)

Benzoylacetone (1·62g.) was heated with ethylenediamine (0·3g) for five minutes. The solid produced was treated with ether (50mls) and filtered off. Yield 1·32g. (76%); recrystallised from ethanol m.pt. 179-180° (lit 182-183°).

(3) Condensations between ethylenediamine and benzoylacetone under conditions of different acidity.

Each reaction mixture was prepared and treated as follows:-

To an aqueous 80% ethanol solution (20mls.) containing benzoylacetone (1g.), acetic acid (Xg.) was added, followed by ethylenediamine (3g.) The solution was kept cool during the addition of ethylenediamine. The reaction mixture was placed in a stoppered flask and kept in a thermostated water bath at 25° for ten days. The precipitated 1,2-bis-(2-benzoyl-1-methylvinylamino) ethane was filtered from the solution, dried, weighed, and its m.pt. noted. The results obtained are shown in Table II.

TABLE II

X (g. of acetic acid)		0·5	1·0	1·5	2·0	2·5	3·0	3·5	4·5	7·0	9·0
YIELD of (VI)	mg.	35	135	375	620	800	860	920	800	740	50
	%	3·5	12·5	34	58	74·5	80	86	74·5	69	47
	m.pt. °C	←			177-180						→

Ph·CO·CH:CMe·NH·CH_2·CH_2·NH·CMe:CH·CO·Ph.

(VI)

(4) 2,3-Dihydro-5-methyl-7-phenyl-1,4-diazepinium perchlorate (V)

Benzoylacetone (8·1g.) was added to a solution of ethylenediamine (3g.) in acetic acid (50g.) at 120°. After the mixture had been heated for 1 hr. at 120° it was poured into water (500 mls.) and extracted with ether (3x50 mls.) to remove any unreacted benzoylacetone. Perchloric acid (60% 25 mls.) was added to the aqueous layer and the mixture concentrated on a rotary film vacuum evaporator until crystals appeared. After cooling, the crystals were removed by filtration. Yield 7·7g. (54%); recrystallised from ethanol m.pt. 123-124·5°. (Found: C,50·13; H,5·55; N,9·87 $C_{12}H_{15}N_2ClO_4$ requires C,50·27; H,5·27; N,9·77%) U.V. Spectrum in methanol λ max 257mμ (ε=9,600), 341·5mμ (ε=18,500). N.M.R. spectrum in Table VIII.

Conversion of compound (VI) into the dihydro diazepine (V).

1,2-Bis-(2-benzoyl-1-methylvinylamino) ethane (VI) (1·74g.) was heated in acetic acid (2·5g.) and water (0·15 mls.) for 1 hour at 120°. The reaction mixture was worked up as above. Yield of 2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium perchlorate 0·86g. (60%).

(D) Preparation of 2,3-dihydro-5,7-diphenyl-1,4-diazepine.

(1) Preliminary attempt.

Dibenzoylmethane (11·2g.) was added to a mixture of acetic acid (33·3g.) and ethylenediamine (3·0g.) The mixture was heated under reflux for 1½ hours and after cooling, poured into water (330 mls.) and then extracted with ether (3x50mls) to remove unreacted dibenzoylmethane. The two layers were treated as follows:-

Ether layer

Sodium bicarbonate solution followed by solid sodium bicarbonate was added until no more carbon dioxide was evolved. The crystals which separated from the ether were removed by filtration Yield 1·6g.; recrystallised from ethanol/ether m.pt. 125-126°. This compound was shown to be 1-acetylamino-2-(2^1-benzoyl-1^1-phenylvinylamino) ethane (VIII). Found: C,74·09; H,6·66; N,9·06 $C_{19}H_{20}N_2O_2$ requires C,74·00; H,6·54; N,9·08%.

The ether was separated from the aqueous layer and dried. Distillation of the ether left unreacted dibenzoyl methane 6·8g. (60·8%).

Aqueous layer

Perchloric acid (60%; 17 mls.) was added and the mixture kept overnight. The crystals which appeared were removed and dried. Yield 4·4g. (25·2%); recrystallised from ethanol m.pt. 154-156°. This compound was shown to be 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate from its N.M.R. spectrum (Table VIII) and by elemental analysis of the free base, m.pt. 160-162°, which was liberated by treatment of the salt with concentrated sodium hydroxide solution and extraction with benzene. Found: C,82·68; H,6·70; N,10·87. $C_{17}H_{16}N_2$ requires C,82·23; H,6·49; N,11·28%. U.V. spectrum in methanol λmax 265mμ (ε=15,700) 358mμ (ε=24,100).

(2) Attempt to increase yield of compound (VIII).

Ethylenediamine (0·45g.) was added to acetic acid (5g.), and

acetic acid (1ml.) was distilled from the mixture at atmospheric pressure. Dibenzoylmethane (1·67g.) was added to the remaining mixture. After being refluxed for 1½ hours the mixture was poured into water (40 mls.) and worked up in a similar manner to the above preparation.

Yields. 1-acetylamino-2- (2^1-benzoyl-1^1-phenylvinyl)amino ethane 1·5g. (65%).

Recovered dibenzoylmethane 0·35g.(21%).

2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate 0·04g. (1·1%).

(3) Preparations with different ethylenediamine/acetic acid ratios.

Each reaction was carried out in the following manner. Ethylenediamine (xg.) was added, with cooling to acetic acid (27 g), followed by dibenzoylmethane (11·2g.) The mixture was refluxed for 1½ hours and worked up for the diazepinium perchlorate as described on page 77. The results are shown in Table III.

TABLE III

Ethylenediamine(g.) x	Acetic acid/ethylenediamine	Yield of diazepinium salt.	
		g.	%
3·0	9	4·4	25·2
6·0	4·5	7·2	41·4
7·8	3·46	10·0	57·4
12·0	2·25	12·5	71·8

2,3-Dihydro-5,7-diphenyl-1,4-diazepinium perchlorate

Ethylenediamine (6·0g) was added to acetic acid (16·5g.) cooling the mixture meanwhile, followed by dibenzoylmethane (11·2g.) The mixture was heated at reflux temperature for 1½ hours and worked up for the diazepinium perchlorate as on page 77. Yield 11·14g. (64·0%).

(E)

(1) Preparation of p-nitrobenzoylacetophenone

Method(a)[28]

A suspension of sodium amide (0·3M) was prepared in liquid ammonia (300 mls.) The liquid ammonia was removed by the passage of dry nitrogen while dry ether (100 mls.) was added. The suspension of sodium amide in ether was heated at reflux temperature for ½ hour. Dry ether (200 mls.) was added, the whole being stirred meanwhile, followed by acetophenone (0·3M) dissolved in dry ether (75 mls). Dry nitrogen was passed through to remove the ammonia liberated. The suspension of sodioketone, protected by a drying tube, was cooled in an ice bath. p-Nitrobenzoyl chloride (0·1M) dissolved in dry ether (125mls.) was added quickly to the stirred mixture and after 15 mins. the ice bath was removed and stirring continued for a further 15 mins. The reaction mixture was poured on to a mixture of conc. hydrochloric acid (27 mls.) and crushed ice (100g). The ether layer was removed and washed with sodium carbonate solution until no more carbon dioxide was evolved. After being dried, the ether was distilled off and the unreacted acetophenone removed by

vacuum distillation. The residue was black and sticky, but on treatment with a little ether a dark brown solid was obtained. Thin layer chromatography revealed the presence of two major components, which were separated on a silica column by elution with benzene. The less polar compound was shown to be the desired diketone m.pt. 158-159° (Lit 160°). Yield 1·4g. (5%). The more polar material, m.pt. 225-235°, was not identified.

Method (b)[29].

Acetophenone (8g.) was dissolved in methanol (50 mls.) containing potassium hydroxide (2·5g.) p-Nitrobenzaldehyde (10g.) was added and after ½ hr. the p-nitrostyrylacetophenone separated. Yield 15·4g.; recrystallised from methanol m.pt. 162·5° (lit.162·5°).

The recrystallised material (13g.) was dissolved in chloroform (250 mls.) The solution was warmed on a water bath and bromine (8·4g) in chloroform (28mls) was added, the mixture being shaken thoroughly after each addition. The chloroform was removed under vacuum and the residue recrystallised from ethanol, m.pt. 149° (Lit. 151°). Yield 15·7g. (74%).

p-Nitrostyrylacetophenone dibromide (15·7g.) was heated at reflux temperature in ethanol containing potassium hydroxide (6g.). Precipitated potassium bromide was removed and conc. hydrochloric acid (12 mls.) was added to decompose the dissolved potassium salt. The addition of water precipitated the diketone. Yield 7·7g. (75·3%), recrystallised from ethanol m.pt. 158-160° (Lit. 160°).

The I.R. spectrum of this compound was identical to that obtained by method (a) and a mixed m.pt. showed no depression.

(2) 2,3-Dihydro-5-p-nitrophenyl-7-phenyl-1,4-diazepine.

p-Nitrobenzoylacetophenone (4·5g.) was added to a mixture of ethylenediamine (4g.) in acetic acid (20g.) The mixture was heated at reflux temperature for 1½ hrs., then cooled and added to water (100 mls.) containing perchloric acid (60%; 20 mls.). The yellow diazepinium perchlorate which had separated was removed and freed from unreacted diketone by treatment with boiling benzene. Yield 2·6g (39·5%); recrystallised from ethanol m.pt. 216-219°. Found C,52·60; H,4·29; N,10·65. $C_{17}H_{16}N_3O_6Cl$ requires C,51·83; H,4·13; N,10·67%).

Treatment of the salt with conc. sodium hydroxide solution liberated the base which could be extracted with hot benzene. Removal of the benzene gave a crystalline material, m.pt. 125-128°(d).

(F) Condensation reactions between N-methylethylenediamine and acetylacetone.

(1) 1-(2^1-Acetyl-1^1-methylvinylamino) 2-(methylamino) ethane perchlorate.(I).

N-Methylethylenediamine (11·1g.) was dissolved in methanol (10 mls.). Perchloric acid (60%; 15 mls.) was added slowly, the mixture being kept cool, followed by acetylacetone (15g.). On scratching the inside of the vessel a precipitate appeared. After 15 mins. this was removed by filtration. Yield 22·2g (57·7%), recrystallised from methanol m.pt. 130-131° (d). Found C,37·97;

H,6·57. $C_8H_{17}N_2O_5Cl$ requires C,37·44; H,6·67%).

(2) Conversion of (I) into 2,3-dihydro-1,5,7-trimethyl-1,4-diazepinium perchlorate.

1-(2[1]-Acetyl-1[1]-methylvinylamino)-2-(methylamino) ethane in perchlorate (22g.) was heated in acetic acid (40mls.) at reflux temperature for one hour. Acetic acid (approx. 38mls.) was removed from the mixture under vacuum, leaving a viscous golden residue which partially crystallised. The N.M.R. spectrum of this residue showed it to consist of 2,3-dihydro-1,5,7-trimethyl-1,4-diazepinium salts and acetic acid. All attempts to recrystallise the mixture of salts failed.

Liberation of base

3g. of the above mixture of diazepinium salts and acetic acid was treated with sodium hydroxide (10g.) in water (25mls.). The mixture was extracted with ether (4x50mls.) and the extract dried with anhydrous sodium sulphate. Removal of the ether left a pale yellow liquid which did not solidify. Yield 1·6g. Its N.M.R. spectrum in trifluoroacetic acid and chloroform (Tables VI and VII) confirmed that it was 2,3-dihydro-1,5,7-trimethyl-1,4-diazepine.

(G) 2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine.

Dibenzoylmethane (22·4g.) was added to a mixture of N-methylethylenediamine (7·4g.) and acetic acid (25mls.) and the whole was heated at reflux temperature for 1½ hrs. The cooled reaction mixture was poured into water (250mls.) and extracted with ether (5x100mls) to

remove unreacted dibenzoylmethane. Perchloric acid (60%; 25mls.) was added to the aqueous layer. The diazepinium perchlorate was precipitated as an oil, which solidified on standing. The solid was removed and melted in the presence of water (2x50mls.). On cooling the perchlorate solidified and was filtered off and dried in a vacuum desiccator over phosphorus pentoxide. Finally the perchlorate was dissolved in acetonitrile and reprecipitated by the addition of ether. Yield 9·1g. (25·1%), m.pt. 75-80°. Found: N,7·45 $C_{18}H_{19}N_2ClO_4$ required N,7·72%). N.M.R. spectrum in trifluoroacetic acid. Signals at τ 2·05, 2·13, 4·37, 5·94, 6·76 in ratio 1:10:1:4:3. U.V. spectrum in methanol λ max 265mμ(ε=12,700), 356mμ (ε =23,000).

The free base was prepared by treatment of the perchlorate with sodium hydroxide solution and extraction of the resultant basic mixture with benzene.

(H)(I)2,3-Dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine and 2,3-dihydro-1,5-dimethyl-7-phenyl-1,4-diazepine.

Benzoylacetone (32·4g.) was added to a mixture of N-methylethylenediamine (14·8g) and acetic acid (50g.). The mixture was heated at reflux temperature for 1½hrs. and then cooled and poured into water (200mls.). After removal of unreacted benzoylacetone by extraction with ether (3x100mls.), perchloric acid (60%, 25mls.) was added to the aqueous layer. The diazepinium perchlorates separated at first as an oil which solidified within 10 mins. Yield 10·8g. (18%), m.pt.95-110°.

The N.M.R. in trifluoroacetic acid showed 2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepinium perchlorate (IX) and 2,3-dihydro-1,5-dimethyl-7-phenyl-1,4-diazepinium perchlorate (X) to be present in a ratio of 3·4:1.

A lengthy fractional crystallisation from methanol gave 5·3g. of (IX), m.pt.124·5-126° and 0·5g. of (X) m.pt. 167-170°.

Analysis of (IX): Found: C,51·51; H,5·93; N,9·35 $C_{13}H_{17}N_2ClO_4$ requires C,51·92; H,5·70; N,9·31%.

The N.M.R. data of (IX) and (X) are discussed in Chap. 1 p 32 ∝ 33

U.V. data (IX) λ max. 256·5mμ (ε=8,200), 346mμ (ε=18,800)
in methanol (X) λ max. 257·5mμ (ε=7,000), 341mμ (ε=19,600).

The free bases derived from (IX) and (X) are liberated by treatment with sodium hydroxide solution and are extracted by hot benzene. They are waxy materials m. pts. 103-104° and 75-80° respectively.

(2) 1-(2^1-Benzoyl-1^1-methylvinylamino)-2-(methylamino) ethane perchlorate(II)

N-Methylethylenediamine (7·4g.) was carefully added to methanol containing perchloric acid (60%; 10mls.), followed by benzoylacetone (16·2g.) dissolved in warm methanol (10mls.). On cooling, Compound (II) was precipitated. Yield 25·2g. (79·1%), recrystallised from methanol, m.pt. 156-158° (d).

N.M.R. spectrum in trifluoroacetic acid. Signals at τ2·3(complex), 5·04, 5·46(m), 6·09(m), 6·87(t) and 7·23 in ratio of 7:1:2:2:3:3.

The I.R. spectrum (nujol mull) showed an absorption due to perchlorate ion.

(3) Conversion of compound (II) into diazepinium perchlorates.

1-(2^1-Benzoyl-1^1-methylvinylamino)-2-(methylamino) ethane perchlorate (II) (6·31g.) was heated at reflux temperature in acetic acid (10mls.) for 1½ hrs. The mixture was cooled and added to ether (200 mls.). The precipitated diazepinium perchlorates were filtered off. Yield 4·9g. (81%).

A N.M.R. spectrum of the mixed perchlorates showed isomers (IX) and (X) to be present in a ratio of 3·1:1.

RELATED TO CHAPTER 2.

Determination of dissociation constants of 1,4 diazepinium dications by U.V. spectroscopy.

The diazepinium salts used were the perchlorates. The U.V. spectrum in 40% sulphuric acid was taken to be that of the monocation as it was unchanged at lower sulphuric acid concentrations and the U.V. spectrum in 96% sulphuric acid that of the dication as it was unchanged from 90% to 96% sulphuric acid.

Spectral data in sulphuric acid solutions.

2,3 dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (a)

monocation λ max mμ 323 (ε=16,570), 260 (ε=app.1,500)

dication - no appreciable absorption above 200mμ

6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (b)

monocation λ max. mμ 347·5 (ε=12,210), 257 (ε=app.1,000)

dication - no appreciable absorption above 200mμ

2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (c)

Monocation λ max. mμ 358 (ε=22,955), 268 (ε=14,070)

dication λmax. mμ 290 (ε=23,500)

6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (d)

monocation λ max. mμ 373 (ε=15,460), 263 (ε=app7,000), 240 (ε=app.7,000)

dication λ max. mμ 320 (ε=17,850).

Evaluation of $(BH^+)/(BH_2^{++})$

Each solution was prepared separately by dissolving a weighed quantity of the diazepinium perchlorate in sulphuric acid of the

required concentration. The weight of the salt used was such that the recorded U.V. spectrum was in the optimum range of accuracy.

The ratio $(BH^+)/(BH_2^{++})$ was calculated from the extinction coefficient obtained ε_2 and that of the monocation ε_1, using the the relationship

$$(BH^+)/(BH_2^{++}) = \varepsilon_2/\varepsilon_1-\varepsilon_2$$

Results.

(a) 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate

λ max. 323 ε_1 = 16,570

Molarity H_2SO_4	H_I	2	$\varepsilon_2/\varepsilon_1-\varepsilon_2$	$\log(BH^+)/(BH_2^{++})$
8·64	-5·66	15,000	15,000/1,570	+·9702
9·17	-6·04	13,570	13,570/3,000	+·6555
9·70	-6·44	11,250	11,250/5,320	+·3250
10·26	-6·82	7,695	7,695/8,875	-·0619
10·81	-7·26	3,911	3,911/12,661	-·5102

(b) 6-bromo-2,3-dihydro-5,7 dimethyl-1,4-diazepinium perchlorate

λ max. 347·5m ε_1 = 12,210

Molarity H_2SO_4	H_I	ε_2	$\varepsilon_2/\varepsilon_1-\varepsilon_2$	$\log(BH^+)/(BH_2^{++})$
10·81	-7·30	7,590	7,590/4,620	+·2155
11·40	-7·72	4,757	4,757/7,453	-·1951
12·03	-8·16	2,291	2,291/9,919	-·6364

(c) 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate

λ max. 358mμ ε_1 = 22,955

Molarity H_2SO_4	H_I	ε_2	$\varepsilon_2/\varepsilon_2-\varepsilon_1$	$\log(BH^+)/(BH_2^{++})$
12·03	-8·16	18,640	18,640/4,315	+·6354
12·30	-8·36	16,045	16,045/6,910	+·3658
12·61	-8·60	12,600	12,600/10,355	+·0852
13·28	-9·10	5,404	5,404/17,451	-·5115

(d) 6-brono-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate

The calculation of $(BH^+)/(BH_2^{++})$ was more complex in this case due to an overlap of the "phenyl" absorption of the dication and the "diazepine" absorption of the monocation, as shown below.

Monocation λ max 373mμ (ε =15,460) at 320mμ(ε=1,545)

Dication max 320mμ (ε =17,850) at 373mμ(ε=881)

The concentration of mono and dication could be calculated from the absorbance (A) at 373mμ and 320mμ by solving the simultaneous equations below.

$$A_{373m\mu} = 1{,}545(BH_2^{++}) + 15{,}460(BH^+)$$

$$A_{320m\mu} = 17{,}850(BH_2^{++}) + 881(BH^+)$$

Molarity H_2SO_4	H_I	A_{373m}	A_{320m}	$(BH^+)\times10^{-5}$	$(BH_2^{++})\times10^{-5}$	$\log\frac{(BH^+)}{(BH_2^{++})}$
10·81	-7·30	0·56	0·38	3·633	1·959	+·2681
11·10	-7·47	0·42	0·56	2·792	3·018	-·0351
11·40	-7·72	0·33	0·65	2·058	3·555	-·2372

RELATED TO CHAPTER 3.

ELECTROPHILIC SUBSTITUTION IN 2,3-DIHYDRO-1,4-DIAZEPINES

(A) Deuteration

2,3-Dihydro-5,7-dimethyl-1,4-diazepine (0·1892g.) was weighed in a stoppered bottle. Deuteriotrifluoroacetic acid (0·5-0·7ml.) was added and the bottle and its contents reweighed to find the amount of acid used (0·5352g.) The solution was quickly transferred to an N.M.R. tube and a little tetramethylsilane added. The spectrum was examined immediately, and within five minutes after the addition of acid. The amount of exchange which had taken place was calculated with reference to the methyl and methylene protons and found to be 5% for CH protons and 58% for NH protons. The theoretical exchange for the weights of diazepine and acid used was 60·4%. The spectrum was re-examined after half an hour and no further exchange had taken place. The small difference between the theoretical and calculated exchange may be due to contamination of the diazepine with a trace of water.

A similar procedure was followed using 2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·1040g.) and deuteriotrifluoroacetic acid (0·7996g). The exchange which had taken place was 89% for both CH and NH. The theoretical exchange possible was 89·3%.

(B) Preparation of 6-bromo-2,3-dihydro-1,4-diazepines.

The two general methods used are outlined below. Yield, m.pts., analytical results and any differences in method are placed under the

heading of each individual diazepine.

Method 1

The diazepine base (xg.) was dissolved in methanol or chloroform (y mls.). An equimolar quantity of bromine dissolved in the same solvent was added gradually. The brominated diazepinium bromide was precipitated by the addition of ether.

Method 2

The diazepinium perchlorate (xg.) was dissolved in methanol (y mls). An equimolar quantity of bromine dissolved in methanol was added gradually. The brominated diazepinium salts were precipitated by the addition of ether. The brominated base was obtained by treatment of the salts with concentrated sodium hydroxide solution and extraction with ether or benzene. Removal of the solvent under vacuum gave the free base, which could be converted into its perchlorate by the addition of an equimolar quantity of perchloric acid.

6-Bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine.

Method 1 was used. x = 0·465g., y = 2 mls. (methanol) Yield of 2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium bromide 0·805g.(93·1%). Recrystallised from water m.pt. 175-178° (d). (Found: Br, 46·2%. $C_{12}H_{14}N_2Br_2$ requires Br,47·4%).

The free base of this compound was difficult to obtain in a pure state, since some decomposition took place on concentration of the benzene extract. The precipitated base was slightly coloured and did not have a sharp melting point, (80-90°). The N.M.R. spectrum in

trifluoroacetic acid was consistent with the structure of the 6-bromo-2,3-dihydro-5-methyl-6-phenyl-1,4-diazepinium cation. (see Table VIII).

6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine.

Method 1 was used x = 4·96g, y = 25 mls. (methanol). Yield of 6-bromo-2,3-dihydro-5,7-diphenyl diazepinium bromide 7·3g.(89·2%). Recrystalled from ethanol m.pt. 178-180° (d). (Found: C,49·47: H,3·98: Br, 39·40. $C_7H_{16}N_2Br_2$ requires C,50·03: H,3·95: Br 39·16%).

The free base of this compound was obtained in yields of 85-90% by the method outlined in Method 2 and using benzene as the extracting solvent. The base, recrystallised from ethanol, had m.pt. 158-161° (d). Treatment of the free base in methanol solution with perchloric acid and water gave the perchlorate m.pt. 176·5-177°.

6-Bromo-2,3-dihydro-5-p-nitro phenyl-7-phenyl-1,4-diazepine.

Method 1 was used x = 1·6g., y = 5 mls. (chloroform). Yield of 6-bromo-2,3-dihydro-5-p-nitro phenyl-7-phenyl-1,4-diazepinium bromide 2·1g. (84·9%). Recrystalled from ethanol m.pt. 192-197° (d).

The free base was obtained (Method 2) as a resinous material which did not crystallise. The N.M.R. spectrum in trifluoroacetic acid was however, consistent with 6-bromination. A perchlorate m.pt. 180-182° (d), was obtained from the base.

6-Bromo-2,3-dihydro-1,5,7,-trimethyl-1,4-diazepinium perchlorate.

Method 2 was used with x = 10·2g. and y = 25 mls. (methanol). In this preparation the diazepinium perchlorate which was brominated

contained a little acetic acid (see Chap. 1).

After the bromine addition most of the methanol was removed under vacuum before the addition of ether. Yield of 6-bromo-diazepinium salts 7·6g. (app. 60%). Sodium hydroxide solution (25 mls. 20%) was added to the 6-bromo salts (7·6g.) and the mixture extracted with ether (3x50 mls). On addition of perchloric acid (60% 3mls.) to the combined ether extract pale yellow crystals of 6-bromo-2,3-dihydro-1,5,7-trimethyl-1,4-diazepinium perchlorate were obtained. Yield after recrystallisation from methanol 6·3g. (46·4%), m.pt. 133-134°. (Found: C,30·53; H,4·59%. $C_8H_{14}N_2BrClO_4$ requires C,30·26; H,4·44%). The addition of perchloric acid to the ethereal solution of the base is the preferred procedure, as concentration of the solution to obtain the base brings about some decomposition. For N.M.R. spectrum see Table VIII.

6-Bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine.

Method 2 was used with x = 3·62g. and y = 10 mls. (methanol). After addition of bromine the methanol was removed under vacuum. Sodium hydroxide (20%, 10 mls.) was added to the residue and the mixture extracted with benzene (5x10 mls.). The benzene was removed under vacuum leaving a yellow oil which did not crystallise. Perchloric acid (60%, 1 ml.) in methanol (2mls.) was added whereat the 6-bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepinium perchlorate crystallised. Yield 2·6g. (60%). Recrystallised from water m.pt. 165-168° (d). Found: C,49·22; H,4·22; N,6·50; Br,18·43.

$C_{18}H_{18}N_2BrClO_4$ requires C,49·04; H,4·12; N,6·35; Br,17·94%.
The free base m.pt. 89-91° was obtained from the perchlorate.

6-Bromo-2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepinium perchlorate (XII).

Method 2 was used; x = 0·60gms., y = 5 mls. (methanol). The diazepinium perchlorate was obtained using the same method as in the previous preparation, but using sodium hydroxide (20% 3 mls.) and perchloric acid (60% 0·25ml.) in methanol (0·5ml). Yield 0·59g.(77·8%). (Found: C,41·38; H,4·40; N,7·45. $C_{13}N_2H_{16}BrClO_4$ requires C,41·13; H,4·25; N,7·38%).

7-Bromomethyl-2,3-dihydro-1-methyl-5-phenyl-1,4-diazepinium bromide. (XIII).

Method 1 was used with x = 1·6g, y = 10 mls. (methanol).

Crystals of 7-bromomethyl-2,3-dihydro-1-methyl-5-phenyl-1,4-diazepinium bromide were obtained by removing the methanol under vacuum and treating the residue with a little acetone. Yield 1·28g. (44·4%), recrystallised from methanol m.pt. 215-217°. (Found: C,43·25; H,4·94; N,7·86. $C_{13}H_{16}N_2Br_2$ requires C,43·34; H,4·48; N,7·78%.

Treatment of the diazepinium bromide with perchloric acid in methanol gave a perchlorate m.pt. 157-159°.

Bromination of 2,3-dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate.

(1) Using an equimolar quantity of bromine.

2,3-Dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate(1g) was dissolved in methanol (15mls). Bromine (0·43g.) in methanol was

added dropwise with stirring. The addition of ether (50 mls.) gave a product (0·75g.) with m.pt. 120-170°, and with a "diazepine" U.V. absorption at λ max 349mμ. Addition of a further 50 mls of ether gave 0·42g. of a product with a "diazepine" U.V. absorption at λ max 346mμ.

(2) Using a 7-molar quantity of bromine

2,3-Dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate (0·5g.) was dissolved in methanol (5 mls.). Bromine (1·5g.) in methanol was added gradually. A precipitate started to form during the addition. After all the bromine had been added the precipitate was removed by filtration and recrystallised from methanol. Yield 0·54g. m.pt. 137-144°. The I.R. spectrum of this material (XXX) indicated that perchlorate was absent. The analysis of (XXX) suggested that multibromination had taken place. Found: C,35·78; H,3·16; N,4·52. Required for tribromination ($C_{19}H_{18}N_2Br_4$): C,38·4; H,3·6; N,4·7. Required for tetrabromination ($C_{19}H_{17}N_2Br_5$) : C,33·91 H,3·1; N,4·15% (Assuming in each case bromide as anion.)

(3) Hydrolysis of product (XXX).

The brominated product (XXX) was warmed to 50° with methanol (15mls.) and conc. hydrobromic acid (3 mls.). The cream coloured precipitate which formed was removed by filtration (Yield 2·8g., m.pt. 160-205°) and stirred with sodium hydroxide solution (1·5 g. in 4 mls. water) for ten minutes. The colour of the mixture turned from cream to grey. After filtration the liberated bases were

washed with water. Thin layer chromatography on silica and elution with 30% diethylether in petroleum ether (40-60°) showed the presence of at least five compounds. Recrystallisation from ethanol gave 1·4g. of tetrabromodianilinoethane m.pt. 139-140°. (Found: C,32·9; H,2·39; N,5·34; Br 59·65. $C_{14}H_{12}N_2Br_4$ requires C,31·87; H,2·29; N,5·31; Br 60·54%). N.M.R. spectrum in trifluoroacetic acid signals at τ 1·97-2·44 (complex), 5·70(S) in ratio of 6:4.

(4) Hydrolysis of 2,3-dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate.

2,3-Dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate (1g.) was heated at reflux temperature for ten minutes with sodium hydroxide solution (5%, 20 mls.). The mixture was extracted with ether (4 x 25 mls.). After the ether was removed a little methanol was added, followed by water, until a precipitate appeared. Yield 0·56 g. (71·5%), recrystallised from methanol m.pt. 84-86°. This compound was N-(2-acetyl-1-methylvinyl)-N,N^1-diphenylethylenediamine. (Found: C,77·00; H,7·34; N,9·60. $C_{19}H_{22}N_2O$ requires C,77·51; H,7·53; N,9·52. N.M.R. spectrum in deuteriochloroform: signals at 2·7-3·3(cx) 4·63(S), 6·2(m), 6·6(m), 7·66(S), 7·94(S) in ratio of 10:1:1:1:3:3 a signal equivalent to one proton was hidden by 6·2(m).

6,6-Dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine.

Bromine (0·7g.) was added gradually to a stirred solution of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (1·31g.) in

benzene (150 mls.). The precipitated 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide was removed by filtration. Yield 0·81g. (49·7%). 6,6-Dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine was obtained from the filtrate by removal of the benzene under vacuum and recrystallisation of the residue from ethanol (6mls.). Yield 0·66g. (40·8%) m. pt. 119-120°(d). (Found: C,49·79; H,3·31. $C_{17}H_{14}N_2Br_2$ requires C,50·28; H,3·47%). N.M.R. spectrum in deuteriochloroform. Signals at 2·3-2·6(CX) and 5·72(S) in ratio of 10:4.

6-Chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine.

2,3-Dihydro-5,7-diphenyl-1,4-diazepine (1·5g.) was treated with N-chlorosuccinimide (0·81g.) in acetic acid (45 mls) for 2 hours at reflux temperature. Most of the acetic acid was removed under vacuum and a mixture of water (25 mls.) and conc. hydrochloric acid (3 mls.) was added. The precipitated 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepinium chloride was removed by filtration and washed with a small quantity of water. Yield 1·7g. (87·5%) m.pt. 263°(d). N.M.R. in trifluoroacetic acid. Signals at τ 1·6, 2·45 and 5·93 in ratio of 2:10:4.

Liberation of base.

6-Chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepinium chloride (1·7g.) was dissolved in hot water (20 mls). Sodium hydroxide solution (20 mls., 20%) was added and the mixture extracted with benzene (3 x 50 mls). The benzene extract was concentrated under vacuum to

5 mls. and cooled. Crystals of 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine appeared. Yield 1·32g. (87·7%) m. pt. 192-193°. (Found: C,72·45; H,5·46. $C_{17}H_{15}N_2Cl$ requires C,72·21; H,5·34.).

Preparation of 6-bromo-6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine

This compound was prepared by treatment of 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine in benzene solution with a small excess of bromine. The work up was as in the preparation of 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (page 96). Yield recrystallised from methanol 24·6% m.pt. 97-99°. N.M.R. in deuterochloroform. Signals at τ 2·3-2·6(cx) and 5·70 in ratio 10:4.

This compound has not been analysed, but its structure deduced from its I.R. spectrum in hexachlorobutadiene mull. Absorptions at 1,640, 1,480, 1,440, 1,420, 1,350, 1,320, 1,300, 1,280, 1,240, 1,220, 1,080, 1,065, 1,035, 920, 895, 755, 695 cm^{-1}. (cf. 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine, absorptions at 1,640, 1,480, 1,440, 1,350, 1,320, 1,310, 1,280, 1,240, 1,220, 1,080, 1,035, 920, 900, 897, 760, 735, 690 cm^{-1}.)

(C) Nitration of 2,3-dihydro-1,4-diazepinium salts.

(1) 2,3-Dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate.

2,3-Dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (44·9g.) was dissolved in conc. sulphuric acid (175 mls.) Fuming nitric acid (11mls) was added over 1 hour at 0° with stirring. The temperature was then raised to 35-40° for 1½ hours. The nitrated diazepine was precipitated as its perchlorate without the addition of perchloric acid, by pouring

the reaction mixture on to crushed ice (200g.) and application of external cooling. The 2,3-dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate was recrystallised from water. Yield 41·5g. (77·0%), m. pt. 235° (d). (Found: N,15.6°. $C_7H_{12}N_3O_2ClO_4$ requires N,15·58%). N.M.R. spectrum in trifluoroacetic acid see Table IX.

The nitration could also be carried out in fuming nitric acid alone (1 hour at room temperature) and the product isolated as its perchlorate by the addition of 25% perchloric acid.

(2) Bis-(2-acetyl-1-methylvinylamino-2-nitro) ethane [1,2]

2,3-Dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (4·49g.) was dissolved in conc. sulphuric acid (17·5mls.). Fuming nitric acid (1·1 mls.) was added over 1 hour with stirring. The temperature was raised to 35-40° for 1½ hours and the mixture poured into cold water (150 mls). Concentrated sodium hydroxide solution was added until the pH was greater than 11. During the addition the temperature was allowed to rise. The mixture was then allowed to stand for ½ hour after which the pH was adjusted to 8-9 by the addition of sulphuric acid and the mixture extracted with toluene (8 x 500 mls.). Toluene was removed from the extract under vacuum and the residual bis-(2-acetyl-1-methylvinylamino-2-nitro) ethane [1,2] washed with a little methanol. Yield 0·55g. (17·5%) m.pt. 155-160°(d), recrystallised from methanol m.pt. 164-166°. (Found: N,17·06%. $C_{12}H_{18}N_4O_6$ requires N,17·84%).

Evidence for the structure of this compound is given in Chapter 3 part (C).

(3) 2,3-Dihydro-6-nitro-5,7-diphenyl-1,4-diazepinium perchlorate.

2,3-Dihydro-5,7-diphenyl-1,4-diazepine (7·5g.) was added gradually to 83% nitric acid (75mls.) at 0°. The mixture was allowed to stand for ½ hour at room temperature and then poured into cold water (750 mls.). The nitrated diazepinium salt was precipitated as its nitrate m.pt. 198-200°. This was converted into 2,3-dihydro-6-nitro-5,7-diphenyl-1,4-diazepinium perchlorate m.pt. 258-260° by two recrystallisations from perchloric acid in methanol. A good analysis was not obtained for this compound, but its N.M.R. spectrum (Table IX) in trifluoroacetic acid leaves no doubt as to its structure. (Found: C,52·80; H,4·48. $C_{17}H_{16}N_3O_2ClO_4$ requires C,51·85; H,4·10%.)

(4) 2,3-Dihydro-5-methyl-6-nitro-7-phenyl-1,4-diazepinium nitrate.

2,3-Dihydro-5-methyl-7-phenyl-1,4-diazepine (2g.) was gradually added to nitric acid (83% 16 mls.) at 0° and kept for 1 hour at this temperature. The mixture was diluted with water (16 mls.) and 20% sodium hydroxide solution was added with cooling until precipitation of 2,3-dihydro-5-methyl-6-nitro-7-phenyl-1,4-diazepinium nitrate took place. The precipitate was filtered off and washed with a little water. Yield = 1·4g. (43·3%); recrystallised from methanol and ether m. pt. 220° (d). (Found: C,49·78; H,5·2. $C_{12}H_{14}N_4O_5$ requires C,48·98; H,4·80%. N.M.R. spectrum see Table IX.

Attempted nitration of 2,3-dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate.

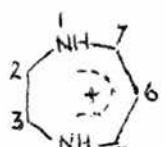
2,3-Dihydro-5,7-dimethyl-1,4-diphenyl-1,4-diazepinium perchlorate (0·5g.) was added to nitric acid (4 mls. 83%) at 0°. The mixture immediately turned red brown. After fifteen minutes it was poured into water 50 mls. A brown precipitate was obtained which became an oil on attempted filtration.

(D) 2,3-Dihydro-1,7-dimethyl-6-p-dimethylaminobenzylidene-5-phenyl 1,4-diazepinium perchlorate.

2,3-Dihydro-1,7-dimethyl-5-phenyl-1,4-diazepinium perchlorate (2g.) and p-dimethylamino benzaldehyde (1g.) were heated at reflux temperature in acetic anhydride (20 mls.) for 1½ hours. Ether (500 mls.) was added to the cooled reaction mixture and the precipitated salts recrystallised from methanol (300 mls). Purple crystals of 2,3-dihydro-1,7-dimethyl-6-p-dimethylaminobenzylidene-5-phenyl-1,4-diazepinium perchlorate were filtered from solution. Yield 0·75g. (25·8%) m. pt. 227-228°. (Found: C,60·80; H,6·19. $C_{22}H_{26}N_3ClO_4$ requires C,61·20; H,6·26%). N.M.R. evidence for structure given in Chap. 3, part (D).

TABLE VIII

N.M.R. SPECTRA OF 2,3-DIHYDRO-1,4-DIAZEPINIUM CATIONS IN TRIFLUOROACETIC ACID SOLUTION



Substituents				Position of Signals τ values						Other signals or comments
1	5	6	7	1,4NH	5,7C_6H_5	6CH	2,3CH_2	1CH_3	5,7CH_3	
H	Me	H	Ph	2·0(b)	2·35	4·5(b)	6·1(m)	–	7·55	
"	Ph	"	"	1·9(b)	2·36	4·05(b)	5·95(m)	–	–	
"	pNO_2 Ph	"	"	hidden under Ph sig.	1·5-2·0(cx) 2·3(5H)	4·1	5·85(m)	–	–	
"	pNH_2 Ph	"	"	1·7(b)	2·1(5H) 2·3(5H)	4·1	5·85	–	–	
"	Me	Br	"	1·4(b)	2·4	–	6·05(m)	–	7·25	
"	Ph	"	"	1·7(b)	2·45	–	5·85(m)	–	–	
"	pNO_2 Ph	"	"	1·1(b)	1·5-2·2(cx) (5H) 2·4(5H)	–	5·75	–	–	
"	Ph	Cl	"	1·6(b)	2·45	–	5·95	–	–	
Me	Me	Br	Me	2·0(b)	–	–	6·1	6·5	7·35 7·45	solution unstable
"	Ph	"	"	2·1(b)	2·6	–	5·4(m) 6·0(m)	6·4	7·2	"
"	"	"	Ph	2·0(b)	2·5	–	5·8	6·7	–	
"	Me	N-piperidinyl	Me	2·1(b)	–	–	5·9	6·4	7·27 7·30	NC_5H_{10} 5·9(m)4H 7·8(m)6H

(b) = broad, (m) = multiplet, (cx)= aromatic complex. Signals are singlets unless otherwise stated. Integrals are correct for structures shown.

RELATED TO CHAPTER 4.

REACTIONS OF SUBSTITUTED-2,3-DIHYDRO-1,4-DIAZEPINES.

(1) Reactions of 6-bromo-2,3-dihydro-1,4-diazepinium salts with acids

(a) Preliminary experiments.

Solutions of the following diazepinium salts were prepared in trifluoroacetic acid and their N.M.R. spectra recorded after 5-10 minutes.

(I) 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide

(II) " " 5-methyl-7-phenyl " "

(III) " " 5,7-diphenyl " "

(I) Gave an N.M.R. spectrum consistent with the brominated diazepine. (II) and (III) gave N.M.R. spectra showing signals corresponding to the 6H-analogues. Integration showed the presence of 30% of the 6H-compound in case (II) and 65% of the 6H-compound in case (III).

(b) Further experiments in trifluoroacetic acid

(i) With 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine.

Solutions of this diazepine and its perchlorate were prepared in trifluoroacetic acid and the N.M.R. spectra recorded at intervals for several days. After one week the solutions showed no change, the spectra recorded being those of the brominated diazepine. The addition of a crystal of potassium chloride to the solution brought about a 20% conversion into the 6H-compound after 1 hour at room temperature. No further changes were observed after 20 days.

The addition of a crystal of sodium bromide to the solution of the base brought about some conversion into the 6H-compound after 1 hour. This amount could not be estimated accurately. After 2 days 30% conversion had taken place and the addition of more crystals of sodium bromide increased this amount to 60%.

(ii) With 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine

Solutions of this diazepine and its bromide and perchlorate were prepared in trifluoroacetic acid and their N.M.R. spectra recorded at intervals. In all cases a methyl signal appeared at τ 7·65 after three days at room temperature. After fourteen days another methyl signal appeared at τ7·55 in the case of the bromide and perchlorate and that at τ 7·65 had increased. No methine protons were observed at τ 4·9 corresponding to signals given by the 6H-compound.

(iii) Effects of addition of water and trifluoroacetic anhydride.

10% Solutions of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide were prepared in (a) Trifluoroacetic acid (b) Trifluoroacetic acid containing 3% water (c) Trifluoroacetic acid containing 3% trifluoroacetic anhydride. Their N.M.R. spectra were recorded at intervals. Solution (c) showed stability after 13 days standing at room temperature. Solutions (a) and (b) showed changes in the methyl proton signals after one day at room temperature. After further time up to thirteen days it was apparent that these changes were taking place more quickly in the case of solution (b)

(c) Experiments in concentrated sulphuric acid.

Solutions of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide (3 mg.) in conc. sulphuric acid (1 ml) and 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide (4 mg.) in conc. sulphuric acid (1 ml.) were prepared in stoppered bottles and allowed to stand at room temperature for twenty-four hours. The solutions (0·5ml.) were diluted with water (100 mls.) and the U.V. spectra recorded immediately. These spectra were characteristic of the brominated compounds. The remaining 0·5 mls. of the sulphuric acid solutions were each diluted by pouring into 0·01M sodium thiosulphate solution, and the U.V. spectra recorded immediately. These spectra were characteristic of the debrominated compounds.

(For U.V. spectra of these compounds see p 86).

(2) Reaction of 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with hydrobromic acid.

A stirred solution of 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·047g.) in benzene (1 ml.) was treated with a solution of hydrobromic acid (0·1 ml. conc. in 1 ml. water). There was an immediate yellow precipitate of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide and the benzene layer became brown in colour and changed the colour of fluorescein paper from yellow to red, suggesting the presence of free bromine. After fifteen minutes the precipitate was removed. Yield 0·048g. (100%). It was identified by I.R. spectrum and mixed m.pt. with the authentic compound.

(B) Reactions of 6-bromo-2,3-dihydro-1,4-diazepines with bases

(1) 2,3-Dihydro-6-methoxy-5,7-diphenyl-1,4-diazepinium perchlorate

A solution of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) in molar methoxide solution (10 mls.) was heated at reflux temperature for thirty minutes. After methanol had been removed under vacuum, water (2 mls.) was added and the mixture extracted with benzene (3 x 5 mls.). After removal of the benzene 2,3-dihydro-6-methoxy-5,7-diphenyl-1,4-diazepine was obtained, m.pt. 177-178·5°. The base was converted into its yellow crystalline perchlorate by the addition of perchloric acid (60%, 0·15 mls. in 0·5 mls. water). Yield 0·24g. (63·4%), recrystallised from methanol m.pt. 238-240°. (Found: C,57·15; H,4·75; N,7·44. $C_{18}H_{19}N_2OClO_4$ requires C,57·09; H,5·10; N,7·39%). U.V. spectrum in methanol λmax 265mμ (ε=9,860), 377mμ (ε=17,080). N.M.R. spectrum see Table X.

(2) 2,3-Dihydro-6-methoxy-5-methyl-7-phenyl-1,4-diazepinium perchlorate.

A solution of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium bromide (3·46g.) in molar potassium methoxide solution (100 mls.) was heated at reflux temperature for thirty minutes. The reaction mixture was worked up as in the previous preparation using benzene (3 x 20 mls.) and perchloric acid (60% 1·5 mls. in 5 mls. water). The base of this diazepine did not crystallise. Yield of 2,3-dihydro-6-methoxy-5-methyl-7-phenyl-1,4-diazepinium perchlorate 2·6g. (82·0%), recrystallised from methanol m.pt. 166-168°. (Found:

C,49·41; H,5·77. $C_{13}H_{17}N_2OClO_4$ requires C,49·42; H,5·42%).
U.V. spectrum in methanol λ max 265mμ (ε=6,680), 367mμ (ε=16,030)
N.M.R. spectrum see Table X.

(3) 6-Ethoxy-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium perchlorate.

A solution of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium bromide (0·346g.) in molar potassium ethoxide solution was heated at reflux temperature for thirty minutes. After removal of the ethanol under vacuum the reaction mixture was worked up as in the previous preparation using benzene (3 x 5 mls.) and perchloric acid (60%, 0·15 mls. in 0·15 mls. water). The base of this diazepine did not crystallise. Yield of 6-ethoxy-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium perchlorate 0·247g. (74·7%), recrystallised from ethanol m.pt. 166-168°. (Found: N,8·34. $C_{14}H_{19}N_2OClO_4$ requires N,8·47%). U.V. spectrum in methanol λ max 260mμ (ε=7,240), 367mμ (ε=14,530). N.M.R. spectrum see Table X.

(4) 2,3-Dihydro-5,7-dimethyl-6-N-piperidinyl-1,4-diazepinium perchlorate.

6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine (10·5g.) was added to piperidine (50 mls.) and heated on a water bath for 1 hour at 60°. Piperidine was removed from the reaction mixture under vacuum and the residue dissolved in warm water (10 mls.). On the addition of perchloric acid (10 mls. 60%) a mixed yellow and white precipitate was obtained. This was recrystallised from water (25 mls.) yielding yellow crystals of 2,3-dihydro-5,7-dimethyl-6-N-piperidinyl-1,4-diazepinium perchlorate. Wt. 13·6g. (95·4%) m.pt. 168-170°

(Found: C,47·08; H,7·45; N,13·4. $C_{12}H_{22}N_3ClO_4$ requires C,46·83; H,7·20; N,13·65%). U.V. spectrum in water λ max 340mμ (ε=7,250). N.M.R. spectrum see Table X.

Treatment of the diazepinium mono perchlorate with 60% perchloric acid gave a colourless diperchlorate m.pt. 200-205° (d). A quantitative determination of the U.V. spectrum of this diperchlorate in aqueous solution showed that it reverted to the monoperchlorate under these conditions.

(5) Preparation of 2,3-dihydro-5-methyl-7-phenyl-6-N-piperidinyl-1,4-diazepinium perchlorate.

6-Bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine (1g.) was added to piperidine (5 mls.) and heated at 60°for 1 hour. Piperidine was removed from the mixture under vacuum and perchloric acid (1 ml. 60% in 5 mls. water) added to the residue. Orange-yellow crystals of 2,3-dihydro-5-methyl-7-phenyl-6-piperidino-1,4-diazepinium perchlorate were obtained. Yield 1·2g. (86·0%), recrystallised from methanol 211-213°. (Found: C,55·59; H,6·42; N,11·39. $C_{17}H_{24}N_3ClO_4$ requires C,55·21; H,6·54; N,11·36%). N.M.R. spectrum see Table X.

(6) 2,3-Dihydro-5,7-dimethyl-6-N-pyrrolidinyl-1,4-diazepinium perchlorate.

6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine (1·42g.) was added to pyrrolidine (20 mls.) and heated for 1 hour at 60°. Excess pyrrolidine was removed under vacuum and water (20 mls.) added to the residue, followed by perchloric acid (3 mls. 60%). Concentrated

sodium hydroxide solution was added dropwise until the pH was approx. 10 and a yellow precipitate of 2,3-dihydro-5,7-dimethyl-6-N-pyrrolidinyl-1,4-diazepinium perchlorate appeared. Yield 0·98g. (47·8%), recrystallised from water m.pt. 159-160°. (Found: C,45·64; H,6·79. $C_{11}H_{20}N_3ClO_4$ requires C,44·98; H,6·86%). N.M.R. spectrum see Table X.

(7) 2,3-dihydro-5-methyl-7-phenyl-6-N-pyrrolidinyl-1,4-diazepinium perchlorate.

6-Bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine (1gm.) was added to pyrrolidine (10 mls.) and heated for 1 hour at 60°. Excess pyrrolidine was removed from the mixture under vacuum and perchloric acid (1ml. 60% in 5 mls. water) was added, followed by water until precipitation of the orange-yellow crystals of 2,3-dihydro-5-methyl-7-phenyl-6-N-pyrrolidinyl-1,4-diazepinium perchlorate was complete. Yield 0·73g. (75·1%), recrystallised from methanol m.pt. 210-212°. (Found: C,53·45; H,6·28. $C_{16}H_{22}N_3ClO_4$ requires C,54·01; H,6·22%). N.M.R. spectrum see Table X.

(8) Reactions of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine in ethoxide solutions.

(a) Using molar ethoxide solution; conc. of diazepine = 0·1M.

(i) 6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) was heated at reflux temperature with molar sodium ethoxide solution (10mls.) for thirty minutes. Ethanol was removed from the mixture under vacuum and water (2 mls.) added to the residue. This mixture was extracted with benzene (4 x 5 mls.). Benzene was removed from the

extract leaving a sandy coloured solid m.pt. 155-158°. Yield 0·105g. (42·3%).

This substance was shown to be 2,3-dihydro-5,7-diphenyl-1,4-diazepine by its I.R. spectrum which was identical to that of an authentic specimen and by a mixed m.pt. determination, which showed no depression. The base was converted into its perchlorate m.pt.154-156° and a mixed m.pt. with an authentic specimen showed no depression.

(ii) A similar preparation to (a) (i) above was carried out using molar potassium ethoxide solution. After concentrating to about 3 mls. potassium bromide was filtered off from the cooled mixture. Yield of potassium bromide 84·2%. Yield of 2,3-dihydro-5,7-diphenyl-1,4-diazepine 36·8%.

(iii) Preparation (a) (i) was repeated with a reaction time of 48 hours at room temperature. At first the bromodiazepine did not completely dissolve in the sodium ethoxide solution, but by the end of the reaction time the mixture was clear. The reaction mixture was worked up in a different way from (a) (i), as follows. After cooling, 30% perchloric acid was added dropwise until the mixture was neutral (pH paper 6-7). The solution was concentrated on a rotary film vacuum evaporator when sodium perchlorate precipitated. Water was slowly added to the residue and the sodium perchlorate dissolved. The addition of more water precipitated 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate. Yield 0·160g. (45·9%) m.pt. 152-155°.

(b) Using molar sodium ethoxide solution; Conc. of diazepine = 0·01M.

(i) 6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) was added to molar sodium ethoxide solution (100 mls.) and the mixture heated at reflux temperature for thirty minutes. The reaction mixture was worked up as in (a) (iii) above and gave a mixture of 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate and 6-ethoxy-2,3-dihydro-5,7-diphenyl diazepinium perchlorate. Yield 0·254g. The N.M.R. spectrum of this mixture in trifluoroacetic acid showed the two compounds to be present in a molar ratio of 0·51 (6H) : 0·49 (6-Oet). This corresponds to a 33·6% yield of the ethoxy compound and 34·8% yield of the 6H compound.

(ii) The above preparation (b) (i) was repeated, but this time instead of the reaction mixture being heated, it was allowed to stand at room temperature for one week, and then worked up in the same way as in (b) (i). A similar mixture of the 6H-and 6-ethoxy-compounds was obtained. Yield 0·277g. The N.M.R. spectrum of this mixture showed the two compounds to be present in a molar ratio of 0·48 (6-H) : 0·52(6-Oet). This corresponds to a 39·2% yield of the 6-ethoxy compound and 28·8% yield of the 6H compound.

(9) Reaction of 6-ethoxy-2,3-dihydro-5,7-diphenyl-1,4-diazepine at 0·1M concentration in molar sodium ethoxide solution.

The above mixture (b) (ii) of 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate and 6-ethoxy- 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (0·140g.) was heated at reflux temperature in molar sodium ethoxide solution (2 mls.) for one hour. The reaction mixture was

worked up as for (b) (i) and a similar mixture of the 6H-and 6-ethoxy-compounds (shown by N.M.R.) was obtained. Yield 0·111g. (app. 80%).

(10) Reaction of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine in potassium isobutoxide solution.

6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide (1·42g.) was added to potassium isobutoxide (2·5g.) in isobutanol (50 mls.). The mixture was heated at reflux temperature for twenty minutes. Isobutanol was removed under vacuum and water (10 mls.) added to the residue. This mixture was extracted with ether (5 x 20 mls.). Ether was removed from the extract leaving a brown oily material which gave crystals of 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate after the addition of perchloric acid (60% 1 ml.) in water (1 ml.). Yield 0·29g. (26·0%) m.pt. 138-140°.

The compound was identified by its I.R. spectrum in nujol mull which was identical to that of an authentic specimen and by a mixed m.pt. determination with the authentic specimen.

(11) Reaction of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine in potassium isopropoxide solution.

Preliminary experiments showed that this diazepine produced 2,3-dihydro-5,7-dimethyl-1,4-diazepine when treated with molar isopropoxide solution at reflux temperature. Experiments were carried out to find whether acetone was also produced in this reaction.

Detection of acetone in reaction mixtures.

The isopropanol/acetone mixture was contained in a flask

connected to a fractionating column which had an outer jacket and inner column, containing methanol. This apparatus had been shown[44] to be effective in the separation of isopropanol and acetone. The outlet of the fractionating column was allowed to dip into a solution of 2,4-dinitrophenylhydrazine. The heating of the mixture was controlled so that the position of reflux of the isopropanol moved up the column very slowly (20-30 mins.). The first few mls. of the isopropanol were allowed to pass into the 2,4-dinitrophenylhydrazine solution.

Using this method it was found that 10 mg. of acetone could be detected in 30 mls. of isopropanol.

Expt. (a).

Potassium (1·1g.) was added in small pieces to isopropanol (40 mls.) contained in a 100 ml. flask, which was connected to the apparatus described above and heated until 5 mls. of distillate had passed into the solution of 2,4-dinitro-phenylhydrazine. No precipitate of acetone 2,4-dinitro-phenylhydrazone was formed.

Expt. (b)

The apparatus was cooled and 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium hydrobromide (1·4g.) was added to the isopropoxide solution. The mixture was heated and a further 5 mls. of distillate allowed to pass into a fresh solution of 2,4-dinitro-phenylhydrazine. No precipitate of acetone 2,4-dinitro-phenylhydrazone was formed.

Expt. (c)

The apparatus was again cooled and 1 ml. of a 1% solution of acetone in isopropanol was added to the reaction mixture. A heavy yellow precipitate formed in the 2,4-dinitro-phenylhydrazine solution when 5 mls. of distillate were allowed to pass into a fresh solution. This was shown to be acetone-2,4-dinitro-phenylhydrazone by comparison with the authentic compound.

Expts. 4 (a) (b) and (c) were repeated with the same results. It was concluded that acetone was not produced in this reaction. The combined reaction mixtures were worked up as described below.

Isopropanol was removed from the mixture under vacuum and water (5 mls.) added to the residue. This mixture was extracted with ether (5 x 40 mls.). Ether was removed from the extract and the residue treated with perchloric acid (1 ml. 60%). The precipitated salt was removed by filtration and washed with a few drops of water. This was shown to be 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate. Yield 0·870g. (38·8%).

(12) Reaction of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine in α-phenylethoxide solution.

This reaction was shown to produce 2,3-dihydro-5,7-diphenyl-1,4-diazepine in approx. 40% yield in preliminary experiments. The formation of acetophenone during this reaction was investigated.

The reaction of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) in α-phenylethanol (5 ml.) containing sodium hydroxide (·2g.) was carried out under nitrogen at 100°. Samples of the reaction

mixture were removed at five minute intervals up to half an hour and examined by thin layer chromatography on silica, eluting with petroleum ether (40-60°) containing 20% diethyl ether. The plates were developed by spraying them with 2,4-dinitro-phenylhydrazine in methanolic sulphuric acid, conditions under which acetophenone appears as an orange-red spot. The α-phenylethanol used contained a small quantity of acetophenone just discernable on the T.L.C. plate. However, no increase in this "blank" was observed on samples removed during the reaction. A 0·1% solution of acetophenone in the α-phenylethanol showed a marked increase in the intensity of coloration of the spot due to acetophenone.

(13) Reactions of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with piperidine.

6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) was added to piperidine (5 mls.) and heated for one hour at 60°. Piperidine was removed from the reaction mixture under vacuum and the residue was treated with perchloric acid (1 ml., 60%), followed by water (10 mls.). An orange solid was thrown from solution (0·42g.) m.pt. 160-170°. Its N.M.R. spectrum showed this to be a mixture of a 2,3-dihydro-5,7-diphenyl-1,4-diazepinium salt and a 2,3-dihydro-5,7-diphenyl-6-N-piperidinyl-1,4-diazepinium salt in an approx. 1:4 molar ratio. Attempts to separate the 6-N-piperidinyl compound by recrystallisation from isopropanol, methanol/ether and ethanol/ether failed.

(14) Reaction of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with benzylamine.

A 2,4-dinitrophenylhydrazine solution was prepared by dissolving the reagent (4·95g.) in conc. sulphuric acid (40 mls.) and diluting to 250 mls. with an equal volume of water and ethanol.

6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·654g.) was added to benzylamine (1 ml.) and heated in an oil bath at 100° for thirty minutes. The reaction mixture was protected from carbon dioxide by use of a drying tube containing potassium hydroxide pellets. Ether (25 mls.) was added to the cooled reaction mixture, and the resinous material which at first separated, crystallised within a few minutes. The crystals were filtered from the ether and washed with further ether (5 mls.). Yield 0·579g. (88·0%) m.pt. 255-265°, recrystallised from methanol m.pt. 270°. This compound was shown to be 2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide since its I.R. spectrum (nujol mull) was identical with that of an authentic specimen, and a mixed m.pt. determination showed no depression.

The ether extracts were combined and added to stirred 2,4-dinitrophenylhydrazine solution (25 mls.). After five minutes the orange precipitate which formed was filtered from solution and washed with a small quantity of water. Yield 0·43g. (75·2%) m.pt.235-236°. This was shown to be benzaldehyde 2,4-dinitrophenylhydrazone by a mixed melting point determination with an authentic specimen and by comparison of its I.R. spectrum (nujol mull) with that of an authentic specimen.

The experiment was repeated and the yields were 2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide 92·2%, and benzaldehyde-2,4-dinitrophenylhydrazone 67·5%.

(15) Treatment of 6-benzylamino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate with benzylamine.

6-Benzylamino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (0·1g.) was heated in benzylamine (3 mls.) at 100° for thirty minutes. After addition of ether 5 mls. the compound was recovered unchanged in almost quantitative yield.

For preparation of starting material see page 131

(16) Reaction of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine in benzylamine.

6-Bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine (0·53g.) was added to benzylamine (1 ml.) and the mixture heated for thirty minutes at 100°. When ether (5 mls.) was added to the mixture a resinous material was thrown out of solution. The ether was decanted and the resinous material was washed with more ether (4 x 5 mls.), but crystallisation did not set in. A little ethanol was added followed by a mixture of ether and acetone and by scratching the side of the tube fine white crystals were obtained. Yield 0·042g. (9·5%) m.pt. 201-202°. N.M.R. spectrum in trifluoroacetic acid signals at τ 1·6(b), 2·1(cx), 5·64(s) in ratio 2:5:4. This was shown to be 2-phenyl-imidazolinium bromide by comparison with an authentic specimen. This was made by preparation of 2-phenyl-imidazoline[45] and conversion into the bromide, m.pt. 201- 202° by addition of a little conc. hydro-

bromic acid followed by acetone. The I.R. spectra of the two compounds were identical and no depression was shown on a mixed m.pt.

The ether extract from this experiment was added to 2,4-dinitrophenylhydrazine solution (25 mls.). The precipitate which formed was filtered from the solution (0·057g. m.pt. 160-190°). The I.R. spectrum of this material was similar to that of benzaldehyde-2,4-dinitrophenylhydrazone, but there were indications of other impurities which recrystallisation did not remove.

(17) Attempted reaction of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine with benzylamine.

6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepine (2·03g.) was added to benzylamine (10 mls.). The mixture was heated one hour at 70°. The addition of ether to the mixture produced a dark brown resinous material. All attempts to crystallise this material failed.

(18) Reactions of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine on heating in various solvents.

(a) Heating in toluene

6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) was dissolved in hot dry toluene (10 mls.) and heated at reflux temperature. After fifteen minutes a precipitate appeared. Heating was continued for a further two hours and the precipitate filtered off. Yield 0·126g. (approx. 38%) m.pt. 250-255°. The I.R. spectrum (nujol mull) of this material indicated that it was mainly 2,3-dihydro-5,7-diphenyl-1,4-diazepinium bromide containing a small quantity of the bromide of the starting material.

The presence of dibenzyl in the toluene filtrate was investigated by G.L.C. in another experiment using diazepine (0·327g.) in toluene (3 mls.). No dibenzyl was detected, though it was shown that dibenzyl could easily be detected as a 0·1% solution in toluene using the same G.L.C. apparatus under identical conditions.

(b) Heating in benzene

6-Bromo-2,3-dihydry-5,7-diphenyl-1,4-diazepine (0·327g.) was dissolved in hot dry benzene (10 mls.) and heated at reflux temperature for 24 hours. The formation of a precipitate became obvious after 3 hours of heating. Yield 0·096g., m.pt. 250-258°. This was shown to be the same material as in (18) (a) by its I.R. spectrum.

(c) Heating in ethanol

6-Bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) was heated in ethanol (10 mls.) at reflux temperature for 24 hours. The ethanol was removed under vacuum and the residue treated with hot benzene (3 x 10 mls.) to remove any unreacted material. Yield of 2,3-dihydro-5,7-diphenyl-1,4-diazepine hydrobromide 0·081g. (24·1%) m.pt. 265-268°. Concentration of the benzene extract yielded the starting material in 48% yield.

(19) 2,3-Dihydro-1,5,7-trimethyl-6H-piperidinyl-1,4-diazepinium perchlorate

6-Bromo-2,3-dihydro-1,5,7-trimethyl-1,4-diazepinium perchlorate (1·0g.) was heated in piperidine (20 mls.) at 60° for one hour. Most of the piperidine was removed from the mixture under vacuum and

water (2 mls.) added to the residue, followed by perchloric acid (60%) until the mixture was just acid. More water was added and some crystals and dark oily material separated. After recrystallisation from ethanol the yield of 2,3-dihydro-1,5,7-trimethyl-6-N-piperidinyl-1,4-diazepinium perchlorate was 0·12g. (7·1%) m.pt. 122-123°. (Found: C,48·68; H,7·54; N,13·15. $C_{13}H_{24}N_3ClO_4$. requires C,48·52; H,7·52; N,13·06%). N.M.R. spectrum in Table VIII.

(20) Reactions of 6-bromo-2,3-dihydro-1,5,7-trimethyl-1,4-diazepine with molar potassium methoxide solution.

(a) 6-Bromo-2,3-dihydro-1,5,7-trimethyl-1,4-diazepinium perchlorate (0·317g.) was added to molar potassium methoxide solution (10 mls.) and heated at 50° for thirty minutes. Methanol was removed from the mixture under vacuum and water (2 mls.) added to the residue. This mixture was extracted with ether (4 x 5 mls.). Perchloric acid (60%, 1 ml.) was added to the extract and a precipitate of starting material was obtained Yield 0·182g. (57·4%). Its identity was shown by mixed m.pt. with the authentic compound and comparison of their I.R. spectra (nujol mull).

(b) The reaction above (20) (a) was repeated, but this time the reaction mixture was heated at reflux temperature for thirty minutes. Starting material only was recovered. Yield 0·038g. (12·3%).

(c) Reaction (20) (a) was again repeated but the reaction mixture was heated for one hour at reflux temperature. After removing the methanol under vacuum, water (2 mls.) was added and the mixture extracted with ether (4 x 5 mls.). The extract was dried

with anhydrous sodium sulphate and the ether removed. The N.M.R. spectrum in trifluoroacetic acid of the brown oily residue was examined in search of other products. The spectrum was rather "dirty", but signals due to C-methyl and N-methyl protons of the starting material and its 6H-analogue were obvious. In addition, signals believed to be due to C-methyl, N-methyl and O-methyl protons of the 6-methoxy compound were also observed at τ 7·52, 7·58, ($C\text{-}CH_3$), 6·59 ($N\text{-}CH_3$) and 6·34 (OCH_3).

(21) Attempted reaction of 6-bromo-2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine with potassium methoxide solution.

a) 6-Bromo-2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepinium perchlorate (0·380g.) was added to molar potassium methoxide solution (10 mls.) and heated at reflux temperature for thirty minutes. Methanol was removed from the reaction mixture under vacuum and water (2 mls.) added to the residue. This mixture was extracted with benzene (3 x 5 mls.), and benzene removed from the extract. Perchloric acid (60%, 0·15 mls.) was added to the residue. The crystals which formed were removed and were shown to be starting material by mixed m.pt. and by comparison of its I.R. spectrum (nujol mull) with that of the authentic compound. Yield 0·220g. (57·9%).

b) The experiment was repeated increasing the heating time to three hours. Dark brown tarry materials were formed when perchloric acid was added during the work-up and no products were isolated.

(22) Attempted reaction of 6-bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine with molar potassium methoxide solution.

6-Bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepinium perchlorate (0·441g.) was heated with molar potassium methoxide solution (10 mls.) for 4 hours at reflux temperature. Methanol was removed from the reaction mixture under vacuum and water (2 mls.) added to the residue. This mixture was extracted with benzene (5 x 5 mls.) and benzene removed from the extract. Perchloric acid (60%, 0·15 mls. in 2 mls. water) was added to the residue and a yellow gummy material separated. The addition of a few drops of methanol started crystallisation of this material which was shown to be starting material by mixed m.pt. and comparison of I.R. spectrum with that of the authentic compound. Yield 0·378g. (85·7%).

(23) Attempted reaction of 6-bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepinium perchlorate with molar potassium ethoxide solution.

The reaction was carried out as in (22) above but using potassium ethoxide solution instead of potassium methoxide solution. Starting material 0·330g. (74·8%) was obtained.

(24) Attempted reaction of 6-bromo-2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepine with piperidine

6-Bromo-2,3-dihydro-1,7-dimethyl-5-phenyl-1,4-diazepinium perchlorate (0·330g.) was heated in piperidine (20 mls.) for one hour at 60°. Piperidine was removed under vacuum and perchloric acid (60% 1·0 ml. in 1 ml. water) was added. The precipitate which formed

was filtered off and was shown to be starting material by mixed m.pt. and comparison of its I.R. and N.M.R. spectrum with those of the authentic compound. Yield 0·310g. (81·6%).

(25) Attempted reaction of 6-bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepine with piperidine

(a) 6-Bromo-2,3-dihydro-1-methyl-5,7-diphenyl-1,4-diazepinium perchlorate (0·441g.) was heated with piperidine (5 mls.) for four hours at 60°. Piperidine was removed under vacuum and the gummy residue treated with a little water and perchloric acid. Crystals of starting material were obtained as shown by its N.M.R. spectrum and I.R. spectrum. Yield 0·240g. (57·0%).

(b) The experiment was repeated, but the reaction mixture was heated at reflux temperature for twenty hours. On working up as above (25) (a) 2,3-dihydro-5,7-diphenyl-1-methyl-1,4-diazepinium perchlorate was obtained. Its identity was shown by its I.R. and N.M.R. spectrum Yield recrystallised from methanol 0·08g. (18·0%).

KINETIC STUDIES OF THE REACTION BETWEEN BROMODIAZEPINES AND METHOXIDE ION

The rates of reaction of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine and 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with methoxide ion were followed by means of U.V. spectroscopy. The 6-methoxy compounds show a larger extinction coefficient than their 6-H-analogues in the "phenyl" portion of their U.V. spectra. The rates of reaction at 25° of 0·01M diazepine with 0·2, 0·4 and 0·6M methoxide ion were followed by recording the U.V. spectra of reaction mixtures at appropriate time intervals. The pseudo 1st order rate constand k_1 was obtained by a plot of log(a-x) against time, and the bimolecular rate constant k_2 obtained by a plot of k_1 against methoxide concentration.

Preparation of reaction mixtures

An approx. molar solution of sodium methoxide solution was prepared by dissolving sodium (11·5g) in dry methanol (250 mls.) and making up the volume to 500 mls. at 25°. The exact strength of the solution was determined by titration against standard hydrochloric acid.

(a) Three portions, (1), (2) and (3), of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine (0·327g.) were weighed out. Each portion was dissolved in methanol and placed in a 100 ml. graduated flask. The volumes of methanol used were for (1) 75 mls. (2) 55 mls. and (3) 35mls. The flasks were placed in a water bath thermostatted at 25° for five minutes and the following volumes of app. molar sodium methoxide

solution at 25° added (1) 20 mls. (2) 40 mls. (3) 60 mls. The volume was immediately made up to 100 mls. after addition of the sodium methoxide solution and placed in the water bath at 25°. 1 ml. portions of the reaction mixture were withdrawn at the time intervals indicated, and diluted to 100 mls. with methanol containing perchloric acid (0·05 ml.,60%). The U.V. spectra were recorded.

(b) Three portions of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium bromide (0·346g.) were weighed out and the above procedure (a) followed. 1·5 ml. protions of the reaction mixture were withdrawn in this case in order to record the U.V. spectrum in the region of maximum accuracy.

(a) RESULTS

U.V. spectra in methanol.

6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepinium cation

λ max 265mμ (ε=5,810), 374mμ (ε=15,460)

2,3-dihydro-5,7-diphenyl-6-methoxy-1,4-diazepinium cation

λ max 265mμ (ε=9,860), 377mμ (ε=17,080)

Kinetic run (a)(1) Initial concs.) methoxide = 0·208M
) diazepine = 0·01M

Time hrs.	Absorbance at 265mμ	(a-x)mole litre^{-1}	log(a-x)
2	0·590	0·0097	-2·0132
4	0·630	0·0088	-2·0555
6	0·680	0·0075	-2·1249
8	0·715	0·0067	-2·1739
10	0·750	0·0058	-2·2366
12	0·770	0·0053	-2·2757
22	0·845	0·0034	-2·4685
25	0·870	0·0028	-2·5528
28	0·900	0·0021	-2·6778

Kinetic run (a)(2) Initial conc.)methoxide 0·416M
)diazepine 0·01M

Time hrs.	Absorbance at 265mμ	(a-x)mole litre^{-1}	log(a-x)
1	0·60	0·0095	-2·0230
2	0·645	0·0084	-2·0757
4	0·720	0·0065	-2·1871
6	0·780	0·0051	-2·2924
8	0·830	0·0038	-2·4202
10	0·870	0·0028	-2·5528
12	0·880	0·0026	-2·5850

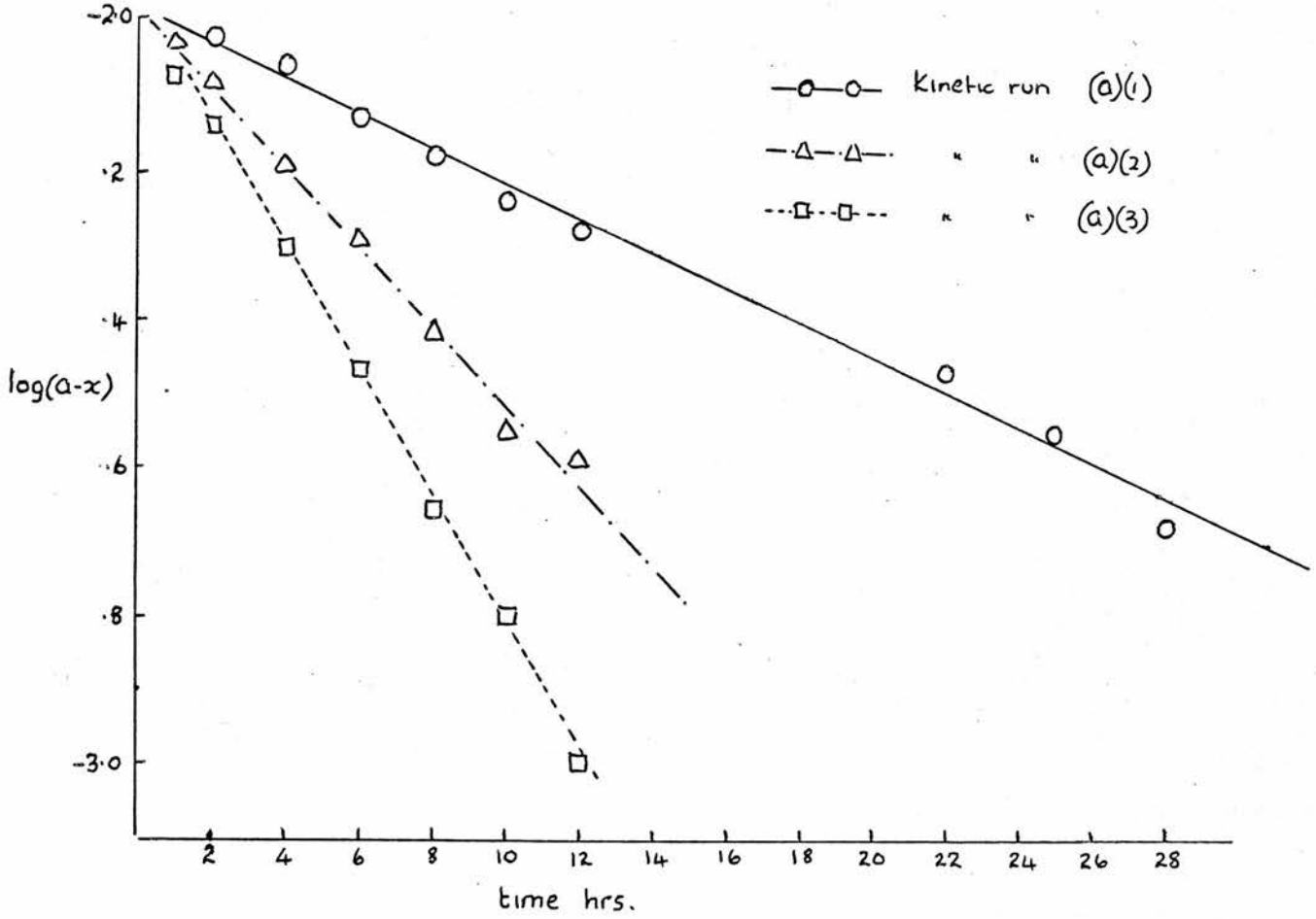
Kinetic run (a)(3) Initial conc.)methoxide 0·624
)diazepine 0·01M

Time hrs.	Absorbance at 265mμ	(a-x)mole litre^{-1}	log(a-x)
0·85	0·64	0·0085	-2·0706
2	0·69	0·0073	-2·1367
4	0·78	0·0050	-2·3010
6	0·85	0·0034	-2·4685
8	0·895	0·0022	-2·6576
10	0·92	0·0016	-2·7959
12	0·945	0·0010	-3·000

FIG. VII

Reaction of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with sodium methoxide

p. Ist. order plot.



(b) U.V. spectra in methanol.

6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepinium cation

λ max 265mμ (ε =4,200), 361mμ (ε =13,740)

2,3-dihydro-6-methoxy-5-methyl-7-phenyl-1,4-diazepinium cation

λ max 265mμ (ε =6,680), 376mμ (ε =16,020)

Kinetic run (b)(1) Initial concs. } methoxide 0·198M
} diazepine 0·01M

Time hrs.	Absorbance at 265mμ	(a-x)mole litre^{-1}	log(a-x)
1	0·635	0·0099	-2·0044
2	0·665	0·0090	-2·0458
3	0·685	0·0085	-2·0706
4	0·710	0·0078	-2·1079
6	0·740	0·0070	-2·1549
8	0·780	0·0059	-2·2291
11·3	0·820	0·0048	-2·3188
26·5	0·920	0·0022	-2·6576

Kinetic run (b)(2) Initial concs.)methoxide 0·406M
)diazepine 0·01M

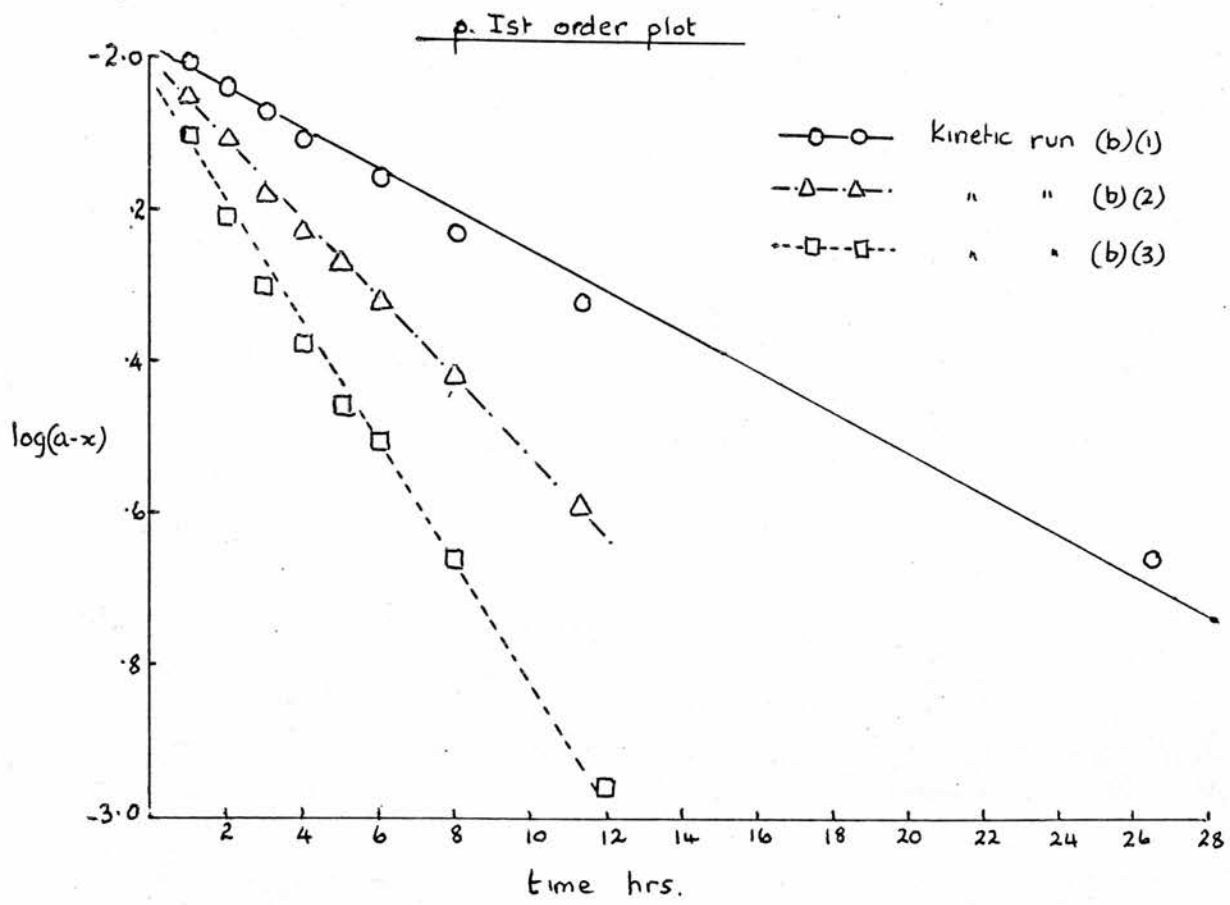
Time hrs.	Absorbance at 265mμ	(a-x)mole litre^{-1}	log(a-x)
1	0·665	0·0090	-2·0458
2	0·705	0·0079	-2·1024
3	0·750	0·0067	-2·1739
4	0·780	0·0059	-2·2291
5	0·800	0·0054	-2·2676
6	0·820	0·0048	-2·3188
8	0·860	0·0038	-2·4202
11·3	0·905	0·0026	-2·5850

Kinetic run (b)(3) Initial concs.)methoxide 0·614M
)diazepine 0·01M

Time hrs.	Absorbance at 265mμ	(a-x)mole litre^{-1}	log(a-x)
1	0·705	0·0079	-2·1024
2	0·770	0·0062	-2·2076
3	0·815	0·0050	-2·3010
4	0·845	0·0042	-2·3768
5	0·870	0·0035	-2·4559
6	0·885	0·0031	-2·5086
8	0·920	0·0022	-2·6576
12	0·960	0·0011	-2·9586

FIG. IX

Reaction of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine with sodium methoxide



Calculation of rate constants.

(a) Rate constants for reaction between 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine and sodium methoxide.

From Fig. VII

Kinetic run No.	molarity of ^-OMe	$\frac{\log(a-x)}{t}$	$K_1=2\cdot303\times-\log\frac{(a-x)}{t}$
(a) (1)	0·208	$-\frac{0\cdot5}{22\cdot1\times3,600}$	$1\cdot45\times10^{-5}$ sec^{-1}
(a) (2)	0·416	$-\frac{0\cdot5}{9\cdot7\times3,600}$	$3\cdot30\times10^{-5}$ "
(a) (3)	0·624	$-\frac{0\cdot5}{6\cdot4\times3,600}$	$5\cdot00\times10^{-5}$ "

From Fig. VIII $K_2 = 8\cdot0\times10^{-5}$ litre mole^{-1} sec^{-1}

(b) Rate constants for reaction between 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine and sodium methoxide.

From Fig. IX

Kinetic run No.	molarity of ^-OMe	$\frac{\log(a-x)}{t}$	$K_1=2\cdot303\times-\log\frac{(a-x)}{t}$
(b) (1)	0·198	$-\frac{0\cdot5}{19\cdot3\times3,600}$	$1\cdot66\times10^{-5}$ sec^{-1}
(b) (2)	0·406	$-\frac{0\cdot5}{9\cdot6\times3,600}$	$3\cdot30\times10^{-5}$ sec^{-1}
(b)(3)	0·614	$-\frac{0\cdot5}{6\times3,600}$	$5\cdot00\times10^{-5}$ sec^{-1}

From Fig X, $K_2 = 3\cdot5 \times 10^{-5}$ litre mole^{-1} sec^{-1}

FIG. VIII

Reaction of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine with sodium methoxide

2nd order plot.

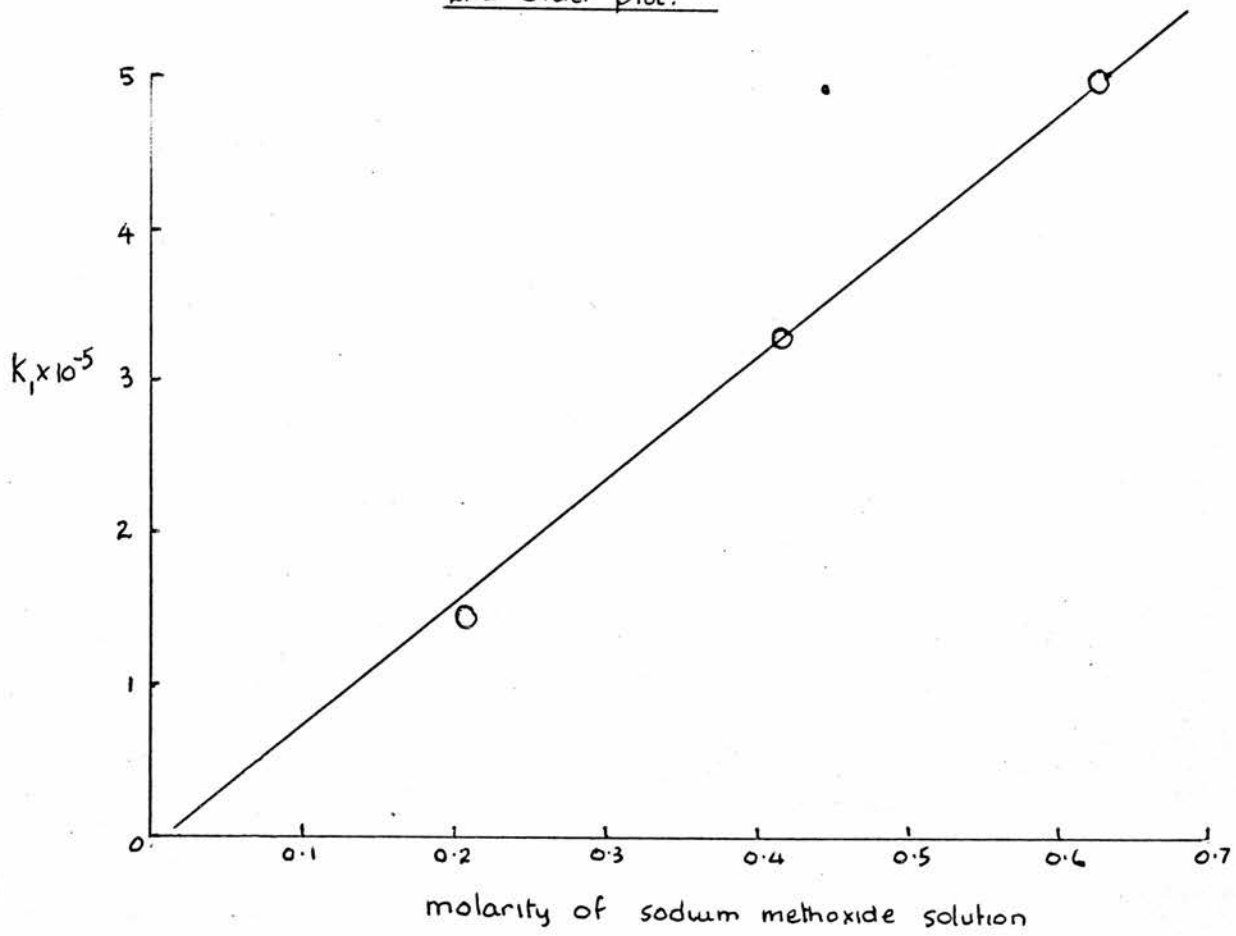
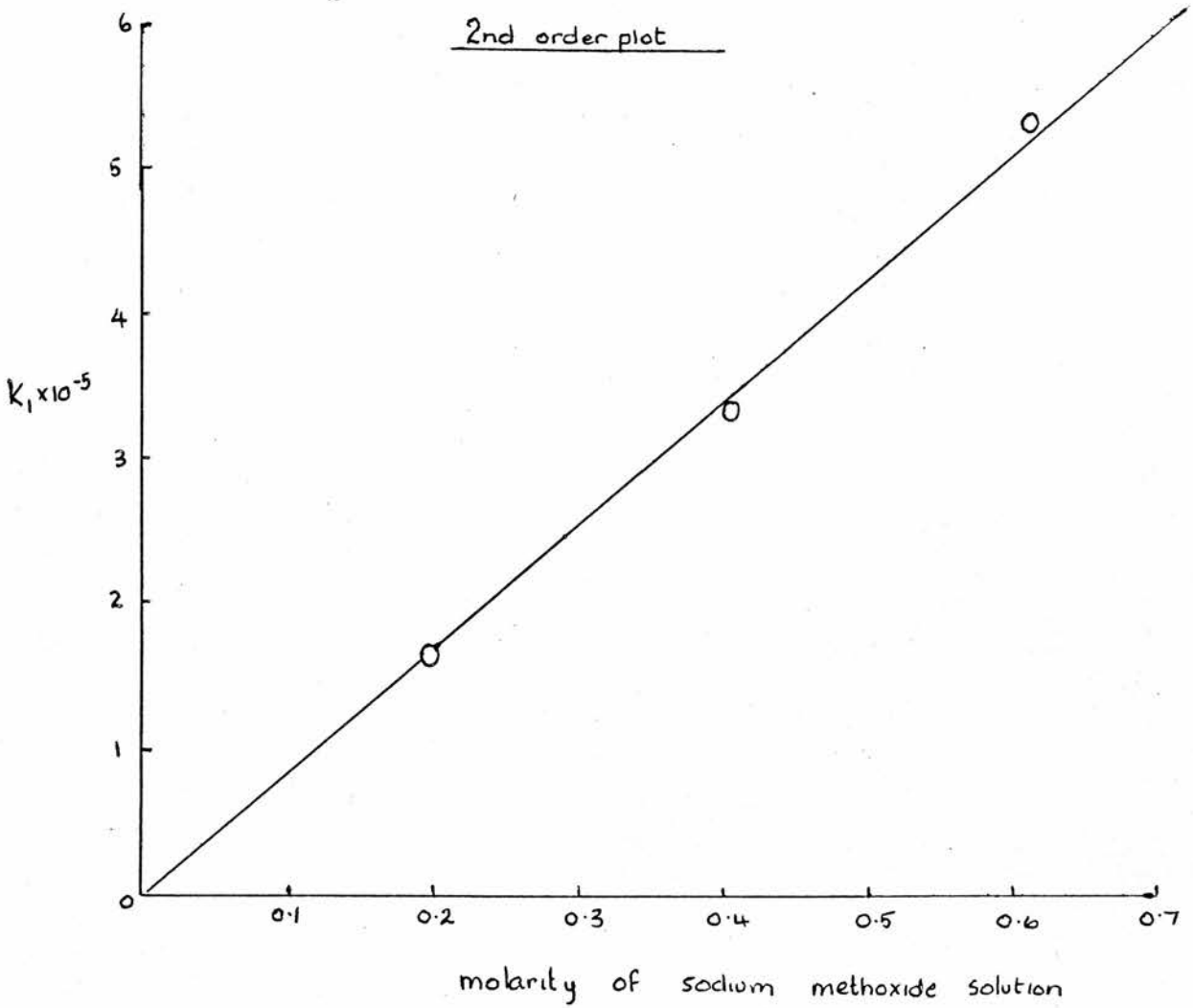


FIG. X

Reaction of 6-bromo-2,3-dihydro-5-methyl-7-phenyl-1,4-diazepine with sodium methoxide



(c) (1) 6-Amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate

Palladium charcoal catalyst (10%,3g.) was added to a hot solution of 2,3-dihydro-5,7-dimethyl-6-nitro-1,4-diazepinium perchlorate (20g.) in methanol (300 mls.) and cyclohexene (100 mls.). The mixture was heated at reflux temperature for twenty four hours when the U.V. spectrum of a sample of the reaction mixture diluted with methanol indicated that reduction was complete. The catalyst was filtered from the mixture and the solvent removed from the filtrate under vacuum. A few drops of ethanol were added to the residue and yellow crystals of 6-amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate were obtained. Yield 12·3g. (69·2%) recrystallised from ethanol m.pt. 123-124·5°. (Found: C,35·29; H,5·67; N,17·40. $C_7H_{14}N_3ClO_4$ requires C,35·08; H,5·89; N,17·53%).

(2) 6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate

Palladium charcoal catalyst (10%,1·5g.) was added to a hot solution of 2,3-dihydro-6-nitro-5,7-diphenyl-1,4-diazepinium perchlorate in ethanol (200 mls.) and cyclohexene (50 mls.). The mixture was heated at reflux temperature for twenty four hours when more catalyst (0·5g.) and cyclohexene (25 mls.) were added; the heating was continued for a further twenty four hours. The catalyst was filtered from the reaction mixture and the solvent removed from the filtrate under vacuum. The addition of a few drops of ethanol gave orange-red crystals of 6-amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate. Yield 3·0g. (70·2%), recrystallised from ethanol m.pt. 217-218°. (Found: C,55·32; H,5·05; N,11·25.

$C_{17}H_{18}N_3ClO_4$ requires C,56·13; H,4·99; N,11·55%).

The N.M.R. spectrum was in accordance with its structure see Table IX.

(D)(i)(a) 6-Benzylideneimino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate.

6-Amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (2·39g.) was added to a solution of benzaldehyde (1·3 mls.) in methanol (2 mls.). The mixture was warmed at 60° for five minutes. Yellow crystals of 6-benzylideneimino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate precipitated on cooling. Ether (25 mls.) was added to complete the precipitation. Yield 3·14g. (95·8%), recrystallised from methanol m.pt. 169·5-171·5°. (Found: C,51·47; H,5·61; N,12·55. $C_{14}H_{18}N_3ClO_4$ requires C,51·30; H,5·54; N,12·82%). N.M.R. spectrum see Table IX.

(b) 6-Benzylamino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate.

6-Benzylideneimino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (2g.) was suspended in water (5 mls.) and warmed to approx. 40°. Sodium borohydride (0·3g.) was added to the suspension in small amounts over thirty minutes. The mixture was cooled and the sticky suspended solid filtered from solution and treated with hot acetone (5 mls). The solid which did not dissolve was filtered from solution. The filtrate was treated with ether and cream coloured crystals of 6-benzylamino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate were obtained. Yield 1·05g. (52·2%)

m.pt. 139-141°. (Found: C,51·11; H,6·27; N,12·59. $C_{14}H_{20}N_3ClO_4$ requires C,50·99; H,6·11; N,12·74%). N.M.R. spectrum see Table IX.

(c) 6-Benzylideneamino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate.

6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (0·2g.) was warmed at 60° for five minutes with benzaldehyde (0·1ml.) in methanol (1·5 ml.). Ether (10 mls.) was added to the cooled reaction mixture and a light brown resinous material separated. All attempts to crystallise this material were unsuccessful, but as this resinous material was reduced to 6-benzylamino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (see prep. below) the initial reaction of benzaldehyde with the aminodiazepine was assumed to have taken place satisfactorily.

(d) 6-Benzylamino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate

6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (0·20g.) reacted with benzaldehyde as in the previous reaction. The resinous material thrown out of solution by the addition of ether was dissolved in methanol (1·5 ml.) and warmed to 40°. Sodium borohydride (0·1 gm.) was added in small portions over half an hour. After cooling the reaction mixture, water (5 mls.) was added and sticky yellow crystals of 6-benzylamino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate were obtained. Recrystallisation from acetone/ether yielded 0·11g. (44·1%). m.pt. 217-219°. (Found: C,64·32; H,5·56; N9·10. $C_{24}H_{24}N_3ClO_4$ requires C,63·50; H,5·33; N,9·26%). N.M.R.spectrum see Table IX.

(e) 2,3-Dihydro-5,7-dimethyl-6-thenylideneimino-1,4-diazepinium perchlorate.

6-Amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (2·39g.) was added to thienyl- 2-aldehyde (0·3 mls.) and the mixture heated at 100° for five minutes. Ether was added to the cooled mixture and yellow crystals of 2,3-dihydro-5,7-dimethyl-6-thenylidenimino-1,4-diazepinium perchlorate separated. Yield 3·21g. (99·4%), Recrystallised from ethanol. m.pt. 112·5-114·5°. (Found: C,43·63; H,4·67. $C_{12}H_{16}N_3SClO_4$ requires C,43·18; H,4·83%). N.M.R. spectrum see Table IX.

(f) Terephthalylidene-bis(N-6-imino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium) diperchlorate.

6-Amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (4·79g) was dissolved in methanol (50 mls.) terephthalaldehyde (1·34g.) added to the solution. The mixture was heated at reflux temperature for thirty minutes. On cooling orange crystals of terephthalylidene-bis(N-6-imino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium) diperchlorate separated, m.pt. 230-232°. Yield 4·7g. (81·4%). (Found: C,46·02; H,5·40; N,14·66. $C_{22}H_{30}N_6Cl_2O_{10}$ requires C,45·76; H,5·23; N,14·55%). N.M.R. spectrum in trifluoroacetic acid signals at τ 0·5, 1·05(b), 2·3, 6·0(m) and 7·42 in ratio of 1:2:2:4:6.

(2) Preparation of 6-diazonium salts of 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate.

(a) In perchloric acid.

A small quantity of 6-amino-2,3-dihydro-5,7-diphenyl-1,4-

diazepinium perchlorate was dissolved in a mixture of water and 60% perchloric acid. A cold concentrated solution of sodium nitrite was added dropwise to the solution at -5°. The yellow precipitate which formed was filtered off. This decomposed very violently at 230-231°. The I.R. spectrum in nujol mull showed the presence of a diazonium salt by an absorption at 2,200cm.$^{-1}$ and perchlorate by a characteristic absorption between 1,000 and 1,200cm.$^{-1}$.

(b) In hydrogen borofluoride solution

6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (0·1g.) was suspended in a mixture of 40% hydrogen borofluoride solution (0·5 mls.) and water (0·5 mls.) and cooled to -5°. A cold concentrated solution of sodium nitrite (0·04g.) in water (0·1ml.) was added dropwise and with agitation to allow the suspended amino salt to react completely. The mixture was tested continuously with potassium iodide paper to make certain that an excess of nitrous acid was present throughout the reaction. A fine yellow precipitate was obtained which decomposed at approx 180°. Yield 0·086g. Its I.R. spectrum in nujol mull showed an absorption at 2,200 cm.$^{-1}$ and also indicated the presence of perchlorate. When a small amount was ignited on a spatula a green flame was given which suggested the presence of borofluoride.

(c) Thermal decomposition of product from (b)

The product from the previous preparation was gently heated in an oil bath at 150°. Decomposition was not immediate, but when

it occurred it was very rapid and a black tarry residue remained. All attempts to isolate a product from this reaction failed.

(d) In hydrochloric acid

6-Amino-2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (0·2g.) was dissolved in a mixture of conc. hydrochloric acid (0·5 ml.) and water (0·5ml.) and cooled to -5°. Sodium nitrite solution (0·1g. in ·4ls. water) was added gradually to the diazepinium salt solution. The yellow precipitate which formed was filtered off, washed with a few drops of ice cold water and dried in a vacuum desicator. Yield = 0·192g. (85%), decomposes at 168°. The I.R. spectrum showed an absorption at 2,200cm.$^{-1}$ and also indicated the presence of perchlorate ion. This diazonium was considered to be a mixed chloride/perchlorate.

(e) Conversion of diazonium salt into 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine

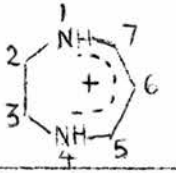
The diazonium salt (0·10g.) from the previous preparation was suspended in water (1 ml.) containing sodium chloride (0·2g.), and cuprous chloride (0·1g.). The mixture was warmed at 90-95° for one hour. After cooling it was treated with sodium hydroxide (0·4g. in 1ml. water) and extrated with benzene (3 x 5 mls.). Removal of the benzene left a small amount of pale brown oily material which partially crystallised when scratched. Yield approx. 5-6 mg. The crystals were removed and pressed out on porous pot. The I.R. spectrum of this material was identical to that of 6-chloro-2,3-dihydro-5,7-diphenyl-1,4-diazepine.

(f) Reaction of 6-amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate with nitrous acid.

Sodium nitrite solution (·04g. in 0·1 ml. water) was added dropwise to a solution of 6-amino-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (0·1g.) in perchloric acid (0·1 ml. 60% in 0·5 ml. water) at -5°. The mixture was allowed to stand for fifteen minutes at 0° and conc. sodium hydroxide solution was added, with cooling, until the mixture was alkaline. This mixture was extracted with ether until the extracts were no longer yellow. The combined extracts were dried over anhydrous sodium sulphate overnight and 60% perchloric acid was added dropwise, the wall of the vessel being scratched meanwhile until precipitation was complete. The white precipitate was filtered off and washed with a few drops of methanol. Yield 0·04g. Decomposes at $210-215^{\circ}$. Its I.R. spectrum (nujol mull) showed a strong absorption at 2,200cm.$^{-1}$ which suggested that this material was a diazonium salt.

TABLE IX

N.M.R. SPECTRA OF 2,3-DIHYDRO-1,4-DIAZEPINIUM CATIONS IN TRIFLUOROACETIC ACID

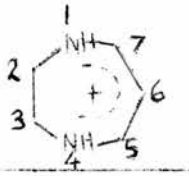


SUBSTITUENTS			POSITION OF SIGNALS - τ VALUES				
5	6	7	1,4NH	5,7-C_6H_5	2,3-CH_2	5,7-CH_3	ADDITIONAL SIGNALS OR COMMENTS
Me	nitro	Me	1·35(b)	-	6·05(m)	7·45	
Me	"	Ph	1·2(b)	2·45	6·05(m)	7·45	
Ph	"	Ph	1·3(b)	2·40	5·95(m)	-	
Me	amino	Me	1·2(b)	-	6·05(m)	7·25	
"	benzylidene imino	"	1·1(b)	-	5·95(m)	7·45	-N=CHPh 0·75(b) -N=CH-C_6H_5 1·65-2·1(cx)
"	benzylamino	"	1·3(b)	-	6·15(m)	7·55	-NHCH$_2$Ph 5·23 -NHCH$_2$C$_6$H$_5$ 2·45 -NHCH$_2$Ph not shown
"	thenylidene imino	"	0·95(b)	-	6·05(m)	7·5	protons of thenylidene gp 2·5(t) 1H, 2·3-2·5 3H
Ph	amino	Ph	1·15(b)	2·25	5·75(m)	-	-NH$_2$ not shown
"	benzyl amino	"	1·6(b)	2·25	5·8(m)	-	-NHCH$_2$Ph 5·8, -NHCH$_2$C$_6$H$_5$ 2·5-3·1(cx) -NHCH$_2$Ph not shown

(b) = broad, (m) = multiplet, (t) = triplet, (cx) = aromatic complex. Signals are singlets unless otherwise stated. Integrals are correct for structures shown.

TABLE X

N.M.R. SPECTRA OF 2,3-DIHYDRO-1,4-DIAZEPINIUM CATIONS IN TRIFLUOROACETIC ACID SOLUTION



Substituents			Position of Signals τ Values				
5	6	7	1,4NH	5,7C_6H_5	2,3CH_3	5,7CH_3	Additional signals or comments
Me	N-piperidinyl	Me	1·2(b)	-	6·05	7·2	$-NC_5H_{10}$ 6·05(m)4H, 7·8(m) 6H
"	N-pyrrolidinyl	"	1·2(b)	-	6·05	7.25	$-NC_4H_8$ 6·0(m)4H, 7·5(m)4H
"	"	Ph	0·95(b) 1·3(b)	2·2	5·9	7·15	$-NC_4H_8$ 5·9(m)4H, 7·8(m)4H
"	N-piperidinyl	"	0·8(b) 1·2(b)	2·15	5·9	7·1	$-NC_5H_{10}$ 6·1(m)4H, 7·7-9·2(m)6H
*Ph	"	"	1·05(b)	2·15	5·7	-	$-NC_5H_{10}$ 6-7(m)4H, 8-9·3(m)6H
Me	methoxy	"	2·0(b)	2·4	6·1	7·45	$-OCH_3$ 6·6
"	ethoxy	"	2·0-2·6	2·35	6·1	7·45	$-OCH_2CH_3$ 6·35(q), $-OCH_2CH_3$ 9·0(t)
Ph	methoxy	"	2·0(b)	2·4	5·95	-	$-OCH_3$ 6·85
*"	ethoxy	"	2·0(b)	2·35	5·9	-	$-OCH_2CH_3$ 6·5(q), OCH_2CH_3 9·4(t)

(b) = broad, (m) = multiplet, (t) = triplet and (q) = quartet. Signals are singlets unless otherwise stated. Integrals are correct for structures shown. * These compounds were not obtained pure and spectra characteristice obtained from mixtures with their 6H analogues.

REFERENCES.

1. J. Thiele & G. Steinnig, Ber., 1907, 40, 955.
2. W. Ried & W. Höhne, Chem. Ber., 1954, 87, 1801.
3. D. Lloyd, R.H. McDougall & D. R. Marshall, J.Chem.Soc., 1965, 3785.
4. W. Ried & E. Torinus, Chem. Ber., 1959, 92, 2902.
5. J. O. Halford & R. M. Fitch, J.Amer.Chem.Soc., 1963, 85 3354.
6. G. Schwarzenbach & K. Lutz, Helv.Chim.Acta., 1940, 23, 1139.
7. M. A. Rosanova, J. Russ. Phys. Chem. Soc., 1915, 47 611.
8. C. A. C. Haley & P. Maitland, J. Chem. Soc., 1951, 3155.
9. D. Lloyd & D. R. Marshall, J. Chem. Soc., 1956, 2597.
10. B. Eistert & F. Haupter, Chem. Ber., 1960, 93 264.
11. C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd, & D. R. Marshall, J. Chem. Soc., (C) 1966, 93.
12. F. E. King & P. C. Spensley, J. Chem. Soc., 1952, 2144.
13. M. Weissenfels, H. Schurig & G. Hühsam, Chem. Ber., 1967, 100, 584.
14. J. M. F. Gagan, personal communication.
15. H. A. Staab & F. Vögtle, Chem. Ber., 1965, 98, 2701.
16. W. Ried & W. Höhne, Chem. Ber., 1954, 87, 1811.
18. G. Schwarzenbach & K. Lutz, Helv. Chim. Acta., 1940, 23 1162.
19. S. Veibel and J. I. Nielson, Mat, Fys. Dan-Vid-Selsk., 35 No6(1966)
20. J. A. Barltrop, C. G. Richards, D. M. Russell & G. Ryback, J. Chem. Soc., 1959, 1132.
21. J. A. Barltrop & C. G. Richards, Chem. & Ind., 1957, 466.
22. D. Lloyd & D. R. Marshall, J. Chem. Soc., 1958, 118.
23. R. P. Bell & D. R. Marshall, J. Chem. Soc., 1964, 2195.

24. D. Lloyd, R. H. McDougall & D. R. Marshall, J. Chem. Soc.(C), 1966, 780.

25. G. O. Dudek & R. H. Holm J. Amer. Chem. Soc., 1961, 83, 2099.

26. S. H. H. Chaston, S. E. Livingstone, T. N. Lockyer & J.S.Shannon Aust. J. Chem., 1965, 18, 1539.

27. A. T. Mason, Ber., 1887, 20, 267.

28. B. O. Linn & C. R. Hauser, J. Amer. Chem. Soc., 1956, 78, 6066.

29. H. Wieland, Ber., 1904, 37, 1148.

30. A. C. Cope, L. E. Estes, J. R. Emery, & A. C. Haven, J. Amer. Chem. Soc., 1951, 73, 1199.

31. F. M. Jaeger & J. A. van Dijk, Proc. Akad, Sci. Amsterdam, 1936, 39, 348; 1937, 40, 12.

32. H. S. Broadbent, E. L. Allred, L. Pendleton & C. W. Whittle, J. Amer. Chem. Soc., 1960, 82, 189.

33. E. G. Rauh, G. F. Smith, C. V. Banks & H. Diehl, J. Org. Chem., 1945, 10, 1945.

34. Hammett "Physical Organic Chemistry", McGraw Hill Book Co., 1940, p.267.

35. C. D. Coryell & R. C. Fix, J. Inorg. Nuclear Chem., 1955, 1, 119.

36. J. C. D. Brand, W. C. Horning & M. B. Thornley, J. Chem. Soc., 1952, 1374.

37. T. G. Bonner & J. C. Lockhart, J. Chem. Soc., 1957, 364.

38. G. Schwarzenbach & K. Lutz, Helv. Chim. Acta., 1940, 23, 1147.

39. C. Barnett, Chem. Comm., 1967, 637.

40. R. L. Hinman & J. Lang, J. Amer. Chem. Soc., 1964, 86, 3796.

41. M. J. Jorgenson & D. R. Hartter, J. Amer. Chem. Soc., 1963,85,878.

42. H. C. Brown & R. A. Wirkkala, J. Amer. Chem. Soc., 1966,88,1447.

43. L. M. Stock & A. Himoe, Tet. Letters, 1960, No. 13, 9.

44. J. Binks, Ph.D. Thesis, University of St. Andrews, 1962.

45. R. Forsyth, V. K. Nimkar & F. L. Pyman, J. Chem. Soc.,1926,800.

46. N. V. Subba Rao & C. V. Ratnam, Current Sci. (India), 1955,24,299.

47. J. I. Nielsen, personal communication.

48. C. Barnett, J. Chem. Soc. (C), 1967, 2436.

49. C. Barnett, D. Lloyd & D. R. Marshall, J. Chem. Soc.(B),1968,in press.

50. L. M. Turton, personal communication.