To Mother, Father and Charlie

INVESTIGATIONS INTO SOME 2,3-DIHYDRO-1,4-DIAZEPINIUM SALTS AND RELATED COMPOUNDS

being a Thesis

presented by

MARGOT STRUTHERS, B.Sc.

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

St. Andrews

September 1982

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, with the approval of the Faculty of Science, in the Departments of Chemistry of the Philipps Universität, Marburg (4 terms) under the supervision of Prof. Dr. Chr. Reichardt, and the University of St. Andrews (8 terms) under the supervision of Dr. D.M.G. Lloyd.

CERTIFICATE

I hereby certify that Miss Margot Struthers has spent the requisite period of research under my supervision, has fulfilled the conditions of the University Court 1967, No. 1, and is qualified to submit the accompanying thesis in application for the degree of Ph.D.

Director of Research

UNIVERSITY CAREER

I entered the University of St. Andrews in October 1975 and graduated B. Sc. with Second Class Honours (Division One) in Chemistry in July 1979.

The research described in this thesis was carried out between October 1979 and September 1980 at the Philipps Universität, Marburg, during which time I held a Scholarship awarded by the British Council in association with the D.A.A.D., and between October 1980 and September 1982 at the University of St. Andrews. During this time I held a Research Studentship awarded by the University of St. Andrews.

ACKNOWLEDGEMENTS

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My thanks are due to the technical staff of both the Philipps Universität and the University of St. Andrews, especially Mrs.M.Smith (N.M.R. spectra), Mr.C.Millar (mass spectra), Mrs.S.Smith (microanalyses, St.Andrews) and Herr Pfeiffer (microanalyses, Marburg). My thanks are also due to my friends and colleagues in the departments whose assistance and advice was, at times, of chemical interest.

I wish to thank the British Council for the award of a scholarship to study in Germany for a year, and to the University of St. Andrews for the award of a Research Studentship.

Finally, I wish to thank the Computing Laboratory of the University of St. Andrews for allowing me to use the "simple text processor" programme which enabled me to type this thesis.

SUMMARY

The preparation of some 6-hydroxy-2,3-dihydro-1,4-diazepinium salts and 5-hydroxy-2-oxo-1,2-dihydro-pyrimidinium salts and their phenylogues from hydroxymalonaldehyde and its derivatives was investigated.

Preparation of the 6-hydroxy-1,4-dimethyl-diazepinium salt was not achieved. Instead, a 2-formyl-1,4-dimethyl-1,4,5,6-tetra--hydropyrazinium salt was obtained ; methylation of this species was investigated. Preparation of the N-unsubstituted salt was unsuccessful. Eistert and Haupter reported the preparation of the 6-hydroxy-1,4-diphenyl-diazepinium salt in 1960. For comparison, the preparation of some 6-methoxydiazepinium salts and some 5-hydroxy-2-oxo-pyrimidinium salts was investigated.

A series of 2,3-dihydro-6-hydroxyphenyl-1,4-diazepinium perchlorates was successfully prepared. The acidity of these salts in comparison with phenol was examined. Also, the reactivity of 6-hydroxyphenyl-diazepinium salts with respect to electrophilic aromatic substitution was investigated. To this end, the diazepinium salts were caused to react with a variety of electrophiles, resulting in the isolation of a number of bromophenyl- and p-nitrobenzeneazophenyl-diazepinium perchlorates.

The alkylation of the hydroxy group of the 6-hydroxyphenyldiazepinium salts was examined. Methylation of the hydroxy group was successful for the N,N´-substituted diazepinium salts, but the N,N´-unsubstituted salts were preferentially methylated on their nitrogen atoms.

The unexpected N-methylation of some 6-hydroxyphenyl-diazepinium salts prompted further study of some other N,N´-unsubstituted diazepinium systems with similar success.

The meta- and para-hydroxyphenyl-diazepinium salts were obtained from their acroleins or vinamidinium salts. These precursors were prepared from the appropriate hydroxyphenyl acetic acids. An attempted analogous reaction to produce the ortho-hydroxyphenyl precursors caused the formation of a benzofuran-type molecule.

Protodehalogenation reactions of some dihydrodiazepinium bromides was investigated. Earlier research had led to the proposal of an "onium anion" as an intermediate in the reaction. Further investigation favoured this intermediate. For the protodehalogenation of some 6-halogeno-dihydrodiazepinium salts at elevated temperatures it was noted that a "cut-off" temperature exists below which no dehalogenation occurs, and above which, in solvent only, the halogen atom is extracted.

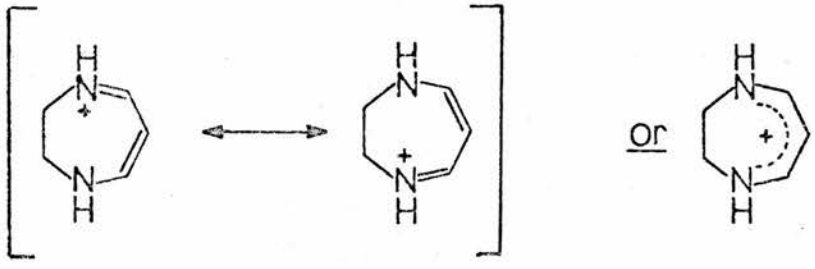
CONTENTS

2,3-DIHYDRO-1,4-DIAZEPINIUM SALTS

INTRODUCTION

The terms "dihydrodiazepine" and "dihydrodiazepinium", as used in this account, refer to 2,3-dihydro-1,4-diazepines (1) and their monocations (2) respectively.

(1)



(2)

The first example of a 2,3-dihydro-1,4-diazepine was prepared in 1940[1]. Because of the chemical resemblance of diazepines to benzenoid compounds, and their quasi-aromatic[2] or meneidic character[3], diazepines and their monocations have, in recent years, been extensively reviewed[4,5,6]. In this review it is therefore considered sufficient to outline only briefly the properties of these compounds.

Dihydrodiazepines, and especially their monocations, are very stable species, the presence of a symmetric delocalised system of π-electrons in the derived cation resulting in a resonance energy of about 19 kcal mol^{-1} [8]. Dihydrodiazepines are very strong bases, sharing with amidines the distinction of being perhaps the strongest

organic bases known, with pK_a values in the region of 13-14[1]. They readily form the monocation - over a wide pH range the monocation is the predominant species, the dication forming only in very strong acid. This is a reflection of the high stability of the monocation system.

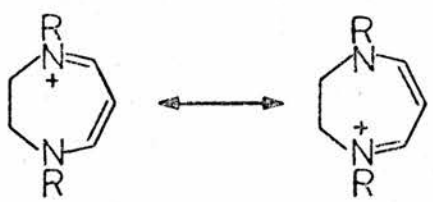
The term "quasi-aromaticity" can be illustrated by a general consideration of the vinamidinium system (3), the dihydrodiazepinium monocation itself providing a good example of this system (atoms 4-7,1).

$$\overset{+}{N}H_2{=}CH{-}CH{=}CH{-}NH_2 \longleftrightarrow NH_2{-}CH{=}CH{-}CH{=}\overset{+}{N}H_2$$

(3)

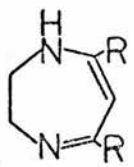
Despite the absence of closed cyclic conjugation, the system has a high resonance stability, and it is this stability which accounts for the tendency to react by substitution rather than by addition. For example, halogenation readily occurs at the 6-position of dihydrodiazepinium cations to give 6-substituted products. "Quasi-aromaticity" or "meneidic" behaviour may be concisely summarised by the phrase "the tendency to retain the type"[7].

It is interesting to note that the vinamidinium system may be represented as a hybrid of two identical canonical forms, analogous to the two Kekulé representations for benzene.



STRUCTURE

The dihydrodiazepine base may have either the conjugated form (4), or the non-conjugated bisimine form (5).



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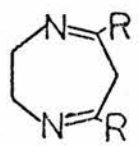


(5)

All spectroscopic evidence[9,10,11,12] implies that the preferred structure is that of the conjugated form (4), with rapid tautomeric exchange of a hydrogen between the two nitrogen atoms[12]:

-The ^{1}H-N.M.R. spectra, for symmetrically substituted dihydrodiazepines, show that the protons at the 2 and 3 positions and also the 5 and 7 positions are, respectively, equivalent at ambient temperature. The spectra also show a single proton peak for the proton at C6 (δ=5.6ppm).

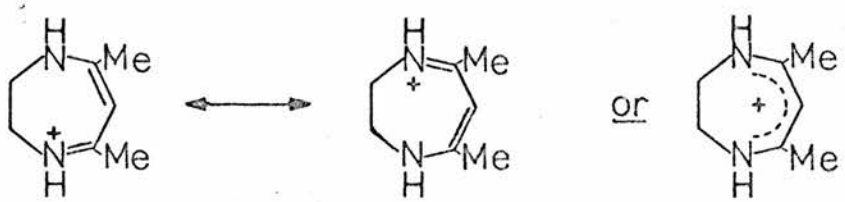
-The I.R. spectra[10,12] of dihydrodiazepines have an N-H absorption between 3150 cm^{-1} and 3190 cm-1, no normal C=N stretching absorption, but instead a characteristic absorption between 1500 cm-1 and 1600 cm-1.

-The U.V. spectra[11,13] have a long wave band below 300 mμ : this is not in agreement with the structure of a bisimine having two isolated

C=N- bonds, but is in agreement with a conjugated π-electron system.

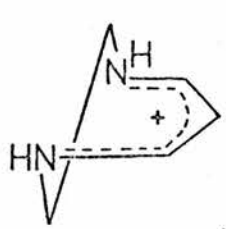
The diazepinium monocation also has a conjugated structure, eg.(2), as indicated by spectroscopic evidence[13].

The ^{1}H-N.M.R. spectrum[13] of the 5,7-dimethyl derivative, (6), showing signals at approx. δ= 7.8 (singlet), 5.1 (singlet), 3.8 (multiplet), and 2.3 ppm. (singlet), ratio (2:1:4:6), is in full accord with the symmetry of the monocation as shown below.



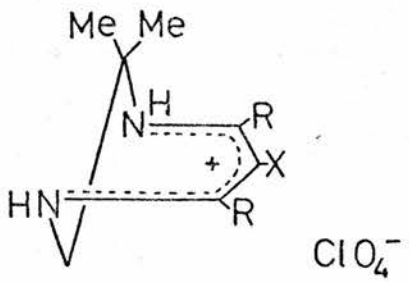
(6)

Models of diazepinium salts[10] indicate that the vinamidinium portion of the ring has the shape of one turn of a rather flat helix, the 2,3-bond forming the connecting "step". N.M.R. studies[14] show coupling constants between the 6-CH and NH groups : for coupling to take place through four bonds in a simple system, a planar W-shaped conformation of bonds is normally required. This therefore shows that the whole delocalised portion of the molecule is effectively coplanar. The representation of the ring as the "half-chair" conformation (7) is also valid since the N-H bonds are then coplanar with the 6-CH bonds.



(7)

Variable temperature ^{1}H- and ^{13}C-N.M.R. studies[14,15] have shown that the dihydrodiazepinium ring has the "half-chair" conformation which rapidly inverts at ambient temperature, but not at lower temperatures. Studies[14] of various 2,2-dimethyl-dihydrodiazepinium salts (8) have provided a range of coalescence temperatures, for example :



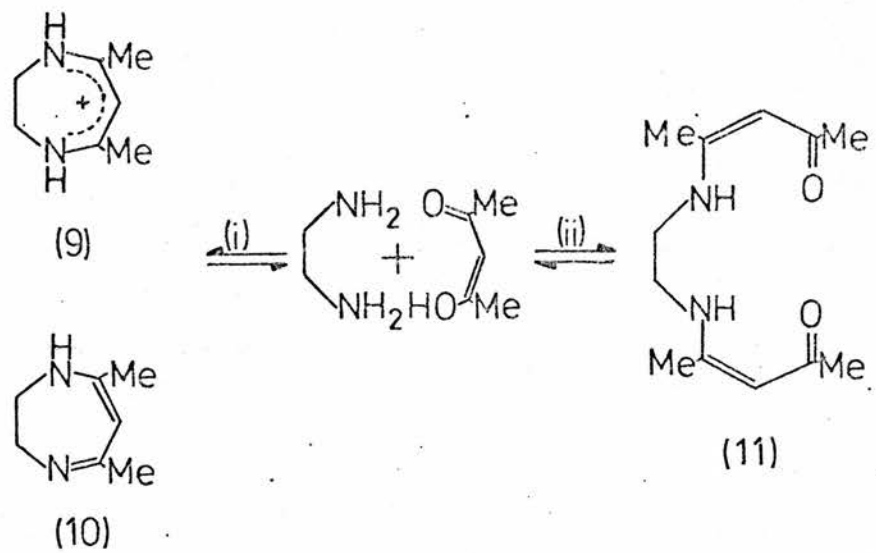
(8)

Compound	Coalescence Temp. °C
R = Me X = H	4 + 1
R = Me X = Br	-25 + 1
R = Ph X = H	-2 + 1

The results of recent X-ray crystallographic studies[16] on the simple 5,7-dimethyl derivative are in complete agreement with previous suppositions in establishing the shape of the molecule and the delocalised nature of the unsaturated portion, the C-C and C-N bond lengths averaging, respectively, 1.390 and 1.319 Å.

PREPARATION

The first reported preparation of a dihydrodiazepine was by Schwarzenbach and Lutz in 1940[1]. They treated ethylenediamine with acetylacetone under acidic conditions ($HClO_4$), and obtained, in good yield, the perchlorate salt (9) as a condensation product. They found the dihydrodiazepinium cation to be extremely stable, and the corresponding dihydrodiazepine base (10), obtained by treating the cation with sodium hydroxide, to be an extremely strong organic base. Earlier workers on the reaction between acetylacetone and ethylenediamine did not record the formation of any dihydrodiazepine derivative, but only an open-chain condensation product (11)[17], formed from two molecules of ketone and one of amine.



(i) pH < 6 or > 10

(ii) RT , neutral or mildly alkali

Schwarzenbach and Lutz obtained both products by varying their reaction conditions and later work has shown that :

-If the reaction is carried out in mildly alkaline or neutral medium at room temperature[1,5,13,18], the bis-oxoenamine (11) forms.

-At higher temperatures the yield of bisoxoenamine drops sharply, even at the pH most favoured for its formation[18].

-At pH less than 6 or greater than 10, the dihydrodiazepine (or its salt) is the main or only product[18].

Assimilation of early research led to general preparative methods for both bisoxoenamines and dihydrodiazepines[5,13]:

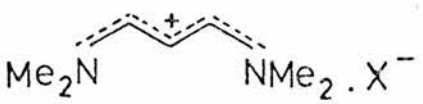
-The bisoxoenamines are generally best prepared by mixing the diketone and the diamine together in a 2:1 molar ratio, either neat or in methanol or ethanol. The product separates on standing[5,13].

-The general dihydrodiazepine preparation involves heating an equimolar mixture of diketone and diamine to ca. 120° in acetic acid for 15 minutes. After cooling, addition of perchloric acid causes precipitation of the diazepinium perchlorate, whereas addition of 2N-potassium hydroxide precipitates out the diazepine base[5,13].

The principal synthetic route to dihydrodiazepines remains that of condensation reactions between 1,2-diamines and 1,3-dicarbonyl compounds, in solutions of appropriate pH[6,19,20,21]. Slight modification of the conditions does sometimes result in improved yields for individual diazepines[10,22,48,49], in particular when using aryl diketones as reactants[23,24,25]. For example, the condensation of benzoylacetone with ethylenediamine yields a bisoxoenamine over a much wider pH range, and indeed, in alkaline solution the bisimine derived from ethylenediamine and acetophenone forms[24]. To obtain the best yield of dihydrodiazepine in this case requires definite modification of the reaction conditions, this being due to the lower reactivity of aryl-substituted carbonyl groups in general[24,25].

A variety of dihydrodiazepines, including some not otherwise readily available, has been made from derivatives of carbonyl compounds, such as diazapentadienium or vinamidinium salts (12),(13), and azaoxapentadienium salts (14), as opposed to the related dicarbonyl compounds themselves[26,27,29,32].

(12)



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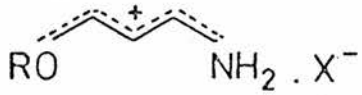
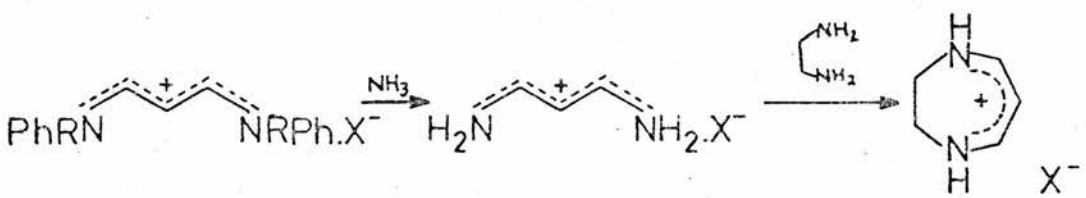


(14)

Direct reaction of these salts with diamines is not always straightforward. In many cases high dilution conditions are required[27], or some other modification must be made. For example, when diazapentadienium salts react with diamines, there is considerable difference in the rates of replacement of the first and second aryl amino groups[27], and therefore in some cases side products may result. This problem may often be resolved by passing ammonia through a solution of the salt before adding the diamine. The driving force of the reaction is thermodynamic, relying on the good leaving tendencies of the aryl amines - passing ammonia through the solution causes displacement of an aryl amino group by $-NH_2$ which is itself displaced by the diamine ; the ammonia can then itself be easily removed from the solution[27].

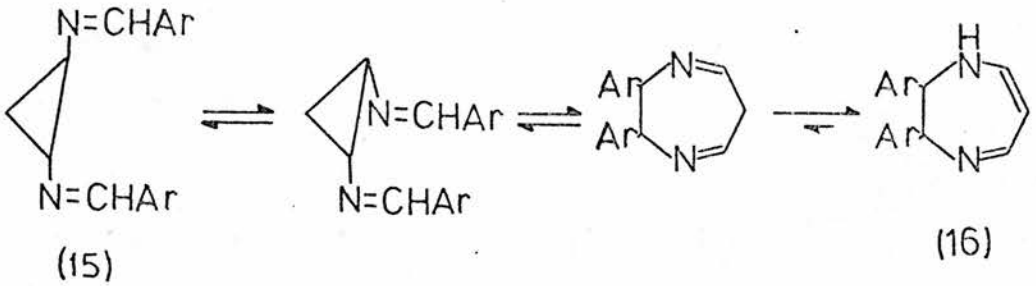


This modification has been used to prepare dihydrodiazepines previously unobtainable by the reaction of the diamine with either a dicarbonyl compound or directly with a vinamidinium salt.

Dihydrodiazepines have also been prepared by methods which do not involve a condensation reaction, for example -

-The addition of excess ethylenediamine to buta-1,3-diyne[30] gives a high yield of 5-methyl- dihydrodiazepine.

-An unusual preparation involves isomerisation of a Schiff base. Bisanils of 1,2-diaminocyclopropanes (15) undergo a Cope rearrangement when heated to 120-130°, thereby forming 2,3-diaryldihydrodiazepines (16)[11,12,31].

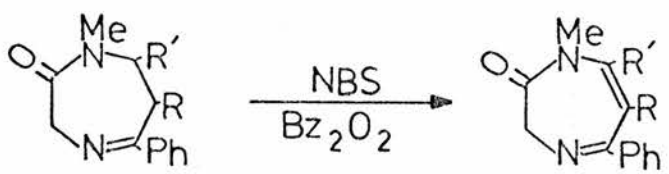


(15) (16)

Ar = Ph , p-$MeOC_6H_4$, p-MeC_6H_4 , ∝-naphthyl

The above reaction sequence was proposed, with the overall equilibrium of the reaction being controlled by the equilibrium of the last step, which is almost entirely on the side of the conjugated form[12].

-The dehydrogenation of 2,3,6,7-tetra-dihydrodiazepines (17) with benzoylperoxide and N-bromosuccinimide results in the formation of 1-methyl-2-oxodihydrodiazepines (18)[5].

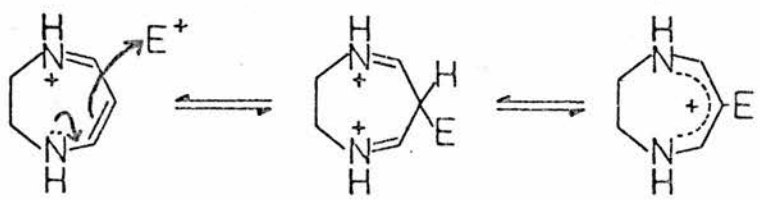


(17) (18)

The preparation of dihydrodiazepines has thus been extensively studied.

REACTIONS

The 2,3-dihydro-1,4-diazepinium cations clearly do not have an aromatic structure as normally accepted, but are nevertheless highly stable[10,13], the extreme stability being ascribed to the presence of a symmetric delocalised system of π-electrons. Their reactivity can be understood by consideration of this delocalised vinamidinium system. This portion is electron rich, and therefore reactive towards electrophiles, despite the positive charge. Electrophiles characteristically attack dihydrodiazepinium cations at the 6-position, this being the electron-rich site, to give 6-substituted derivatives ; reaction is thought to proceed via an intermediate -complex (19) analogous to the Wheland intermediate in the electrophilic substitution of benzenoid compounds.



(19)

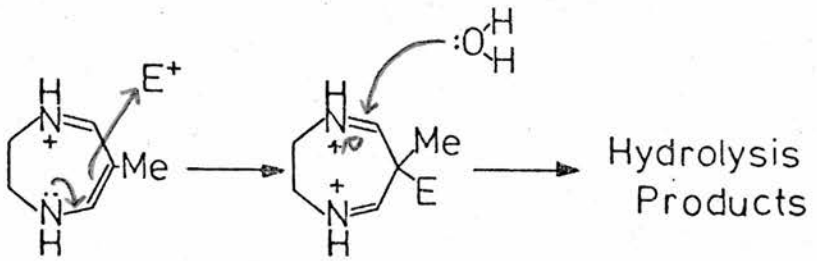
E = D,Br,Cl,I,NO_2

Thus, 2,3-dihydro-1,4-diazepinium cations are readily deuteriated[12,33,34,35,42] halogenated[13,22,34,36,37] nitrated[38,39,40,41] and also couple with diazonium salts[49]. An interesting feature of these reactions is that some of them represent rare examples of electrophilic attack by a cation on another cation.

The electrophilic substitution reactions of the 2,3-dihydro-1,4-diazepinium cations occur under conditions similar to those used for benzene derivatives, kinetic studies having shown the involvement of the dihydrodiazepinium cation in the reaction. The kinetics of halogenation[34,50] and nitration[50] reactions closely resemble those of benzenoid compounds, in the case of halogenation resembling those for activated benzene derivatives, such as phenols or amines.

For attack of an electrophile at the 6-position a stable intermediate dication structure can be drawn, however a similar structure cannot be drawn for electrophilic attack at the 5- and 7-positions[7,33,42,43]. This is reflected in the enormous difference in reactivity towards electrophiles between the 6-position and the 5- and 7-positions[33,43]. Deuteriation studies on the unsubstituted cation using deuteriotrifluoroacetic acid confirm the unreactivity of the 5,7-positions towards electrophiles - the 1,4,6-protons are exchanged very rapidly whereas no exchange of the 5,7-protons had occurred after 9 days[42].

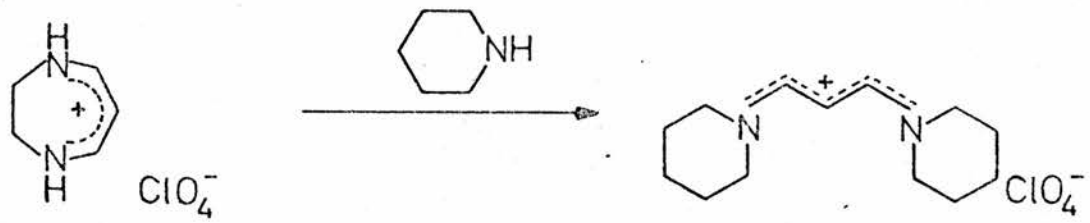
Electrophiles will also react with 6-bromo- and 6-methyl-substituted dihydrodiazepinium cations at the 6-position, despite the loss of resonance stabilisation in the process[43,44]. The dication intermediate formed cannot lose a proton to regain this resonance stabilisation, and the intermediate, as a bisiminium salt (20), is readily hydrolysed.



(20)

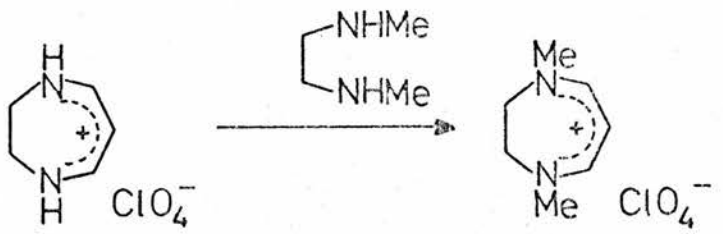
The reactivity of the 6-position of dihydrodiazepinium salts can be transmitted through, for example, a phenyl ring. Thus, a 6-phenyldiazepinium cation undergoes electrophilic aromatic substitution at the <u>para</u> position of the phenyl ring[45].

The 5- and 7-positions of dihydrodiazepines are electronically favourable for nucleophilic attack, however these sites are often surprisingly inert to nucleophiles. Studies of 5,7-unsubstituted derivatives have shown that this observed unreactivity is due to the inhibiting effect of substituents in the 5,7-positions[42], presumably for steric reasons. Reaction of the unsubstituted salt with piperidine results in elimination of $NH_2CH_2CH_2NH_2$ and formation of an open-chain vinamidinium salt (21), whereas the 5,7-dimethyl derivative remains unchanged even after keeping it in a methanolic solution of piperidine for a week[42].



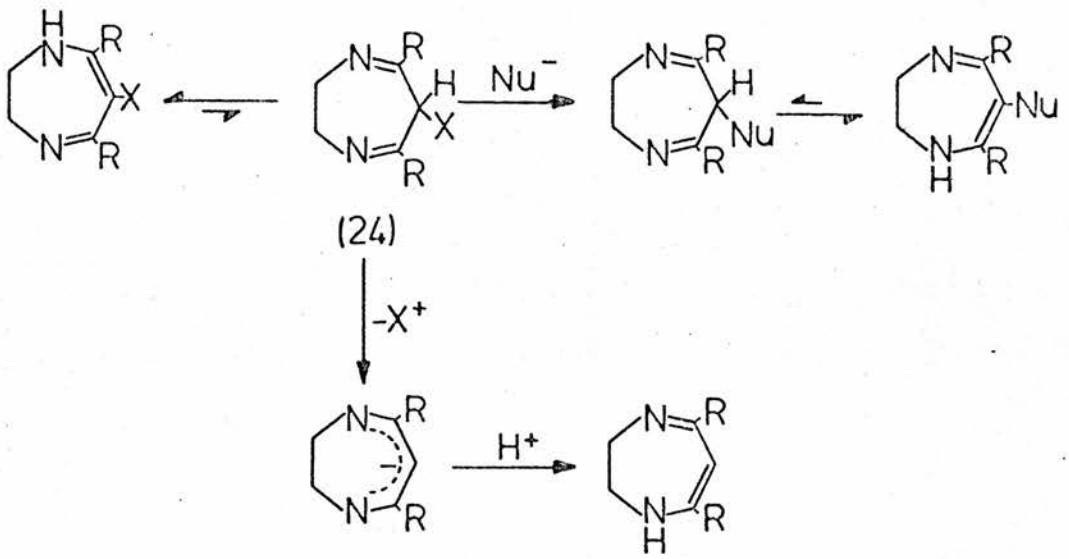
(21)

In some cases transdiazepination may occur, for example, the reaction of an unsubstituted dihydrodiazepine (22) with 1,2-dimethylethylenediamine to give a 1,4-dimethyldihydrodiazepinium salt (23)[42].



(22) (23)

With 6-halogenodihydrodiazepines, nucleophilic attack has unexpectedly been observed at the 6-position resulting in either substitution of the halogen atom by the nucleophile, or alternatively by hydrogen [36,37,46,77]. The 6-position of the dihydrodiazepine is electron rich and normally a site for electrophilic attack. Reaction with nucleophiles at the 6-position has therefore been taken to involve the bisimine tautomer (24), the 6-position then being adjacent to three electron-withdrawing groups and consequently prone to nucleophilic attack[5]. Bisimine formation involves loss of conjugation and is therefore disfavoured, although energetic considerations suggest that it might be present to the extent of ca.10%[47]. The course of the reaction is determined by steric factors; if X, R, or Nu^- are large, protodehalogenation may take place, the 6-unsubstituted compound being isolated[5,36,46]. Thus, when X = Br, R = Me and Nu^- = Bu^tO^- the 6-unsubstituted compound results, but if Nu^- = MeO^- the 6-methoxydihydrodiazepine is obtained[46].



Nu^- = nucleophile

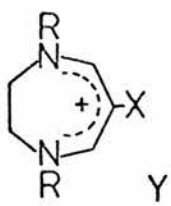
Less investigated are a variety of rearrangement reactions which dihydrodiazepines undergo. For example, 2,3-diphenyl-dihydrodiazepine decomposes to yield ammonia and 2,3-diphenylpyridine[29]. Also dihydrodiazepines undergo a degenerate Cope rearrangement[11,12,29,31], as previously mentioned.

DISCUSSION

INTRODUCTION

A number of 6-substituted-2,3-dihydro-1,4-diazepinium salts has been prepared. The presence of the 6-substituent often has a marked effect on the overall properties of the meneidic system, so that the introduction of a hydroxy group into a diazepinium salt should affect the properties of the system, and the hydroxy group will itself be affected by the delocalised system. The preparation of such systems (25) was investigated.

As previously considered, the reactivity of the 6-position of dihydrodiazepinium salts can be transmitted through a phenyl ring[45], substituted at this position. The introduction of a hydroxy group into such a phenyl ring poses some interesting questions - will the resulting compound react as a phenol, and how will it be affected by the diazepinium system, for example, with respect to electrophilic aromatic substitution in the phenyl ring, and with respect to the acidity of the compound ? The hydroxy group and the diazepinium system are both "donor" groups, and as such are strongly activating and ortho/para directing.



Y^-

X = OH , $\underline{p}$-C_6H_4OH , $\underline{m}$-C_6H_4OH , $\underline{o}$-C_6H_4OH

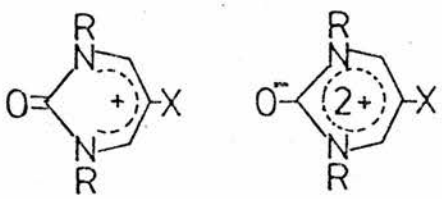
R = H , Me , Ph

Y = ClO_4^- , BF_4^-

(25)

In addition, some 2-oxo-1,2-dihydropyrimidinium salts, (26), were studied. In comparison with the 2,3-dihydro-1,4-diazepinium ions, the 2-oxo ions show a lower reactivity of their vinamidinium system. To illustrate this, the rate of deuteriation of 5,7-dimethyldihydrodiazepinium salts and their 2-oxodihydropyrimidinium analogues can be considered[62] : the rate of deuteriation is about 10^{10} times slower for the 2-oxodihydropyrimidinium salts. This is because the 2-oxodihydropyrimidinium nucleus has two stable delocalised systems, namely, the 1,5-diazapentadienium system and the urea type system, which both compete for the excess of electrons. This competition results in greatly reduced reactivity of the normally electron-rich 1,5-diazapentadienium system towards electrophiles as compared with an unperturbed 1,5-diazapentadienium system .

The 2-oxodihydropyrimidinium nucleus could have an alternative resonance form (27). N.M.R. studies have shown that the signals due to the pyrimidinium nucleus occur at significantly lower field than those of a dihydrodiazepinium nucleus. This is consistent with an inductive deshielding and with a mesomeric deshielding due to the resonance structure (27)[62].

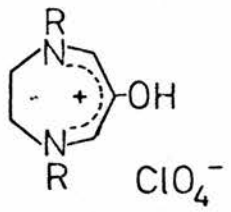


(26) (27)

X = OH , <u>p</u>-C_6H_4OH , <u>m</u>-C_6H_4OH , <u>o</u>-C_6H_4OH

R = H , Me , Ph

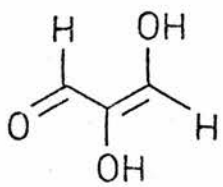
2,3-DIHYDRO-6-HYDROXY-1,4-DIAZEPINIUM PERCHLORATES



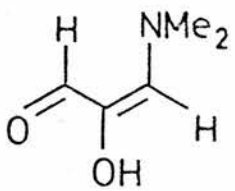
a) R = H
b) R = Me
c) R = Ph

(28)

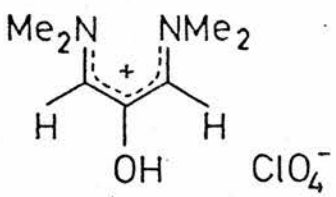
The 6-hydroxy-1,4-diazepinium perchlorates (28) might be preparable by the condensation reaction of a substituted N,N´-ethylenediamine with hydroxymalonaldehyde (29), or a derivative such as the acrolein (30) or the vinamidinium salt (31), in the presence of perchloric acid. Of these reactants, the ethylenediamines are commercially available, but of the hydroxy compounds only hydroxymalonaldehyde is readily available.



(29)



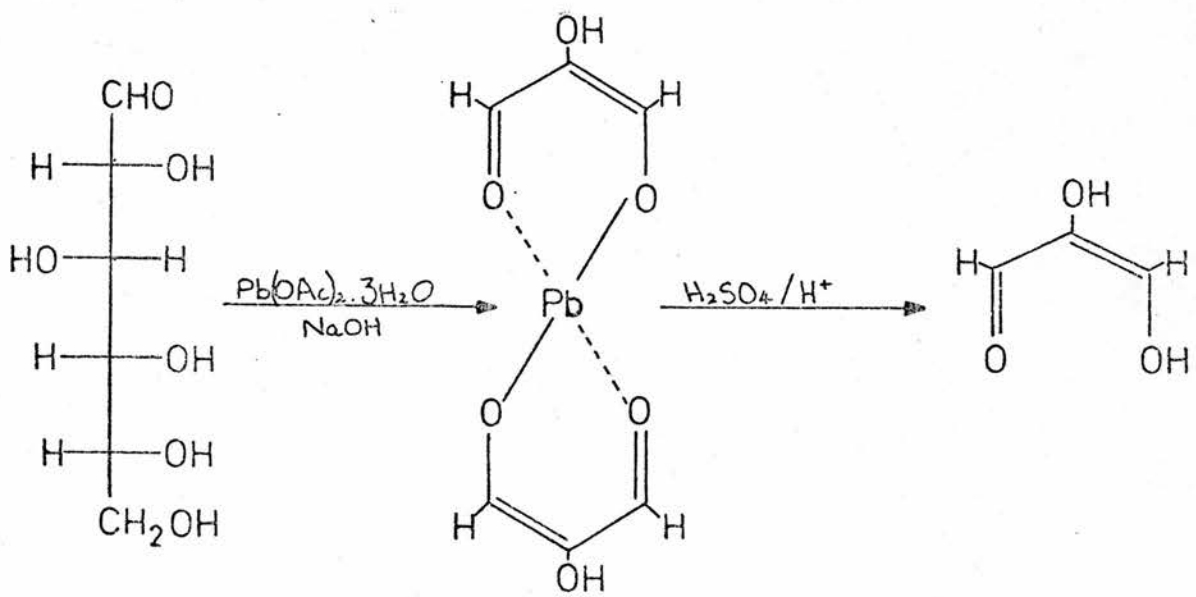
(30)



(31)

A : Preparation from hydroxymalonaldehyde

Hydroxymalonaldehyde, or triose-reductone, as it is also known, has been well studied[51-61], and there are a number of synthetic methods by which it can be made[54,55,58-61]. The method used was somewhat tedious ; however, it involved only a two-step process[60] (31), and the starting materials were relatively inexpensive.



(32)

6-Hydroxy-1,4-diphenyl-1,4-diazepinium perchlorate (28c) was first synthesised in 1960 by Eistert and Haupter[55]. They obtained this diazepinium salt by the condensation reaction of N,N'-diphenylethylenediamine with hydroxymalonaldehyde in the presence of methanolic perchloric acid.

By analogy, it was hoped to obtain the 6-hydroxy-1,4-diazepinium and the 6-hydroxy-1,4-dimethyl-1,4- diazepinium perchlorates, starting from ethylenediamine and N,N´-dimethylethylenediamine respectively. Preparation of these two compounds was not achieved, but the attempts did however provide some interesting results.

(i) ETHYLENEDIAMINE + HYDROXYMALONALDEHYDE

Reaction of ethylenediamine with hydroxymalonaldehyde in the presence of methanolic perchloric acid resulted in the formation of a dark red solution. Removal of the solvent yielded a thick tar, from which no product could be isolated. Attempts to characterise this tar by ^{1}H-N.M.R. spectroscopy were unsuccessful.

In some respects this result is not surprising. 6-Hydroxy-1,4-diazepinium perchlorate (28a) is likely to be highly reactive, and might consequently react further, for example, dimerisation may occur.

(ii) N,N´-DIMETHYLETHYLENEDIAMINE + HYDROXYMALONALDEHYDE

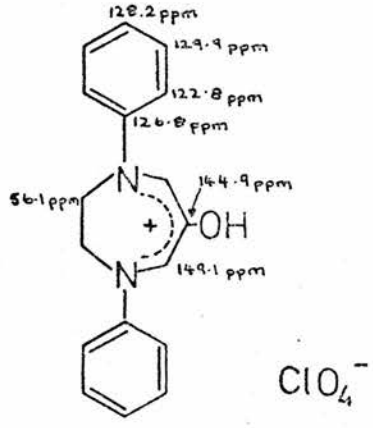
Reaction of N,N´-dimethylethylenediamine with hydroxymalonaldehyde in the presence of methanolic perchloric acid resulted in the precipitation of white needles. These were initially believed to be the 6-hydroxy-1,4-dimethyl-1,4-diazepinium perchlorate (28b), however, spectroscopic investigation proved otherwise.

Microanalysis results support the possibility of the product being the diazepinium perchlorate, ($C_7H_{13}ClN_2O_5$). ^{1}H-N.M.R.- and ^{13}C-N.M.R.-spectroscopy, on the other hand, imply something else. A comparison of the N.M.R. data of the product with that obtained from the 6-hydroxy-1,4-diphenyl-1,4-diazepinium perchlorate allows this to be easily seen (see table, page 22).

^{1}H- and ^{13}C-N.M.R. data

Experimental* (28b) , R = Me		(28c) , R = Ph	
^{13}C-N.M.R. (ppm.)	^{1}H-N.M.R. (ppm.)	^{13}C-N.M.R. (ppm.)	^{1}H-N.M.R. (ppm.)
41.4	2.9 (s)	56.1	4.0 (s)
42.8	3.2 (s)	122.8	7.2 (s)
47.6	3.5 (m)	126.8	7.9 (s)
112.9	7.9 (s)	128.2	OH-peak absent
149.9	8.8 (s)	129.9	
177.5		144.9	
		149.1	
^{1}H-N.M.R. ratio		^{1}H-N.M.R. ratio	
3 : 3 : 4 : 1 : 1		4 : 10 : 2	

(spectra obtained using d_6-DMSO as solvent)



(28c)

(* Product from reaction of hydroxymalonaldehyde with N,N´-dimethylethylenediamine)

By comparison with the 1,4-diphenyldiazepinium perchlorate, the expected N.M.R. data for the 6-hydroxy-1,4-dimethyl-diazepinium salt would be approximately as follows :

^{1}H-N.M.R. : δ = 3.0 (s) , 3.8 (m) , 7.9 (s) and 9.0 (br) ppm.
ratio 6 : 4 : 2 : 1 .

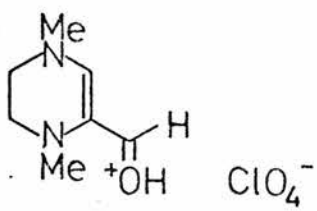
^{13}C-N.M.R.: δ = 42 , 50 , 145 and 150 ppm.

Other relevant spectroscopic evidence concerning the white needles is as follows :

Mass spectrum : m/e = 140

Infra-red spectrum : strong absorption band at 1650 cm^{-1}
(characteristic absorption of an aldehyde carbonyl)

By considering all the relevant information, the white needles are believed to have a six-membered ring structure (33).



(33)

This result was, indeed, surprising. When the reaction was carried out using tetrafluoroboric acid instead of perchloric acid, the cation formed remained the same ; changing the anion of the reaction did not alter the basic reaction.

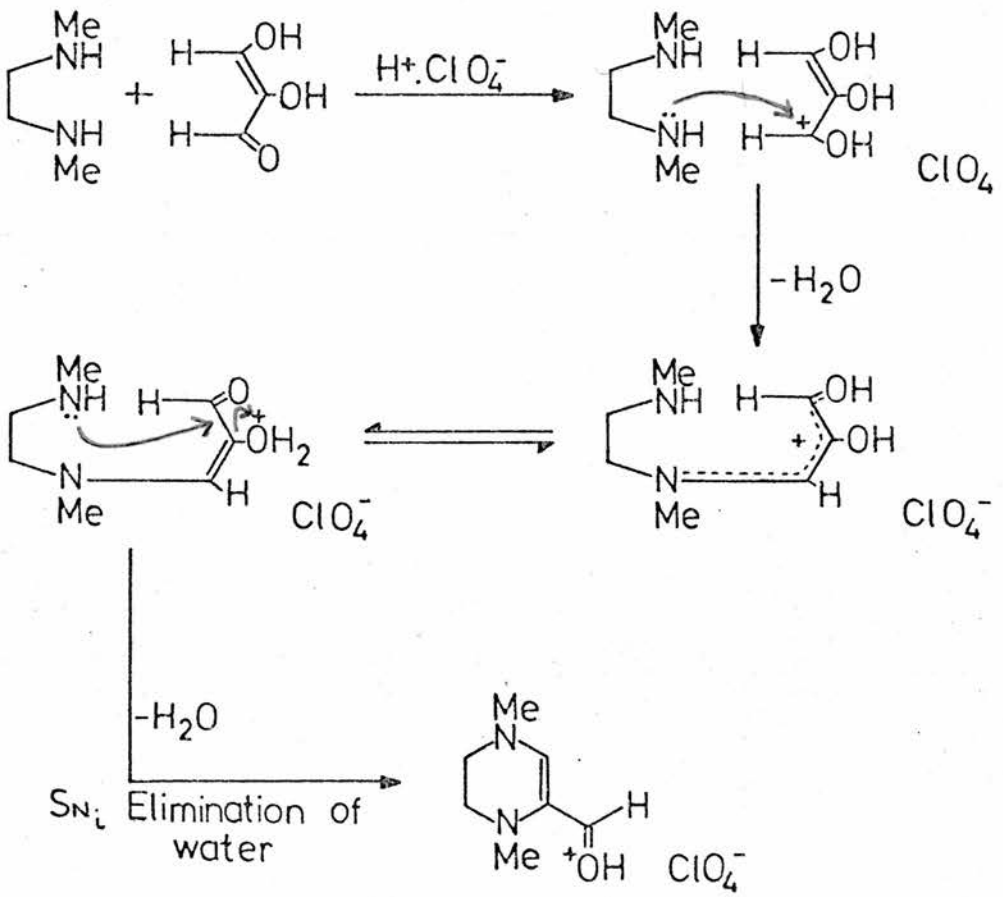
The spectrocopic data obtained for the tetraflouroborate salt is as follows :

^{1}H-N.M.R. : δ = 2.9 (s) , 3.2 (s) , 3.5 (m) , 7.9 (s) ,
(d_6-DMSO) 8.8 (s) and 10.7 (br) ppm..
ratio 3 : 3 : 4 : 2 : 1 : 1

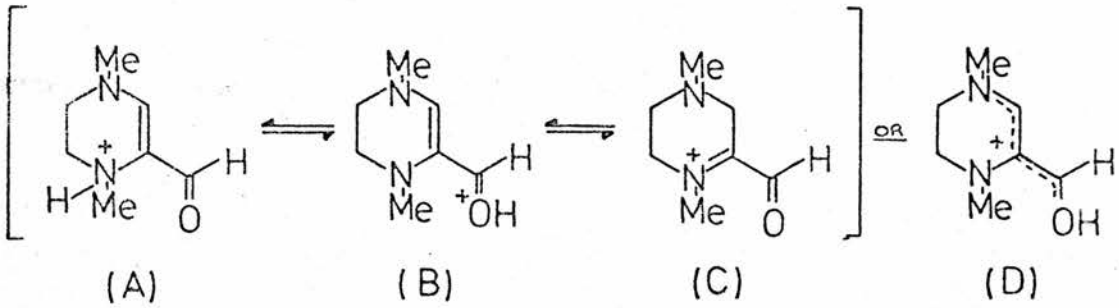
^{13}C-N.M.R. : δ = 41.5 , 43.0 , 43.1 , 47.8 , 113.2 , 150.3
(DMSO) and 178.1 ppm..

Mass spectrum: m/e = 140.2

A mechanistic possibility for the reaction is :



Possible tautomeric forms for the compound



(A) (B) (C) (D)

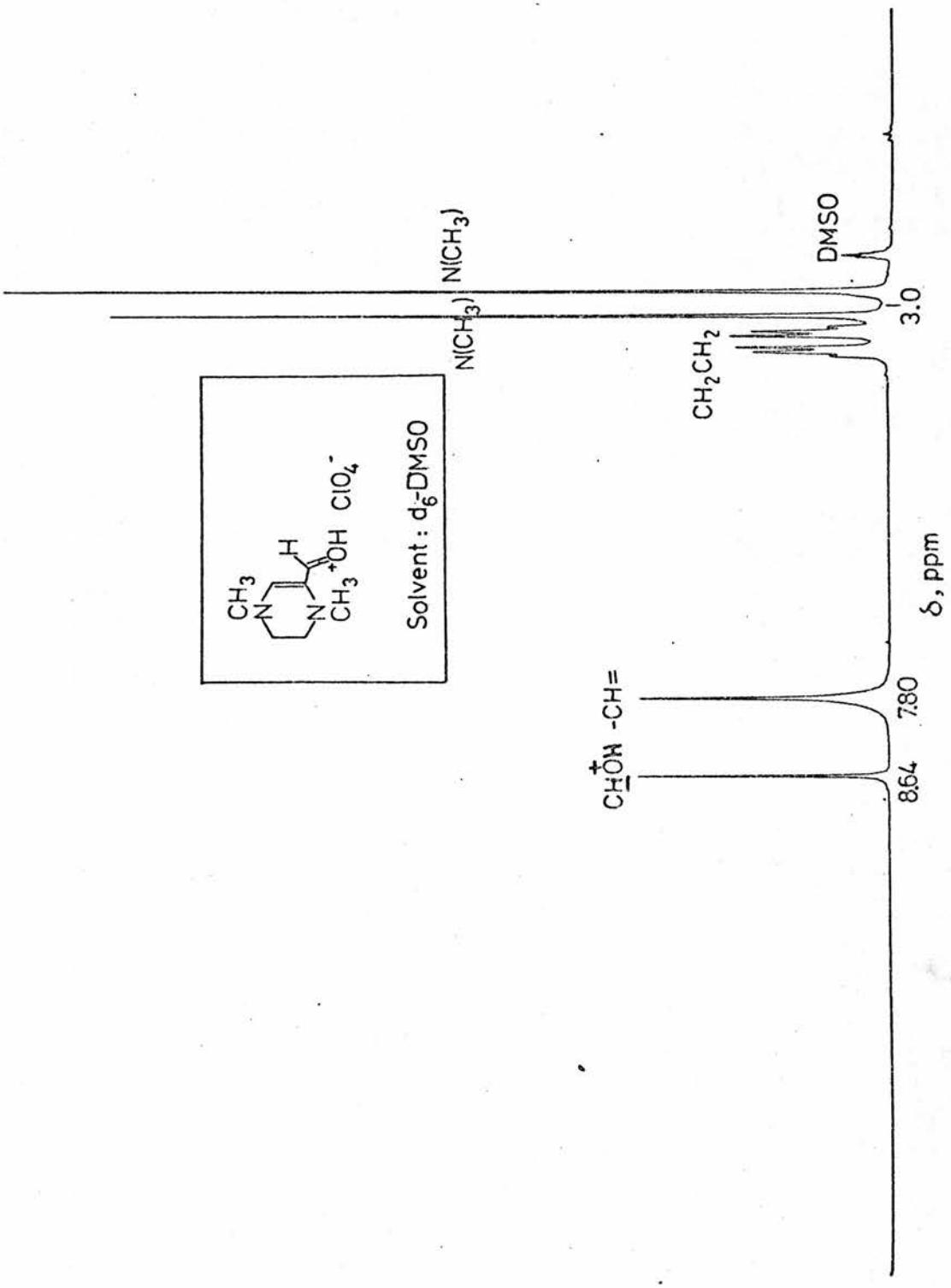
In the case of the proposed structure (B) there is a delocalised azaoxapentadienium system (D).

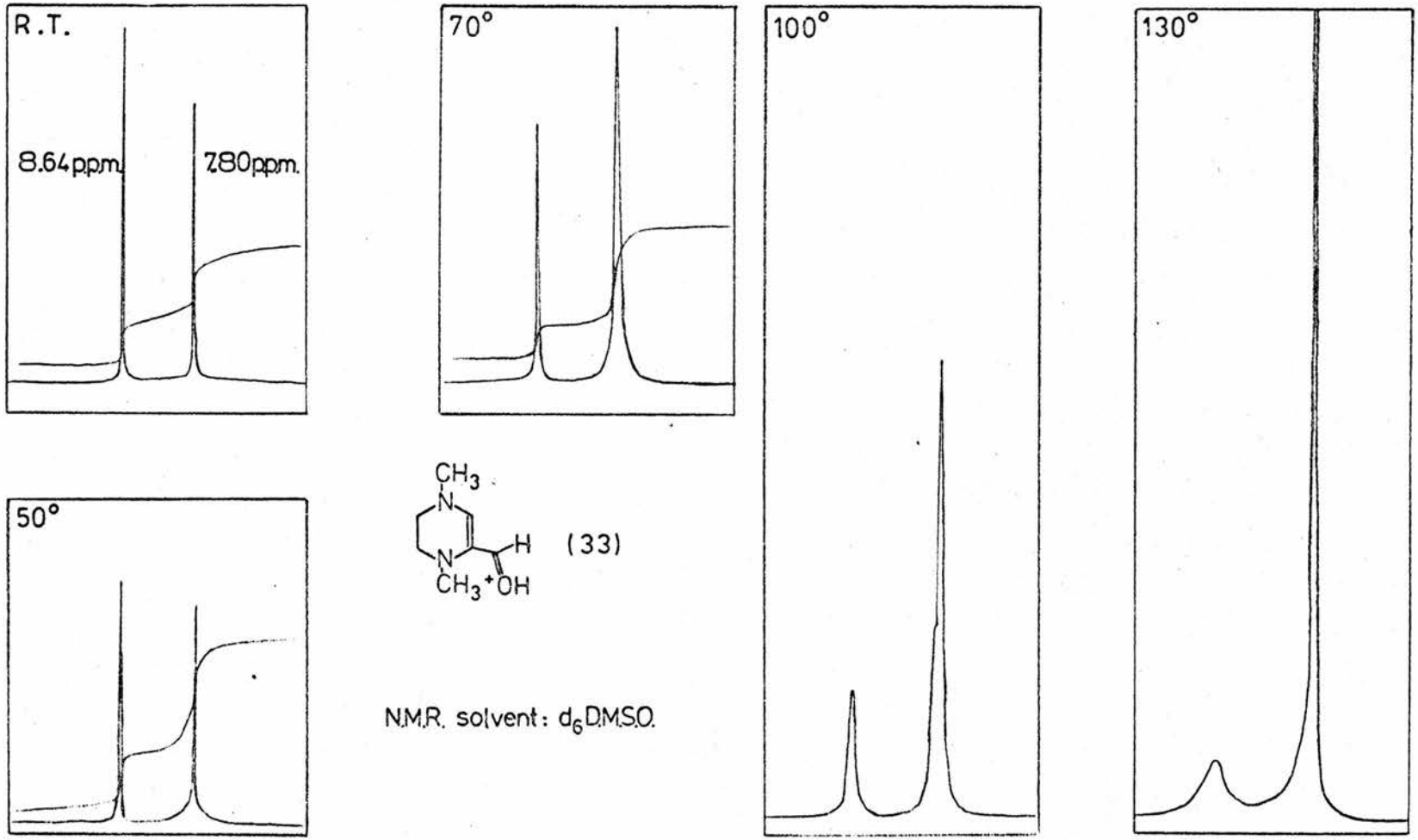
In addition to the routine spectroscopic work, variable temperature ^{1}H-N.M.R. data was obtained for the 6-membered ring (see table, page 28).

The room temperature ^{1}H-N.M.R. spectrum indicates only the presence of 12 protons, with the possibility of a thirteenth proton showing a low broad peak at approximately 7.9 ppm. At elevated temperatures it becomes more apparent that a thirteenth proton is present.

Higher temperatures cause tautomerism within the molecule, such that, for example, the two types of methyl protons become equivalent. On returning the sample to room temperature, the spectrum reverts back to its original form : heating the molecule to temperatures in the region of 130^{o}, does not, therefore, cause any permanent change to it.

^{1}H-N.M.R. Spectrum of (33) at normal temperature





(33)

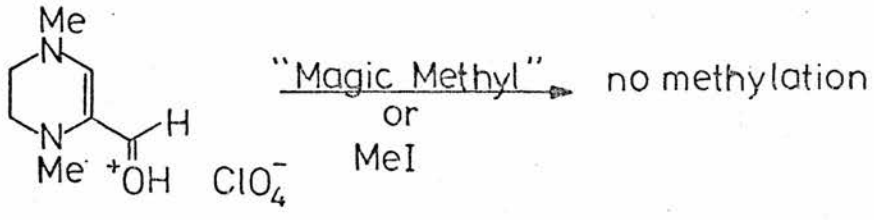
N.M.R. solvent: d_6 D.M.S.O.

Variation of a section of the ^{1}H-N.M.R. spectrum with temperature

Temperature	Variation of the spectrum with temp.(d_6-DMSO)
R.T. (ca.30°C)	δ= 2.9 (s) , 3.2 (s) , 3.5 (m) , 7.9 (s) , 8.8 (s) ppm.. ratio 3 : 3 : 4 : 1 : 1 .
-50°C -20°C 10°C	No apparent change w.r.t. spectrum at R.T.
50°C	Integral slope for peak at 7.9 ppm. tends to 2 units instead of 1, although this integral in the R.T. spectrum may conceivably be 2 units (see spectra , pages 26 & 27) Basically , no change in the spectral form .
72°C	Basically , no change in the spectral form , but integral ratio now tends to a definate 3 : 3 : 4 : 2 : 1 .
100°C	General broadening and merging of peaks . Peak at 7.9 ppm. develops a shoulder peak .
130°C	Two methyl peaks (δ = 2.9 and 3.2 ppm.) appear as a single peak . Peak at 7.9 ppm. is very sharp . Rest of spectrum very broad.
R.T. (after heating)	Spectrum returns to its original form .

If the reaction of N,N′-dimethylethylenediamine with hydroxymalonaldehyde is carried out in methanol, with absence of $HClO_4$, it is interesting to note that a white precipitate still occurs. This precipitate is unstable at room temperature and rapidly decomposes. Because of its instability, no data is available on the species, but information regarding the analogous reaction between N,N′-diphenylethylenediamine and hydroxymalonaldehyde leads one to assume that the product has an open-chain structure[10,18,24]. In the absence of H^+, one end of the hydroxymalonaldehyde has added on to one end of the N,N′-diphenylethylenediamine, but for ring-closure to occur H^+ must be present.

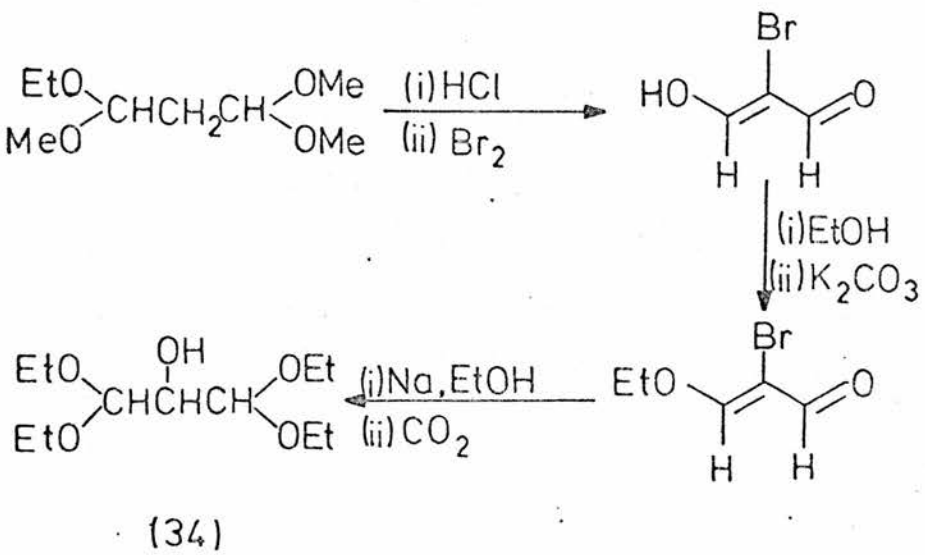
With regard to the 6-membered ring system (33), it may be possible to methylate the hydroxy group. Attempts to methylate using "Magic Methyl" (FSO_3CH_3) and methyl iodide as methylating agents were unsuccessful. Because of the nature of the hydroxy group in this case, this outcome is not totally unexpected. The $=OH^+$ group may be considered as a protonated carbonyl group. This may account for the fact that the methylation reaction was unsuccessful.



(33)

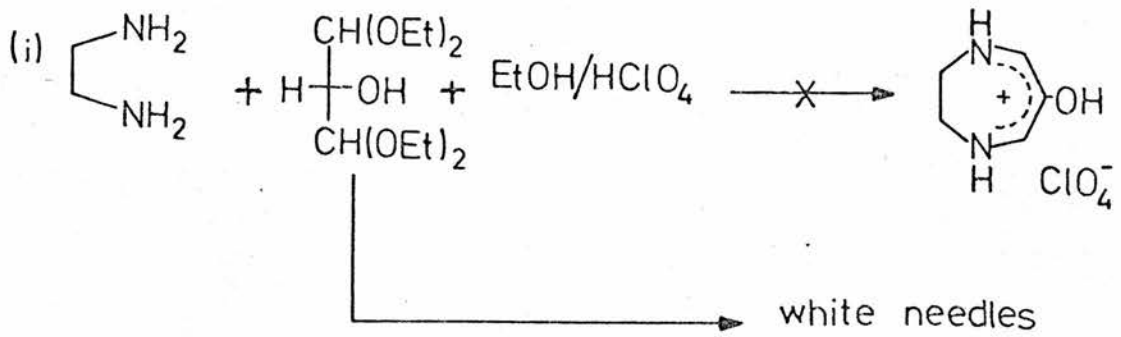
B : Preparation from tartronic Aldehyde

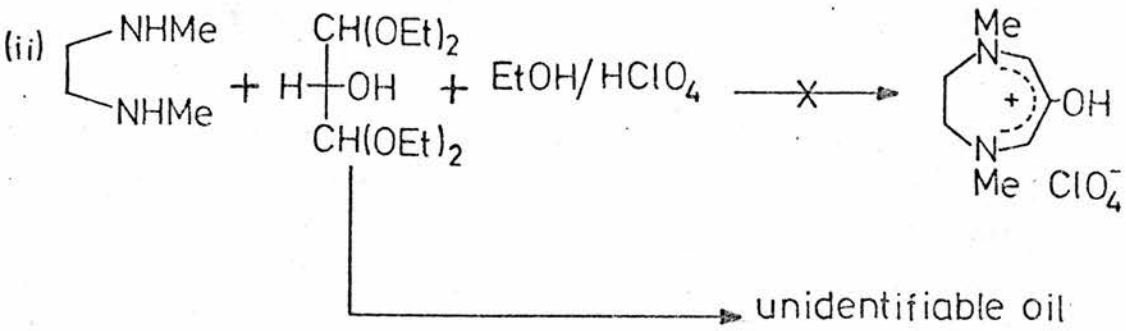
An alternative precursor to hydroxymalonaldehyde in the preparation of 6-hydroxydiazepinium salts by condensation reaction with an ethylenediamine, is tartronic aldehyde (34). This can be obtained from 3-ethoxy-1,1,3-trimethoxypropane, reaction proceeding via bromomalonaldehyde as an intermediate[63,64,65].

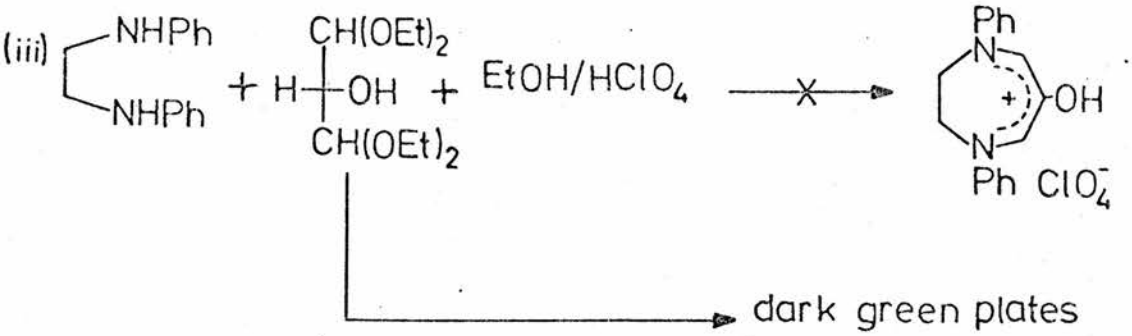


(34)

It was hoped that by using tartronic aldehyde instead of hydroxymalonaldehyde, the 6-hydroxy- , 6-hydroxy-1,4-dimethyl- , and the 6-hydroxy-1,4-diphenyl-1,4-diazepinium perchlorates could be obtained. This was not achieved but the reactions, once again , gave unusual results.

(i) 
NH2
NH2
CH(OEt)2
H
OH
CH(OEt)2
EtOH/HClO4
H
N
OH
N
H
ClO4-
white needles

(ii) 
NHMe
NHMe
CH(OEt)2
H
OH
CH(OEt)2
EtOH/HClO4
Me
N
OH
N
Me
ClO4-
unidentifiable oil

(iii) 
NHPh
NHPh
CH(OEt)2
H
OH
CH(OEt)2
EtOH/HClO4
Ph
N
OH
N
Ph
ClO4-
dark green plates

(i) ETHYLENEDIAMINE + TARTRONIC ALDEHYDE

The white needles produced as a result of the reaction of ethylenediamine with tartronic aldehyde were identified as a simple perchlorate salt of ethylenediamine ie. reaction between the aldehyde and the diamine has not occurred. Why the condensation reaction does not occur may be explained by one of two reasons :

- the tartronic aldehyde in some way reacts with itself, leaving no species available for a condensation reaction with ethylenediamine.

OR

- the ethylenediamine reacts preferentially with the perchloric acid to form the ethylenediamine perchlorate rather than with the tartronic aldehyde.

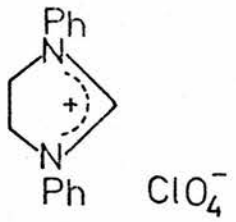
(ii) N,N'-DIMETHYLETHYLENEDIAMINE + TARTRONIC ALDEHYDE

Reaction of N,N'-dimethylethylenediamine with tartronic aldehyde did not result in the formation of either the 6-membered ring system (33), or of the diazepinium salt. The thick red oil produced remains unidentified.

(iii) N,N'-DIPHENYLETHYLENEDIAMINE + TARTRONIC ALDEHYDE

Reaction of N,N'-diphenylethylenediamine with tartronic aldehyde results not in the formation of the orange crystalline 6-hydroxy-1,4-diphenyl-diazepinium salt[55], but in the formation of dark green, almost black needles. The darkness of colour, in this case, is thought to be due to the presence of trace amounts of the conjugated dimerised species, (36). It is believed, by consideration

of the data available, that the main product of the reaction is a 5-membered ring, (35). This type of compound is known[66,67,68,69], and reports of it do not imply any intense colouration.

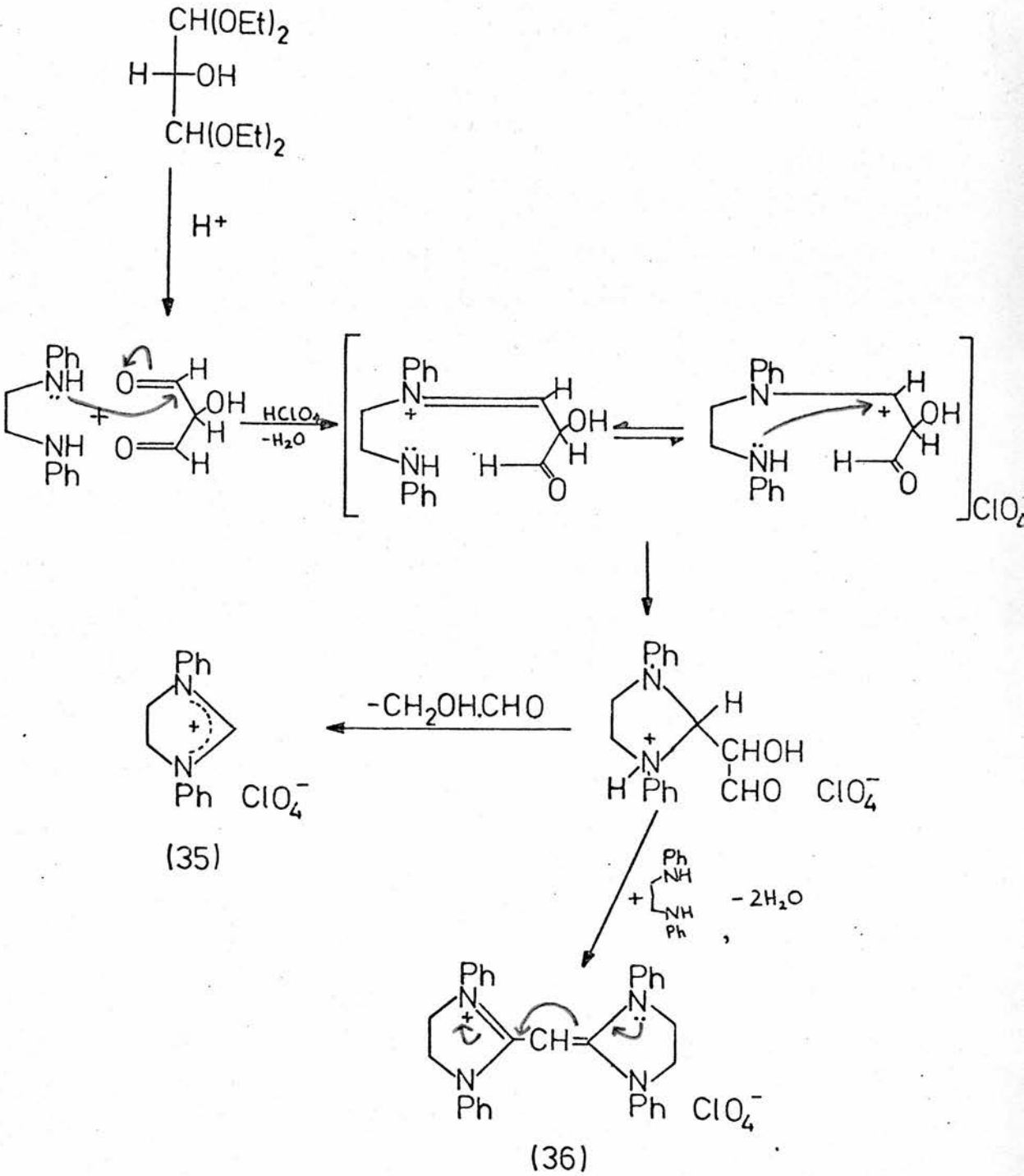


(35)

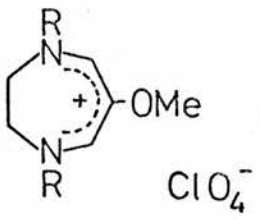
(36)

Mechanistically, formation of this compound is quite feasible, (see page 34).

The reaction conditions for formation of the 6-hydroxy-1,4-diphenyl-diazepinium salt (28c), the 2-formyl--1,4-dimethyl-1,4,5,6-tetrahydropyrazinium salt (33) and the 1,3-diphenyl-imidazolinium salt (35) have all been similar. It would seem that a fine balance of conditions determines whether the reaction product in each case is a 5- , 6- or 7-membered ring.


CH(OEt)2
H
OH
CH(OEt)2
H+
HClO4
-H2O
-CH2OH.CHO
CHOH
CHO
ClO4
(35)
-2H2O
(36)

2,3-DIHYDRO-6-METHOXY-1,4-DIAZEPINIUM PERCHLORATES



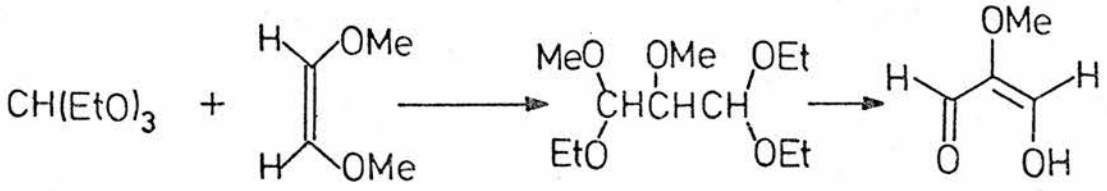
a) R = Me

b) R = Ph

(37)

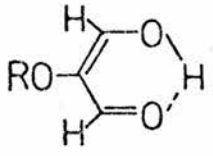
The formation of the tetrahydropyrazinium salt (33) from the reaction of hydroxymalonaldehyde and N,N´-dimethylethylenediamine was certainly unexpected. As an altemative, methoxymalonaldehyde might react with a substituted ethylenediamine to produce the appropriate diazepinium salt (37).

Methoxymalonaldehyde can be prepared by a variety of methods[70,71,72] ; in this case the methoxymalonaldehyde was obtained from triethylorthoformate and 1,2-dimethoxyethene, reaction proceeding via 2-methoxymalondialdehyde-monomethyl-triethyl acetal as an intermediate[70].



Using conditions similar to those for reaction with hydroxymalonaldehyde, methoxymalonaldehyde and N,N'-dimethyl--ethylenediamine, and methoxymalonaldehyde and N,N'-diphenyl--ethylenediamine were caused to react together in the presence of perchloric acid. The products, as hoped, were the 6-methoxy-1,4-dimethyl-1,4-diazepinium perchlorate (37a) and the 6-methoxy-1,4-diphenyl-1,4-diazepinium perchlorate (37b) respectively.

As substituents, the hydroxy group and the methoxy group generally affect a reaction to similar extents. In this case, hydroxymalonaldehyde and methoxymalonaldehyde differ considerably due to the nature of their intermolecular hydrogen bonding[73]. For methoxymalonaldehyde (38) and hydroxymalonaldehyde (39), one would expect the presence of a 6-membered protonic chelate.

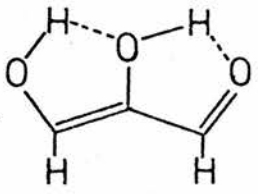


(38) R = Me

(39) R = H

However, hydroxymalonaldehyde is an α-carbonyl enediol in which the carbonyl function allows formation of a hydroxyvinylene homologous carboxylic acid which, together with the central hydroxy group, is capable of forming a double 5-membered ring protonic chelate (40). This hypothesis has been shown to be correct by X-ray structural

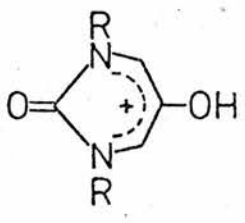
analysis[57] which shows that the three oxygen atoms in hydroxymalonaldhyde all lie on one side of the carbon chain.



(40)

Hence, a possible reason why reaction of methoxymalonaldehyde with an ethylenediamine forms a diazepinium salt, whereas reaction of hydroxymalonaldehyde with an ethylenediamine need not necessarily form a diazepinium salt, is the differing structures and stereochemistry of the two malonaldehydes due to intramolecular interaction.

1,2-DIHYDRO-5-HYDROXY-2-OXO-PYRIMIDINIUM PERCHLORATES



ClO_4^-

a) R = H

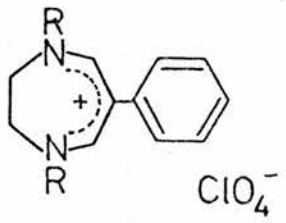
b) R = Me

(41)

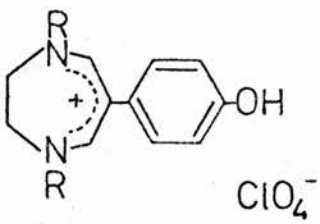
Compounds of this type, where R = Me but with a substituent other than hydroxy at the 5-position are known, for example, when the substituent at the 5-position is p-methoxyphenyl, methyl or halogen[62]. Preparation of the 5-hydroxypyrimidinium salts by the condensation reaction of a urea with hydroxymalonaldehyde (29), or tartronic aldehyde (34), in the presence of perchloric acid, was not achieved.

Any attempts to prepare these pyrimidinium perchlorates yielded an intractable tar, presumably the product of any pyrimidinium salt which was formed reacting further, or some alternative products may result. 2-Oxopyrimidinium salts, in general, show reduced reactivity of their 1,5-diazapentadienium system in comparison with the analogous diazepinium salts. However, the introduction of a hydroxy group at the 5-position may result in a species with different reactivity and properties.

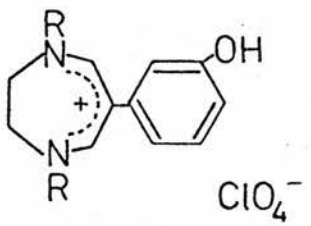
2,3-DIHYDRO-6-HYDROXYPHENYL-1,4-DIAZEPINIUM PERCHLORATES



(42)



(43)



(44)

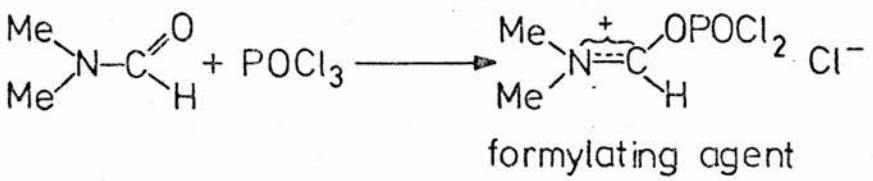
a) R = H

b) R = Me

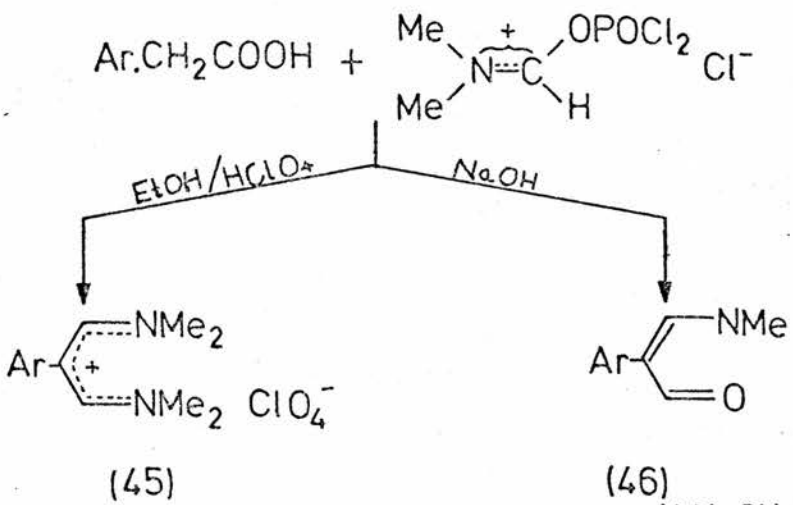
The synthesis of 6-hydroxy- and 6-hydroxy-1,4-dimethyl-1,4-diazepinium salts (28a and 28b) has not been achieved. As the reactivity of the 6-position of dihydrodiazepinium salts can be transmitted through a phenyl ring substituted at this position[45], it is interesting to speculate as to whether the analogous series of 6-hydroxyphenyldiazepinium salts (43 and 44) is preparable.

As with the preparation of 6-hydroxy-1,4-diazepinium perchlorates, synthesis of 6-hydroxyphenyl-diazepinium perchlorates might be achieved by the condensation reaction of a substituted N,N´-ethylenediamine with a hydroxyphenylmalonaldehyde, or a derivative such as the acrolein or the vinamidinium salt, in the presence of perchloric acid. The hydroxyphenylmalonaldehyde derivatives were unknown and their preparation involved modification of some literature methods[74,75]. The ethylenediamines are commercially available.

The preparation of a number of vinamidinium salts, by the Vilsmeier-Haack bisformamination of some substituted phenylacetic acids, has been reported in the literature[74,75]. Reaction of a substituted phenylacetic acid with dimethylformamide and phosphoryl chloride generally affords a vinamidinium salt (45), which may be isolated or, without isolation, converted in to the acrolein (46). The acrolein can then be hydrolysed to the free malonaldehyde (47).



formylating agent

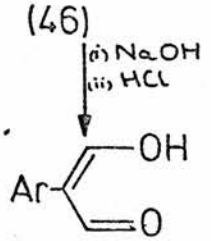


(45) (46)

a) Ar = C_6H_5

b) Ar = $\underline{p}$-C_6H_4OH

c) Ar = $\underline{m}$-C_6H_4OH



(47)

In this case, the arylacetic acids used were phenylacetic acid and meta- and para-hydroxyphenylacetic acid. Preparation of the vinamidinium salts (45), acroleins (46), and malonaldehydes (47) was attempted using modified literature methods[72,74,76].

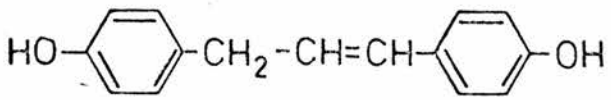
For further experiments, it was only necessary in each case to have either the vinamidinium salt, the acrolein or the free malonaldehyde. In general, the vinamidinium salts are the most easily obtained, but the malonaldehydes are the most reactive in condensation reactions with ethylenediamines.

The phenylvinamidinium salt (45a) has been obtained by the bisformamination of phenylacetic acid[74,75]. The p-hydroxyphenyl- and the m-hydroxyphenylvinamidinium salts (45b and 45c) were similarly obtained. Conversion to the acroleins was successful for the p-hydroxy- and m-hydroxyphenylacroleins (46b and 46c). Hydrolysis of the acroleins to the free malonaldehydes (47) was successful only in the preparation of m-hydroxyphenylmalonaldehyde (47c).

Hydrolysis of p-hydroxyphenylacrolein (46b) resulted in the formation of a white powder which rapidly decomposed to yield a deep purple compound and later a black tar. Isolation of p-hydroxyphenylmalonaldehyde would be quite interesting - oxidation of the species would theoretically yield a highly conjugated and highly reactive compound (48). Indeed, the development of colour might be due to oxidation by atmospheric oxygen.

(48)

However, isolation of p-hydroxyphenylmalonaldehyde was unsuccessful, and the white, unstable compound obtained is possibly the required product which rapidly reacts further, or a self-condensed species (49).



(49)

Evidence for this is somewhat uncertain ; a high resolution mass spectrum implies the formula $C_{15}H_{14}O_2$, and the ^{1}H-N.M.R spectrum and microanalysis results could possibly fit in with the proposed structure, however, the ^{13}C-N.M.R. spectrum indicates the presence of only 10 types of carbon atom (whereas 11 should be apparent).

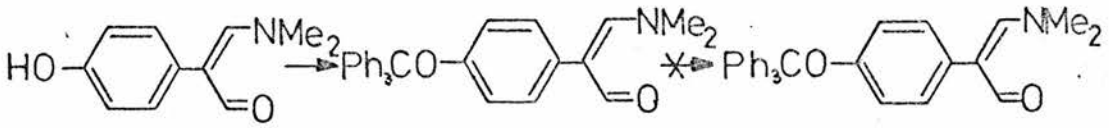
^{1}H-N.M.R. spectrum : δ = 3.2 (d) , 6.9 (broad) , 9.6 (s) and 9.8 ppm. (s)

ratio 2 : 10 : 1 : 1

Found : C,75.96 ; H,6.19 %

$C_{15}H_{14}O_2$ requires C,79.62 ; H,6.24 %

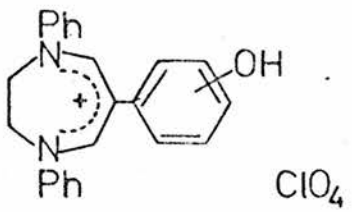
Possibly the influence of the p-hydroxy group in some way affects the formation of free malonaldehyde. Protection of the hydroxy group might therefore allow formation of the malonaldehyde. Addition of a protecting group was relatively simple (50), but still conversion to the free malonaldehyde remained unsuccessful.



(50)

Having prepared some p-hydroxyphenyl-vinamidinium salts, -acroleins, and -malonaldehydes their reaction with ethylenediamines in the presence of perchloric acid was investigated.

Despite the fact that, in general, the free malonaldehydes are more reactive than the acroleins than the vinamidinium salts, all, when condensed with ethylenediamines, afforded the appropriate diazepinium salts (42,43 and 44). The 6-hydroxyphenyl-1,4-diphenyl-diazepinium salts (51) were, however, not preparable by this method. Similar diazepinium salts have been prepared by the liberation of free malonaldehydes from their sodium salts and by then adding N,N´-diphenylethylenediamine[78]. In this case, the preparation of the sodium salts of meta- and para-hydroxymalonaldehyde was not achieved.



(51)

The 6-hydroxyphenyldiazepinium salts possess both a hydroxy group and a diazepinium system. It is interesting to speculate -

a) whether the 6-hydroxyphenyldiazepinium salts will be more or less acidic than phenol. Phenol itself has a pK_a of 9.99[77]. The pK_a of the 6-hydroxyphenyldiazepinium salts is expected to be lower than this - because the diazepinium system is an electron donor, there would be less tendency for the hydroxy group to also donate electrons into the phenyl ring, therefore the hydrogen of the hydroxy would be more firmly attached, this resulting in a lower hydrogen ion concentration, and consequently a lower pK_a.

b) whether, with respect to the site of electrophilic aromatic substitution, the diazepinium system or the hydroxy group will have the dominant effect; both the hydroxy group and the diazepinium system are "donor groups" and are therefore strongly activating and ortho/para directing.

c) whether the phenolic hydroxy group can be alkylated. A phenol is often converted into its ether to provide protection against oxidation or other undesired side reactions during transformations not involving the oxygen function.

A: The acidity of 6-hydroxyphenyldiazepinium salts

The acidity of the 6-hydroxyphenyldiazepinium salts in comparison with phenol is of interest. Comparison of the relative acidities was achieved by measurement of pH values in aqueous and methanolic solutions.

This can be determined by the application of the Henderson Equation and by doing a simple pH determination.

Henderson Equation $pH = pK_a + \log [salt]/[acid]$

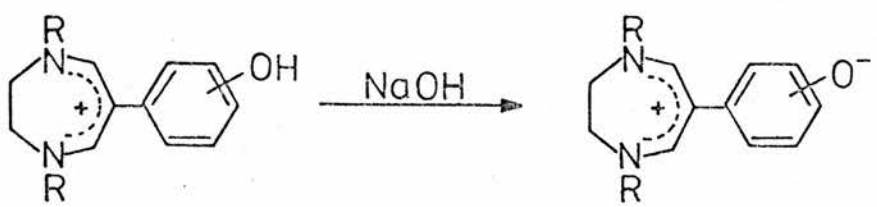
The pH measurements were carried out on methanolic solutions such that

$$[salt] = [acid]$$

therefore $\log [salt]/[acid] = 0$

therefore $pH = pK_a$

(The species "salt" and "acid" as used here refer to the diazepinium salt (52) and the salt after treatment with sodium hydroxide (53).



(52) (53)

The diazepinium salt solutions were made up to a concentration of 0.01M in methanol. To this was added a 0.005M sodium hydroxide solution such that:

[diazepinium salt solution] = 0.005M = [sodium salt solution]

RESULTS :

R	Position of -OH	$pH = pK_a$ (methanol)	$pH = pK_a$ (water)
H	meta	10.2	9.9
Me	meta	9.6	9.4
H	para	9.5	9.6
Me	para	9.9	9.8
Phenol		10.5	10.2

Results of pH determination are accurate to approx. 0.1

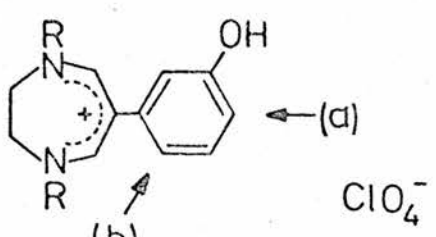
As expected, the hydroxyphenyldiazepinium salts have a lower pK_a than phenol.

B: The reactivity of 6-hydroxyphenyl-1,4-diazepinium salts with respect to electrophilic aromatic substitution

If the hydroxy group controls the reactivity of the diazepinium salt, then electrophilic aromatic substitution will occur ortho/para to it, and meta to the diazepinium system. However, if the diazepinium system is the more strongly activating then the reverse will occur i.e. substitution ortho/para to the diazepinium system and meta to the hydroxy group.

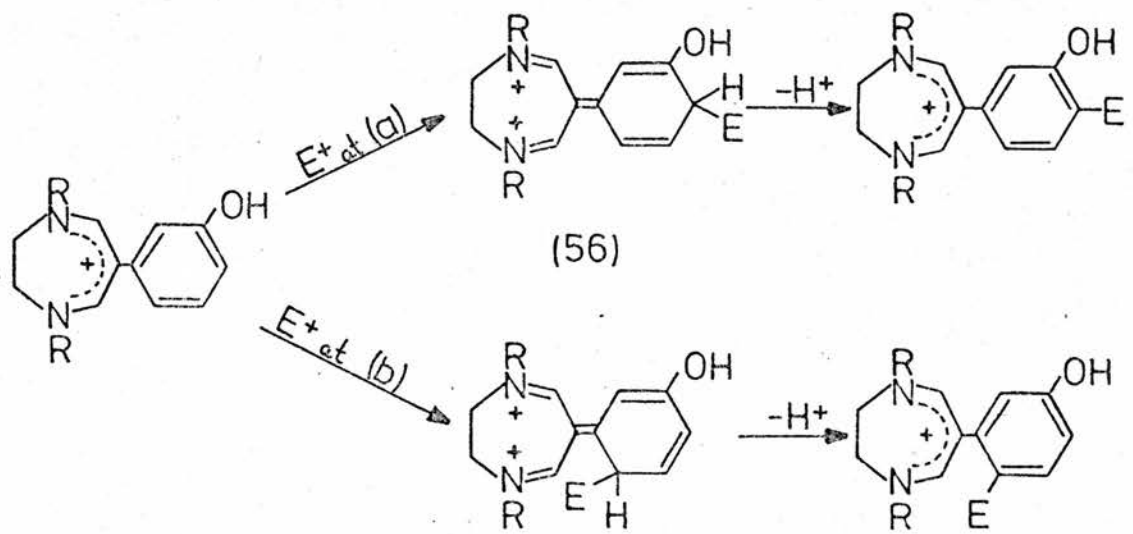
The reactivity of 6-hydroxyphenyl-diazepinium salts with respect to electrophilic aromatic substitution was therefore studied using different electrophiles. The halogens are useful electrophiles because they are fairly reactive and their introduction into reactive aromatic systems requires no catalyst. Some other useful reactions are those with diazonium ions, which are sufficiently electrophilic to couple with reactive aromatic nuclei to give azo dyes, and nitration.

If the 6-phenyl substituted diazepinium salts have a hydroxy group at the meta-position of their phenyl ring, then there is little doubt as to the position of electrophilic substitution. The diazepinium system and the hydroxy group will both activate the same positions ie.(55), positions (a) and (b).



(55)

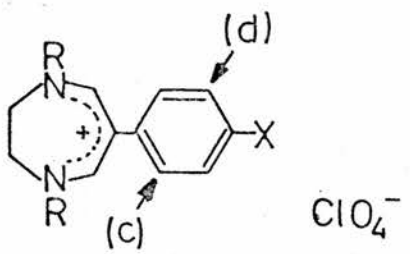
Substitution will occur preferentially at position (a) because of steric hinderance at position (b), in each case reaction proceeding via a dication intermediate (56) and (56′).



(56)

(56′)

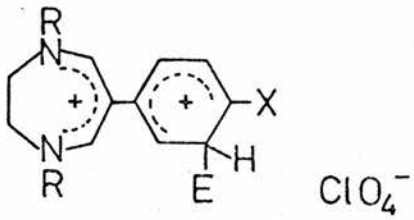
If the 6-phenyl substituted diazepinium salts have an electron-donating group at the para-position of their phenyl ring, then electrophilic substitution might occur at either position (c) or (d), (57).



(57)

Attack of an electrophile at position (c), which would be activated by the diazepinium system, is sterically hindered, such that even if the diazepinium system is more activating than the p-substituent, electrophilic substitution may still not occur. Attack at

position (d), which would be activated by the p-substituent, would produce a Wheland type intermediate (58) which would be destabilised by interaction between the two neighbouring positively charged systems.



(58)

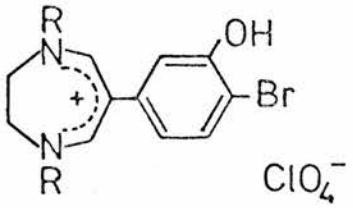
Consequently, irrespective of the fact that the p-substituent and the diazepinium systems are activating, electrophilic aromatic substitution might still not occur. Indeed, when the phenyl ring is substituted by the p-methyl or p-methoxy groups electrophilic attack does not occur[80].

(i)BROMINATION

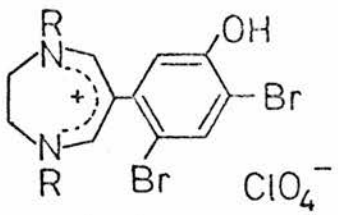
This reaction was effected by the simple addition of a methanolic solution of bromine, in stoichiometric amounts, to a methanolic solution of the diazepinium salt. In this way, the mono- and dibromo-derivatives of the m-hydroxy- and p-hydroxy--phenyldiazepinium salts were obtained. The products obtained from the m-hydroxyphenyldiazepinium salt, when using excess quantities of bromine, were seen (from mass spectroscopic data) to contain some tri- and tetrabrominated salt. These were, however, present only in very small amounts and could not be isolated. No tri- or tetrabromo compounds were observed for the p-hydroxyphenyldiazepinium salts.

The success of all the bromination reactions was unexpected:

The ease of bromination of the m-hydroxyphenyldiazepinium salts at the site para to the diazepinium system [(55),site (a)] was to be expected as it is doubly activated, monobromination yielding the species (59). Dibromination resulted in the insertion of a second bromine atom into a sterically unfavourable position [(55),site (b)]. However, the combined activating effect of the hydroxy group and the diazepinium system must be considerable as the second bromine atom was substituted without difficulty (60). As a substituent, bromine is deactivating and ortho/para directing; with regard to insertion of the second bromine atom, the first bromine seems to have had little effect in determining the site of further substitution. An important contributing factor in the ease of bromination is that, for mono- and dibromination, reaction proceeds via stabilised Wheland intermediates (56).



(59)



(60)

a) R = H

b) R = Me

The splitting patterns observed for the aromatic protons in the ^{1}H-N.M.R. spectra confirm the sites of bromination. This was achieved by a comparison of the spectra with other aromatic compounds substituted at the same positions.

A complex mixture of substituent effects comes into play for any further brominations.

Bromination of the p-hydroxyphenyldiazepinium salts was also achieved without difficulty, substitution occurring ortho to the hydroxy group [(57),site (d)]. The activating and ortho/para directing effect of the hydroxy group must therefore have a dominant effect over that of the diazepinium system.

But bromination of p-methyl and p-methoxyphenyldiazepinium salts does not occur under similar conditions[80]. This was explained by the fact that only a destabilised Wheland type intermediate (58) could be drawn for the reaction. So, why does bromination occur on the p-hydroxyphenyldiazepinium salts and not on, for example, the analogous p-methoxyphenyldiazepinium salts ? - one might expect a similar destabilised Wheland type intermediate to form on bromination of the p-hydroxyphenyldiazepinium salts. There are two points to be considered here:

(i) The methoxy group, the hydroxy group and the diazepinium system are all ortho/para directing and will activate an aromatic nucleus to electrophilic substitution. If the diazepinium system is more activating than another substituent at the para position, then substitution will be favoured at the positions ortho/para to the diazepinium system. The para position is blocked by the other substituent and the ortho position is sterically hindered, therefore substitution may not occur. If, on the other hand, the para-substituent has a greater activating effect than the diazepinium system, then electrophilic substitution may occur ortho/para to it. Again the para position is blocked, this time by the diazepinium

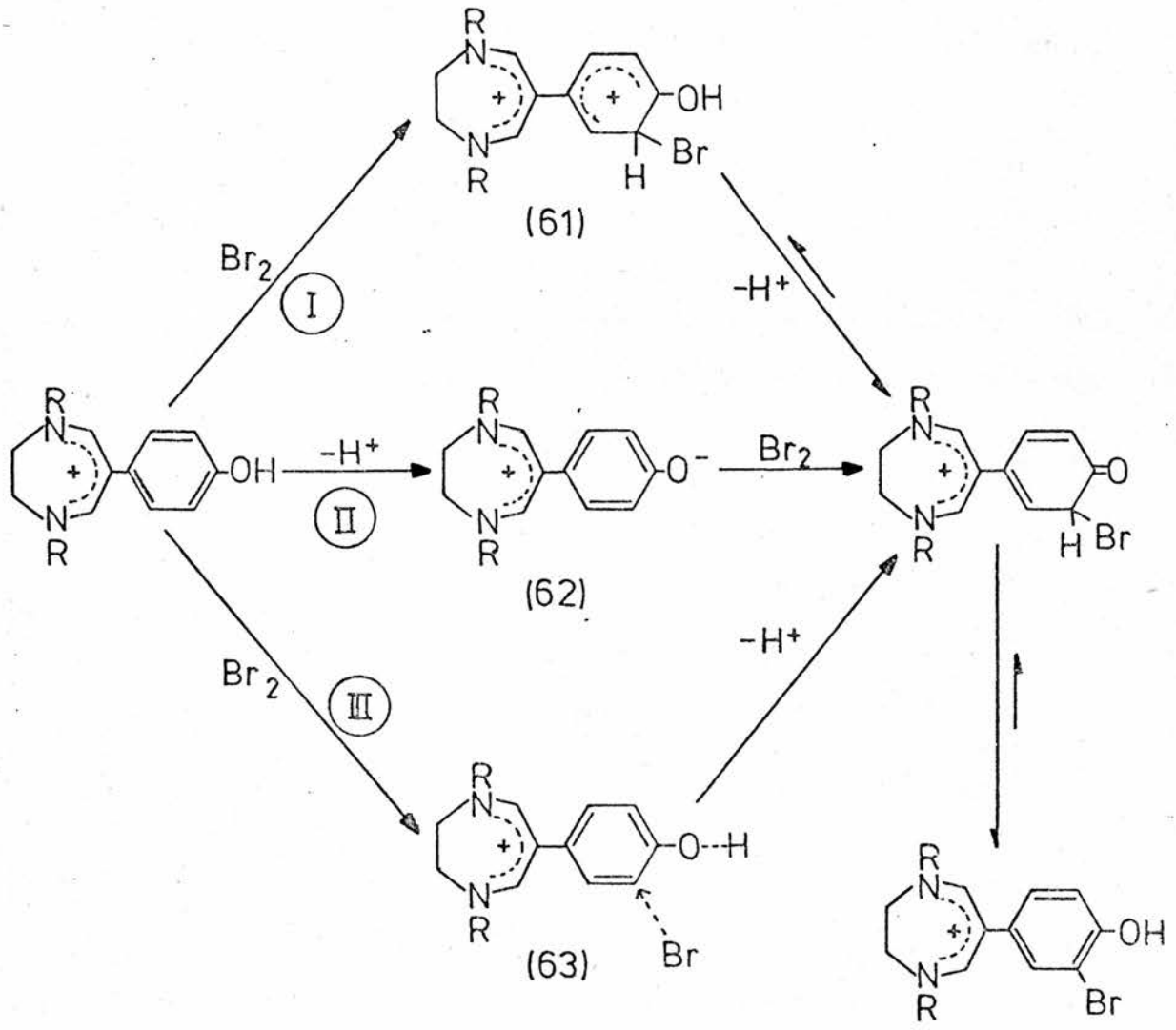
moiety, however the ortho position is available for a substitution reaction.

A possible reason why the p-hydroxyphenyldiazepinium salts are brominated whereas the p-methoxyphenyl salts are not may be to do with the relative activating effects of the various substituents attached to the phenyl ring. This argument requires the relative effects to be

hydroxy group > diazepinium system > methoxy group

It is known that a hydroxy group will activate an aromatic nucleus more than a methoxy group will, but the degree to which the diazepinium system will activate is not known.

(ii) The properties of the hydroxy group, in that it can sometimes lose a proton, may account for the fact that the p-hydroxyphenyldiazepinium salts can be brominated, whereas the analogous p-methoxyphenyldiazepinium salts can not. As previously mentioned, reaction is unlikely to proceed via an intermediate with two adjacent positively charged portions. To account for the reaction an alternative mechanism is proposed:

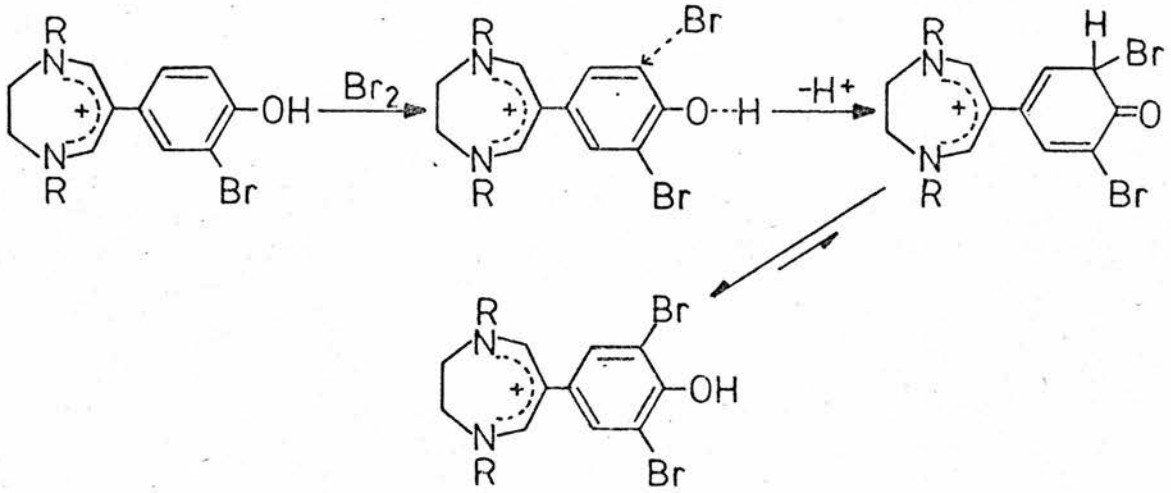


a) R = H

b) R = Me

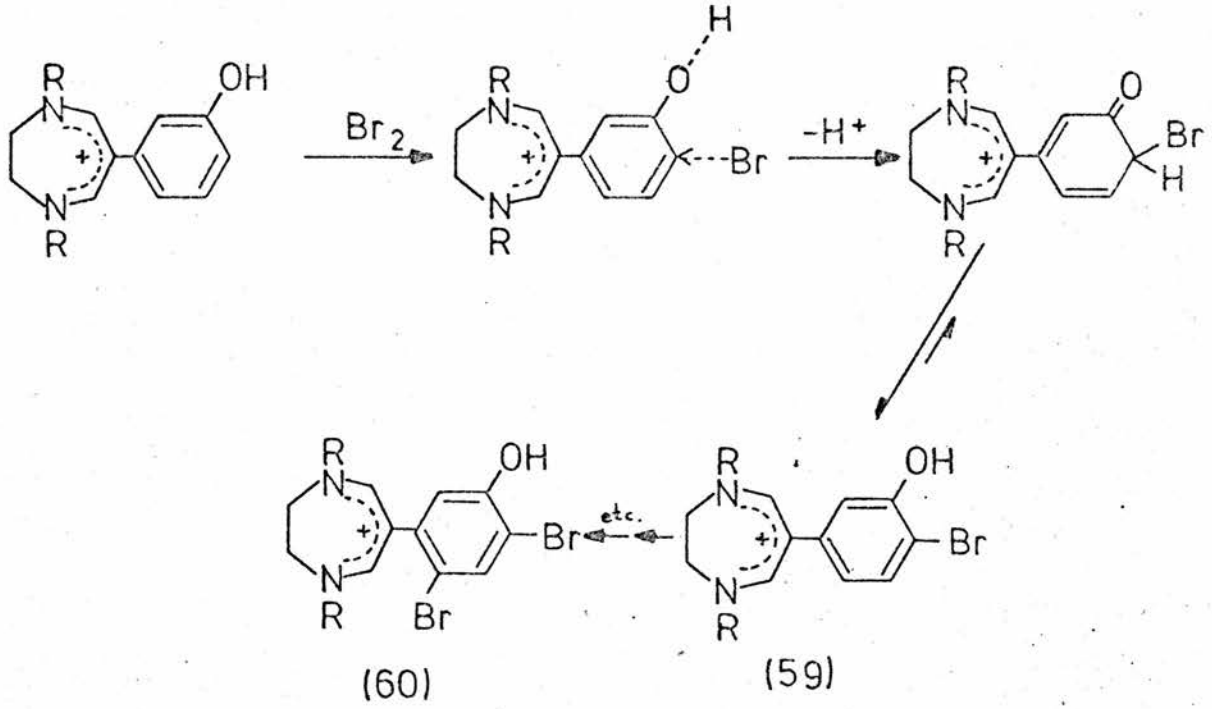
The argument against route (I) is whether the intermediate (61) will form or not. If it does, proton loss would occur very rapidly. Alternatively, the diazepinium salt could first lose a proton, route (II), and then bromination occur. An alternative representation of the reaction may be to consider it as a concerted process, route (III) i.e. bromination and loss of a proton occur simultaneously.

A similar argument can be applied for insertion of a second bromine atom i.e.



(65)

and also for bromination of the m-hydroxyphenyldiazepinium salts i.e.

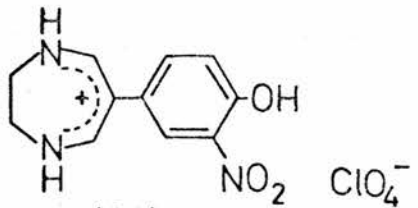


(60) (59)

(ii)NITRATION

Nitration of an aromatic nucleus involves the introduction of the nitro group, NO_2. This can be achieved by a variety of ways, for example, from an aqueous nitric acid solution or from a solution of nitronium tetrafluoroborate[81,82,83], the conditions chosen being appropriate to each substrate.

A number of attempts were made to nitrate the hydroxyphenyldiazepinium salts but with only limited success. Mass spectroscopic data implied, for example, some formation of the nitrated product of the 6-(p-hydroxyphenyl)-diazepinium salt since a peak was observed corresponding to a mono-nitrated species (66).



(66)

Found (accurate mass) : $\underline{M}^+$,233.0795

$C_{11}H_{11}N_3O_3$ requires $\underline{M}$,233.0800

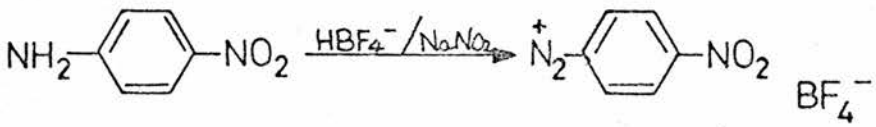
Other analytical and spectroscopic data was inconclusive.

During the course of the nitration reactions, the solutions invariably took on the expected red colouration. Isolation of any product was hampered by solubility factors : in aqueous acidic solutions the diazepinium salts are very soluble, and any nitrated diazepinium salts would be equally soluble. Addition of a base to precipitate any product or starting material would only result in breakdown of the diazepinium ring[38]. For reactions in non-aqueous solutions, the product remained as an intractable tar.

(iii)DIAZOTISATION

Diazonium ions can couple with reactive aromatic nuclei to give azo dyes. Since the colouration of these dyes is due to the absorption of light in the visible part of the spectrum by the extended delocalised system of π-electrons present in the dye molecule, electrophilic attack by diazonium ions on diazepinium salts should therefore produce highly coloured species.

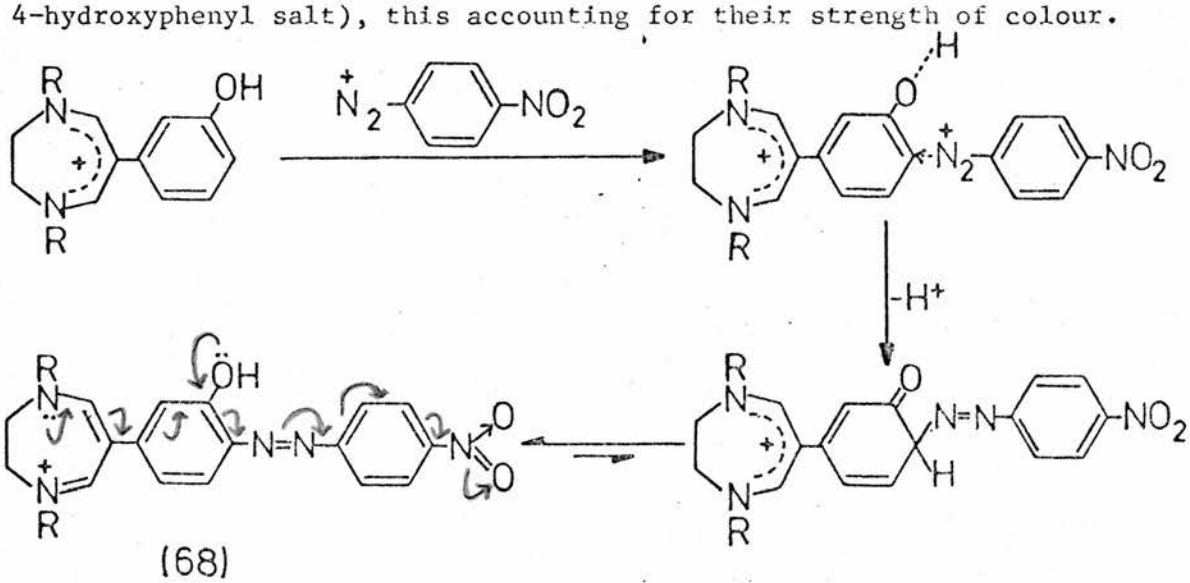
The diazonium ion used in this case was p-nitrobenzenediazonium tetrafluoroborate (67) which can be prepared from p-nitroaniline[84,85].



(67)

This diazonium salt can then be coupled with a diazepinium salt by simply adding together, with stirring, methanolic solutions of the two salts. In all cases of the p-hydroxy- and m-hydroxyphenyldiazepinium salts, a deep red or orange colouration ensued, implying formation of the azo dye. Unfortunately, these azo dyes could not be obtained in an analytically pure form, but N.M.R. results nevertheless implied success of the reactions.

As with the electrophilic substitution of bromine, the mechanism of reaction is believed to involve a concerted process. The delocalised system of π-electrons for both the 4-hydroxy-3-(p-nitrobenzeneazo)-phenyl- (69) and the 3-hydroxy--4-(p-nitrobenzeneazo)-phenyldiazepinium salts (68) is indeed extensive (in the 3-hydroxyphenyl salt more so than in the 4-hydroxyphenyl salt), this accounting for their strength of colour.



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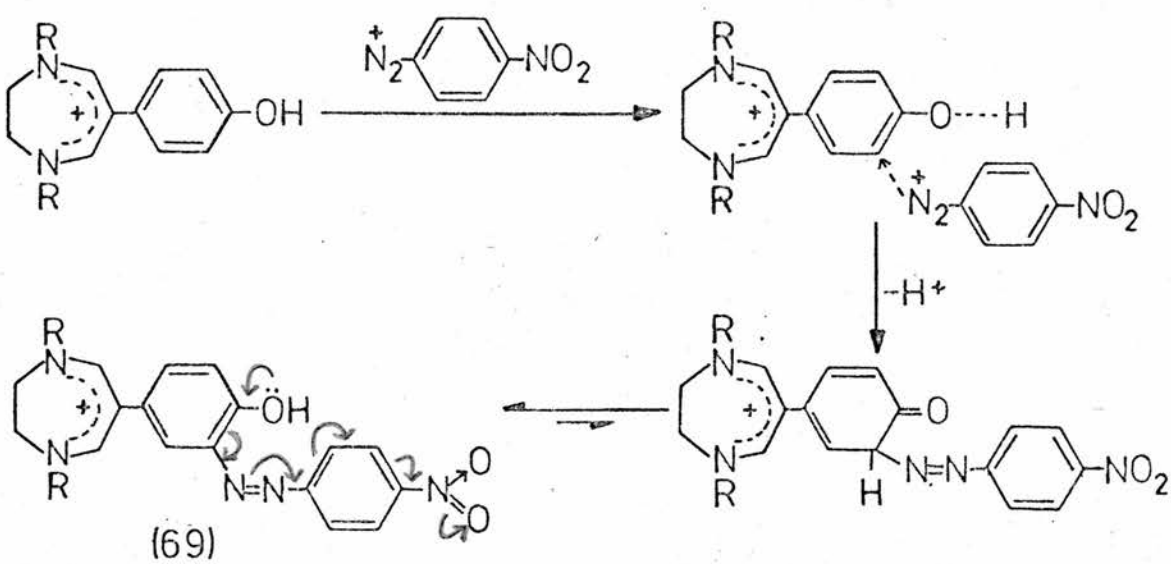


(69)

a) R = H

b) R = Me

C: The alkylation of 6-hydroxyphenyldiazepinium salts

O-Alkylation of a phenol is often done in order to protect the hydroxy group during reactions not involving the oxygen function. This generally requires fairly gentle conditions, for example, dimethyl or diethyl sulphate in a weakly alkaline aqueous medium. However, the diazepinium salts are, in some cases, sensitive to alkali, therefore some alternative methods of methylation were investigated.

(i) Methyl iodide can be used to methylate a phenolic hydroxy group. The most usual way in which to do this reaction is to reflux the phenol, methyl iodide and some potassium carbonate in acetone for a few of hours[86].

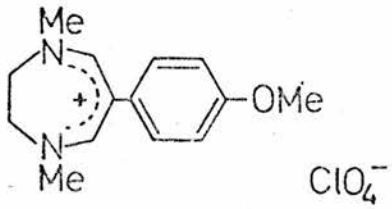
(ii) Diazomethane is a powerful, if somewhat hazardous, methylating agent and its use can be applied to phenolic hydroxy groups.

(iii) "Magic Methyl" is also a powerful methylating agent.

(iv) A method which is not so well known is that of using methyl iodide with potassium carbonate and dimethylformamide as a solvent[87]. This method may be successful in instances when the use of acetone as a solvent is not.

The methylation reactions using (i) methyl iodide and potassium carbonate in acetone, (ii) diazomethane, and (iii) "Magic Methyl" were unsuccessful. The reaction using methyl iodide and potassium carbonate with dimethylformamide as a solvent was successful beyond expectation, and some unexpected results were obtained.

With respect to the 6-hydroxyphenyl-1,4-dimethyl-diazepinium salts (43b) and (44b), methylation occurred on the oxygen function to produce the 6-methoxyphenyl-1,4-dimethyl-diazepinium salts (70)/(71).



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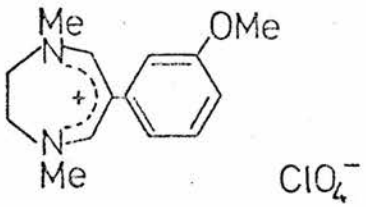
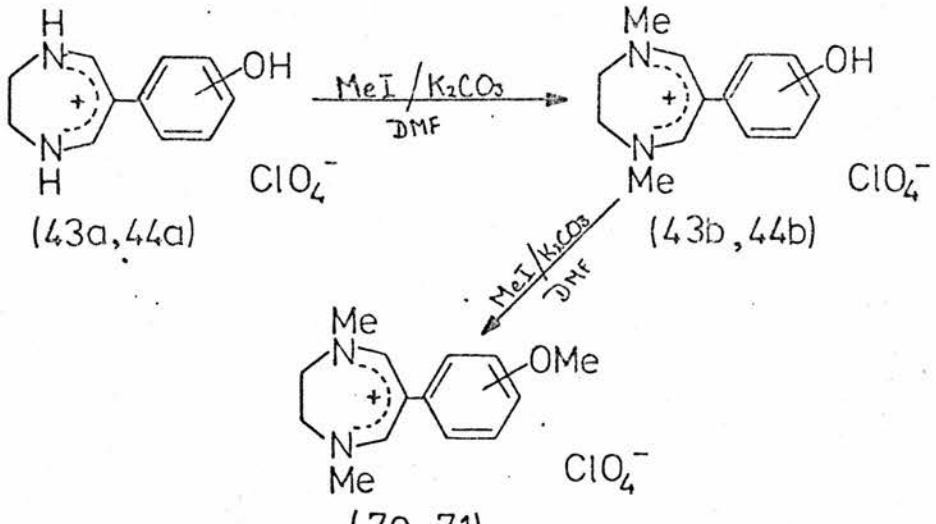


(71)

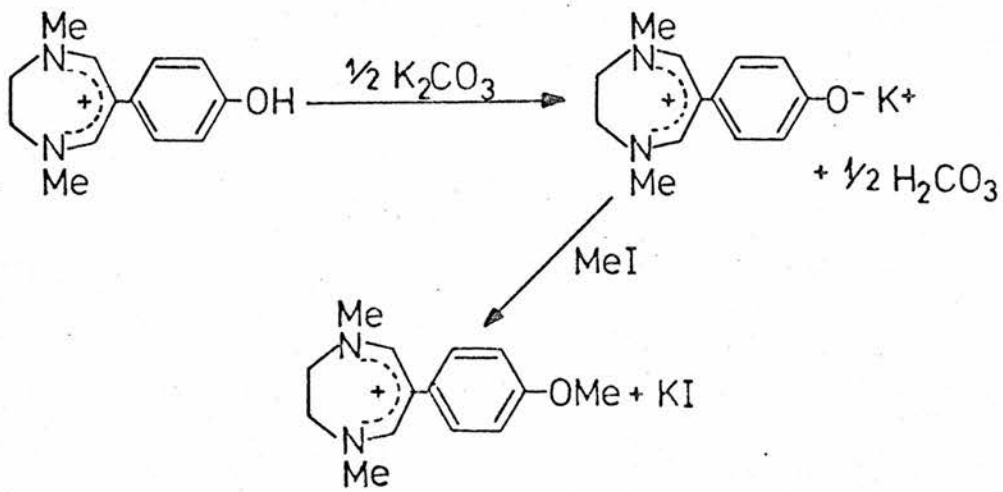
Methylation of the analogous 6-hydroxyphenyldiazepinium salts (43a,44a) did not, however, produce the 6-methoxyphenyldiazepinium salts. Instead, methylation occurred on the nitrogen function, to produce the 6-hydroxyphenyl-1,4-dimethyl-diazepinium salts. By using a three-fold excess of methyl iodide, methylation then occurred on the hydroxy group as well.



(43a,44a) (43b,44b) (70,71)

The way in which methylation occurs, using methyl iodide and potassium carbonate, is that the potassium carbonate abstracts an acidic proton and then methylation of the resulting potassium salt occurs.

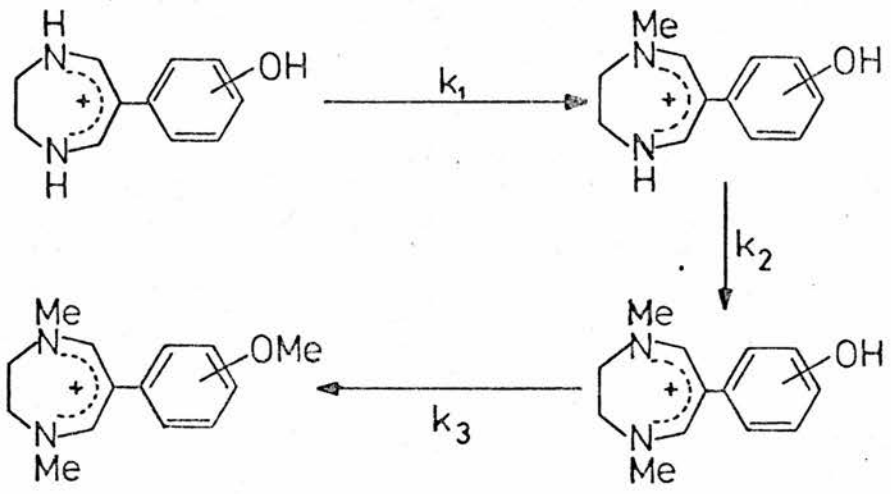
eg.



With the 6-hydroxyphenyl-1',4-dimethyl-diazepinium salts this is quite straightforward. With the N-unsubstituted 6-hydroxy--phenyldiazepinium salts the situation may be different. It is possible that the nitrogen proton is abstracted in preference to the hydroxy proton, implying that the hydrogen of the $\overset{\delta+}{N}\text{-}\overset{\delta+}{H}$ of the 6-hydroxyphenyldiazepinium salts is more acidic than that of the $\text{-O-}\overset{\delta+}{H}$. The hydroxy group can be methylated only when the two nitrogen atoms have been methylated.

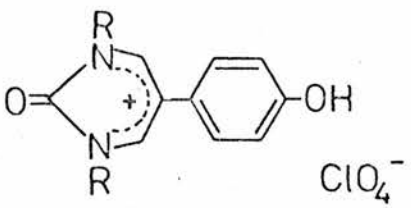
By using equimolar quantities of methyl iodide and the diazepinium salt it was hoped that mono-methylation would result. However, using smaller amounts of methyl iodide still resulted in formation of the N,N´-dimethyl compounds, the products merely being formed in lower yields. It would seem that the methylation of one nitrogen atom activates the second nitrogen atom towards methylation, such that

$$k_2 > k_1 > k_3.$$



If this assumption is correct, as results have implied, then it will not be possible to isolate N-mono-methylated products of the 6-hydroxyphenyldiazepinium salts, and N,N´-dimethylation will always occur before methylation of the oxygen function.

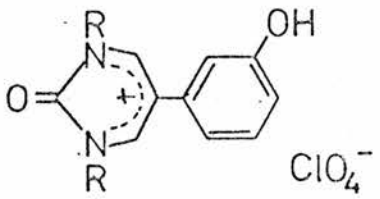
1,2-DIHYDRO-5-HYDROXYPHENYL-2-OXO-PYRIMIDINIUM PERCHLORATES



(72)

a) R = H

b) R = Me



(73)

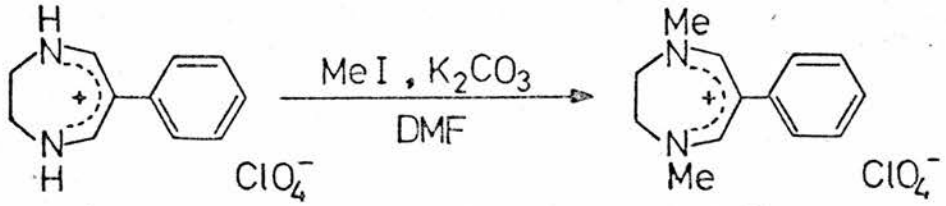
It was thought that preparation of the 1,2-dihydro--5-hydroxyphenyl-2-oxo-pyrimidinium perchlorates might be achieved by using conditions similar to those used for the analogous 6-hydroxyphenyldiazepinium perchlorates. Attempted preparation of the 1,2-dihydro-5-p-hydroxyphenyl-2-oxopyrimidinium perchlorate (72a) resulted in an intractable tar, presumably the product either of any formed pyrimidinium salt reacting further with itself or of an alternative reaction. Similarly, the m-hydroxyphenyl compound (73a) was only obtained as an impure solid. However, both the p-hydroxyphenyl-1,3-dimethyl- (72b) and the m-hydroxyphenyl-1,3-dimethyl-2-oxo-pyrimidinium salts (73b) were obtained successfully.

The analogous 6-hydroxyphenyldiazepinium salts successfully underwent electrophilic aromatic substitution of the phenyl ring. In comparison, all attempts to brominate the pyrimidinium salts were relatively unsuccessful, although mass spectroscopic data did imply the presence of some bromo-compounds. The failure of the pyrimidinium salts to undergo electrophilic substitution is understandable when one considers that the urea group competes with the vinamidinium system for excess electrons, and hence lowers the nucleophilicity of the latter system (see page 17).

SOME N-METHYLATION REACTIONS

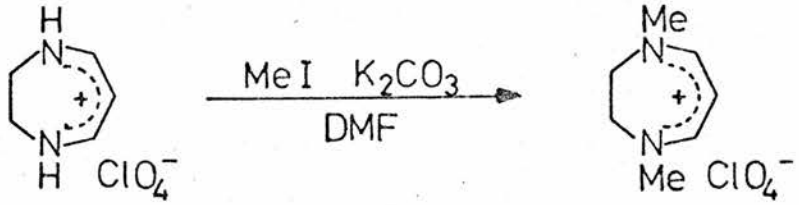
The ease with which methylation of the nitrogen atoms of the 2,3-dihydro-6-hydroxyphenyl-1,4-diazepinium perchlorates occurred prompted the investigation of N-methylation of some other diazepinium salts. The use of methyl iodide, potassium carbonate and dimethylformamide had been successful, and consequently this method was again used.

a) The 2,3-dihydro-1,4-dimethyl-6-phenyl-1,4-diazepinium perchlorate (42b) was successfully obtained from the 6-phenyldiazepinium perchlorate (42a).



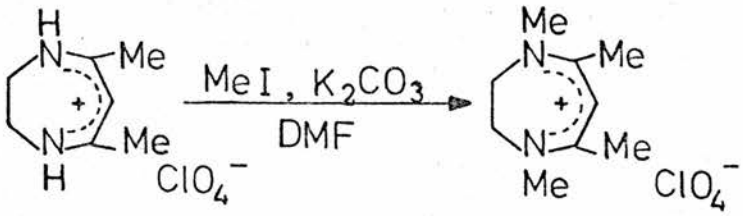
(42a) (42b)

b) Similarly, the 1,4-dimethyl-2,3-dihydro-1,4-diazepinium perchlorate (75) was successfully obtained from the unsubstituted diazepinium salt (74)[26].



(74) (75)

c) The 2,3-dihydro-1,4,5,7-tetramethyl-1,4-diazepinium perchlorate (77) is normally obtained with some difficulty[22]. However, N-methylation of the 5,7-dimethyldiazepinium perchlorate[1] (76) allowed the tetramethyl salt to be obtained easily.



(76) (77)

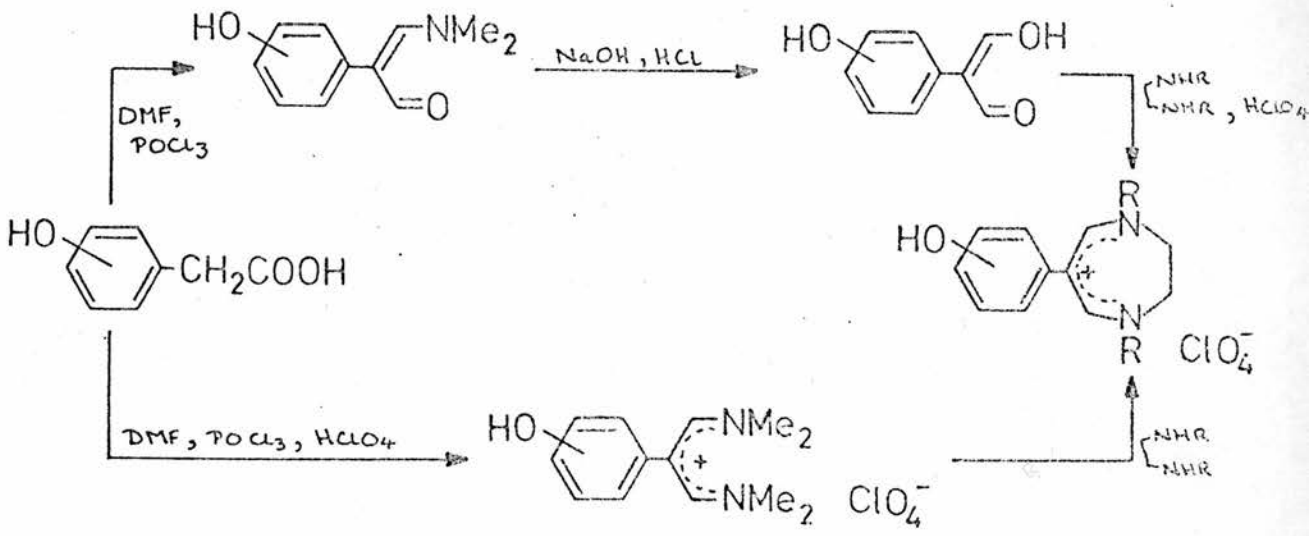
d) The 2,3-dihydro-1,4-dimethyl-5,7-diphenyl-1,4-diazepinium perchlorate (79) was previously unknown. However, N-methylation of the 5,7-diphenyldiazepinium salt (78)[25] allowed it to be prepared.

(78) (79)

From the success of the N-methylation reactions it would seem that this method may be widely used to methylate the nitrogen atoms of 1,4-diazepinium salts. There is also no reason to think that, in general, N-alkylation of N-unsubstituted diazepinium salts will not occur by using an alkyl halide, potassium carbonate and dimethylformamide. In this way a variety of alkyl groups may be introduced onto the 1,4-positions of 1,4-diazepinium salts.

AN UNEXPECTED BENZOFURAN

p-Hydroxyphenylacetic acid was the initial starting material used for the preparation of a variety of p-hydroxyphenyldiazepinium salts. Similarly, the m-hydroxyphenyldiazepinium salts were derived from the m-hydroxyphenylacetic acid. As the o-hydroxyphenylacetic acid is also commercially available, it was hoped that a similar series of o-hydroxyphenyldiazepinium salts could be prepared.



The initial stage of the reaction involves the conversion of the phenylacetic acid to the acrolein or the vinamidinium salt. It is at this stage, the Vilsmeier-Haack bisformamination of o-hydroxyphenylacetic acid, that an alternative product was obtained. With the p-hydroxyphenyl- and the m-hydroxyphenylacetic acids the formation of the acrolein, or the vinamidinium salt, as a solid precipitate occurs only after treatment of the reaction mixture. With the o-hydroxyphenylacetic acid, on the other hand, a red precipitate forms during the course of the reaction.

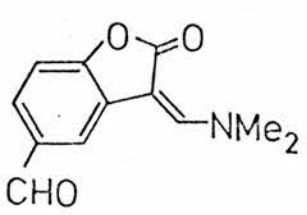
The precipitate derived from the Vilsmeier-Haack bisformamination of o-hydroxyphenylacetic acid was characterised as a benzofuran-type compound (80). Consistent with this formulation are the following :

^{1}H-N.M.R. : δ = 3.3 - 3.7 (m), 7.4 - 7.7 (m), 8.0 (s) and 9.9 (s) ppm.

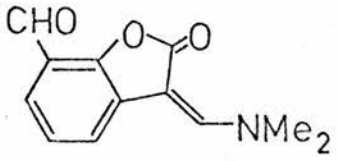
Intensity ratio 6 : 3 : 1 : 1

Found : C,66.41 ; H,5.23 ; N,6.32 % ; $\underline{M}^+$,217.07

$C_{12}H_{11}NO_3$ requires C,66.35 ; H,5.10 ; N,6.45 % ; $\underline{M}$,217.07



(80a)



(80b)

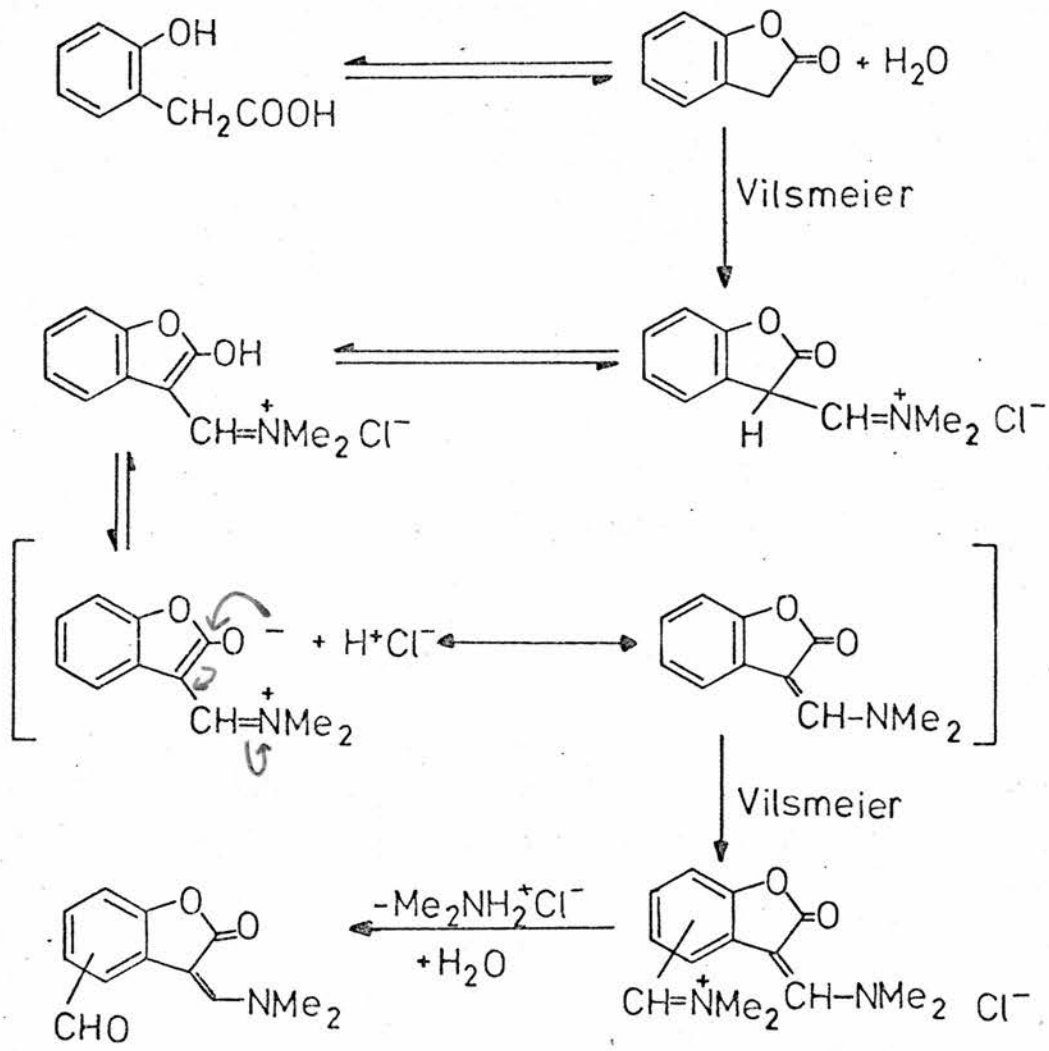
o-Hydroxyphenylacetic acid is known to exist in equilibrium with benzofuran-2(3H)one, and it is this species which, in all probability, reacted with the Vilsmeier formylating agent. Since the hydroxy group in o-hydroxyphenylacetic acid is adjacent to the acid group it is not surprising that chemical interaction between the two sites took place.

Also, the hydroxy group is activating and ortho/para directing with respect to electrophilic aromatic substitution, and this seems to have resulted in formylation of the benzene ring.

The complexity of the ^{1}H-N.M.R.-spectra (see page 68) led to the assumption that two isomers were present, the 3-(dimethylaminomethylene)-5-formyl- (80a) and the 3-(dimethylaminomethylene)-7-formyl-benzofuran-2(3H)one (80b), but no attempt was made

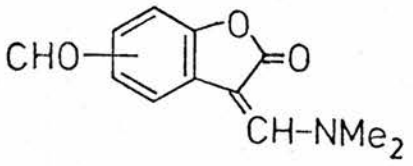
to separate the two isomers.

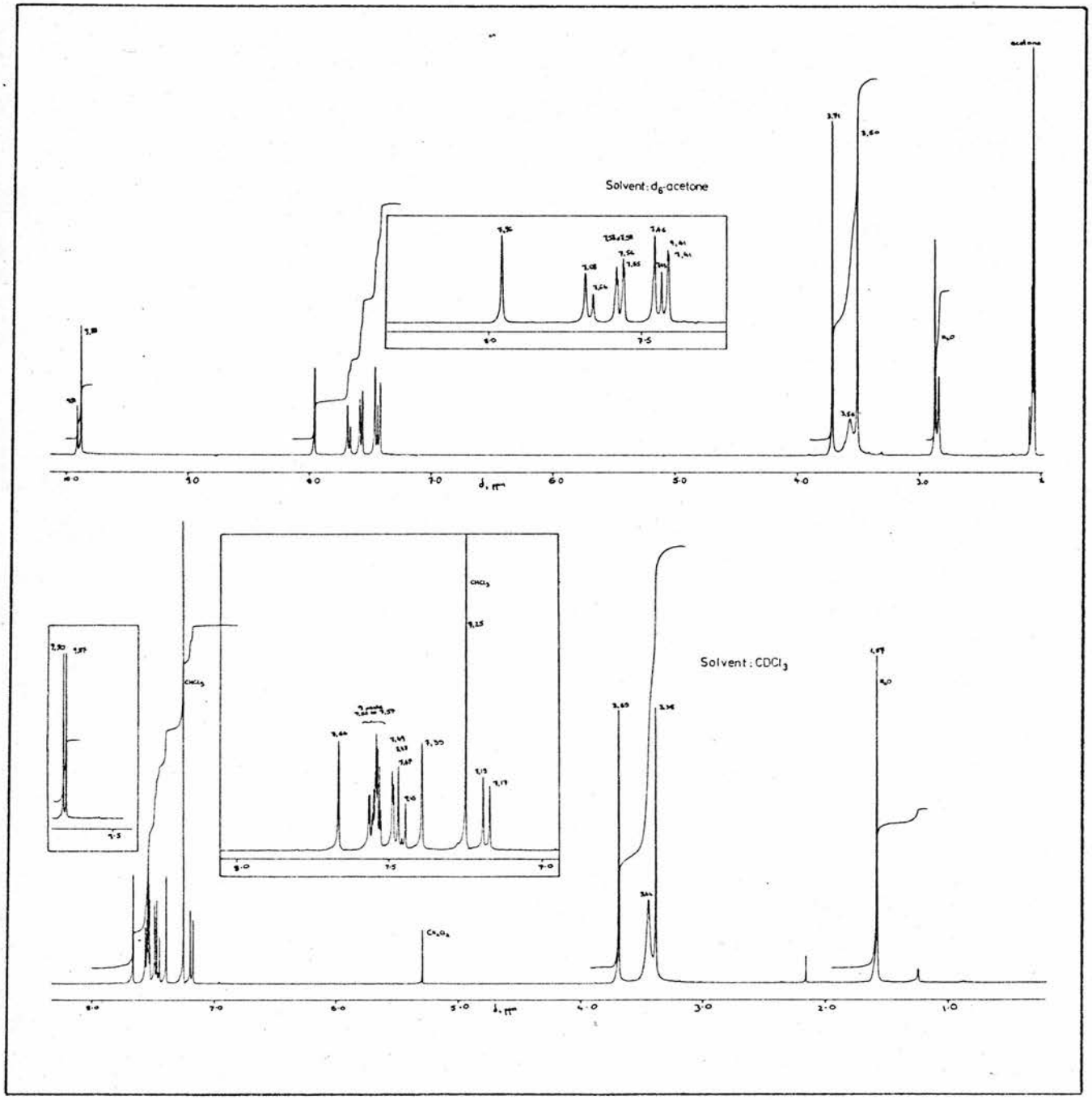
A postulated reaction mechanism for the formation of the benzofuran system may be drawn:



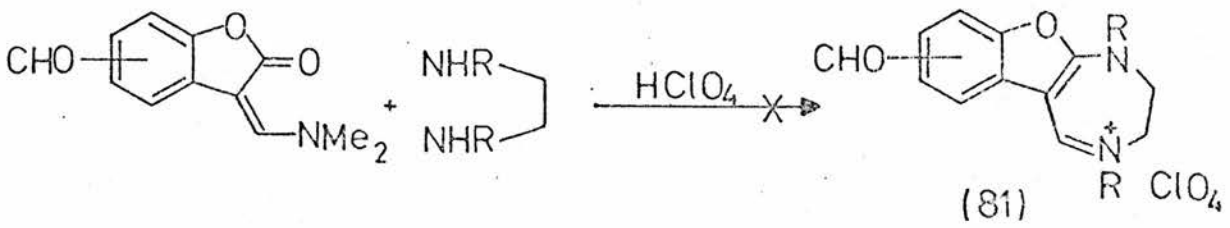
(80)

^{1}H-N.M.R. Spectra of





The benzofuran (80), although not the compound hoped for, still has a system which might have reacted with an ethylenediamine to produce a diazepinium salt (81).



(81)

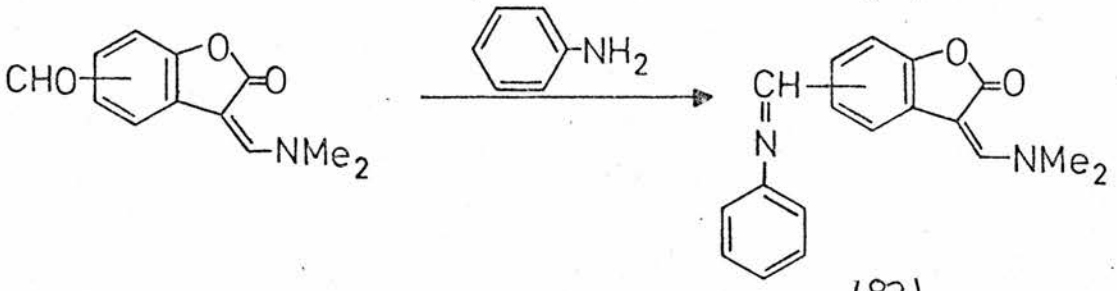
This result was, unfortunately, not achieved. Two possible explanations for this are:

(i) the arylaldehyde is likely to be more reactive towards an ethylenediamine therefore reducing the likelihood of reaction occurring across the "acrolein" portion.

(ii) reaction to form a diazepinium salt involves a state of equilibrium between the reactants and the products, this generally favouring formation of the diazepinium salt. In this case the equilibrium may lie on the side of the reactants and hence no diazepinium salt forms.

Of these two problems, there is little that could be done about the second, but the first can be overcome by protection of the arylaldehyde group. A frequent means of protecting an aldehyde group is to react it with an amine to produce a Schiff base. With this in

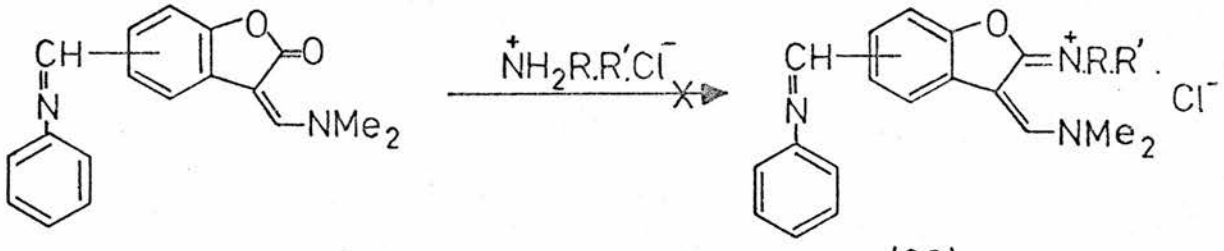
mind, 3-(dimethylaminomethylene)-5(7)-formyl-benzofuran-2(3H)one was treated with aniline to produce the Schiff base (82)



(82)

Regrettably, this, when treated with an ethylenediamine, still did not produce a diazepinium salt.

As an alternative, the "acrolein" portion having failed to produce a diazepinium salt, the carbonyl group might be converted into a dialkylamino or an arylamino group, with the possibility that the resulting vinamidinium system would be more reactive towards an ethylenediamine than the acrolein system. However, attempts to convert the carbonyl group into a dialkylamino or arylamino group were also unsuccessful (83).



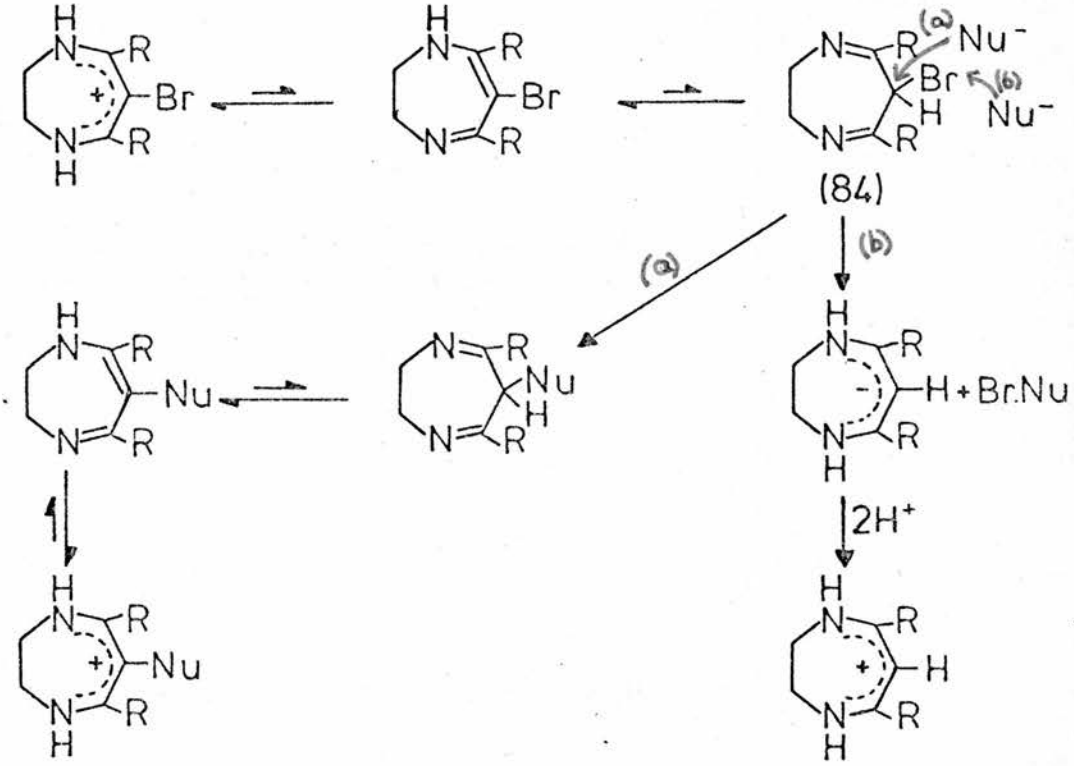
(83)

(i) R = Ph , R' = H

(ii) R = R' = Me

PROTODEHALOGENATION OF SOME 2,3-DIHYDRO-6-HALOGENO-1H-1,4-DIAZEPINIUM SALTS

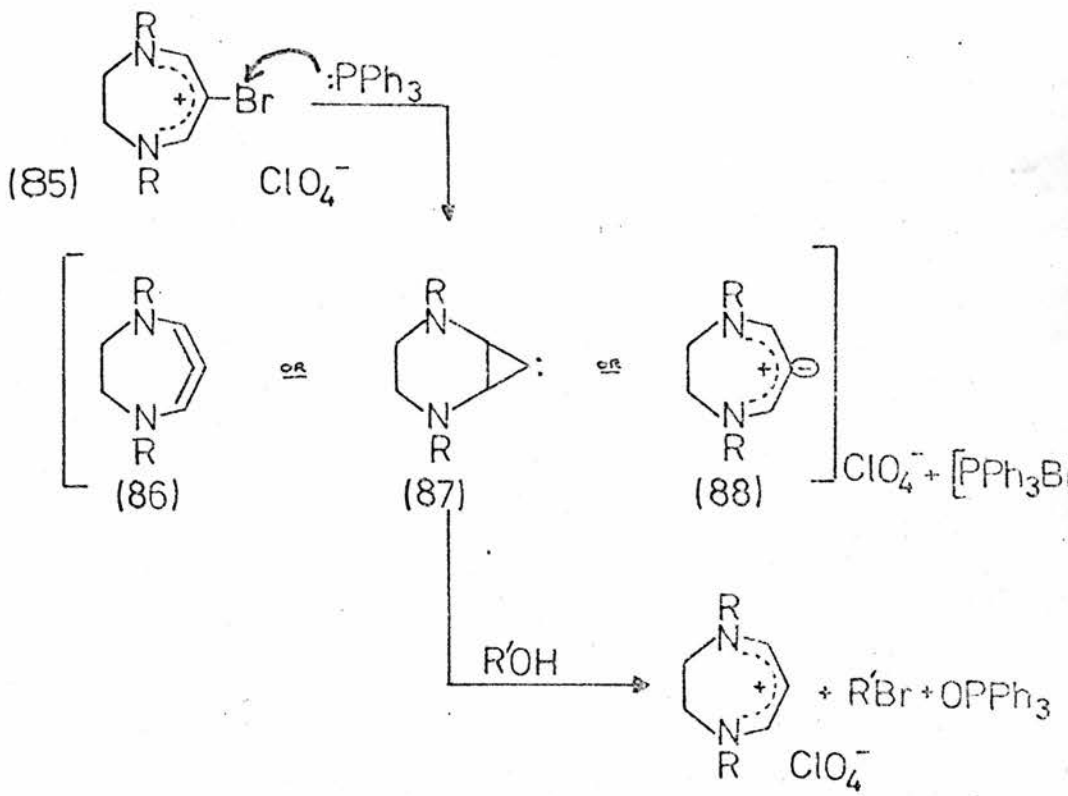
6-Halogenodihydrodiazepinium salts react with nucleophiles to produce a compound in which the halogen atom has been replaced by either the nucleophile or by a proton[36,37,46,77]. The active species for the reaction of the 6-halogenodihydrodiazepinium salts is believed to be the bisimine tautomer of the base form (84).



Whether or not the product of this reaction is the protodehalogenated species is determined by the size of the nucleophile and of the 5,7-substituents. The smaller the substituent R, or the halogen atom, the easier it will be for the nucleophile to react at the 6-position, and consequently produce less protodehalogenated species - route (a). Similarly, the larger the

halogen atom or the 5,7-substituents the more likely it is that the protodehalogenated species will form - route (b).

Protodehalogenation, as detailed previously, requires the initial formation of the dihydrodiazepine base which then tautomerises to the reactive bisimine form. However, recent studies[88,91] have shown that salts which cannot form a dihydrodiazepine base, for example the 6-bromo-1,4-dimethyldiazepinium perchlorate (85b), may also undergo protodebromination when heated with a molar equivalent of triphenylphosphine in n-pentanol. This requires the reaction to proceed *via* an alternative intermediate, whose structure might be an allene (86), a carbene (87), and a species which is at the same time an onium ion and a carbanion - the onium anion (88)[88]. Also for *N*,*N*′-unsubstituted diazepinium salts (85a), when treated with triphenylphosphine in alcohol, the triphenylphosphine is unlikely to allow formation of sufficient base to allow protodebromination to occur *via* the base as an intermediate. Consequently a different intermediate must be proposed.



Formation of the allene or the carbene would involve substantial distortion of the geometry of the ring[16] together with loss of the delocalisation energy of the vinamidinium system (ca.19 kcal mol^{-1})[8]. On the other hand, calculations of the molecular geometries for these intermediates, using the MNDO method*, imply that the allenic system (86) is preferred[89] for an isolated system. However the reactions under consideration were carried out in solution and under these conditions the intermediate might have a different structure.

All in all, there is a reasonable amount of evidence in support of this mechanism, i.e. that the bromine atom is abstracted to yield an onium anion, for example :

- use of perdeuteriomethanol with the 5,7-dimethyldiazepinium salt results in a 6-deuteriodihydrodiazepinium salt[88,91].

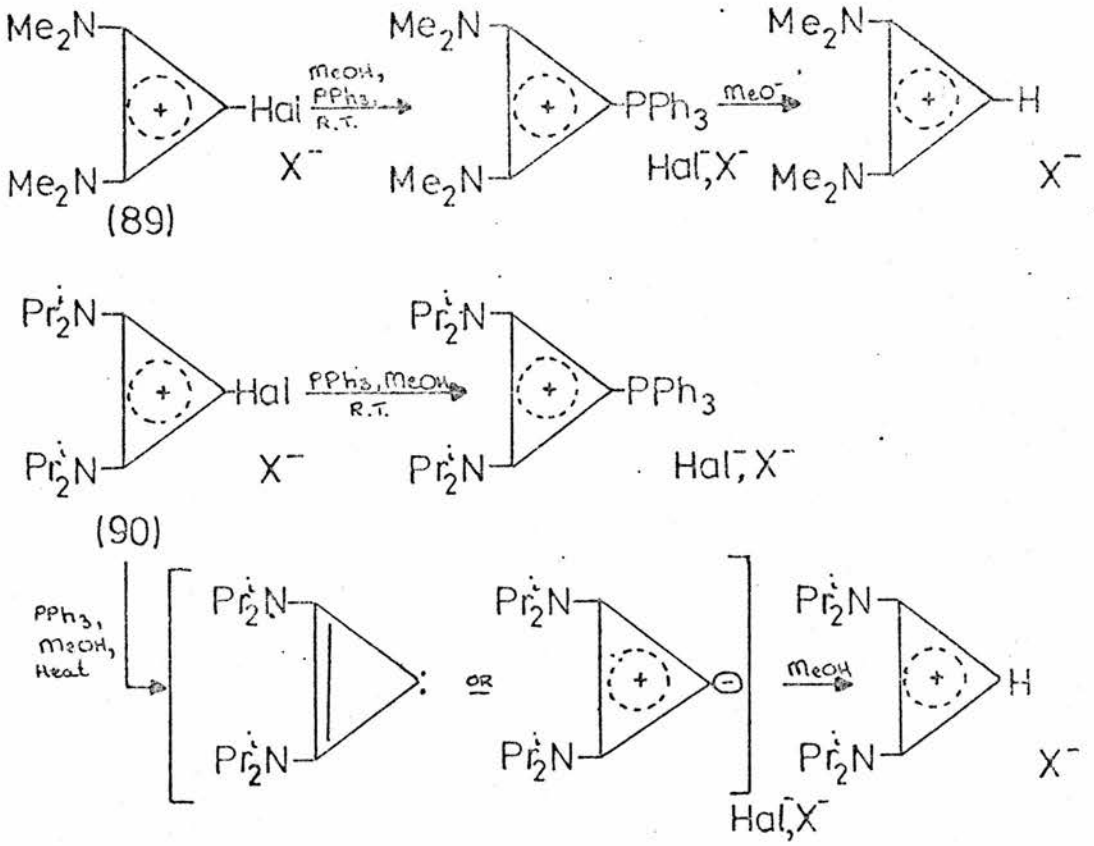
- salts which cannot form dihydrodiazepine bases can still undergo protodebromination[88,91].

- protodebromination of the 5,7-dimethyldihydrodiazepinium salt in

(* MNDO = Modified Neglect of Diatomic Overlap[90])

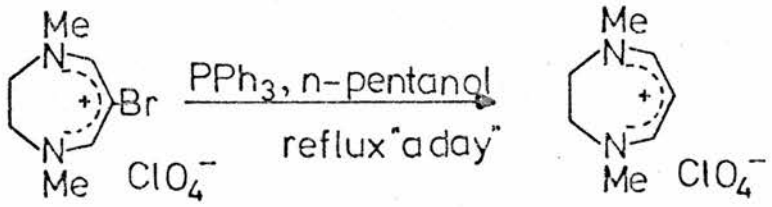
1-propanol also provides the other expected products, 1-bromopropane and triphenylphosphine oxide[88,91].

Other instances have been reported in the literature[92-100] in support of a similar type of intermediate, although they have not been formulated as such. An example of this is the dehalogenation of bisaminocyclopropenium salts which has been described as proceeding *via* a carbene as an intermediate[92,93,94]. Protodehalogenation of the salt (89) at room temperature will not proceed with triphenylphosphine in methanol only, but requires the addition of some methoxide ion. Similarly, dehalogenation of the salt (90) at room temperature with methanol and triphenylphosphine produces a triphenylphosphine salt, but no dehalogenated salt. If the reaction is carried out at elevated temperatures then a protodehalogenated species ensues - reaction is described as proceeding *via* a carbene, but the intermediate may be better described as an onium anion[95].



Protodebromination reactions of the 6-halogeno-dihydrodiazepinium salts had been studied in sufficient depth to decide that an intermediate, like the onium anion, must be involved[88,91]. Further work was carried out on such systems to gain additional information.

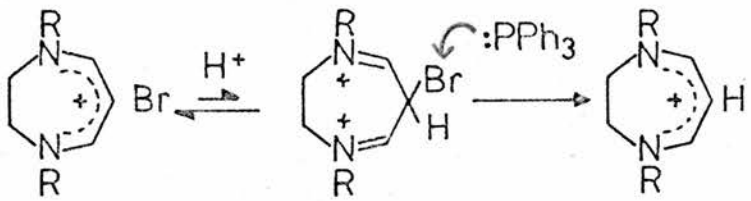
(i) The protodebromination of 6-bromo-2,3-dihydro-1,4-dimethyl--diazepinium perchlorate (91) was studied. G.Richardson[91] reported that this compound protodebrominated by refluxing the salt with triphenylphosphine in n-pentanol for "a day". However, no debromination occurred using n-propanol or methanol as the solvent (n-propanol and methanol both have lower boiling points than n-pentanol).



(91) (75)

Repeating this experiment led to the introduction of a number of modifications to the original method. First it was observed that "a day" must be a length of time in excess of 12 hours. Refluxing the salt with triphenylphosphine in n-pentanol for less than 12 hours resulted in the reprecipitation of the bromo derivative.

As the reaction is basically that of bromine/hydrogen exchange, it was thought that the addition of more hydrogen ions to the reaction mixture might induce protodebromination. Refluxing the salt with triphenylphosphine and a few drops of 70% perchloric acid in n-pentanol for just 3.5 hours resulted in precipitation of the protodebrominated species. In these circumstances a modified mechanism may be drawn.

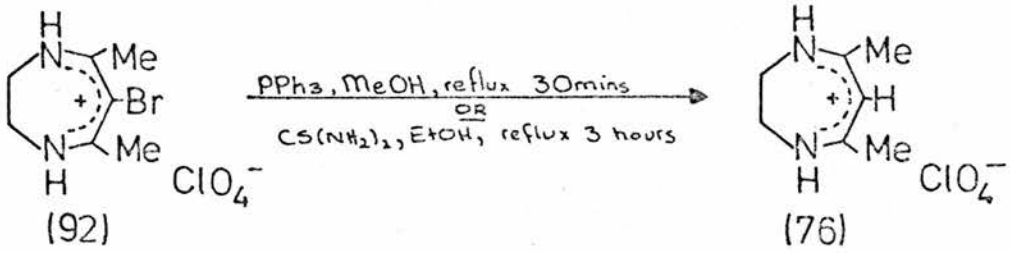


Addition of too much perchloric acid, however, caused a darkening of the reaction mixture and attempts to isolate any proto- or bromo-species were unsuccessful. The colouration of the solution is probably due to the formation of decomposition products. Refluxing the salt in n-pentanol with 70% perchloric acid only does not afford the proto-derivative.

Another possible means of promoting protodebromination is by the addition of a bromine acceptor. Potassium bromide was added to the reaction mixture (of salt, triphenylphosphine and n-pentanol) and this was heated under reflux for 6 hours, resulting in no debromination. This may have been because the potassium bromide remained, for the most part, as a suspension in the solution, and may not therefore have dissolved sufficiently to take part in the reaction.

Summarising this work, the protodebromination of the 6-bromo-1,4-dimethyldiazepinium salt (91) can best be carried out in n-pentanol with triphenylphosphine refluxing, say, for 20 hours, or in n-pentanol with triphenylphosphine and a drop of perchloric acid and refluxing for 3.5 hours.

(ii) The protodebromination of 6-bromo-2,3-dihydro-5,7-dimethyl--1,4-diazepinium perchlorate (92) was investigated. It has been reported[91] that this compound underwent protodebromination by refluxing the salt with triphenylphosphine in methanol for 30 minutes.



(92) (76)

Using this method, the protodebromination reaction was found to be unsuccessful. However, addition of a few drops of 70% perchloric acid induced the loss of bromine and the consequent formation of the proto-derivative (76).

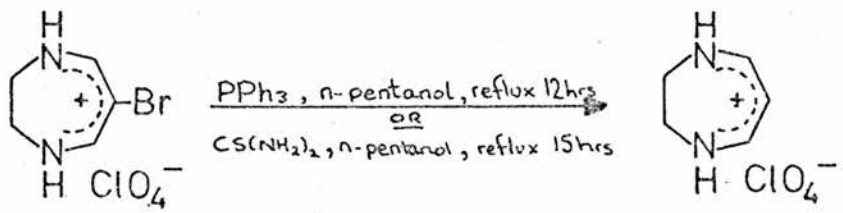
As an alternative to triphenylphosphine, thiourea can be used to bring about abstraction of the bromine atom. Attempts to debrominate the 6-bromo-5,7-dimethyldiazepinium salt (92) by using thiourea in ethanol and refluxing for 3 hours were successful[46,96].

(iii) The successful protodebromination of 6-bromo-2,3-dihydro-

-1,4-diazepinium perchlorate (93) has been reported[91]. The reaction involves heating the salt and triphenylphosphine in n-pentanol under reflux for 12 hours.

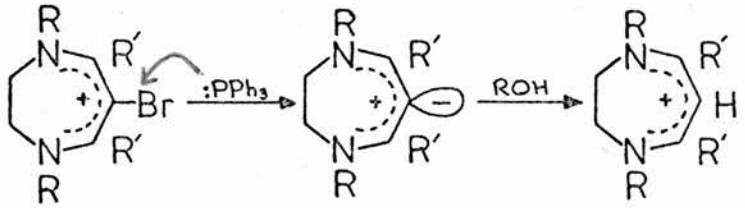
Addition of a few drops of 70% perchloric acid to the reaction mixture also allows the 6-proto derivative to be achieved. So, protodebromination occurs with or without the perchloric acid, however it was observed that the product obtained with the addition of acid was more easily isolable and obtainable in better yield. The use of perchloric acid causes the product to be entirely the perchlorate salt, whereas without the acid the product is a mixture of the bromide and the perchlorate. This accounts for the fact that, in comparison with the reaction without acid, the product of the reaction with acid is more readily isolated.

Similarly, the protodebromination was carried out using thiourea in place of triphenylphosphine. The 6-bromo derivative was refluxed for 15 hours in n-pentanol with only perchloric acid, with only thiourea and with both thiourea and perchloric acid. The only unsuccessful reaction was that without thiourea, although the reaction with both thiourea and perchloric acid afforded a more isolable product.



(93) (74)

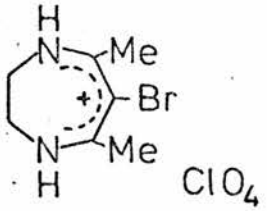
The protodebromination reactions considered so far have all been successful as long as a bromine abstractor, namely thiourea or triphenylphosphine, has been present. This substantiates the idea that, in the absence of acid, the intermediate which forms is an onium anion.



onium anion

In the case of reaction where acid is also present debromination of a dication (see page 76) is a probable alternative mechanism.

Protodebromination reactions which do not require triphenylphosphine or thiourea have been further investigated using the 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (92). This diazepinium salt is protodebrominated by refluxing it in methanol for 30 minutes with triphenylphosphine, or by refluxing in ethanol for 3 hours with thiourea. However, addition of silver nitrate as a bromine acceptor does not induce protodebromination if the reaction is carried out in ethanol or methanol.



(92)

Investigation of protodebromination reactions in solvent only was carried out in a variety of solvents of varying boiling points. Previously the reaction had always been carried out in alcohols, but now non-alcoholic solvents were also used. By heating the salt in solvent for 20 hours it was observed that reaction in solvents having a boiling point greater than 120° were successful i.e. protodebromination took place, whereas reaction in solvents of boiling point lower than 110° resulted in reprecipitation of the 6-bromo derivative.

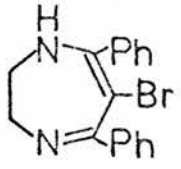
RESULTS

Solvent	B.pt.°	Has protodebromination occurred?
Dimethylformamide	153	Yes
Xylene	138	Yes
n-Pentanol	139	Yes
4-Methyl-pentan-2-ol	133	Yes
Cyclopentanone	130	Yes
n-Butanol	116-118	mixture of 6-bromo- and 6-protodiazepinium salt
2-Methyl-butan-2-ol	100-103	No
n-Propanol	96-99	No
Ethanol	78	No

All the above reactions were carried out by refluxing the reaction mixture for approx. 15 hours. The successful protodebromination reactions yielded only protonated species.

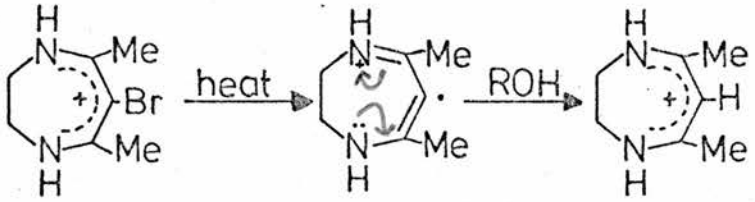
These results implied that protodebromination of the 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (92) in solvent only is temperature dependent and the "cut-off" temperature is approximately 116-118°. A similar temperature dependent effect had been observed for the debromination of the 6-bromo-5,7-diphenyldiazepine base (94)[36]. In this case the yield of protodebrominated species increased with the boiling point of the solvent used.

Solvent	B.pt°	Yield
Ethanol	78	24%
Benzene	80	29%
Toluene	111	38%



(94)

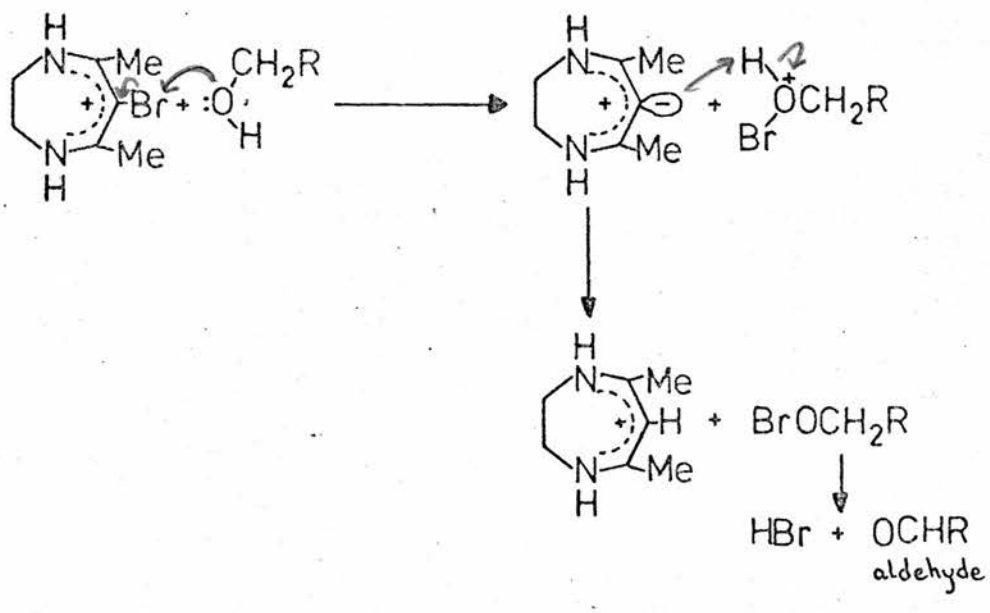
The question arose as to whether this implied that the protodebromination reaction of (92) had proceeded via a radical intermediate. According to Viehe[101], radicals are stabilised and particularly readily formed if their site of formation lies between a donor and an acceptor group (a "capto-dative environment"). The 6-position of a diazepine fits this criterion, hence radical formation may make the protodebromination reaction proceed readily.



(92)

Investigation of this possibility was carried out by means of an E.S.R spectroscopic investigation on the 6-bromo salt (92) in solution but with negative results. Further E.S.R. work was done on a solution of the salt in dimethyl sulphoxide together with a nitroxide solution in dimethyl sulphoxide. The nitroxide produces a radical signal - if the 6-bromodiazepinium salt was protodebrominated via a radical intermediate, then radical combination will occur resulting in a decrease in the size of the nitroxide radical signal. However, this was not observed, and therefore the conclusion can be made that protodebromination of the 6-bromo-5,7-dimethyldiazepinium perchlorate does not proceed by a radical reaction at temperatures greater than 120°.

When considering a mechanism for the protodebromination reaction the destiny of the bromine atom must be considered. A proposed mechanism for the reaction in alcohol is :



This requires one of the side products to be an aldehyde. Investigation into the products of the reaction in n-pentanol was carried out, specifically testing for the presence of n-valeraldehyde. The protodebromination was carried out in the usual way, but before isolation of the 6-proto derivative the reaction solvent was distilled off and tests were done on the first few drops of distillate, which should contain most of the n-valeraldehyde.

B.pt. n-valeraldehyde, 103°

B.pt. n-pentanol, 136°

The low concentration of aldehyde made preparation of any derivatives extremely difficult. However, the 2,4-dinitrophenylhydrazone was isolated and characterised by mixed melting point. An infra red spectrum on the distillate also showed a small absorption in the carbonyl region, possibly attributable to n-valeraldehyde.

Although not conclusive, these results do provide positive evidence for the proposed reaction mechanism.

An interesting point to note is that protodehalogenation of the 6-bromo-5,7-dimethyldiazepinium perchlorate (92) also occurred in xylene, a solvent in which it is not soluble, but which has a boiling point greater than 120°. The explanation for this could be that the xylene contained some aqueous or alcoholic solvent and it is this which actually reacted with the 6-bromo salt, the refluxing xylene merely providing an adequate reaction temperature.

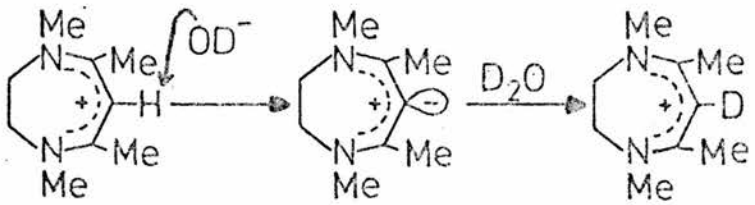
The 6-chloro- and 6-iodo-5,7-dimethyldiazepinium perchlorates were briefly studied, dechlorination and deiodination occurring in an analogous manner to debromination. Dechlorination occurs less readily than debromination and this may be attributable to the reluctance of the chlorine, in comparison with bromine, to form a positive ion. Deiodination, however, occurs more readily, the "cut-off" temperature for the reaction being about 80°. The largeness of the iodine atom, its presence in the 6-iodo-5,7-dimethyldiazepinium salt causing some steric strain, together with a greater readiness to form a positive ion may be the reason for this.

The success of the dehalogenation reactions of the 6-halogeno-5,7-dimethyl-2,3-dihydrodiazepinium salts prompted the study of the analogous bases. Heating these bases in a variety of solvents led to the conclusion that debromination occurs at much lower temperatures for the diazepine bases than for their salts. Protodebromination of the 6-bromo-5,7-dimethyl-2,3-dihydro-diazepine base can occur in methanol (65°) whereas the corresponding salt requires temperatures in excess of about 120°. Initially it was suggested that dehalogenation of the 6-halogenodiazepinium salts proceeded by formation of the bisimine tautomer of the base form (see page 71). Obviously, in comparison with the salts, the diazepine bases are more easily converted to the bisimine form, and their easier debromination may be connected with this.

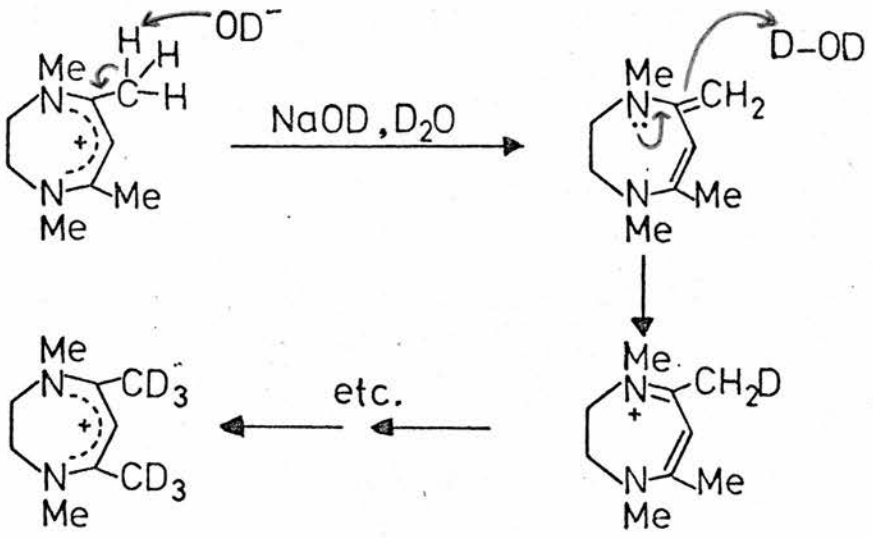
N,N'-disubstituted diazepinium salts cannot be converted to a base and dehalogenation of the 6-halogeno derivatives must proceed by an alternative route.

As an adjunct to this study of some dehalogenation reactions and the subsequent formation of an onium anion, a simple ^{1}H-N.M.R. experiment was carried out, not involving dehalogenation.

The idea behind the experiment was that a diazepinium salt substituted at the 1,4,5,7-positions, when treated with sodium deuteroxide solution, might be converted via its onium anion into the 6-deuterio derivative.



The experiment was done by recording a ^{1}H-N.M.R. spectrum of the diazepinium salt in deuterium oxide. Then a small piece of sodium was added to the sample, thereby creating sodium deuterioxide solution. It was hoped that the 6-H signal would disappear. Unexpectedly, deuteriation occurs instead at the 5,7-dimethyl groups implying that these positions are more reactive towards nucleophilic attack than the 6-H position.



Analogous deuteriation studies were done on the 1,4-dimethyl-5,7-diphenyl- and the 5,7-dimethyl-1,4-diphenyl--diazepinium perchlorates. No interesting results were obtained ; unfortunately, treatment with sodium deuterioxide solution caused hydrolysis of the diazepinium perchlorates.

N.M.R. SPECTRA

ABBREVIATIONS AND MATERIALS

All N.M.R. spectra were recorded in DMSO unless otherwise stated, and shifts are in ppm. downfield from TMS.

The ^{1}H-N.M.R. spectra were recorded on a Bruker WP-80.

The ^{13}C-N.M.R. spectra were recorded on a Varian CFT-20.

s = singlet

d = doublet

t = triplet

m = multiplet

q = quartet

br = broad

DMSO = dimethylsulphoxide

TMS = tetramethylsilane

ac = acetone as solvent

Mass spectra were recorded on an AEI MS902.

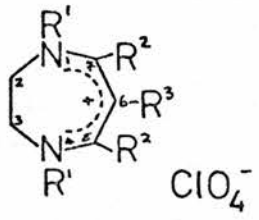
Accurate masses were recorded with perfluorotri-n-butylamine as an internal reference.

Melting points were obtained on a Gallenkamp apparatus using open capillary tubes and are uncorrected.

Yields for these reactions have usually not been optimised.

DIAZEPINIUM PERCHLORATES OTHER THAN 6-PHENYLSUBSTITUTED SALTS

Compound	Substituent groups		
	R^1	R^2	R^3
28c	Ph	H	OH
37a	Me	H	OMe
37b	Ph	H	OMe
77	Me	Me	H
79	Me	Ph	H



^{1}H-N.M.R. shifts

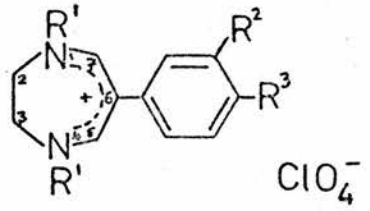
Compound	δ R^1	δ R^2	δ R^3	δ $-CH_2CH_2-$	Intensity Ratio
28c	7.2(s)	7.9(s)	no peak	4.0(br)	10 : 2 : 4
37a	3.3(s)	8.1(s)	3.5(s)	3.6(s)	6 : 2 : 3 : 4
37b	7.5(s)	8.1(s)	3.6(s)	4.2(br)	10 : 2 : 3 : 4
77	3.3(s)	2.2(s)	5.3(s)	3.8(s)	6 : 6 : 1 : 4
79	3.3(s)	7.7(s)	5.1(s)	4.1(br)	6 : 10 : 1 : 4

^{13}C-N.M.R. shifts

Compound	δ C(2,3)	δ C(5,7)	δ C(6)	δ other C
28c	56.1	149.1	144.9	1,4-Ph,122.8,126.8,128.2, 129.9
37b	56.0	152.1	144.8	6-OMe,64.7 ; 1,4-Ph,123.0, 128.3,129.7,131.4
79	57.5	97.2	166.6	1,4-Me,45.6 ; 5,7-Ph,128.4, 129.4,131.0,137.3

HYDROXY- AND METHOXYPHENYLDIAZEPINIUM PERCHLORATES

Compound	Substituent Groups		
	R^1	R^2	R^3
42a	H	H	H
42b	Me	H	H
43a	H	H	OH
43b	Me	H	OH
44a	H	OH	H
44b	Me	OH	H
70	Me	H	OMe
71	Me	OMe	H



^{1}H-N.M.R. shifts

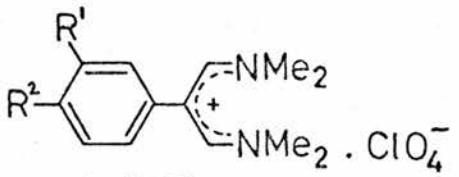
Compound	δ R^1	δ H(5,7)	δ CH_2CH_2	δ Ar	δ OH/OMe	Intensity Ratio
42a	7.4(br)	8.0(s)	3.7(s)	7.45(s)	-	2 : 2 : 4 : 5
42b	3.2(s)	7.7(s)	3.6(s)	7.1(s)	-	6 : 2 : 4 : 5
43a	9.3(br)	7.7(s)	3.7(s)	6.7-7.3(q)	with NH	3 : 2 : 4 : 4
43b	3.4(s)	7.9(s)	3.7(s)	6.6-7.4(q)	9.4(br)	6 : 2 : 4 : 4 : 1
44a	6.4(br)	7.7(s)	3.7(s)	6.6-7.3(m)	with NH	3 : 2 : 4 : 4
44b	3.4(s)	7.9(s)	3.7(s)	6.4-7.2(m)	with Ar	6 : 2 : 4 : 5
70[ac]	3.7(s)	8.0(s)	4.0(s)	6.9-7.4(q)	3.8(s)	6 : 2 : 4 : 4 : 3
71	3.5(s)	8.0(s)	3.8(s)	6.8-7.5(m)	with CH_2	6 : 2 : 7 : 4

^{13}C-N.M.R. shifts

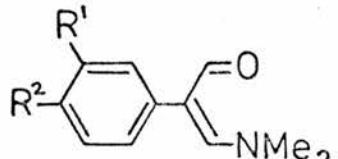
Compound	δ C(2,3)	δ C(5,7)	δ C(6)	δ other C
42a	48.9	157.4	102.7	6-Ph,126.2,127.3,128.7, 138.8 ; C-OH,156.0
42b	55.4	157.5	102.1	6-Ph,126.2,127.6,128.5, 139.0 ; 1,4-Me,47.5
43a	50.6	156.1	104.0	6-Ph,116.1,129.1,131.3 ; C-OH,156.0
43b	55.4	157.2	102.2	6-Ph,115.2,129.1,129.9 ; C-OH,156.1 ; 1,4-Me,47.3
44a	50.5	154.7	103.8	6-Ph,112.5,113.6,117.4, 129.5 ; C-OH,157.5
44b	55.4	157.4	102.2	6-Ph,113.2,114.7,118.5, 129.5 ; C-OH,157.4 ; 1,4-Me,47.4
70	55.5	157.3	101.8	6-Ph,113.9,129.1,131.5 ; C-OMe,158.0 ; OCH_3,55.3 ; 1,4-Me,55.5
71	56.1	158.4	103.1	6-Ph,112.9,114.0,120.9, 130.8,141.4 ; C-OMe,160.3 ; 1,4-Me,48.4 ; OCH_3,67.8

VINAMIDINIUM SALTS, ACROLEINS, AND HYDROXYPHENYLMALONALDEHYDES

Compound	Substituent groups	
	R^1	R^2
45a	H	H
45b	H	OH
45c	OH	H
46b	H	OH
46c	OH	H
47	OH	H
50	H	Ph_3CO-



(45)



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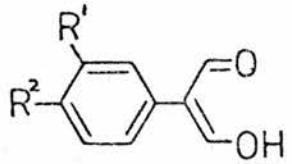


(47)

^{1}H-N.M.R. shifts

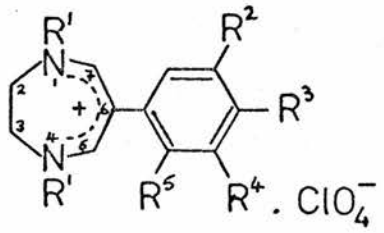
Compound	δ OH/Ph_3CO	δ Ar	δ NMe_2	δ -CH=	Intensity Ratio
45a	-	7.6(s)	2.6(s),3.5(s)	8.0(s)	5 : 6 : 6 : 2
45b	9.7(br)	6.4-7.0(q)	2.3(s),3.1(s)	7.5(s)	1 : 4 : 6 : 6 : 2
45c	no peak	6.6-7.4(m)	2.4(s),3.1(s)	7.6(s)	4 : 6 : 6 : 2
46b	9.0(br)	6.2-6.7(q)	2.6(s)	6.8(s),8.7(s)	1 : 4 : 6 : 1 : 1
46c	9.2(br)	6.3-6.9(m)	2.7(s)	7.0(s),8.9(s)	1 : 4 : 6 : 1 : 1
47c	9.5(br)	6.4-7.1(m)	-	8.7(s)	2 : 4 : 2
50	7.1-7.5(m)	6.6-6.8(q)	2.6(s)	9.0(s),other peak with Ph_3CO	16 : 4 : 6 : 1

^{13}C-N.M.R. shifts

Compound	δ N-CH_3	δ C(Ar)	δ -CH=	δ C-Ar	δ other C
45a	48.4,39.1	128.2,128.6,132.1 132.4	162.8	105.1	-
45b	39.1,48.5	115.2,122.1,133.2	163.2	105.3	C-OH,157.6
45c	38.9,48.5	115.8,118.9,123.1 129.6,133.7	162.8	105.2	C-OH,157.2
46b	42.8	114.3,125.0,132.0	158.8	113.0	C-OH,155.8;C=O,188.4
46c	42.0	113.2,118.1,121.9 128.2,136.1	158.6	114.1	C-OH,156.4,C=O,187.0
47c	-	113.7,116.2,120.1 128.5,132.6	180.0	121.0	C-OH(Ar),156.7
50	43.3	90.7,100.4,121.0 144.2	155.2	111.4	C=O,189.2;-C-O-,39.6; Ph,126.9,127.4,128.9 130.9

BROMO-HYDROXYPHENYL-DIAZEPINIUM PERCHLORATES

Compound	Substituent groups				
	R^1	R^2	R^3	R^4	R^5
59a	H	OH	Br	H	H
59b	Me	OH	Br	H	H
60b	Me	OH	Br	H	Br
64a	H	Br	OH	H	H
64b	Me	Br	OH	H	H
65a	H	Br	OH	Br	H
65b	Me	Br	OH	Br	H



^{1}H-N.M.R. shifts

Compound	δ R^1	δ H(5,7)	δ CH_2CH_2	δ Ar	δ OH	Intensity Ratio
59a	10.5(br)	8.0(d)	3.8(s)	6.6-7.7(m)	with R^1	3 : 2 : 4 : 3
59b	3.5(s)	8.0(s)	3.8(s)	6.7-7.6(m)	no peak	6 : 2 : 4 : 3
60b	3.5(s)	7.9(s)	3.8(s)	7.0(s) & with H(5,7)	no peak	6 : 3 : 4 : 1
64a	10.4(br)	7.9(d)	3.8(s)	6.8-7.6(m)	with R^1	3 : 2 : 4 : 3
64b	3.5(s)	8.0(s)	3.8(s)	6.9-7.6(m)	10.2(br)	6 : 2 : 4 : 3 : 1
65a	10.4(br)	8.0(d)	3.8(s)	7.6(s)	with R^1	3 : 2 : 4 : 2
65b	3.5(s)	8.0(s)	3.8(s)	7.6(s)	9.3(br)	6 : 2 : 4 : 2 : 1

^{13}C-N.M.R. shifts

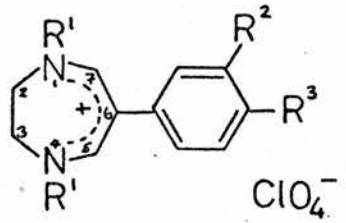
Compound	δ C(2,3)	δ C(5,7)	δ C(6)	δ C-Br	δ C-OH	δ other C
59a	49.0	157.3	102.0	107.6	154.2	6-Ph,115.4,120.0, 133.3,139.8
59b	55.5	157.4	101.5	107.6	154.1	6-Ph,116.0,120.3, 132.8,140.0; 1,4-Me,47.6
64a	49.7	158.0	101.3	110.4	153.3	6-Ph,117.4,129.0 132.0,134.3
64b	56.2	158.1	102.0	110.3	153.2	6-Ph,117.2,129.3 133.0; 1,4-Me,48.4
65a	49.8	158.1	101.4	112.4	150.0	6-Ph,132.0,134.0
65b	56.1	158.1	100.7	112.2	149.8	6-Ph,132.2,134.6; 1,4-Me,48.5

NOTES : Compound (60a) was not sufficiently pure, and N.M.R. data afforded no useful information. Theoretical shifts for ^{13}C-N.M.R. spectra can be calculated by adding an appropriate correction factor to the shift values of the basic molecule. The basic molecules for these bromo-diazepinium salts are the hydroxyphenyldiazepinium salts.

The theoretical values fit the experimental values exceedingly well except for the carbon attached to the hydroxy group. Mono-bromination of the molecule causes a deviation to this C-OH value of approx.6 ppm from the expected, whereas insertion of two bromine atoms results in a deviation of approx. 12ppm. This is most likely due to crowding within the molecule.

HYDROXY-(p-NITROBENZENEAZO)-PHENYLDIAZEPINIUM PERCHLORATES

Compound	Substituent Groups		
	R^1	R^2	R^3
68a	H	N_2PhNO_2	OH
68b	Me	N_2PhNO_2	OH
69a	H	OH	N_2PhNO_2
69b	Me	OH	N_2PhNO_2

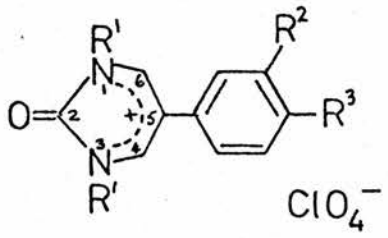


^{1}H-N.M.R. shifts

Compound	δ R^1	δ H(5,7)	δ CH_2CH_2	δ Ar	δ OH	Intensity Ratio
68a	10.4(br)	8.1(s)	3.8(s)	7.1-7.8(m), 8.2-8.6(q)	with R^1	3 : 2 : 4 : 3 : 4
68b	3.4(s)	8.1(s)	3.9(s)	7.2-7.8(m), 8.2-8.7(q)	no peak	6 : 2 : 4 : 3 : 4
69a	10.1(br)	8.1(s)	3.9(s)	6.9-8.6(m)	9.4(br)	2 : 2 : 4 : 7 : 1
69b	3.4(s)	8.0(s)	4.0(s)	6.9-7.9(m), 8.0-8.7(q)	10.5(br)	6 : 2 : 4 : 3 : 4 : 1

1,2-DIHYDRO-2-OXO-PYRIMIDINIUM PERCHLORATES

Compound	Substituent groups		
	R^1	R^2	R^3
72b	Me	H	OH
73a	H	OH	H
73b	Me	OH	H



^{1}H-N.M.R. shifts

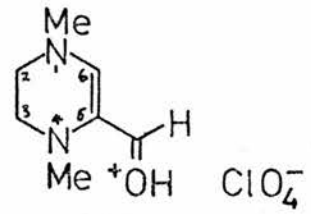
Compound	δ R^1	δ H(4,6)	δ OH	δ Ar	Intensity Ratio
72b	3.8(s)	9.5(s)	no peak	6.9-7.7(q)	6 : 2 : 4
73a	8.7(br)	8.8(s)	with R^1	6.7-7.4(m)	3 : 2 : 4
73b[ac]	2.8(s)	9.5(s)	8.7(s)	6.8-7.4(m)	6 : 2 : 1 : 4

The only ^{13}C-N.M.R. spectrum recorded was for compound (72b).

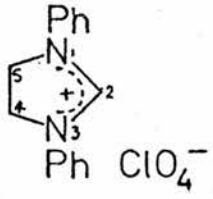
δ = 1,3-Me, 40.3 ; C(5),116.5 ; C(Ar),116.0,120.7,127.4 ;

C=O, 147.2 ; C(4,6), 157.2 ; C-OH, 158.2 ppm

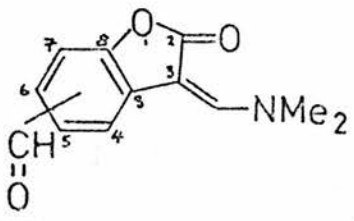
MISCELLANEOUS PRODUCTS



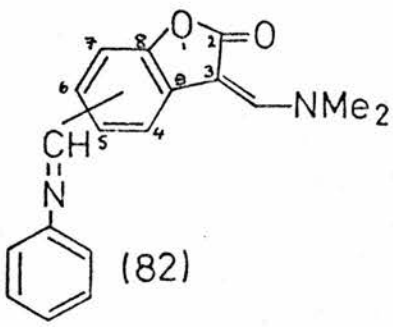
(33)



(35)



(80)



(82)

Compound (33)

^{1}H-N.M.R. : δ = 2.9 & 3.2 (s : Me), 3.5 (m : CH_2), 7.9 (s : -CH=), 8.8 (s : -CH=O) ppm

Integral ratio : 3 : 3 : 4 : 1 : 1

^{13}C-N.M.R. : δ = C(2,3),41.4 & 47.6 ; 1,4-Me,42.8 ; C(5),112.9 ; C(6),149.9 ; CH=OH,177.5 ppm

Compound (35)

^{1}H-N.M.R. : δ = 4.6 (s : CH_2), 7.3-7.8 (m : Ph), 10.0 (s : H(2)) ppm

Integral ratio 4 : 10 : 1

^{13}C-N.M.R. : δ = C(4,5),48.7 ; 1,3-Ph,118.8,127.5,130.1,136.3 ; C(2),152.0 ppm

Compound (80)

^{1}H-N.M.R. : δ = 3.3-3.7 (m : Me), 7.4-7.7 (m : Ar), 8.0 (s : =CH-N), 9.9 (d : CHO(Ar)) ppm

Intensity ratio 6 : 3 : 1 : 1 (see page 67)

^{13}C-N.M.R. : δ = Me,47.4 ; C(3),114.8 ; C(Ar),107.8,126.1,153.3 ; C(8),131.8 ; C(9),138.1 ; =CH-N,153.3 ; CHO,191.4 ppm

Compound (82)

^{1}H-N.M.R.^{ac}: δ = 3.3-3.8 (m : Me), 6.6-7.9 (m : Ar), 8.6 (s : CH=N), 9.9 (s : CH=NAr) ppm

Integral ratio 6 : 8 : 1 : 1

EXPERIMENTAL

2,3-Dihydro-6-hydroxy-1,4-diphenyl-1,4-diazepinium perchlorate (28c)[55]

A solution of N,N´-diphenylethylenediamine (0.7g) and 70% perchloric acid (1g) in methanol (10ml) was added to a solution of hydroxymalonaldehyde[60] (0.22g) in methanol (10ml). This solution was warmed to approx. 60°. When it had cooled, the yellow needles were filtered off, washed with a little methanol and ether, and recrystallised from methanol.

M.pt 197-198° (Lit. 197°)[55] Yield 0.65g (80%)

Found : C,56.11 ; H,4.52 ; N,7.59 % ; m/e=264

$C_{17}H_{17}N_2O]ClO_4$ requires C,55.97 ; H,4.70 ; N,7.68 % ; m/e=265

2-Formyl-1,4-dimethyl-1,4,5,6-tetrahydropyrazinium perchlorate (33)

A solution of N,N´-dimethylethylenediamine (0.3g) and 70% perchloric acid (1g) in methanol (10ml) was added to a solution of hydroxymalonaldehyde[60] (0.22g) in methanol (10ml). This solution was warmed to approx. 60°. After being kept for 12 hours white needles were filtered off, washed with a little methanol and ether, and recrystallised from methanol.

M.pt 203-204° Yield 0.3g (50%)

Found : C,35.09 ; H,5.54 ; N,11.45 % ; m/e=140

$C_7H_{13}N_2O]ClO_4$ requires C,34.94 ; H,5.45 ; N,11.64 % ; m/e=141.2

To prepare the tetrafluoroborate salt (33´), 50% aq. fluoroboric acid (1.5g) was used, yielding a white crystalline product.

M.pt 194-196° Yield 0.25g (44%)

Found : C,36.98 ; H,5.66 % ; m/e=140

$C_7H_{13}N_2O]BF_4$ requires C,36.88 ; H,5.75 % ; m/e=141

1,3-Diphenyl-imidazolinium perchlorate (35)

A solution of N,N´-diphenylethylenediamine (0.5g) and 70% perchloric acid (0.5g) in ethanol (10ml) was added to a solution of tartronic aldehyde[63,64,65] (0.6g) in ethanol (10ml). This solution was heated under reflux for 30 minutes. On cooling, dark green plates crystallised out. These were filtered off, washed with a little ethanol and ether, and recrystallised from ethanolic perchloric acid.

M.pt 238-240° Yield 0.53g (76%)

Found : C,55.98 ; H,5.01 ; N,8.63 %

$C_{15}H_{15}N_2]ClO_4$ requires C,55.82 ; H,4.68 ; N,8.68 %

2,3-Dihydro-6-methoxy-1,4-dimethyl-1,4-diazepinium perchlorate (37a)

A solution of N,N´-dimethylethylenediamine (0.3g) and 70% perchloric acid (1g) in methanol (10ml) was added to a solution of methoxymalonaldehyde[70] (0.25g) in methanol (10ml). This solution was heated under reflux for 20 minutes, and then left standing for 24 hours. Removal of the solvent resulted in an oil. To this was added a little ether/methanol solution, and with scratching, a yellow precipitate formed. This was filtered off, washed with a little methanol and ether, and recrystallised from methanol.

M.pt 138-142° Yield 0.1g (16%)

Found : C,36.89 ; H,5.84 ; N,10.76 % ; m/e=155

$C_8H_{15}N_2O]ClO_4$ requires C,37.73 ; H,5.94 ; N,11.00 % ; m/e=155.2

(Note : this compound was obtained with some difficulty)

2,3-Dihydro-6-methoxy-1,4-diphenyl-1,4-diazepinium perchlorate (37b)

A solution of N,N'-diphenylethylenediamine (0.8g) and 70% perchloric acid (1g) in methanol (10ml) was added to a solution of methoxymalonaldehyde[70] (0.25g) in methanol (10ml). This solution was warmed to approx. 60°. After 24 hours the yellow precipitate was filtered off, washed with a little methanol and ether and recrystallised from methanol.

M.pt 214-216° Yield 0.79g (84%)

Found : C,57.23 ; H,5.03 ; N,7.42 % ; m/e=278

$C_{18}H_{19}N_2O]ClO_4$ requires C,57.07 ; H,5.06 ; N,7.40 % ; m/e=279

2,3-Dihydro-6-phenyl-1,4-diazepinium perchlorate (42a)[27]

A solution of 1,5-diaza-1,1,5,5-tetramethyl-1H-3-phenylpentadienium perchlorate (45a) (0.75g) in methanol (10ml), plus a few drops of 70% perchloric acid, was added to a solution of ethylenediamine (0.15g) in methanol (10ml). This solution was warmed to approx. 60° and was then kept for 24 hours. The fine, pale yellow precipitate could be filtered off and recrystallised from ethanol. If no precipitate formed, either trituration or the addition of ether encouraged formation of a solid.

M.pt 179-181° (Lit. 179-180°)[27] Yield 0.52g (77%)

Found : C,48.29 ; H,4.75 ; N,10.17 % ; m/e=173

$C_{11}H_{13}N_2]ClO_4$ requires C,48.45 ; H,4.81 ; N,10.27 % ; m/e=173

2,3-Dihydro-1,4-dimethyl-6-phenyl-1,4-diazepinium perchlorate (42b)

A solution of 1,5-diaza-1,1,5,5-tetramethyl-1H-3-phenylpentadienium perchlorate (45a) (0.75g) in methanol (10ml), plus a few drops of 70%

perchloric acid, was added to a solution of N,N'-dimethyl-ethylenediamine (0.22g) in methanol (10ml). This solution was warmed to approx. 60° and was then kept for 24 hours. The pale yellow needles were filtered off and recrystallised from ethanol. If no precipitate formed, either trituration or the addition of ether encouraged formation of a solid.

M.pt 157-158° (Lit. 154-156°)[102] Yield 0.49g (65%)

Found : C,51.64 ; H,5.65 ; N,9.26 % ; m/e=201

$C_{13}H_{17}N_2]ClO_4$ requires C,51.92 ; H,5.70 ; N,9.31 % ; m/e=201

(42b) was also prepared by the N-methylation of the 6-phenyldiazepinium perchlorate (42a) - see page 116.

1,2-Dihydro-6-(p-hydroxyphenyl)-1,4-diazepinium perchlorate (43a)

The same procedure was followed as for the preparation of (42a), except that 1,5-diaza-3-(p-hydroxyphenyl)-1,1,5,5-tetramethyl-1H-pentadienium perchlorate (45b) (0.8g) was used, affording a precipitate of yellow powder.

M.pt 197-199° Yield 0.59g (82%)

Found : C,45.84 ; H,4.51 ; N,9.55 % ; m/e=189

$C_{11}H_{13}N_2O]ClO_4$ requires C,45.77 ; H,4.54 ; N,9.70 % ; m/e=189

1,2-Dihydro-6-(p-hydroxyphenyl)-1,4-dimethyl-1,4-diazepinium perchlorate (43b)

The same procedure was followed as for the preparation of (42b), except that 1,5-diaza-3-(p-hydroxyphenyl)-1,1,5,5-tetramethyl-1H-pentadienium perchlorate (45b) was used, affording a precipitate of

yellow needles.

M.pt 163-165° Yield 0.5g (50%)

Found : C,49.42 ; H,5.43 ; N,8.93 % ; m/e=217

$C_{13}H_{17}N_2O]ClO_4$ requires C,49.30 ; H,5.41 ; N,8.84 % ; m/e=217

(43b) was also prepared by N-methylation of the 6-(p-hydroxyphenyl)diazepinium perchlorate (43a) - see page 114.

2,3-Dihydro-6-(m-hydroxyphenyl)-1,4-diazepinium perchlorate (44a)

The same procedure was followed as for the preparation of (42a), except that 1,5-diaza-3-(m-hydroxyphenyl)-1,1,5,5-tetramethyl-1H-pentadienium perchlorate (45c) (0.8g) was used, affording a precipitate of off-white crystals.

M.pt 159-161° Yield 0.32g (45%)

Found : C,45.82 ; H,4.56 ; N,9.81 % ; m/e=189

$C_{11}H_{13}N_2O]ClO_4$ requires C,45.77 ; H,4.54 ; N,9.70 % ; m/e=189

6-(m-Hydroxyphenyl)-1,4-dimethyl-2,3-dihydro-1,4-diazepinium perchlorate (44b)

The same procedure was followed as for the preparation of (42b), except that 1,5-diaza-1,1,5,5-tetramethyl-1H-3-(m-hydroxyphenyl)-pentadienium perchlorate (45c) was used, affording a precipitate of yellow needles.

M.pt 165-167° Yield 0.73g (92%)

Found : C,49.20 ; H,5.34 ; N,8.68 % ; m/e=217

$C_{13}H_{17}N_2O]ClO_4$ requires C,49.30 ; H,5.41 ; N,8.84 % ; m/e=217

(44b) was also prepared by N-methylation of the

6-(m-hydroxyphenyl)diazepinium perchlorate (44a) - see page 115.

The 6-phenyl- and 6-hydroxyphenyldiazepinium salts were also prepared from either the acrolein or the free malonaldehyde by the same method:

For (43a), ethylenediamine (0.3g), α-(p-hydroxyphenyl)-β-dimethylaminoacrolein (46b) (0.96g) and 70% perchloric acid (0.8g) were warmed in methanol (40ml).

For (43b), N,N'-dimethylethylenediamine (0.44g), α-(p-hydroxyphenyl)-β-dimethylaminoacrolein (46b) (0.96g) and 70% perchloric acid (0.8g) were warmed in methanol (40ml).

For (44a), ethylenediamine (0.3g), α-(m-hydroxyphenyl)-β-dimethylaminoacrolein (46c) (0.96g) [or m-hydroxyphenylmalonaldehyde (47c) (0.82g)] and 70% perchloric acid (0.8g) were warmed in methanol (40ml).

For (44b), N,N'-dimethylethylenediamine (0.44g), α-(m-hydroxyphenyl)-β-dimethylaminoacrolein (46b) (0.96g) [or m-hydroxyphenylmalonaldehyde (47c) (0.82g)] and 70% perchloric acid (0.8g) were warmed in methanol (40ml).

In each case, the yields, although not accurately recorded, were less than those obtained for the compounds derived from vinamidinium salts. The authenticity of the 6-hydroxyphenyldiazepinium salts was confirmed by microanalytical and ^{1}H-N.M.R spectroscopic data.

1,5-Diaza-1,1,5,5-tetramethyl-1H-3-phenylpentadienium perchlorate(45a)[74]

To chilled dimethylformamide (100ml) was added phosphoryl chloride (46g). The solution was allowed to stand for 5 minutes, then phenylacetic acid (13.6g) was added. The mixture was gradually brought up to 70° (bath temperature) at which it was maintained, with stirring, for 2 hours. The bath temperature was then raised to and maintained at 85° until the evolution of gas was complete (ca.4 hours). Excess dimethylformamide was removed at reduced pressure. To the cooled residue, rendered homogenous by the addition of ethanol (ca.100ml), was added a solution of 70% perchloric acid (30ml) in ethanol (100ml). After keeping the solution in a cool place for 48 hours, the precipitated white needles were filtered off and recrystallised from ethanol.

M.pt 200-202° (Lit. 200-201°)[74] Yield 17.3g (57%)

Found : C,51.78 ; H,6.43 ; N,9.22 % ; m/e=203

$C_{13}H_{19}N_2]ClO_4$ requires C,51.57 ; H,6.32 ; N,9.25 % ; m/e=203

1,5-Diaza-3-(p-hydroxyphenyl)-1,1,5,5-tetramethyl-1H-pentadienium perchlorate (45b)

The same procedure was followed as for the preparation of (45a), except that p-hydroxyphenylacetic acid (15.2g) was used, affording a precipitate of off-white needles.

M.pt 224-226° Yield 22.2g (70%)

Found : C,49.12 ; H,5.82 ; N,8.91 % ; m/e=219

$C_{13}H_{19}N_2O]ClO_4$ requires C,48.98 ; H,6.01 ; N,8.79 % ; m/e=219

1,5-Diaza-3-(m-hydroxyphenyl)-1,1,5,5-tetramethyl-1H-pentadienium perchlorate (45c)

The same procedure was followed as for the preparation of (45a), except that m-hydroxyphenylacetic acid (15.2g) was used, affording a

precipitate of white crystals.

M.pt 194-196° Yield 14.9g (47%)

Found : C,48.97 ; H,5.94 ; N,8.72 %

$C_{13}H_{19}N_2O]ClO_4$ requires C,48.98 ; H,6.01 ; N,8.79 %

α-(p-Hydroxyphenyl)-β-dimethylaminoacrolein (46b)

To chilled dimethylformamide (100ml) was added phosphoryl chloride (46g). The solution was allowed to stand for 5 minutes, then p-hydroxyphenylacetic acid (15.2g) was added. The mixture was gradually brought up to 70° (bath temperature) at which it was maintained, with stirring, for 2 hours. The bath temperature was then raised to 85° until the evolution of gas was complete (ca.4 hours). The resulting cold solution was poured over 300g of ice, and to this was added solid sodium hydroxide (36g). The suspension was stirred until all the solid had dissolved. The solution was then made strongly alkaline by the addition of 10M sodium hydroxide solution (200ml), and chilling to ensure that the temperature did not exceed 40°. After 2 hours, concentrated hydrochloric acid was added, until a precipitate resulted. This was filtered off, washed with water and recrystallised from ethanol to yield a yellow crystalline product.

M.pt. 192-194° Yield 17.8g (93%)

Found : C,69.06 ; H,6.83 ; N,7.22 % ; m/e=191

$C_{11}H_{13}NO_2$ requires C,69.09 ; H,6.85 ; N,7.32 % ; m/e=191

α-(m-Hydroxyphenyl)-β-dimethylaminoacrolein (46c)

The same procedure was followed as for the preparation of (46b), except that m-hydroxyphenylacetic acid (15.2g) was used, affording a

precipitate of pale yellow crystals.

M.pt 206-209° Yield 13.8g (72%)

Found : C,69.00 ; H,6.89 ; N,7.22 % ; m/e=191

$C_{11}H_{13}NO_2$ requires C,69.09 ; H,6.85 ; N,7.32 % ; m/e=191

m-Hydroxyphenylmalonaldehyde (47c)

∝-(m-Hydroxyphenyl)-β-dimethylaminoacrolein (46c) (0.95g) was suspended in ethanol (8ml) and to this was added a 10M sodium hydroxide solution (10ml). This solution was heated under reflux for 3 hours. To the cooled solution was added conc. hydrochloric acid, ensuring that the temperature did not rise above 40°. A brown solid formed. The reaction mixture was extracted three times with ether and the combined ethereal phases were dried over anhydrous magnesium sulphate. The ether was removed under vacuum, leaving a residual fine white powder.

M.pt 135° (decomp.) Yield 0.61g (74%)

Found : C,65.57 ; H,4.88 ; N,0.00 % ; m/e=164

$C_9H_8O_3$ requires C,65.85 ; H,4.91 ; N,0.00 % ; m/e=164

∝-(p-Triphenylmethoxyphenyl)-β-dimethylaminoacrolein (50)

∝-(p-Hydroxyphenyl)-β-dimethylaminoacrolein (46b) (1.91g) was suspended in chloroform (10ml) and to this was added triethylamine (1.01g) and triphenylmethylchloride (2.68g). The solution was stirred at room temperature for 4 hours, after which time any solids were filtered off. All the solvent was removed from the filtrate (under vacuum) yielding a white powder which could be washed with ethanol.

M.pt 181-182° Yield 2.36g (55%)

Found : C,83.02 ; H,6.23 ; N,3.22 %

$C_{30}H_{27}NO_2$ requires C,83.11 ; H,6.28 ; N,3.23 %

6-(4-Bromo-3-hydroxyphenyl)-2,3-dihydro-1,4-diazepinium perchlorate (59a)

To a stirred solution of 2,3-dihydro-6-(m-hydroxyphenyl)--1,4-diazepinium perchlorate (44a) (0.29g) in methanol (10ml) was added, dropwise, a solution of bromine (0.16g) in methanol (10ml), ensuring that the temperature did not rise above 30°. After a short time the reaction mixture decolourised, signifying the absence of any excess bromine. Some of the solvent was removed under vacuum, and to the remainder was added ether. The resulting pale yellow precipitate was filtered off and recrystallised from ethanolic perchloric acid.

M.pt 258-260° Yield 0.15g (41%)

Found* : C,37.24 ; H,3.53 ; N,7.80 % ; m/e=266 & 268

$C_{11}H_{12}N_2BrO]ClO_4$ requires C,35.94 ; H,3.29 ; N,7.62 % ; m/e=267 & 269

6-(4-Bromo-3-hydroxyphenyl)-2,3-dihydro-1,4-dimethyl-1,4-diazepinium perchlorate (59b)

To a stirred solution of 2,3-dihydro-6-(m-hydroxyphenyl)--1,4-dimethyl-1,4-diazepinium perchlorate (44b) (0.32g) in methanol (10ml) was added dropwise a solution of bromine (0.16g) in methanol (10ml), ensuring that the temperature did not rise above 30°. After a short time the reaction mixture decolourised, signifying the absence of any excess bromine. Some of the solvent was removed under vacuum, and to the remainder was added ether. The resulting pale yellow needles were filtered off and recrystallised from ethanolic perchloric acid.

M.pt 172-174° Yield 0.13g (33%)

Found* : C,39.05 ; H,4.10 ; N,7.01 %

$C_{13}H_{16}N_2BrO]ClO_4$ requires C,39.47 ; H,4.08 ; N,7.08 %

6-(2,4-Dibromo-3-hydroxyphenyl)-2,3-dihydro-1,4-diazepinium perchlorate (60a)

The same procedure was followed as for the preparation of (59a), except that double the amount of bromine was added (0.32g), affording a very pale yellow precipitate.

M.pt 222-224° Yield 0.17g (38%)

Found* : C,26.01 ; H,2.15 ; N,5.43 % ; m/e=344,346 & 348

$C_{11}H_{11}N_2Br_2O]ClO_4$ requires C,29.59 ; H,2.48 ; N,6.27 % ; m/e=345,347 & 349

6-(2,4-Dibromo-3-hydroxyphenyl)-2,3-dihydro-1,4-dimethyl--1,4-diazepinium perchlorate (60b)

The same procedure was followed as for the preparation of (59b), except that double the amount of bromine was added (0.32g), affording a precipitate of white needles.

M.pt 212-215° Yield 0.11g (23%)

Found* : C,31.44 ; H,3.28 ; N,5.37 % ; m/e=372,374 & 376

$C_{13}H_{15}N_2Br_2O]ClO_4$ requires C,32.90 ; H,3.19 ; N,5.90 % ; m/e=373,375 & 377

* As mentioned in the discussion (pp.47-48), for electrophilic substitution, the m-hydroxyphenyldiazepinium salts have an aromatic nucleus which is doubly activated, therefore bromination is expected to occur very readily. To account for the inconsistency of the analysis results, it is suggested that the products were contaminated with traces of polybrominated products or, in the case of (59a), of unbrominated material.

6-(3-Bromo-4-hydroxyphenyl)-2,3-dihydro-1,4-diazepinium perchlorate (64a)

The same procedure was followed as for the preparation of (59a), except that the 2,3-dihydro-6-(p-hydroxyphenyl)-1,4-diazepinium perchlorate (43a) (0.29g) was used, affording a pale yellow precipitate.

M.pt 203-205° Yield 0.27g (73%)

Found : C,35.49 ; H,3.37 ; N,7.37 % ; m/e=266 & 268

$C_{11}H_{12}N_2BrO]ClO_4$ requires C,35.94 ; H,3.29 ; N,7.62 % ; m/e=267 & 269

6-(3-Bromo-4-hydroxyphenyl)-2,3-dihydro-1,4-dimethyl-1,4-diazepinium perchlorate (64b)

The same procedure was followed as for the preparation of (59b), except that the 2,3-dihydro-6-(p-hydroxyphenyl)-1,4-dimethyl-1,4-diazepinium perchlorate (43b) (0.32g) was used, affording a precipitate of pale yellow needles.

M.pt 206-208° Yield 0.35g (89%)

Found : C,38.91 ; H,4.19 ; N, 6.91 %

$C_{13}H_{16}N_2BrO]ClO_4$ requires C,39.47 ; H,4.08 ; N,7.08 %

6-(3,5-Dibromo-4-hydroxyphenyl)-2,3-dihydro-1,4-diazepinium perchlorate (65a)

The same procedure was followed as for the preparation of (64a), except that double the amount of bromine was added (0.32g), affording a pale yellow precipitate.

M.pt 198-202° Yield 0.39g (87%)

Found : C,29.56 ; H,2.74 ; N,6.24 % ; m/e=344,346 & 348

$C_{11}H_{11}N_2Br_2O]ClO_4$ requires C,29.59 ; H,2.48 ; N,6.27 % ; m/e=345,347 & 349

6-(3,5-Dibromo-4-hydroxyphenyl)-2,3-dihydro-1,4-dimethyl--1,4-diazepinium perchlorate (65b)

The same procedure was followed as for the preparation of (64b), except that double the amount of bromine was added (0.32g), affording a pale yellow precipitate.

M.pt 192-194° Yield 0.38g (80%)

Found : C,32.64 ; H,3.46 ; N,5.60 % ; m/e=372,374 & 376

$C_{13}H_{15}N_2Br_2O]ClO_4$ requires C,32.90 ; H,3.19 ; N,5.90 % ; m/e=373,375 & 377

p-Nitrobenzenediazonium tetrafluoroborate (67)[84,85]

p-Nitroaniline (6.9g) was dissolved in 20% fluoroboric acid (100ml). The solution was filtered and cooled in an ice bath. To this was added dropwise, with stirring, a cold filtered solution of sodium nitrite (3.45g in 10ml water). The resulting solution was allowed to stand in the ice-bath for a further 5 minutes. The precipitated pale yellow crystals were filtered off, washed with a little cold filtered fluoroboric acid solution, twice with ethanol and four times with ether, and were then dried under vacuum.

M.pt 166° (Lit.173°)[84] Yield 9.83g (84%)

2,3-Dihydro-6-(4-hydroxy-3-(p-nitrobenzeneazo)phenyl)-1,4-diazepinium perchlorate (68a)

To a stirred solution of 2,3-dihydro-6-(p-hydroxyphenyl)--1,4-diazepinium perchlorate (43a) (0.29g) in water (20ml) was added a solution of p-nitrobenzenediazonium tetrafluoroborate (67) (0.47g) in water (20ml), ensuring that the temperature did not rise above 5°. This solution was stirred for 30 minutes and was then kept in a cool

place for 20 hours. The red precipitate was filtered off, washed with ether and then dried under vacuum at 60°. The product was recrystallised from methanolic perchloric acid.

M.pt 202-205° Yield 0.13g (30%)

Analytical and mass spectroscopy data were inconclusive

2,3-Dihydro-6-(4-hydroxy-3-(p-nitrobenzeneazo)phenyl)-1,4-dimethyl--1,4-diazepinium perchlorate (68b)

To a stirred solution of 2,3-dihydro-6-(p-hydroxyphenyl)--1,4-dimethyl-1,4-diazepinium perchlorate (43b) (0.32g) in water (20ml) was added a solution of p-nitrobenzenediazonium tetrafluoroborate (67) (0.47g) in water (20ml), ensuring that the temperature did not rise above 5°. This solution was stirred for 30 minutes and was then kept in a cool place for 20 hours. The red precipitate was filtered off, washed with ether and then dried under vacuum at 60°. The product was recrystallised from ethanolic perchloric acid.

M.pt 186-188° Yield 0.13g (28%)

Found : C,48.18 ; H,4.14 ; N,14.37 % ;

$C_{19}H_{20}N_5O_3]ClO_4$ requires C,48.99 ; H,4.33 ; N,15.03 %

2,3-Dihydro-6-(3-hydroxy-4-(p-nitrobenzeneazo)phenyl)-1,4-diazepinium perchlorate (69a)

The same procedure was followed as for the preparation of (68a), except that the 6-(m-hydroxyphenyl)-diazepinium salt (44a) (0.29g) was used, affording a dark red precipitate.

M.pt 262-264° Yield 0.35g (80%)

Analytical and mass spectroscopy data were inconclusive

2,3-Dihydro-6-(3-hydroxy-4-(p-nitrobenzeneazo)phenyl)-1,4-dimethyl--1,4-diazepinium perchlorate (69b)

The same procedure was used as for the preparation of (68a), except that the 6-(p-hydroxyphenyl)diazepinium salt (44b) (0.32g) was used, affording a dark red precipitate.

M.pt 184-186° Yield 0.39g (83%)

Found : C,48.17 ; H,4.22 ; N,14.58 %

$C_{19}H_{20}H_5O_3]ClO_4$ requires C,48.99 ; H,4.33 ; N,15.03 %

2,3-Dihydro-6-(p-methoxyphenyl)-1 4-dimethyl-1,4-diazepinium perchlorate (70)

To a solution of 2,3-dihydro-6-(p-hydroxyphenyl)-1,4-dimethyl--1,4-diazepinium perchlorate (43b) (0.63g) in dimethylformamide (20ml) was added methyl iodide (0.28g) and potassium carbonate (0.56g). The resulting mixture was shaken for 18 hours, after which time the undissolved potassium carbonate was filtered off. The filtrate was then reduced to a solid by removing all the dimethylformamide on the rotary evaporator. To this solid was added ethanol such that the diazepinium salt went into solution and the remaining potassium carbonate stayed as a solid which could then be filtered off. To the ethanolic diazepinium salt solution was added a few drops of perchloric acid. The solution was then reduced to a volume of approximately 10ml and was then allowed to stand in a cool place. Trituration or the addition of ether encouraged precipitation. The

product was filtered off and recrystallised from ethanolic perchloric acid, yielding pale yellow crystals.

M.pt 107-109° Yield 0.50g (76%)

Found : C,50.42 ; H,5.87 ; N,8.42 % ; m/e=230

$C_{14}H_{19}N_2O]ClO_4$ requires C,50.84 ; H,5.79 ; N,8.47 % ; m/e=231

Alternatively - the same procedure using 6-(p-hydroxyphenyl)diazepinium salt (43a) (0.58g) and a three fold excess of methyl iodide (0.84g) gave 6-(p-methoxyphenyl)-1,4-dimethyl-diazepinium salt (70) as pale yellow crystals.

M.pt 108-109° Yield 0.35g (53%)

A similar reaction with 6-(p-hydroxyphenyl)diazepinium salt (43a) (0.58g) and a two-fold excess of methyl iodide (0.56g) gave the 6-(p-hydroxyphenyl)-1,4-dimethyl-diazepinium salt (43b).

M.pt 163-165° Yield 0.41g (64%)

Found : C,49.00 ; H,5.39 ; N,8.74 %

$C_{12}H_{15}N_2O]ClO_4$ requires C,49.30 ; H,5.41 ; N,8.84 %

2,3-Dihydro-6-(m-methoxyphenyl)-1,4-dimethyl-1,4-diazepinium perchlorate (71)

The same procedure was followed as for the preparation of (70), except that the 6-(m-hydroxyphenyl)-1,4-dimethyl-diazepinium salt (44b) (0.63g) was used, affording pale yellow needles.

M.pt 127-129° Yield 0.48g (73%)

Found : C,48.90 ; H,5.61 ; N,8.21 % ; m/e=230

$C_{14}H_{19}N_2O]ClO_4$ requires C,50.84 ; H,5.79 ; N,8.47 % ; m/e=231

Alternatively - the same procedure using a three-fold excess of methyl iodide (0.84g) and the 6-(m-hydroxyphenyl)diazepinium salt (44a) (0.58g) gave the 6-(m-methoxyphenyl)-1,4-dimethyldiazepinium salt (71) as pale yellow needles.

M.pt 127-129° Yield 0.41g (62%)

A similar reaction using the 6-(m-hydroxyphenyl)diazepinium salt (44a) (0.58g) with a two-fold excess of methyl iodide (0.56g) gave the 6-(m-hydroxyphenyl)-1,4-dimethyl-diazepinium salt (44b).

M.pt 165-167° (page 103, 165-167°) Yield 0.41g (65%)

1,2-Dihydro-5-p-hydroxyphenyl-1,3-dimethyl-2-oxo-pyrimidinium perchlorate (72b)

A solution of N,N'-dimethylurea (0.22g) in methanol (10ml) was added to a solution of 1,5-diaza-3-(p-hydroxyphenyl)-1,1,5,5-tetra--methyl-1H-pentadienium perchlorate (45b) (0.75g) in methanol (10ml), plus a few drops of 70% perchloric acid. This solution was warmed to approx.60°. After 24 hours, the yellow plates were filtered off and recrystallised from ethanolic perchloric acid.

M.pt 242-244° Yield 0.36g (48%)

Found : C,44.85 ; H,4.19 ; N,8.76 %

$C_{12}H_{13}N_2O_2]ClO_4$ requires C,45.51 ; H,4.14 ; N,8.84 %

1,2-Dihydro-5-m-hydroxyphenyl-1,3-dimethyl-2-oxo-pyrimidinium perchlorate (73b)

A solution of N,N'-dimethylurea (0.22g) in methanol (10ml) was added to a solution of 1,5-diaza-3-(m-hydroxyphenyl)-1,1,5,5-tetra-

-methyl-1H-pentadienium perchlorate (45b) (0.75g) in methanol (10ml), plus a few drops of 70% perchloric acid. This solution was warmed to approx.60°. After 24 hours, the yellow needles were filtered off and recrystallised from ethanolic perchloric acid.

M.pt 178-180° Yield 0.35g (46%)

Found : C,45.24 ; H,4.00 ; N,8.71 %

$C_{12}H_{13}N_2O_2]ClO_4$ requires C,45.51 ; H,4.14 ; N,8.84 %

2,3-Dihydro-1,4-dimethyl-6-phenyl-1,4-diazepinium perchlorate (42b)

The same procedure was followed as for the preparation of (70), except that the 6-phenyldiazepinium salt (42a) (0.54g) was used, with twice the amount of methyl iodide (0.56g).

M.pt 156-157° (Lit. 154-156°) Yield 0.33g (55%)

2,3-Dihydro-1,4-dimethyl-1,4-diazepinium perchlorate (75)[26]

The same procedure was followed as for the preparation of (70), except that the 2,3-dihydro-1,4-diazepinium perchlorate (74) (0.39g) was used, with twice the amount of methyl iodide (0.56g), affording an off-white powder.

M.pt 90-94° (Lit. 95-96°)[26] Yield 0.08g (18%)

2,3-Dihydro-1,4,5,7-tetramethyl-1,4-diazepinium perchlorate (77)[22]

The same procedure was followed as for the preparation of (70), except that the 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (76) was used, affording an off-white powder.

M.pt 123-124° (Lit. 126-127°)[22] Yield 0.30g (59%)

Found : C,42.34 ; H,6.74 ; N,10.85 %

$C_9H_{17}N_2]ClO_4$ requires C,42.78 ; H,6.78 ; N,11.09 %

2,3-Dihydro-1,4-dimethyl-5,7-diphenyl-1,4-diazepinium perchlorate (79)

The same procedure was used as for the preparation of (70), except that the 2,3-dihydro-5,7-diphenyl-1,4-diazepinium perchlorate (78) (0.70g) was used, affording a precipitate of white needles.

M.pt 193-194° Yield 0.48g (63%)

Found : C,60.08 ; H,5.63 ; N,7.43 %

$C_{19}H_{21}N_2]ClO_4$ requires C,60.56 ; H,5.62 ; N,7.43 %

3-(Dimethylaminomethylene)-5(7)-formyl-benzofuran-2(3H)one (80a)/(80b)

To chilled dimethylformamide (100ml) was added phosphoryl chloride (46g). The solution was allowed to stand for 5 minutes, then o-hydroxyphenylacetic acid (15.2g) was added. The mixture was gradually brought up to a temperature of 70° (bath temperature) at which it was maintained, with stirring, for 2 hours. The bath temperature was then raised to and maintained at 85° until the evolution of gas was complete (ca.4 hours). The precipitate formed after this time was filtered off, recrystallised from acetone/water and dried under vacuum. After recrystallisation the product was a bright pink crystalline solid.

M.pt 138-139° Yield 8.8g (41%)

Found : C,66.41 ; H,5.23 ; N,6.32 % ; m/e=217

$C_{12}H_{11}NO_3$ requires C,66.35 ; H,5.10 ; N,6.45 % ; m/e=217

3-(Dimethylaminomethylene)-5(7)-phenyliminomethyl-benzofuran-2(3H)one (81)

2-Dimethylamino-3,5(7)-diformyl-benzofuran (80) (0.3g) was dissolved in methanol (30ml) and to this was added aniline (0.13g). This solution was heated under reflux for 10 minutes and was then poured into water (100ml). After the mixture had cooled, the precipitate was filtered off and dried under vacuum at 60° for 6 hours. The brown powder was recrystallised from ethanol/water to yield a pale orange powder.

M.pt 153-155° Yield 0.23g (43%)

Found : C,72.32 ; H,5.29 ; N,8.84 % ; m/e=292

$C_{18}H_{16}N_2O_2$ requires C,73.96 ; H,5.52 ; N,9.58 % ; m/e=292

(Difficulty in recrystallisation accounted for the poor analytical data)

Protodebromination of 6-bromo-2,3-dihydro-1,4-dimethyldiazepinium perchlorate (91)

A solution of the 6-bromodiazepinium salt (91) (0.04g) and triphenylphosphine (0.034g) in n-pentanol (20ml), plus a few drops of 70% perchloric acid, was heated under reflux for 3.5 hours. After the solution had cooled, ether was added to precipitate the 6-proto derivative (75). This was characterised by the melting point and ^{1}H-N.M.R. spectrum.

M.pt. of 6-bromo derivative, 180-181° (Lit. 180-181°)[103]

M.pt. of 6-proto derivative, 95-96° (Lit. 95-96°)[26]

Similarly, the same procedure with the omission of perchloric acid and heating under reflux for 20 hours gave the 6-proto derivative.

Protodebromination of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4--diazepinium perchlorate (92)

A solution of the 6-bromodiazepinium salt (92) (0.1g) and triphenylphosphine (0.086g) in methanol (20ml), plus a few drops of 70% perchloric acid, was heated under reflux for 30 minutes. After the solution had cooled, ether was added to precipitate the 6-proto derivative (76). This was characterised by the melting point and the ^{1}H-N.M.R. spectrum.

M.pt. of 6-bromo derivative, 160-163° (Lit.160-162°)[42]

M.pt. of 6-proto derivative, 140-142° (Lit.139-141°)[1]

The same procedure was followed using thiourea (0.03g) instead of triphenylphosphine, in ethanol (20ml) and heating under reflux for 3 hours.

Protodebromination of 6-bromo-2,3-dihydro-1,4-diazepinium perchlorate (93)

A solution of the 6-bromodiazepinium salt (93) (0.034g) and triphenylphosphine (0.034g) in n-pentanol (20ml), plus a few drops of 70% perchloric acid, was heated under reflux for 12 hours. After the solution had cooled, ether was added to precipitate the 6-proto derivative (74). This was characterised by the melting point and the ^{1}H-N.M.R. spectrum.

M.pt. of 6-bromo derivative, 154-155° (Lit.154-155°)[42]

M.pt. of 6-proto derivative, 308-312°(decomp.) (Lit.310-312°)[1]

The same procedure was followed as above using thiourea (0.03g) in n-pentanol (20ml) and heating under reflux for 15 hours.

Yields for all the protodehalogenation reactions were in excess of 75%.

E.S.R. Spectroscopic Studies (see page 82)

All E.S.R. spectra were obtained on a Bruker ER 200 D

An E.S.R. spectrum was obtained for a solution of the 6-bromo-5,7-dimethyldiazepinium perchlorate (92) in hexanol at 120°. No radical signal was observed, therefore protodebromination either occurred by a non-radical process, or radical concentration was too low to be detected.

A protodebromination reaction was attempted by heating the 6-bromo salt (92) under reflux for 15 hours in ethanol with a catalytic amount of benzoyl peroxide. Benzoyl peroxide is known to act as a radical promoter. However, the protodebromination reaction was unsuccessful, the benzoyl peroxide having been unable to promote a radical debromination.

An E.S.R. spectrum at 50° was obtained for a solution of ditertiary butyl nitroxide in dimethylsulphoxide (0.5×10^{-3}M). To the nitroxide solution was added an equal volume of a solution of the 6-bromo-5,7-dimethyldiazepinium perchlorate (92) in dimethylsulphoxide (10^{-3}M). No decrease in the size of the nitroxide radical signal was observed implying that at 50° the 6-bromo-diazepinium salt produced no appreciable radical concentration.

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