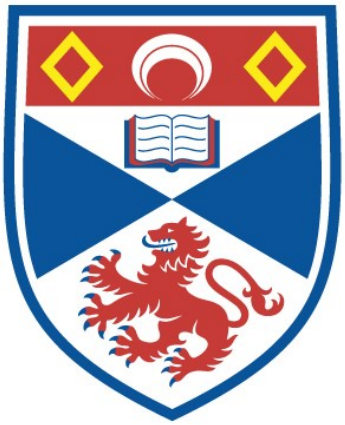
STUDIES OF MENEIDIC SYSTEMS

Hamish McNab

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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STUDIES OF MENEIDIC SYSTEMS

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HAMISH McNAB, B.Sc.

to the

UNIVERSITY OF ST. ANDREWS

in application for

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DECLARATION

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

The work was carried out in the Department of Chemistry of the University of St. Andrews, under the direction of D.M.G. Lloyd.

CERTIFICATE

I hereby certify that Mr. Hamish McNab, B.Sc., has spent 11 terms at research work under my supervision, has fulfilled the conditions of the Resolution 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 1967 as the William J. Matheson Scholar, and graduated B.Sc. with First Class Honours in Chemistry in July 1971.

The research described in this thesis was carried out between September 1971 and July 1974, during which time I held a Research Studentship awarded by the Science Research Council.

ACKNOWLEDGEMENTS

I am most grateful to Dr. D. Lloyd for his advice, interest and encouragement over the past three years.

Parts of this thesis could not have been written without the help of Dr. A.R. Butler (kinetics) and Dr. R.K. Mackie (spectra). I am indebted to my friends and colleagues in the lab. for many interesting and valuable discussions, some pertaining to chemistry.

My thanks are also due to the technical staff of the Department, especially Miss M. Pocwiardowska (nmr spectra), Mr. C. Millar (mass spectra) and Mr. J.R. Bews (microanalyses). The ^{13}C nmr spectra were recorded by Dr. A. Boyd at the University of Edinburgh.

I am indebted to Mrs. W. Pogorzelec, Mr. T. McQueen, and Mr. J. Gray for their help in the production of this thesis.

Finally, I am grateful to the Science Research Council for the award of a Research Studentship.

SUMMARY

The nmr spectra of 2,3-dihydro-1,4-diazepinium salts are discussed. From the magnitude of the coupling constants around the conjugated part of the molecules, a planar partial structure with complete electron delocalisation is indicated. The molecule as a whole adopts a half-chair configuration which rapidly inverts at room temperature. The effect of ring substitution on this exchange process is correlated with the size of the substituents.

The mass spectra of a variety of 2,3-dihydro-1,4-diazepinium salts are reported. The molecular ion of the cation is only rarely observable due to thermal dissociation of the salt. The major breakdown process involves the loss of the (N^1-C^2) fragment but other pathways are also considered. The factors governing some anomalous fragmentation patterns are discussed.

The rates of bromination in methanol of a number of 2,3-dihydro-1,4-diazepinium salts were measured under first-order conditions, normally by stopped flow methods. Differences in rate of factors of up to 10000 between dihydrodiazepines with only alkyl or aryl substituents, are correlated with steric effects in the region of the reaction site.

5,6,7-Unsubstituted 2,3-dihydro-1,4-diazepinium salts are tedious to make by standard methods. Their facile preparation from 1,5-diaryl-1,5-diazapentadienium salts under high dilution conditions, is discussed, and the scope of the synthesis was explored. The mechanism of the reaction was investigated using mono-amine model compounds. Attempts to prepare 5,7-dimethyl-dihydrodiazepinium salts by this method generally resulted in the formation of 2-methylimidazolines.

The parent 2,3-dihydro-1,4-diazepinium perchlorate was obtainable by this high dilution synthesis in sufficient quantities for a study of its properties to be made. It is active towards electrophiles, giving 6-substitution products, and reacts

with nucleophiles at the 5(7) position. In contrast to 5,7-substituted dihydrodiazepines, the 6-halogeno derivatives are inert towards nucleophiles at the 6-position.

A series of 1,2-dihydropyrimidines was prepared, and the chemical and spectroscopic properties of these heterocycles are compared with those of the isoelectronic 2,3-dihydro-1,4-diazepines. Dihydropyrimidines show meneidic reactions with electrophiles at the 5-position, but only 6-unsubstituted derivatives react with nucleophiles at the 6-position. A convenient synthetic route from 4-methyldihydropyrimidines to 5-methyldihydrodiazepinium salts is described.

The effect of electronic perturbation on the 1,5-diazapentadienium system was investigated using series of 1,3-dimethyl-1,2-dihydro-2-oxo- and 2-thiopyrimidinium salts. Substitution reactions of 4,6-unsubstituted derivatives with electrophiles have been shown to proceed by alternative mechanisms; those pyrimidines with 4(6)-methyl substituents also show substitution reactions in the methyl groups. Stable adducts are formed by reaction of the 4,6-unsubstituted compounds with bases. The structure and chemical properties of these pseudobases are discussed.

The electronic structure of 2,3-dihydro-1,4-diazepinium perchlorates and the other 1,5-diazapentadienium salts considered in this thesis, was investigated by ^{13}C nmr spectroscopy.

CONTENTS

INTRODUCTION

Nomenclature

The terms 'dihydrodiazepine' and 'dihydropyrimidine' as used in this thesis, refer to 2,3-dihydro-1,4-diazepines and 1,2-dihydropyrimidines unless otherwise stated. The numbering in α,ω-diazapolymethines, which includes the nitrogen atoms, follows the precedent of Dreiding[1]. The 6-position in dihydrodiazepines, which is electronically equivalent to the 5-position in dihydropyrimidines and the 3-position in open-chain 1,5-diazapentadienes, is also referred to as the 'meso' position by analogy with porphyrin and cyanine nomenclature. The name 'vinamidine' has been suggested for the 1,5-diazapentadiene system[2].

Quasi-aromaticity and Meneidic Character

The term 'quasi-aromatic' was defined in 1964 as follows: "Molecules should be called quasi-aromatic only if they contain an acyclic conjugated π-electron system and show chemical properties typical of aromatic compounds, especially reaction by substitution with retention of type. A significant mesomeric stability is implied"[3]. Nevertheless, the meaning of quasi-aromaticity has become almost as hackneyed as that of aromaticity itself. Although it was originally used to describe the structure of osazones[4], it was latter defined as above[3] in terms of reactivity. More recently, the hydrogenated ring of tetralin has been dubiously described as 'quasiaromatic' on the basis of the results of a variety of physical measurements[5], and to add to the confusion, the term was redefined in 1972, this time on a structural basis[6].

In view of this semantic confusion - which exists over the whole field of aromaticity[7] - it has been suggested[8,9] that the terms 'regenerative' or 'meneidic' (from Greek, menein, to persist; and eidos, type) might be introduced, "to refer to chemical reactivity, namely the tendency of an unsaturated molecule to react by

substitution rather than addition". Meneidic behaviour may be concisely summarised by Robinson's phrase[10] "The tendency to retain the type". 'Aromatic Reactivity' is one example of meneidic behaviour, but the concept is clearly a more general one. Carboxylic acid derivatives, for example, show retention of type in the interconversions of esters, amides, acid halides etc[9]. Tropolone may be considered meneidic, both in its substitution reactions with electrophiles and in its conversion to 2-substituted tropones, in which reactions it behaves as an extended acid[11]. Even alkenes undergo substitution reactions with Friedel-Crafts reagents and may be designated 'meneidic' in this context[12].

Compounds containing the 1,5-diazapentadienium or vinamidinium[2] system (1) form perhaps the best examples of quasi-aromaticity or

$$H_2\overset{+}{N}{=}CH{-}CH{=}CH{-}NH_2 \longleftrightarrow H_2N{-}CH{=}CH{-}CH{=}\overset{+}{N}H_2$$

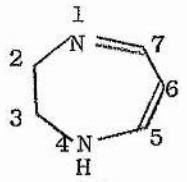
(1)

meneidic behaviour, and so their chemistry is discussed in some detail. The system has a high resonance stability despite the absence of closed conjugation, and it is this stability which explains the importance of substitution reactions in the chemistry of such compounds. Three geometrical isomers are possible: all-cis ('U'), all-trans ('W') and cis-trans ('sickle'). The second is the most stable form in isolation, but the others may be important when constrained in ring systems.

'U'-vinamidines

The simplest cyclic 1,5-diazapentadiene is pyrazole, but since it is also fully conjugated, it cannot be described as quasi-aromatic.

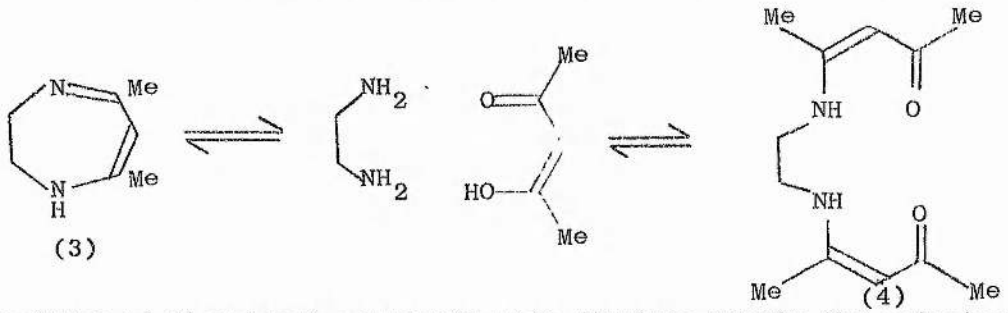
Perhaps the most extensively studied vinamidine system is the 2,3-dihydro-1,4-diazepine (2). Such compounds have recently been



(2)

the subject of a comprehensive review[13], and so only a summary of the salient features of their chemistry is presented here.

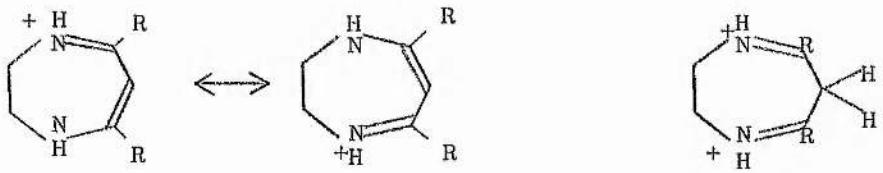
The first authentic dihydrodiazepine was isolated by Schwarzenbach and Lütz[14], who obtained the 5,7-dimethyl derivative (3), from the reaction of ethylenediamine with acetylacetone under acidic conditions. The course of the reaction is markedly pH dependent, however, and the bisoxo-enamine (4) is obtained as the major product in mildly alkaline or neutral media[15,16]. Condensation



(3) (4)

reactions of dicarbonyl compounds with diamines remain the principal synthetic route to dihydrodiazepines, although modified conditions may be necessary[17,18], especially in the preparation of aryl-substituted compounds[19,20,21]. Some isolated examples of the preparation of dihydrodiazepines by other methods have recently appeared in the literature[22-27].

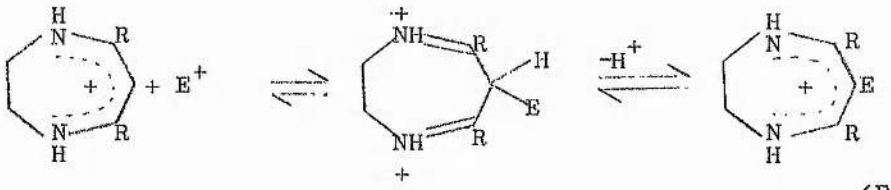
Dihydrodiazepine bases share with amidines the distinction of being perhaps the strongest organic bases known, with pK_a values in the region 13-14[28]. This is due principally to the resonance stability of the monocation (5), estimated to be about 20 kcalmol^{-1} [29], which is further exemplified by the large pH range over which the monocation is the predominant species. The dication (6) is formed



(5) (6)

significantly only in acids of comparable strength to 70% sulphuric acid[16]. Dihydrodiazepinium salts are also resistant to oxidation, dehydrogenation, and hydrolysis[16], although the latter may occur under strongly alkaline conditions. One example of a catalytic reduction of a dihydrodiazepine has been reported[22].

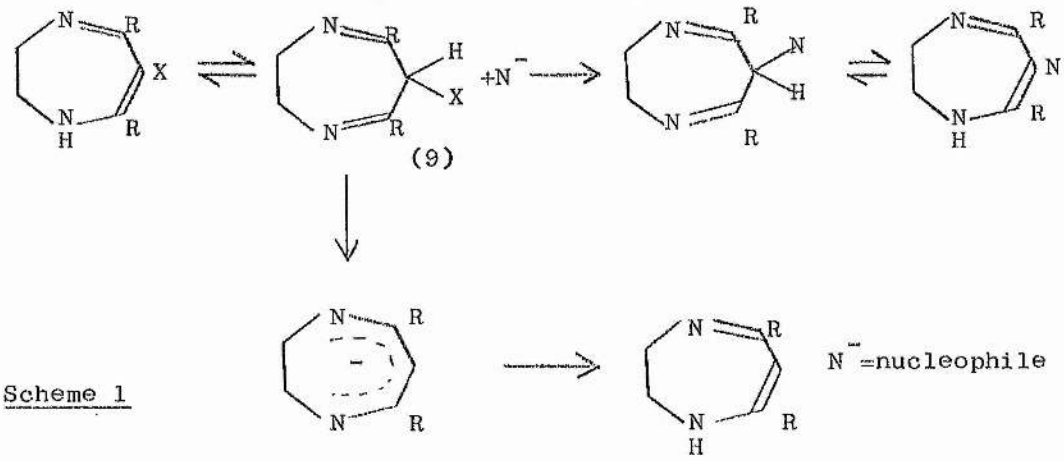
Surprisingly, in view of their positive charge, dihydrodiazepinium salts are active towards electrophiles, and reaction characteristically occurs by substitution at the 6-position rather than by addition. A less naive analysis indicates that this reactivity is not unexpected. As modified enamines, dihydrodiazepinium cations are paradoxically electron-rich, despite their charge. These compounds, therefore, are readily deuteriated by acids[24,30-32], brominated with bromine in methanol[33,34], halogenated with N-halogenosuccinimides in chloroform or acetic acid[34], and nitrated by nitric acid-sulphuric acid mixtures[35-38]. The reaction proceeds via an intermediate σ-complex (7), analogous to the Wheland intermediate in the electrophilic substitution of benzenoid compounds[13]. This intermediate loses a proton to give the 6-substituted product (8). Kinetic studies[31,39,40] have shown that



(7) (8) (E = D, Br, Cl, I, NO_2)

these reactions bear more than a superficial similarity to reactions of active benzenoid compounds, and it was for this reason that the term 'quasi-aromatic' was defined to describe them[3]. Further similarities are evident; the 6-nitro compounds may be reduced to amines[35,41] which yield stable anils and diazonium salts[35], while the 6-unsubstituted compounds are themselves sufficiently active to couple with diazonium salts, although the dihydrodiazepines so produced are hydrolytically unstable and are not isolable[42].

As might be expected since no stable intermediate structure can be drawn, dihydrodiazepines are inert to electrophiles at the 5(7) positions[30,39]. Even 6-substituted dihydrodiazepines react preferentially at the 6-position despite the loss of resonance stabilisation in the process[39,43]. Surprisingly, 5,7-disubstituted dihydrodiazepines are also inert to nucleophiles at the 5(7) positions although attack at these sites is electronically favourable. Totally unexpected is the facile reaction of 6-halogeno-dihydrodiazepines with nucleophiles at the 6-position to give substitution products[33,34,44]. A variety of oxygen, nitrogen, iodide and sulphur nucleophiles have been used. This reaction is unlikely to involve the conjugated tautomer of the dihydrodiazepine, which is electron-rich at the 6-position, but rather the bis-imine tautomer (9), where that position is adjacent to three electron-withdrawing groups and is therefore prone to nucleophilic attack (scheme 1). In agreement with this, N-substituted-6-halogeno-dihydrodiazepines, which cannot exist as a bis-imine tautomer, do not react with nucleophiles[34]. There is no spectroscopic evidence for the presence under any conditions of the bis-imine tautomer, although energetic considerations suggest it may be present to the extent of about 10%[40]. Such concentrations may not be observable spectroscopically because of rapid exchange.

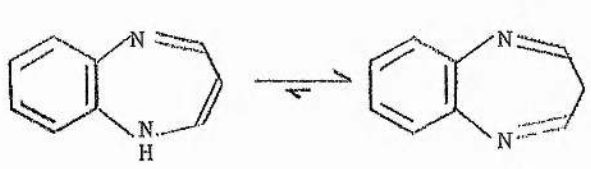


Scheme 1

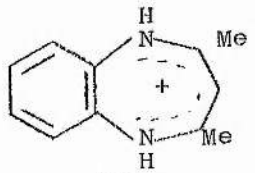
An alternative reaction with nucleophiles may take place when the site of the reaction is sterically crowded, due to large X, R,

or N^-, and the 6-unsubstituted compound is isolated (see Scheme 1)[34,44]. Attack of the nucleophile on the 6-substituent in the bis-imine tautomeric form is thought to yield an anion which abstracts a proton from the medium to give the product. This 'abnormal substitution'[34] is a competitive reaction with the conventional nucleophilic substitution[34].

The 1,5-diazapentadiene system also exists potentially in benzo-1,5-diazepines (10)[45] which have been known since 1907[46], but



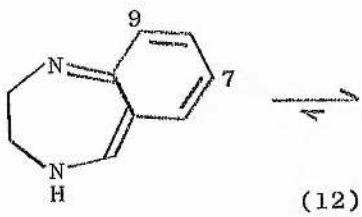
(10a) (10b)



(11)

in these compounds the bis-imine tautomer (10b) is the predominant form[45,47]. The monocations, however [eg. (11)] do contain the vinamidinium system[47], but this species is stable over only a moderate pH range[48]. The lack of meneidic character of these compounds is further exemplified by their unpredictable behaviour with electrophiles[48]. The system is complicated by conjugation with the benzene ring.

2,3-Dihydrobenzo-1,4-diazepines (12) have been extensively studied[49] on account of the pharmacological importance of certain derivatives, such as the tranquiliser 'valium' (13)[50]. These



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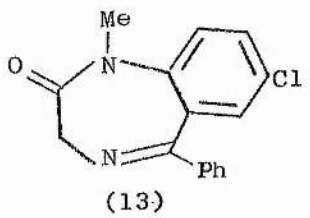
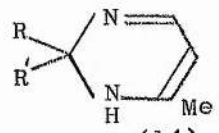


(13)

compounds are formally 1,9-diazanonatetraenes and so might be active towards electrophiles at positions 7 and 9. Indeed, the 7-nitration of one such diazepine has been reported[51].

There have been very few reports on 1,5-diazapentadienes constrained in rings other than seven-membered. The 1,2-dihydropyrimidines (14) (R,R' = alkyl) have been made[52,53] and their

properties are reported in this thesis. The eight-membered ring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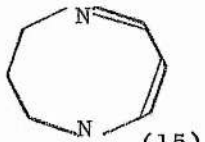
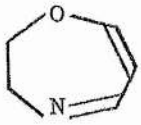

(15)

analogue, 1,2,3,4-tetrahydrodiazocine (15), is unknown, and molecular models indicate that the structure is rather strained.

Although not specifically studied in this thesis, the possibility of replacing the nitrogen atoms of 1,5-diazapentadienes with other electron-donating heteroatoms is clearly an attractive one. Such compounds, whether of six or seven-membered rings, in general remain to be investigated. The 2,3-dihydrooxazepine system (16) has never been prepared, and no simple derivatives of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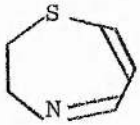
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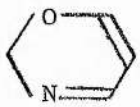
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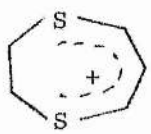
(19)

2H-1,3-thiazines (19) have been isolated. The 2,3-dihydro-1,4-thiazepine ring (17) has excited more interest because of its similarity to penicillin derivatives, and three rather specialised syntheses have been reported[54,55,56], including one of a thiazepinium salt[56]. 6-Substituted derivatives were prepared in each case: the reactions of the compounds were not studied. The only known derivatives of the 2H-1,3-oxazine system (18) contain a 2-ethoxy substituent, and were formed by reaction of oxoenamines with triethyl-orthoformate[57]. The 2,3-dihydro-1,4-dithiepinium cation (20) is unknown, while the only 1,4-dioxepin derivatives which have been prepared contain the 5,6,7-trihydrodioxepin nucleus (21)[58].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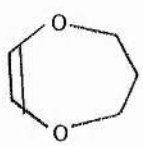
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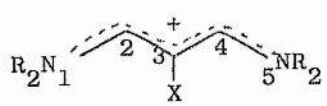

(22)

'W'-vinamidines

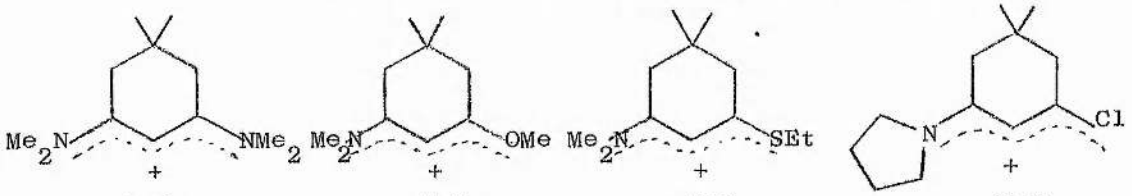
The most extensive class of vinamidines with the all-trans configuration is that of open-chain 1,5-diazapentadienium salts (22). Although the corresponding bases are predominantly all-cis[47,59,60], stabilised by hydrogen-bonding as are β-diketone enols, the large vic coupling constants (J ca.13Hz) of protons 1-5 in the nmr spectra of the cations unambiguously establish their structure as all-trans[60,61]. The possibility[62] of the bases having a non-classical 6π-electron structure by conjugation through the hydrogen bond, has been ruled out[63].

A variety of methods of preparation of these compounds has been reported. In certain cases, they may be made directly from the corresponding dicarbonyl compound or its mono-[62] or di-acetal[47] derivatives, but two steps may be necessary[64]. The normal route to N,N'-dialkyl-2,3,4-unsubstituted derivatives, however, is by a sequence involving successively Micheal addition, and condensation of the alkylamine on propargylaldehyde[65]; they can also be prepared from the more readily available N,N'-diaryl derivatives[66]. The preparation of 2-aryl and 2,4-diaryl-1,5-diazapentadienes from dithiolium salts[67], and the isolation of the 3-methyl-1,5-diphenyl compound via a six-stage synthesis from iso-butyraldehyde[68] are examples of alternative synthetic routes. 2,4-Dichlorovinamidinium salts have been made from phosgenimmonium salts[69,70].

The literature on these open chain diazapentadienes and their higher vinylogues is diverse. In some cases they have been studied as model compounds for cyanine dyes[71], but spectroscopic comparison with dihydrodiazepines has also excited interest[60,63,72]. They have been used as synthetic intermediates, for example in the preparation of phenanthrenes[73], quinolines[74], cyanines[75] and dihydro-diazepines[26,27]. The use of the 2,4-dichloro derivatives in the synthesis of a variety of heterocycles has recently been reviewed[76].

The majority of these cyclisations involve the electrophilicity of the 2(4) positions, a property not normally associated with the corresponding positions in the dihydrodiazepine system. In contrast, comparatively little work has been done on the nucleophilicity of the 3-position. Arnold and co-workers have studied the formylation[77], bromination[78] and nitration[78,79] of the 1,1,5,5-tetramethyl compound (22, R = Me, X = H) which in each case gave the 3-substituted product (22, R = Me, X = CHO, Br, NO_2). Deuteriation at the 3-position has also been reported[80]. The bromination and nitration work was later repeated on the 2-aryl derivatives, and similar results were obtained[81]. It is nevertheless noticeable that the conditions used were necessarily milder than for the corresponding reactions in the dihydrodiazepine series. For example, bromination of these open-chain compounds with molecular bromine (the reagent of choice in dihydrodiazepine chemistry) is unsatisfactory due to the formation of unstable addition products. The rigidity of the transition state in the reactions of the cyclic compounds would therefore appear to have some influence on their meneidic properties.

The bis-imide derivative of dimedone (23) is an example of a rigid all-trans vinamidinium salt, and, neglecting steric effects due to the dimethylamino group, it seems to show similar properties to dihydrodiazepines. The 'U' and 'W' systems have similar



(23) (24) (25) (26)

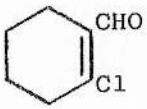
resonance energies, and their rates of deuteriation are almost identical[82]. In contrast, the dimedone ON and SN derivatives (24) and (25)[83] show a reduction in rate of deuteriation by a factor of about 10^6 over the bis-imide[82]. This is to be expected since the

electron-donating ability of nitrogen (ie. its Lewis basicity) is greater than for the other two heteroatoms. Unfortunately, no such quantitative results are available for the ClN system (26)[84] or for the 2-aryl open-chain SN systems which have been recently prepared[85]. On the basis of the above data, it has been predicted[82] that the 2,3-dihydro-1,4-dithiepinium cation may be too unreactive to show meneidic properties. The closest analogue to this system which has been prepared is the 1,5-diethyl-1,5-dithia-pentadienium cation (27)[86], but only its uv spectrum was recorded.

(27)

'Sickle' vinamidines

Very little work has been published on vinamidines of this configuration, although they have been prepared photochemically from those of the all-trans structure[26,60]. On steric grounds, it seems likely that the dianil derivatives (29)[74,79,87] of β-chlorovinyl-aldehydes[88] [eg. (28)] should be sickle-shaped.



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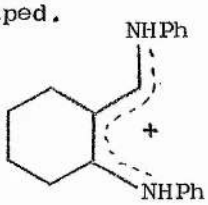
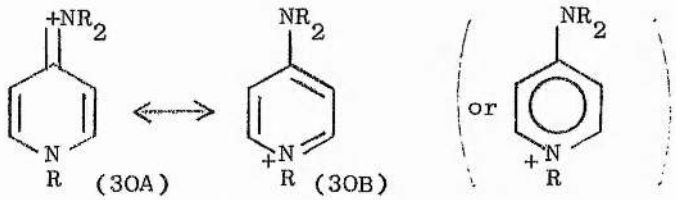
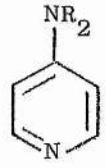


(29)

The 4-aminopyridinium system (30) is an example of an electronically perturbed cis-trans vinamidine, and its resonance forms show competition between the 1,5-diazapentadiene (30A) and the pyridine (30B) structures. A detailed analysis of vibrational spectra



(30A) (30B)



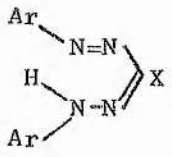
(31)

of (30) (R = H) has shown that the vinamidine is indeed the favoured canonical form[89]. Nitration of (30) (R = Me) and of the free base (31) (R = Me) at the 3-position show similar rates over a wide pH

range[90]. This suggests that the reaction of (31) proceeds via the cation, presumably by a typical vinamidine mechanism.

Polyazapentadienes

An interesting series of 1,2,4,5-tetra-azapentadienes, the formazans (32)[91] has been studied in some detail. These compounds are readily prepared by the action of diazonium salts on hydrazones[92] or on compounds containing active methylene groups[93]. Formazan bases rigidly adopt an all-cis structure[94], and there has been some discussion concerning the nature of the hydrogen bond in these systems[94,95,96]. Surprisingly, they are rather weak bases, and no



(32)

salt has ever been isolated, probably due to ready hydrolysis. In some cases, an acid-catalysed rearrangement may take place to give benzo-1,2,4-triazine derivatives[97]. The mechanism of this reaction presumably parallels that of quinoline formation from 1,5-diaryl-1,5-diazapentadienes[87]. Formazans nevertheless show meneidic character in their activity towards electrophiles at the 3-position. They couple with diazonium salts[98] and undergo the Mannich reaction[98]. Bromination of (32) (Ar = Ph, X = H) takes place not only at the 3-position, but also in the N-phenyl substituents[99]. Such behaviour is also found with some N,N'-diaryldihydrodiazepines[34]. The 3-bromo derivatives are active towards nucleophiles, and the corresponding iodo-compound and thiol have been made in this way[99].

A number of 1,3,5-triazapentadienes have been prepared[66,73,76].

Diazapolymethines

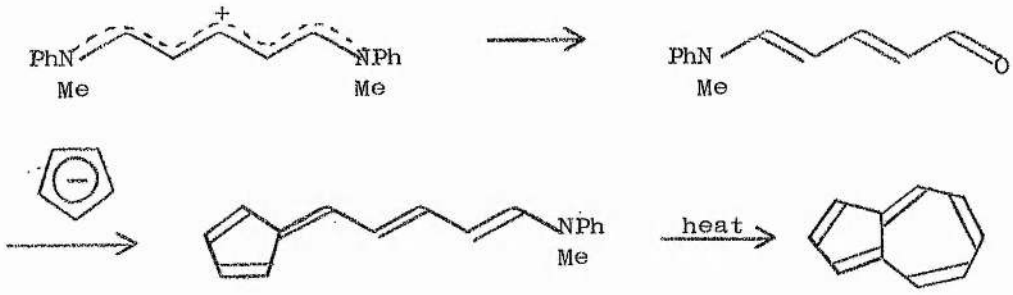
Like the pentadienium cations, these polymethinium salts (33) adopt the all-trans configuration when in isolation[61]; clearly the

possibilities of geometrical isomerism are manifold.

$$R_2N\text{-}(CH)_n\text{=}\overset{+}{N}R_2 \longleftrightarrow R_2\overset{+}{N}\text{=}(CH)_n\text{-}NR_2$$

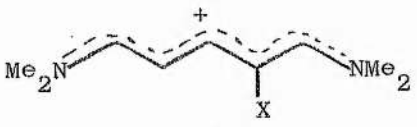
(33)

The syntheses of (33), (R = Me, n = 1-13) have been described by Malhotra and Whiting[65]. The compounds most readily available are those where n = 5, the dianils of glutacondialdehyde, which are prepared in two steps by the action of amines on pyridinium salts[65]. The reverse process has also been reported[100]. Glutacondialdehyde dianils are imporant synthetic intermediates, and are used in the classic Ziegler-Hafner synthesis of azulenes (Scheme 2)[101].



Scheme 2

Like the vinamidines, the conjugated system in these heptamethinium salts is essentially electron-rich, and so the compounds may be expected to be active towards electrophiles. There is only one report of such reactions in the literature. Kučera and Arnold prepared the 3-substituted compounds (34) (X = Br, NO_2)[78] by the same methods as they used for pentamethines[78], although the yields



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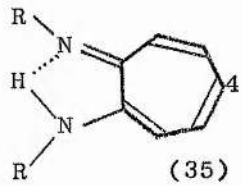
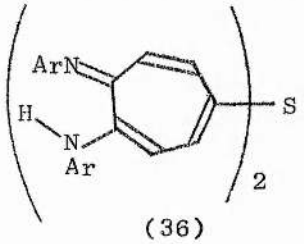


(35)

in this case were slightly lower. The structures of the products were established by cyclisation to pyridine derivatives. No attempts were made to observe disubstitution; a comparison with benzene derivatives of the activating effects of substituents already present would be of interest.

No chemical studies have been carried out on the next member of the series, an all-trans diazanonamethine, but the isoelectronic cycloheptatriene derivatives (35) have been investigated. These are most readily prepared by the action of the appropriate amine on the 1,2-diethoxytropylium ion[102], although other methods have been reported[103,104,105]. Structural work has shown that the NH may be symmetrically located between the nitrogens[106], possibly giving a 10 π-electron system[107], and so some ambiguity exists as to the exact mechanism of electrophilic substitution in these compounds. The bases may be brominated or chlorinated, and coupled with diazonium salts, the reaction taking place at the 4-position of the cycloheptatriene ring[103]. No work of this kind has been carried out on the salts. The 4-halogeno substituents are active towards nucleophiles, but do not necessarily yield simple products. For example, both hydrogen sulphide and thiourea react with the 4-bromo compound to give the sulphide (36)[103].



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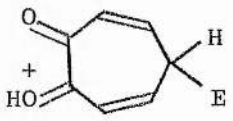
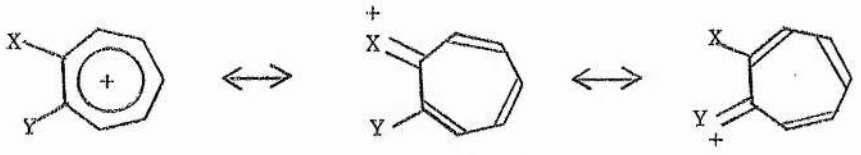


(37)

Tropolone itself readily undergoes substitution reactions at the 4-position with electrophiles, and it has been suggested[108] that the mechanism of these reactions is parallel to that of vinamidines, via a stable cation (37) analogous to the Wheland intermediate. A wide variety of 1,2-disubstituted tropylium salts (38) are known[109], and a comparison of their behaviour with

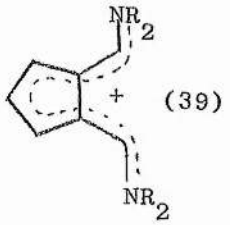


(38A) (38B) (38C)

electrophiles would be of interest. When X and Y are poor Lewis bases (eg. O,S,Cl), form (38A) would be important and reaction with

electrophiles slow. Forms (38B) and (38C), which give a higher electron density at the 4-position should be of increased importance when X and/or Y is nitrogen. ^{13}C nmr studies could also indicate this trend.

Isoelectronic with these cycloheptatrienes, are the cyclopentadiene derivatives (39)[110] and (40)[111]. A detailed analysis of the



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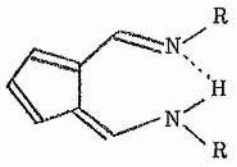
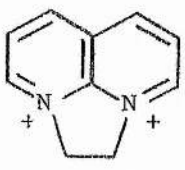


(40)

spectra of the base (40) was interpreted in terms of an intramolecular hydrogen bond, which undergoes rapid exchange[111]. These conclusions have been confirmed recently by an X-ray crystal structure determination and by ESCA results on compound [(40), R = Ph][111a]. Some doubt was cast[111,111a] on the 'non-classical aromatic' concept which had been proposed earlier for related systems[62,106,107]. These cyclopentadienes have been used in the synthesis of hydrocarbons[112,113], using methods related to the Ziegler-Hafner azulene preparation. Meneidic reactions in these systems have not been studied, although they can proceed only at the 3-position of the ring because of the position of the bridge.

It is of interest that the pseudobase derived from the diquaternary salt (41) of 1,8-naphthyridine adopts the fully conjugated nonamethine form (42)[114,115].



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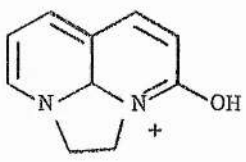


(42)

Miscellaneous Diazapolymethine Systems

From the foregoing account, it is clear that the unique properties of α,ω-diazapolymethines depend substantially on two physical consequences of their structure. First, the high stability

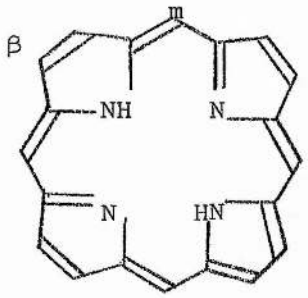
of the monocation, especially notable in the dihydrodiazepine series, is related to its symmetrical 'push-pull' mesomeric system. Second, the alternation in charge along this system causes selected positions to be active towards electrophiles and others towards nucleophiles. That these reactions tend to be substitution rather than addition is a further consequence of the stability of the structure.

This thesis is concerned primarily with the effect of the geometric and electronic environment on the properties of vinamidines. It is appropriate at this stage to consider a selection of other recent examples where these characteristic properties are evident, despite electronic perturbation of the system. The chemistry of one such species, the 4-aminopyridinium cation (30) has already been discussed.

Perhaps the most important modified vinamidines are the corrin and porphyrin systems[116,116a], which occur in a diverse variety of natural products[117,118]. Electrophilic substitution has been shown to take place at the meso (m) positions in porphyrins (43) and their metal complexes, although the β-position is said to be more active[119,120]. Metal-free porphyrins may be deuteriated[121,122], halogenated[123] and nitrated[120,124], and the nitro-compound reduced to an amine[120]. The corresponding complexes are deuteriated more rapidly than the bases[121], and can be formylated under Vilsmeyer conditions[121]. A meso-thiocyanato derivative has also been prepared[125].

The resemblance of the tetradehydrocorrin system (44) to that of dihydrodiazepines has been remarked upon by Johnson[126]. Complex salts of the former may be halogenated, deuteriated, or nitrated[126,127], reaction occurring at the 5, 10 or 15 positions. The immediate substitution products, however are unstable to oxidation[126,127]. Reaction of the 5,15-dibromo-derivative with nucleophiles gave the 5,15-unsubstituted compound.[126], a mode of reaction also found in the dihydrodiazepine series[34]. That

tetradehydrocorrin complex salts may be reduced specifically to



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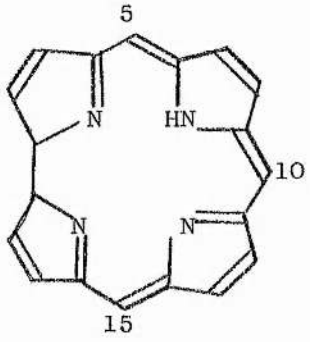

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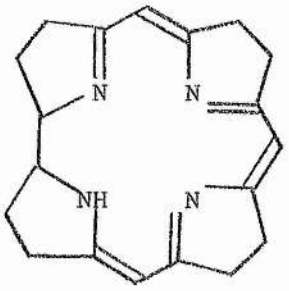
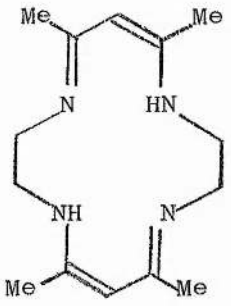


(45)

corrins (45)[128] reflects once again the stability of the vinamidine system. Little work appears to have been done on the reactions of corrins themselves with electrophiles. Similarly, the reactions of simpler macrocycles[129,130] [eg. (46)] prepared as routes to possible model compounds for corrins and porphyrins, have not been studied.



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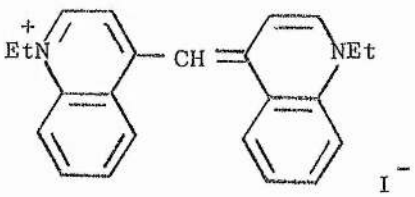


(47)

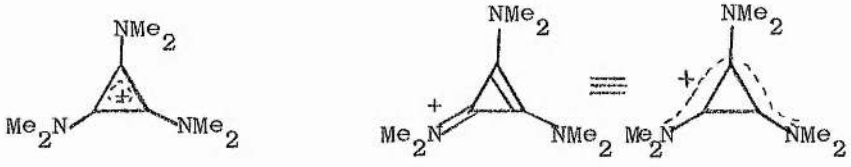
Some other natural products containing the α,ω-diazapolymethine nucleus have been reported[1,131].

Commercially, the most important diazapolymethines are without doubt the cyanines, which, as photographic sensitisers "have made colour photography and high-speed photography possible"[132]. Many variations in the structure of cyanine (47) have been reported: other heterocycles may replace either or both of the quinoline nuclei for example, while polymethine or azapolymethine chains may separate the two rings. Clearly the permutations are endless* and

* Some impression of this may be gained by the 790 page review by Hamer[132].

furthermore the literature of the subject is complicated by much of the work being reported as patents. Because of the photographic interest, the spectroscopic properties of cyanines are well documented, but little work has been done on their chemistry. Activity towards electrophiles, however, has been demonstrated by their ability to couple with diazonium salts[133,134].

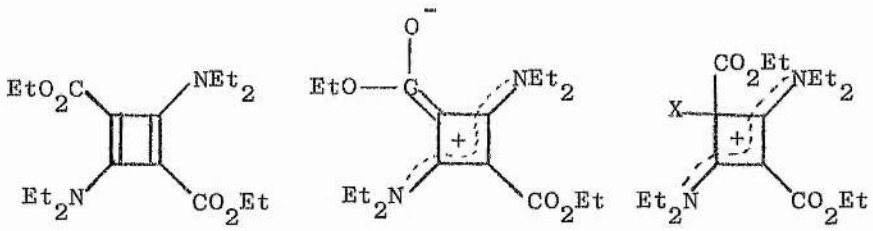
A variety of normally reactive systems may be stabilised by the vinamidine group. Whereas cyclopropenium salts react additively in the cold with weak nucleophiles (eg. alcohols)[135,136], the 1,2,3-tris(dimethylamino) derivative (48) is unaffected by hot



(48) (48A) (48B)

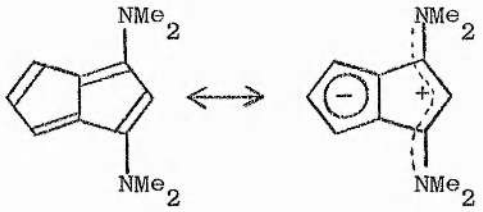
water.[137] The contribution of the imine canonical forms (48A) is evident from the X-ray crystal structure of the compound, which shows short C-N bonds[138]. It is tempting to consider these compounds as bridged 3-aminovinamidines (48B). If this argument is valid, the scarcely studied 1,2-diaminocyclopropenium system should exhibit comparable stability and might undergo electrophilic substitution (unlike other cyclopropenium salts), at the 3-position. As may be predicted, the corresponding trialkoxy-[139] and tris(alkylthio)cyclopropenium[140] salts are markedly less stable.

Cyclopropenium salts, although reactive, are inherently stable species. In contrast, cyclobutadienes are thermodynamically unstable and simple derivatives may be isolated only with great difficulty[141,142,143]. Push-pull cyclobutadienes[144] eg. (49), which can be obtained comparatively readily[145], can be drawn in a vinamidinium canonical form (49A). In this case, however, structural data show that the ester-ring bond is of 'normal' length, and not shortened as would be expected if the form (49A) were prevalent[146]. These cyclobutadienes have strong basic and



(49) (49A) (50)

nucleophilic properties[144], and some of the driving force in their reactions (eg. with acids, bromine, or methyl iodide) may be the resultant formation of the stable 1,5-diazapentadienium system (50)

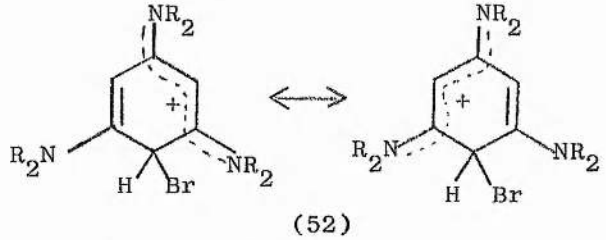


(51) (51A)

(X = H, Br, CH_3). The cyclobutadiene itself may be generated by the action of sodium hydride on the salt (50) (X = H)[145].

Simple pentalene derivatives have only recently been prepared, and were shown to be highly reactive[147]. 1,3-Bis(dimethylamino)-pentalene (51), however, is stable towards atmospheric oxygen for several hours at room temperature, possibly due to the contribution of the vinamidinium/cyclopentadienide canonical form (51A)[148]. A 2-aza derivative has also been prepared[149].

In the chemistry of benzenoid compounds, the importance of the Wheland intermediate in the course of electrophilic substitution reactions has long been recognised. Recently, the benzenium ion itself has been observed spectroscopically in super-acid media[150], but the first Wheland intermediates to be isolated and to be stable at ambient temperatures, eg.(52)[151], employed vinamidines to delocalise the positive charge. It is of interest that halogeno-



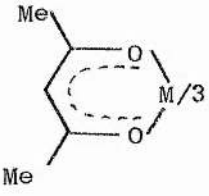
(52)

benzenes are produced by the action of bases on the cation (52),

whereas strong nucleophiles cause debromination[152] in a manner reminiscent of dihydrodiazepines[34] and tetradehydrocorrins[126].

Other Quasi-aromatic Compounds

A few other systems are known which display quasi-aromatic or meneidic properties, chief among these being the metal chelates of acetylacetone (53). After much discussion[153,154,155] it is now

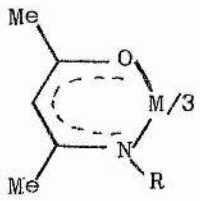


(53)

agreed from nmr evidence[156] that the conjugation in these systems does not include the metal, and so is truly acyclic. Electrophilic substitution reactions on these compounds have been known for nearly fifty years[157] and a considerable selection of syntheses has been carried out[158]. As well as undergoing halogenation[157,159] and nitration[160,161] at the methine position, these chelates may be formylated under Vilsmeyer conditions[161] and acylated by the Friedel-Crafts method[162]. The nitro-compound may be reduced catalytically to an amine, which gives a diazonium salt with nitrous acid[163]. This salt couples with β-naphthol, is reduced by ethanol, and yields a fluoro derivative under Schiemann conditions[163]. As with benzenoid compounds, groups other than hydrogen may be replaced by electrophiles[158], but the 3-halogeno compounds are inert towards nucleophiles[159]. This is not unexpected in view of the high charge density of the methine position; indeed the chemical shift of this position in the nmr spectra of these chelates (ca. τ 4.5)[164] is comparable to that of the equivalent (6-) position in dihydrodiazepines (ca. τ 4.9).

Some related chelates have been made and their reactions studied. Thus the oxo-enamine complexes (54) and (55) have been brominated[165,166] and an isocyanato derivative of (55) has been

prepared[167].



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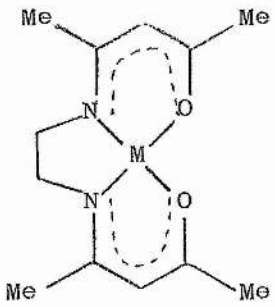


(55)

The presence of the metal is not necessary in these reactions. The bromination of acetylacetone itself is well known[108], and it may be C-alkylated under acidic conditions[168]. Similarly, oxo-enamines (in a rigid all-trans configuration) have been acylated[169], thiocyanated[170,171], halogenated[171] and deuteriated[171]. It is an interesting coincidence that this series provides another example of nucleophilic dehalogenation[171].

DISCUSSION

PART I

DIHYDRODIAZEPINES

SECTION 1

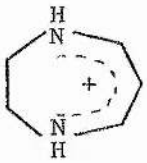
NUCLEAR MAGNETIC RESONANCE SPECTRA OF DIHYDRODIAZEPINIUM SALTS[172]

Nmr spectroscopy has found extensive use in the study of dihydrodiazepines, but the technique has in general been applied only as an empirical tool in structure determination. For example, the position of substitution in reactions with electrophiles has been confirmed by the absence of the 6-proton signal in the spectra of the products[34,35]. On a more sophisticated level, the nmr spectra of dihydrodiazepines have been quoted as models in the resolution of the 'non-classical aromaticity' controversy concerning open-chain 1,5-diazapentadienes[72], and attempts have been made to correlate the chemical shifts with theoretical charge densities[173]. The technique has also been used kinetically in studies of deuteriation reactions[30]. However, the spectral parameters have never been related to the structure and conformation of the dihydrodiazepine ring itself, although work has been reported for 1,5-benzodiazepines[174].

The majority of early determinations of dihydrodiazepine spectra employed trifluoroacetic acid (TFA) as solvent, but [$^2H_6$]-acetone or [$^2H_6$]dimethylsulphoxide (DMSO) were found to be more convenient. Under these conditions, the NH signals occur as broad peaks at low field, whose position may be clarified by the addition of a little TFA. This solvent mixture also resolved NH-CH coupling, which otherwise is not observable because of proton exchange.

As has been noted for other 1,5-diazapolymethinium salts[1], the chemical shifts of the protons in the vinamidinium portion of the dihydrodiazepinium cation (56), reflect the charge distribution in the system. The protons at the 5(7) position resonate at low

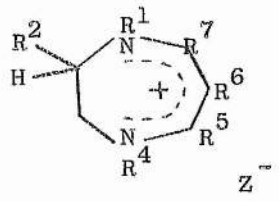
field (ca. τ 2.5), while those at the 6-position are more shielded, the peaks occurring at ca. τ 5.0. Simple first-order spectra are therefore generally obtained.



(56)

The vicinal coupling constants (J_{vic}) due to the interaction between the protons of this conjugated part of the molecule, are of interest because of empirical correlations with π-bond order (p)[175,176,177]. Equations relating J_{vic} and p have been derived for five- and six-membered rings, but no extension to seven-membered rings has been reported. However, the inspection of molecular models has suggested that the geometry of the conjugated portion of the dihydrodiazepine may approximate to that of a six-membered ring, with bond angles little perturbed from 120°. Table 1 lists the vicinal coupling constants of the majority of known 5,6(7)-unsubstituted dihydrodiazepinium salts and the bond orders derived from them[176,177] assuming a six-membered ring geometry. Considering the naivety of the approach, and the total neglect of any effect due to the electronegativity of nitrogen[178], it is remarkable that these empirical bond orders are so close to the 'theoretical' value of 0.75, which may be obtained assuming the complete delocalisation of 6 electrons through 4 bonds. This total delocalisation is also implied by the similarity in magnitude of J_{45} and J_{56}[172].

The effect of vicinal NH coupling is also evident in the resonances due to the methylene protons, although in this case the complexity of the spin system may give rise to peculiar signals (eg. Figures 1 and 2). A similar peak has also been recorded in the spectrum of the bisoxo-enamine (4)[179]; it is possible that these may arise through second-order interactions assuming a different



(56)

a, R^n = H
b, R^1 = Me
c, R^2 = Me
d, R^5 = Me
e, R^6 = Me
f, R^1 = R^4 = Me
g, R^1 = R^4 = CH_2Ph
h, R^1 = R^4 = Ph
i, R^1 = R^5 = Me
j, R^1 = R^4 = R^5 = Me

(where unspecified, R = H)

Table 1 Coupling Constants and Bond Orders for the Dihydrodiazepinium Salts (56)

Compound	Solvent	$J_{45(17)}$ /Hz	$^{176}p_{45}$	$^{177}p_{45}$	$J_{56(67)}$ /Hz	$^{176}p_{56}$	$^{177}p_{56}$	Z	Ref.
56a	$[^2H_6]$acetone (/TFA)	7.2	0.64	0.63	7.8	0.71	0.69	ClO_4	x
56b	$[^2H_6]$acetone (/TFA)	ca.8	0.7	0.7	7.9	0.72	0.69	ClO_4	x
56c	$[^2H_6]$acetone	7.9	0.72	0.69	7.9	0.72	0.69	ClO_4	x
56d	$[^2H_6]$DMSO (/TFA)	7.8	0.71	0.69	8.2	0.76	0.72	picrate	x,22
56e	$[^2H_6]$DMSO /TFA	8.0	0.73	0.70	-	-	-	ClO_4	18,y
56f	$[^2H_6]$acetone	-	-	-	7.8	0.71	0.69	ClO_4	17,y
56g	$[^2H_6]$acetone	-	-	-	8.0	0.73	0.70	ClO_4	x
56h	$[^2H_6]$DMSO	-	-	-	8.2	0.76	0.72	ClO_4	19
56i	$[^2H_6]$DMSO	-	-	-	8.4	0.78	0.74	picrate	x
56j	$[^2H_6]$acetone	-	-	-	8.8	0.83	0.77	picrate	x

Reference x ; this work

y ; I am grateful to Dr. D.R. Marshall for samples of these compounds

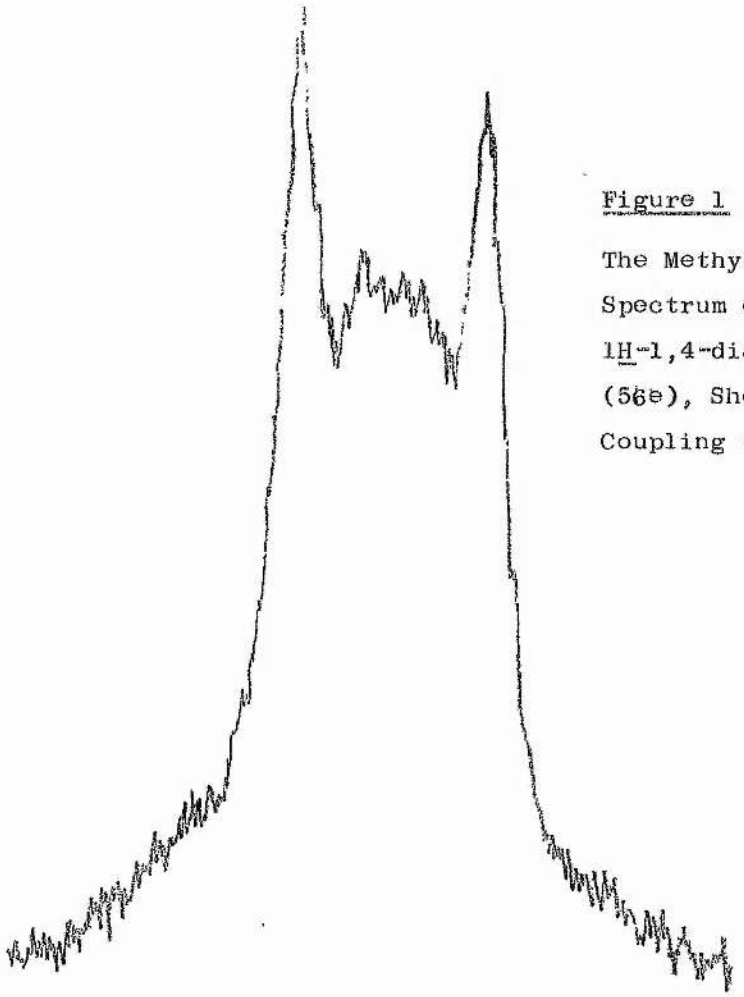


Figure 1

The Methylene Signal in the Nmr Spectrum of 2,3-Dihydro-6-methyl-1H-1,4-diazepinium Perchlorate (56e), Showing the Effect of NH Coupling (Sweep Width 100 Hz)

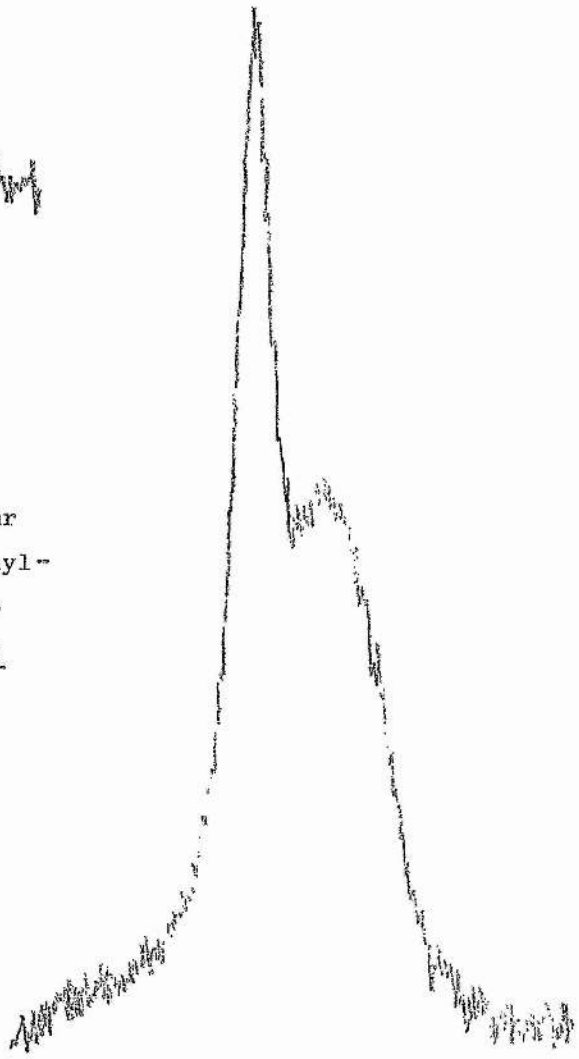
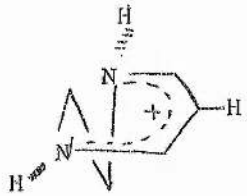


Figure 2

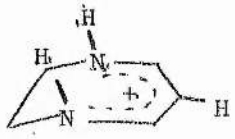
The Methylene Signal in the Nmr Spectrum of 2,3-Dihydro-1-methyl-1H-1,4-diazepinium Perchlorate (56b) Showing the Effect of NH Coupling (Sweep Width 100 Hz)

coupling constant between each methylene and the NH.

Long-range coupling between the 6-proton and the NH has also been observed, which causes the 6-proton signal to appear as a small triplet (J ca. 1.8 Hz), not always fully resolved, in the spectra of N,N'-unsubstituted dihydrodiazepinium salts. The corresponding signal in N-substituted compounds is a doublet (J ca. 1.8 Hz); the assignment has been further confirmed by double resonance experiments. There is much evidence that such coupling through four bonds normally requires a planar 'W'-shaped configuration[180,181]. Hence the effective planarity of the complete vinamidinium system in these compounds is confirmed. Similarly, the earlier supposition[18] that the dihydrodiazepinium system adopts a half-chair (57) rather than a half-boat (58)* conformation is substantiated, since only in the former case are the NH and 6-CH bonds coplanar. In the spectrum of the 2-methyl derivative (56c), 'meta'-coupling between the non-equivalent 5- and 7-protons is observed (J ca. 1.1 Hz). The assignment was confirmed by an INDOR experiment.



(57)



(58)

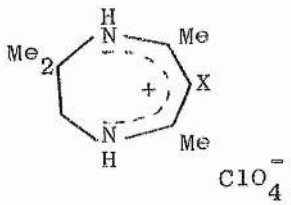
At normal temperatures and in the absence of NH coupling, the signal due to the methylene protons occurs as a singlet. At lower temperatures, however, the resonance becomes broad and flattens, and when the temperature is reduced still further the signal reappears as a complex multiplet. Such behaviour is typical of a conformationally mobile system. Thus at comparatively high temperatures the ring rapidly inverts between forms (57A) and (57B), whilst at lower

* For a critical discussion of similar terms, see reference 182

(57A) (57B)

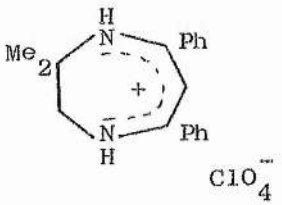
temperatures this process is slowed down so that the system becomes effectively 'frozen' in one conformation.

The strongly coupled signals due to the methylene protons at low temperature render such compounds unsuitable for a kinetic analysis of the ring inversion, and so a series of 2,2-dimethyl-dihydrodiazepinium salts (59) and (60) were synthesised for this purpose. At -50°, the spectra of these salts are fully resolved,

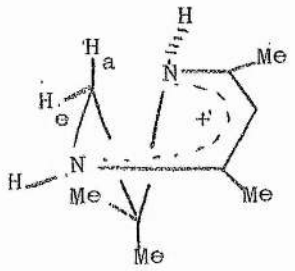


a, X=H d, X=Cl
b, X=NO_2 e, X=Br
c, X=OMe f, X=I
g, X=Me

(59)



(60)



(59a)

and that of the 6-unsubstituted compound (59a) was examined in detail.

The methylene protons occur as an AB system (J 13.6 Hz, $\Delta\tau$ 0.62 ppm) the downfield half of which is further split into two doublets, (J 7.2 Hz), due to coupling with the 4-NH group. Spin decoupling the downfield of the two NH signals causes the multiplet to collapse to an unperturbed AB system. From the relation between

dihedral angle and coupling constant, therefore, the downfield part of the AB system represents the 'equatorial' proton H_e. This observation could be consistentwith a 'homo-homo-aromatic' ring current. However, the equatorial proton in [$^2H_{11}$]cyclohexane is also reported to resonate at lower field than the axial ($\Delta\ \tau$ 0.48 ppm)[183], and so the effect of 1,4-orbital overlap in dihydrodiazepines can probably be neglected.

The two signals for the 2-methyl groups are separated by 38.3 Hz. The upfield resonance is broad, but may be sharpened by decoupling the upfield (axial) methylene proton. Hence the axial methyl-substituent may be assigned to the upfield signal.

The 6-proton signal occurs as a triplet due to long-range coupling with the NH. Spin decoupling each NH in turn causes the signal to collapse to a doublet, the coupling constants being slightly different (J_{16} 1.9 Hz, J_{46} 1.5 Hz).

Due to the dissymmetry of the system, the protons in the 5- and 7-methyl groups give rise to two peaks (separation 2.1 Hz at -50°). Decoupling the upfield (1-) NH sharpens the upfield signal and hence this must be due to the 7-methyl group. Conversely, the downfield signal is sharpened by decoupling the upfield methylene resonance. The separation of these methyl peaks is apparently temperature dependent, and is reduced to 0.4 Hz at 30°. A similar effect is found in the spectrum of the 6-methoxy compound (59c), where the separation varies from ca. 4 Hz at -90°, through 0 Hz (30°) to ca. 2 Hz at +50°. The explanation of this phenomenon, and of the concomitant variation in line-shape, is obscure.

The NH signals in the low temperature spectrum of (59a) are separated by ca 30 Hz. The downfield resonance, due to the 4-proton, is the broader of the two, because of coupling with the adjacent methylene group.

The spectrum of 2,3-dihydro-2,5,7-trimethyl-1H-1,4-diazepinium perchlorate was also recorded at -50°. In this case the signals

due to the 2-methyl group occurred as doublets of equal intensity. Hence there is no preference for bulky groups in dihydrodiazepines to adopt the equatorial position. This is not unexpected in view of the absence of any axial interactions.

The kinetic analysis of the ring inversion process is particularly simple for the 2,2-dimethyldihydrodiazepines (59) and (60). The 2,2-dimethyl groups give rise to one sharp singlet at high temperature, which becomes broad and eventually disappears as the temperature is lowered. Below this 'coalescence temperature' (T_c), the inversion rate is slow on the nmr time scale and two singlets are observed (Figure 3). Equations have been derived relating the rate constant for the exchange process to spectral parameters such as line width[174,184], and from an Arrhenius plot, an estimate of the activation energy (E_a) and hence enthalpy ($\Delta H^{\ddagger}$) for the inversion may be calculated. Temperatures in the range T_c to $T_c + 25^{o}$ were experimentally convenient; a typical Arrhenius plot is shown in Figure 4. Furthermore, application of transition-state theory to the situation at the coalescence temperature gives an expression for the free energy of activation ($\Delta G^{\ddagger}$) for the inversion, from which may be calculated the entropy of activation ($\Delta S^{\ddagger}$)[174]. These quantities are compiled for the dihydrodiazepinium cations (59) and (60) in table 2. $\Delta G^{\ddagger *}$ is an estimate of $\Delta G^{\ddagger}$ based on an empirical relation[185], $\Delta G^{\ddagger *}$ 57.3 + 0.21 T_c ± 1.9 kJ mol^{-1}; the agreement between this and the rigorous thermodynamic $\Delta G^{\ddagger}$ is remarkable.

It is apparent from the table that the electronic nature of the 6-substituent has little effect on the ease of inversion, the free energies of activation for the 6-nitro and 6-methoxy compounds differing by less than 0.2 kJ mol^{-1}. Unexpectedly, however, large

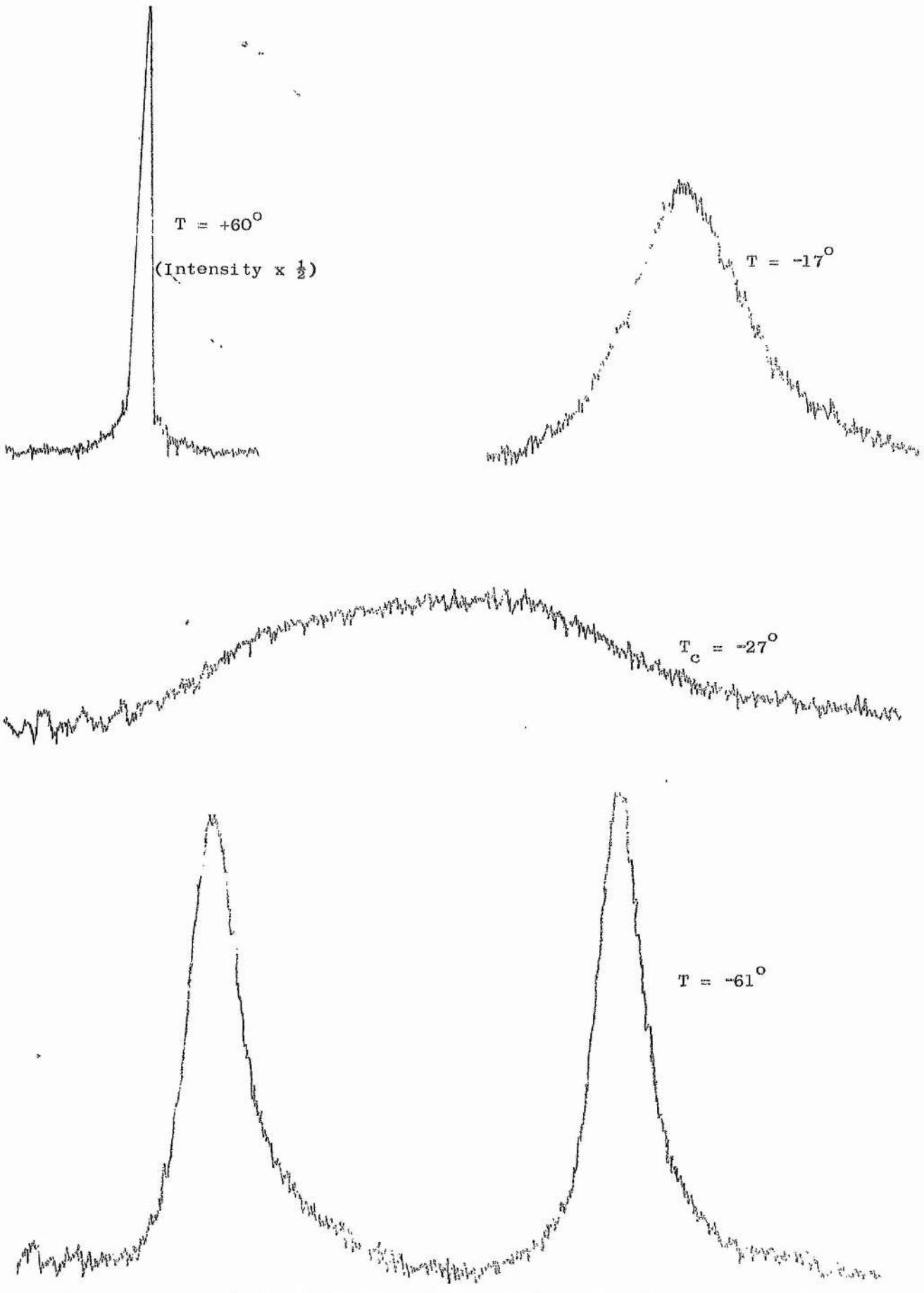


Figure 3 Temperature Dependence of the 2,2-Methyl signal in the Nmr spectrum of 2,3-Dihydro-2,2,5,7-tetramethyl-6-nitro-1H-diazepinium Perchlorate (59b) (Sweep Width 50 Hz)

Figure 4 Arrhenius Plot for the Ring Inversion Process of the 6-Nitrodihydrodiazepinium Perchlorate (59b)

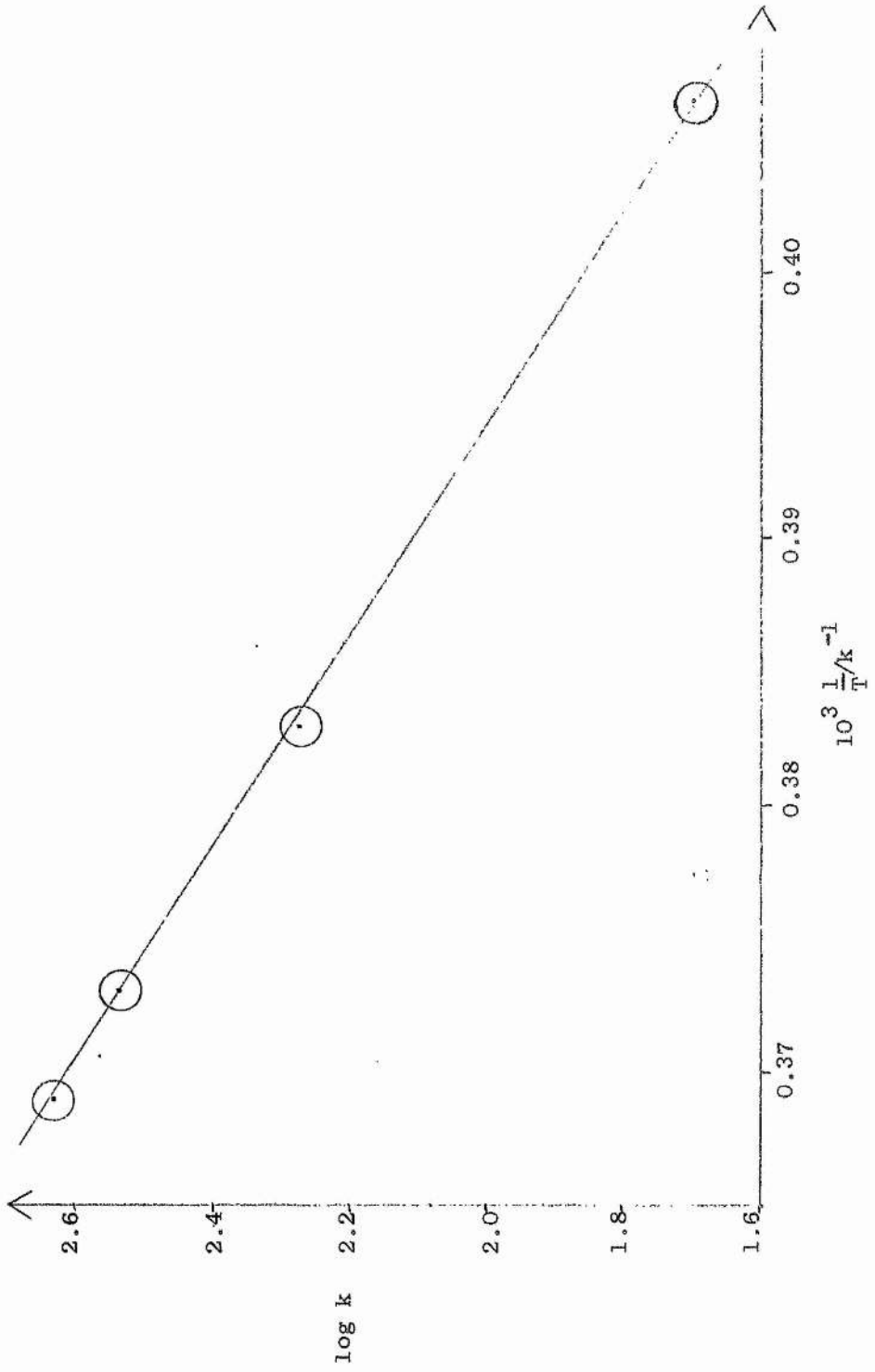


Table 2 Activation parameters for ring-inversion in 2,2-dimethyldihydrodiazepinium salts (59) and (60)

Compound	T_c (°C)	$\Delta G^{\ddagger}$ / kJ mol^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	E_a / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J mol^{-1} K^{-1}	$\Delta G^{\ddagger *}$ / kJ mol^{-1}
59a	4±1	58.7±0.6	57.2±1.3	59.5±1.3	- 5.3±1.9	58.1±1.9
59b	-27±1	51.8±0.5	46.0±0.7	48.1±0.7	-23.5±1.2	51.6±1.9
59c	-25±1	52.0±0.5	51.0±2.5	53.1±2.5	- 3.8±3.0	52.0±1.9
59d	-23±1	52.6±0.5	46.2±1.5	50.2±1.5	-17.6±2.0	52.5±1.9
59e	-25±1	52.2±0.5	50.5±2.1	52.5±2.1	- 7.0±2.6	52.0±1.9
59f	-32±1	50.8±0.5	46.7±0.1	48.7±0.1	-16.8±0.6	50.6±1.9
59g	-49±1	47.1±0.5	40.5±1.0	42.4±1.0	-29.1±1.5	47.0±1.9
60	- 2±1	56.9±0.6	54.5±2.1	56.7±2.1	- 9.3±2.7	56.9±1.9

groups at the 6-position facilitate the exchange. This phenomenon could have its origins either in a ponderal or a size effect. A graph of formula weight of substituent versus $\Delta G^{\ddagger}$ gave an irregular curve (Figure 5), while a plot of van der Waals radius[186] of monatomic substituents against $\Delta G^{\ddagger}$ gave a straight line, with standard deviation in gradient of about 10% (Figure 6). It is likely, therefore, that the large substituents must influence the geometry of the ring. The vicinal repulsions between the groups on the 5,6 and 7 positions may cause a slight lengthening of the ring bonds*, or may perhaps distort the planarity of the vinamidinium system. In either case, the rigidity of the molecule would be affected.

The case of the 6-methyldihydrodiazepinium salt is anomalous. It is known[186] that the van der Waals radius of a methyl group is roughly comparable to that of a bromine atom, yet the inversion process in the 6-methyl compound is much more facile than would be predicted from the graph (Figure 6). A related anomaly has been found

* I am grateful to Professor J.H. Ridd for a valuable discussion.

Figure 5 Plot of $\Delta G^{\ddagger}$ versus Atomic Weight of 6-Substituents for the Dihydrodiazepines (59a,d,e,f)

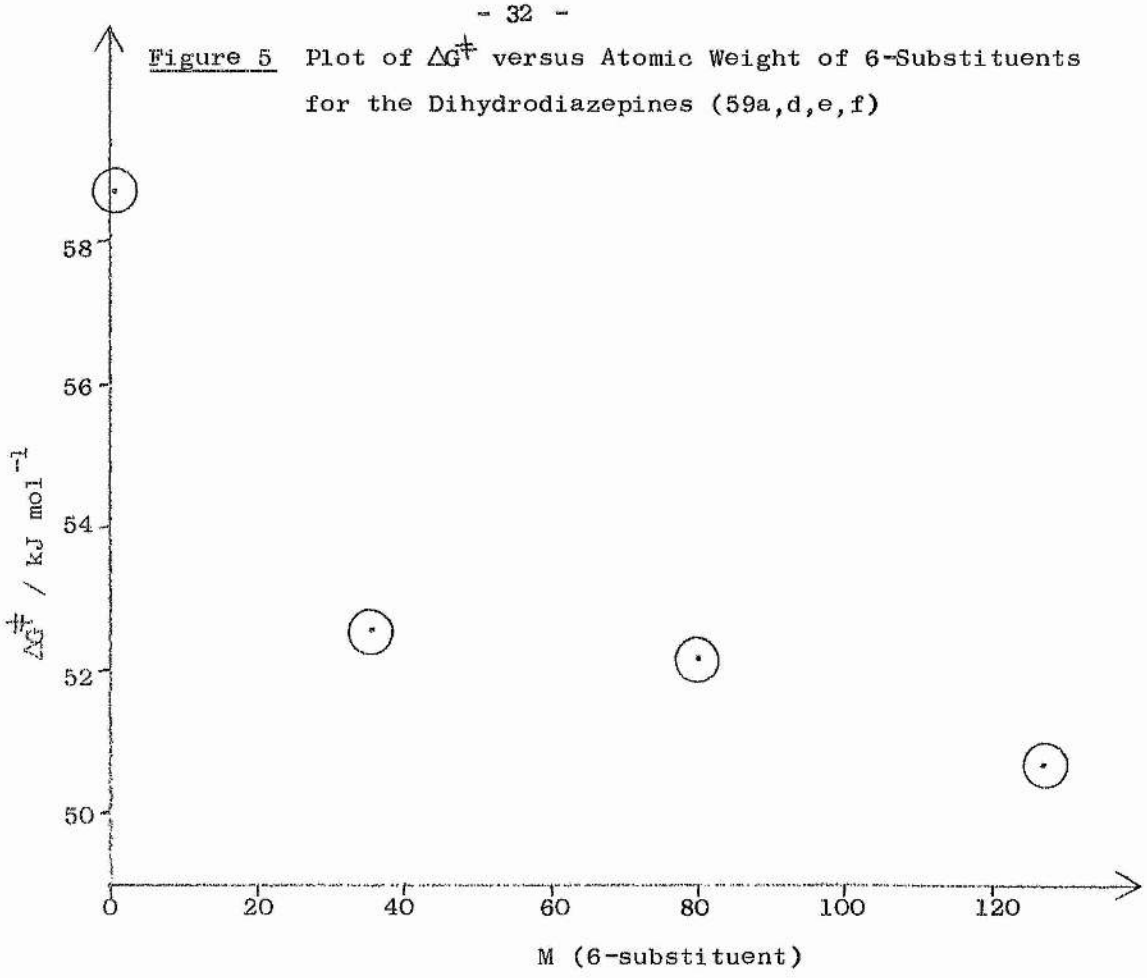
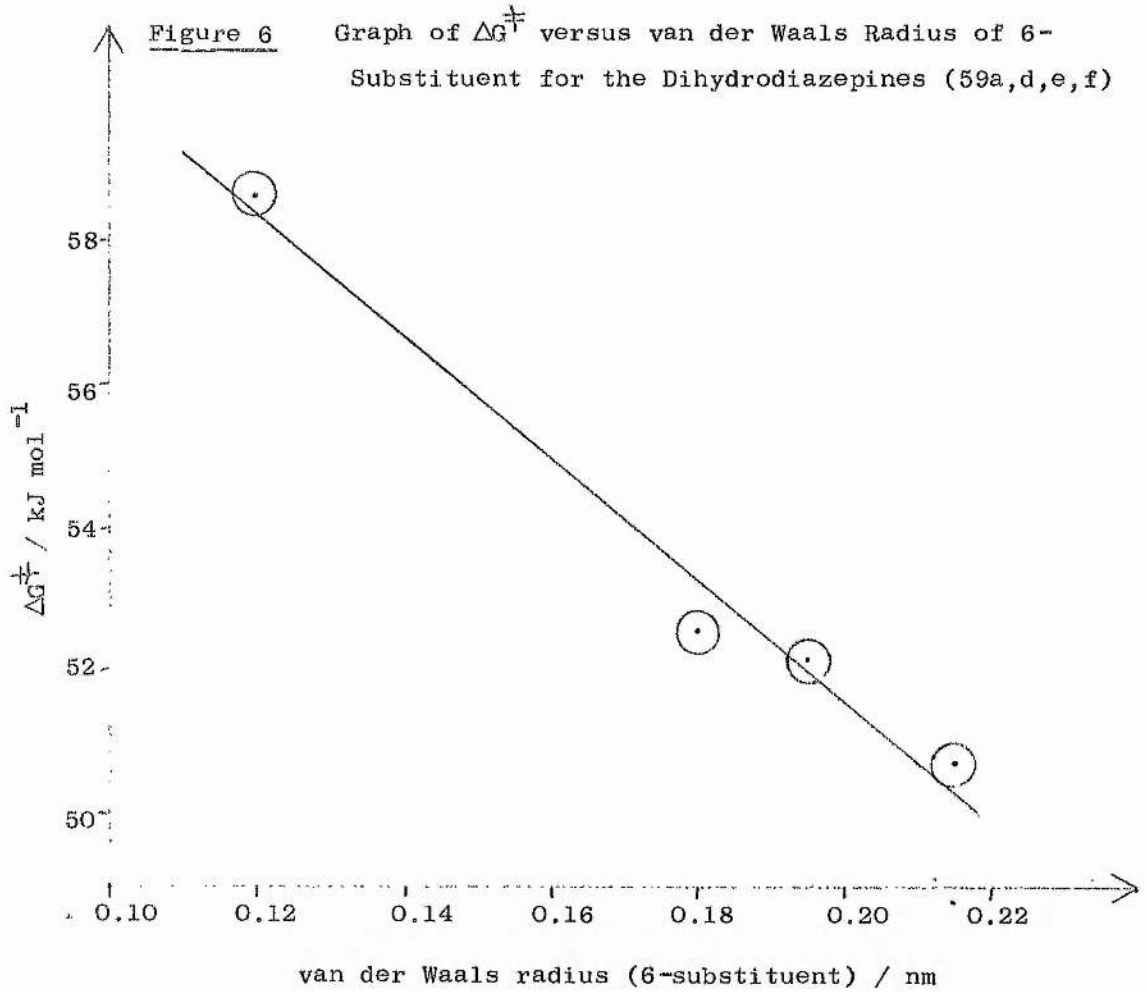


Figure 6 Graph of $\Delta G^{\ddagger}$ versus van der Waals Radius of 6-Substituent for the Dihydrodiazepines (59a,d,e,f)



in the study of cyclohexane derivatives, where methyl groups show a greater tendency to take up equatorial positions than do bromine atoms[187]. Both effects may be explained by the shorter bonding distance of the methyl group which will cause greater interaction with vicinal substituents.

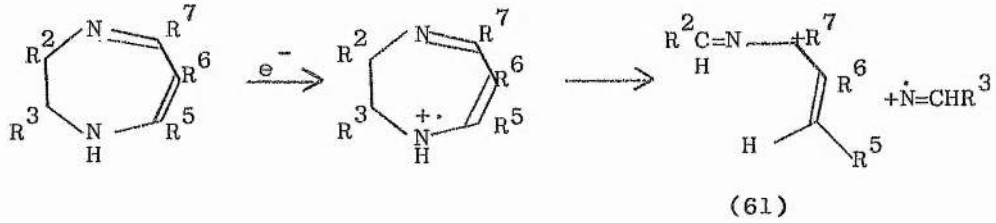
Replacement of the 5- and 7-methyl groups with phenyl substituents causes a slight decrease in $\Delta G^{\neq}$. Although not studied quantitatively, increasing the size of substituents at the 1,4- and especially the 2,3-positions appears to increase $\Delta G^{\neq}$, as might be expected from simple ponderal arguments.

The values for the entropy of activation ($\Delta S^{\neq}$) given in table 2 are probably not quantitatively meaningful. They are of small magnitude, and negative in sign, consistent with a slight ordering effect in the transition state for the inversion.

SECTION 2

MASS SPECTRA OF DIHYDRODIAZEPINIUM SALTS

In contrast to the importance of nmr spectroscopy in the investigation of dihydrodiazepines, their mass spectra have been but little studied. Staab and Wünsche[188] reported the breakdown patterns of a selection of 2,3-diaryl derivatives, obtained both by standard condensation methods[189], and by the Cope rearrangement of double anils formed from 1,2-diaminocyclopropane[23,24]. Intense molecular ions were present for all the compounds studied; the chief fragmentation process, confirmed by the presence of metastable peaks, was the elimination of the N^1-C^2 fragment, leaving a positively charged linear compound (61) (Scheme 3). Further decomposition of



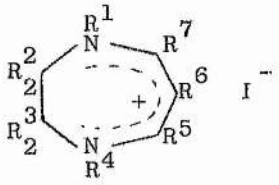
(61)

Scheme 3

(61) resulted in the formation of ethylene, hydrogen cyanide and tropylium ion (R^2 = Ph). Other breakdown processes such as the direct loss of $C_7H_7^+$ from the molecular ion gave rise to peaks of lesser intensity, and in any event are applicable only to the special case of 2(3)-aryldihydrodiazepines.

Because of the problem of involatility, there have been comparatively few reports in the literature of mass spectral work on organic salts[190]. However, in this study, satisfactory spectra of dihydrodiazepinium salts were obtained, although the molecular ions were rarely observable. The perchlorate salts were in general thermally unstable, and for this reason a series of dihydrodiazepinium iodides (62) was prepared. These are readily available from the perchlorates by metathetic reaction with potassium iodide

in methanol[2].



(62)

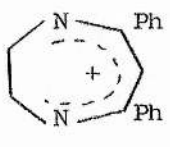
a, $R^5=R^7=Me$
b, $R^2=R^5=R^7=Me$
c, $R^5=R^7=Ph$
d, $R^2=Me, R^5=R^7=Ph$
e, $R^5=R^6=R^7=Me$*
f, $R^1=R^5=R^7=Me$

(where unspecified, R=H)

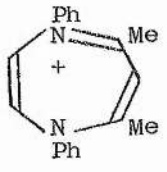
g, $R^5=Me, R^7=Ph$
h, $R^1=R^4=Ph$, $R^5=R^7=Me$
i, 2,3-cyclohexano, $R^5=R^7=Me$
j, 2,3-cyclohexano, $R^5=R^7=Ph$
k, $R^1=R^4=R^6=Me$*
l, $R^1=R^4=Me$*

The mass spectrum of the 5,7-diphenyl compound (62c) (Figure 7) was studied in detail, and the peak assignments checked by high resolution mass measurement. These results are summarised in table 3.

All the dihydrodiazepinium iodides investigated showed low intensity peaks at the m/e value corresponding to the molecular ion of the salt, but this is most likely to be the ^{13}C-isotope peak of the free base. Thermal dissociation of the salt, where possible, would therefore appear to precede electron bombardment. For alkyl-substituted dihydrodiazepinium salts, the most intense peak in the molecular ion cluster is indeed characteristically that of the base. For aryl-substituted derivatives, however, the (M_{base}-1) peak is the most abundant, probably due to the loss of the second N-hydrogen atom to give a resonance stabilised cation eg. (63), isoelectronic with the Wheland intermediate. This explanation



(63)

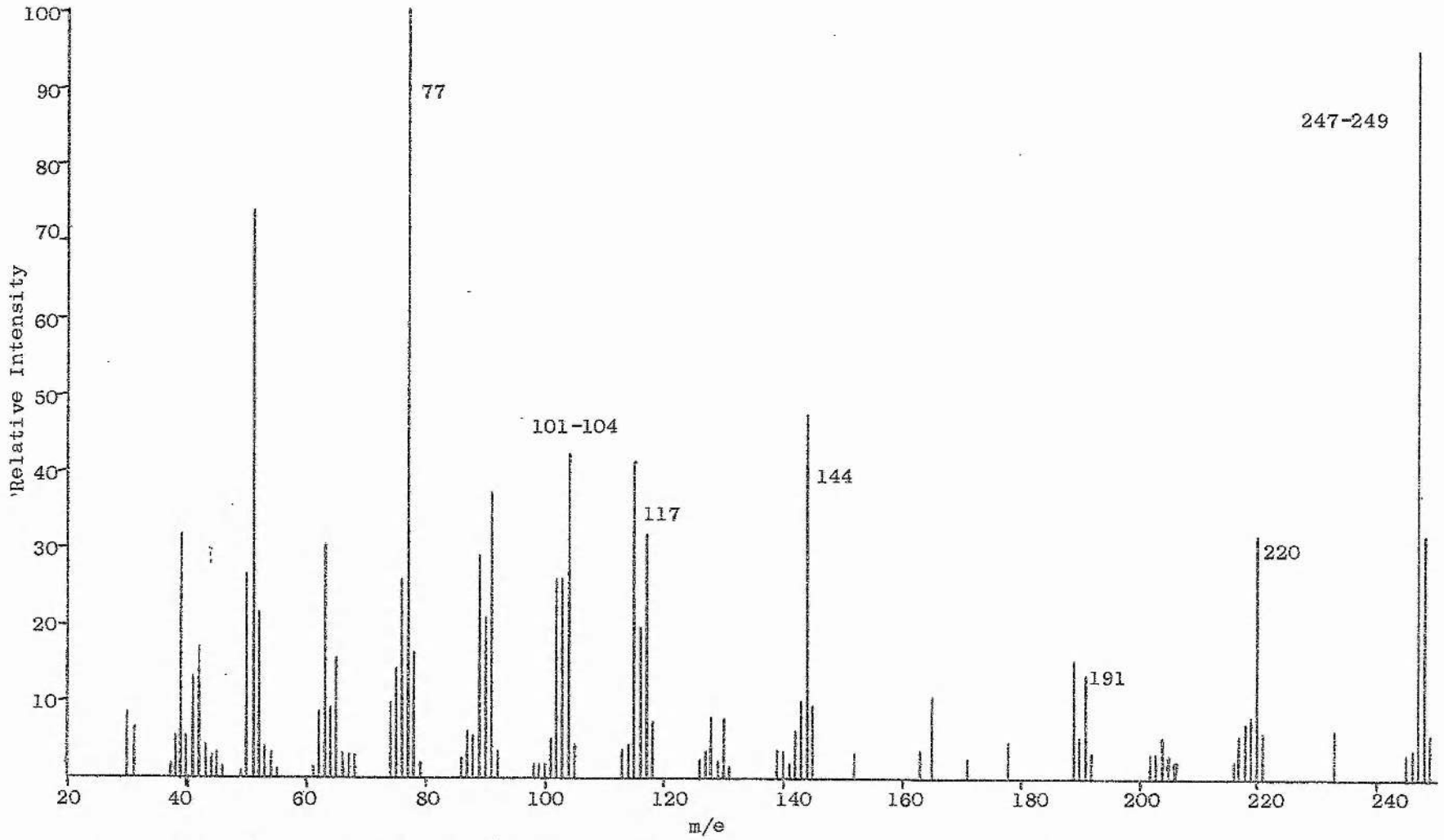


(64)

cannot hold for the intense (M_{cation}-2) peak in the mass spectrum of the 1,4-diphenyl compound (62h), however, in which case the

* I thank Dr. D.R. Marshall for samples of the perchlorates of these compounds.

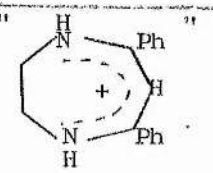
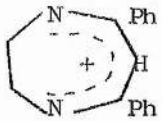
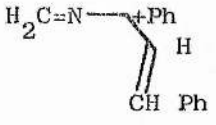
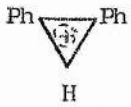
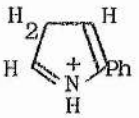
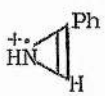
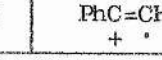
Figure 7 Mass Spectrum of the 5,7-Diphenyldihydrodiazepinium Iodide (62c)



formation of the 1,4-diazepinium nucleus (64), possibly by a retro [8+2] cycloaddition, would appear to be most likely.

For compounds in which the 1,4- and 6- positions are blocked by alkyl groups, the molecular ion of the cation may be observable

Table 3 Summary of high resolution results for 2,3-dihydro-5,7-diphenyl-1H-1,4-diazepinium iodide (62c)

m/e	Structure	Formula	Found	Required
249		$C_{17}H_{17}N_2$ $C_{16}^{13}CH_{16}N_2$	249.132774	249.139167 249.134697
247		$C_{17}H_{15}N_2$	247.122506	247.123517
220		$C_{16}H_{14}N$	220.112552	220.112619
191		$C_{15}H_{11}$	191.085824	191.086071
144		$C_{10}H_{10}N$	144.081782	144.081320
117		C_8H_7N	117.057833	117.057846
104		C_7H_6N	104.050051	104.050022
102		C_8H_6	102.047179	102.046948

(eg. Compound (6.2k), Found, 139.123601; $C_8H_{15}N_2$ requires 139.123517). Explanations for the apparent vaporisation of an organic salt have included the postulation of an unstable cation-anion adduct which subsequently dissociates, or of the decomposition of a charge-transfer

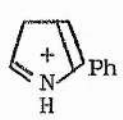
complex[190].

For the alkyl-(but not aryl) substituted dihydrodiazepinium iodides, the simple cleavage of the substituent is an important breakdown path in the mass spectrum. (eg. Compound (62a), Found m^* 96; 124 ⟶ 109 requires m^* 95.8). The relative intensity of this (M_{base}-15) peak, referred to the standard (M_{base}), is affected by the number of methyl groups in the molecule, but is almost independent of the position of substitution.

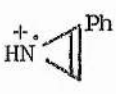
As was found previously[189], the most intense breakdown peak in each spectrum is due to the loss of the (N^1-C^2) fragment. This is unexpected, since the ejected radical is not resonance stabilised as it is in the case of 2-aryldihydrodiazepines. An alternative pathway[191], involving thermal loss of ethylene to give a pyrazole, was rejected on the basis of the high-resolution results. The 2,2-dimethyl compounds (62b) and (62d) almost exclusively lose the radical $Me_2C{=}N\cdot$ in preference to $H_2C{=}N\cdot$, while for the N-methyl dihydrodiazepinium salt (62f), it is the loss of $H_2C{=}N\cdot$ which has preference over $H_2C{=}\dot{N}Me$.

The linear cation (61) may itself decompose; metastable peaks have been found for the direct loss of a methyl group (eg. Compound (62a), perchlorate salt, Found m^* 68.5; 96 ⟶ 81 requires m^* 68.4).

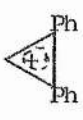
A second, less favourable, breakdown of the dihydrodiazepine is the ejection of the (N^1-C^7) fragment; the loss of cyanides is known to be a favourable process in the mass spectra of many nitrogen heterocycles[192]. The residue of the molecule may be written as a cyclic species [eg. (65)].



(65)



(66)

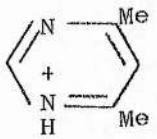


(67)

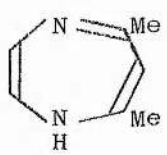
The peak at m/e 117 in the mass spectrum of the 5,7-diphenyl derivative (62c) may be assigned the azirine structure (66). This forms an example of another general decomposition route, the driving force of which is probably the concomitant production of an ethylene and a cyanide, two small, stable, neutral fragments. That the azirine formation is not the major driving force is clear from the spectrum of the 5-methyl-7-phenyl compound (62g), in which peaks due to methyl and phenyl substituted azirines occur with similar intensities. The steric requirements of the reaction are met by the planarity of the 1,5-diazapentadiene system, which allows facile overlap between the p-orbitals of the 1- and 6-positions.

A further breakdown mechanism may lead to a three-membered ring, in this case a cyclopropenium ion [eg. (67)]. This decomposition may be regarded as an offshoot of the major pathway leading to the linear cation (61), probably due to the rearrangement of an intermediate cation radical. Once again, the concomitant formation of neutral species is probably the driving force. The simplest identifiable decomposition fragments which give rise to peaks in the mass spectra are generally protonated or unprotonated cyanides and acetylenes (table 3).

Because the primary decomposition process involves the breaking of the C^2-C^3 bond, this mechanism cannot lead to products in the case of the 2,3-cyclohexanodihydrodiazepinium salts (62i) and (62j). Instead, the dimethyl derivative (62i) shows an intense peak at m/e 109 (Found, 109.076615; $C_6H_9N_2$ requires 109.076569), which probably corresponds to the formation of the pyrimidinium cation (68). This assignment is confirmed by the occurrence of a



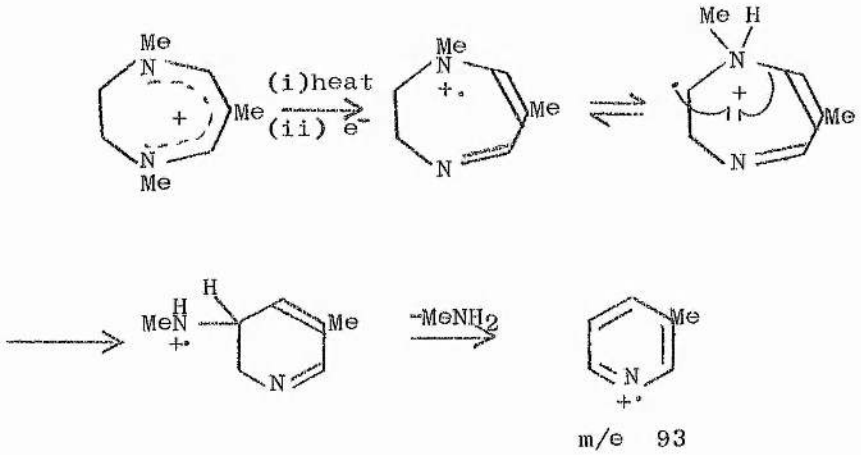
(68)



(69)

corresponding cluster of peaks centred at m/e 233 in the mass spectrum of the diphenyl derivative (62j). The 1,3-interaction necessary for this breakdown is probably enhanced by the rigidity of these dihydrodiazepines. A small peak at m/e 122 (relative intensity 27%) in the spectrum of the dimethyl compound may be due to the 1,4-diazepine (69) (Found,122.084255; $C_7H_{10}N_2$ requires 122.084394).

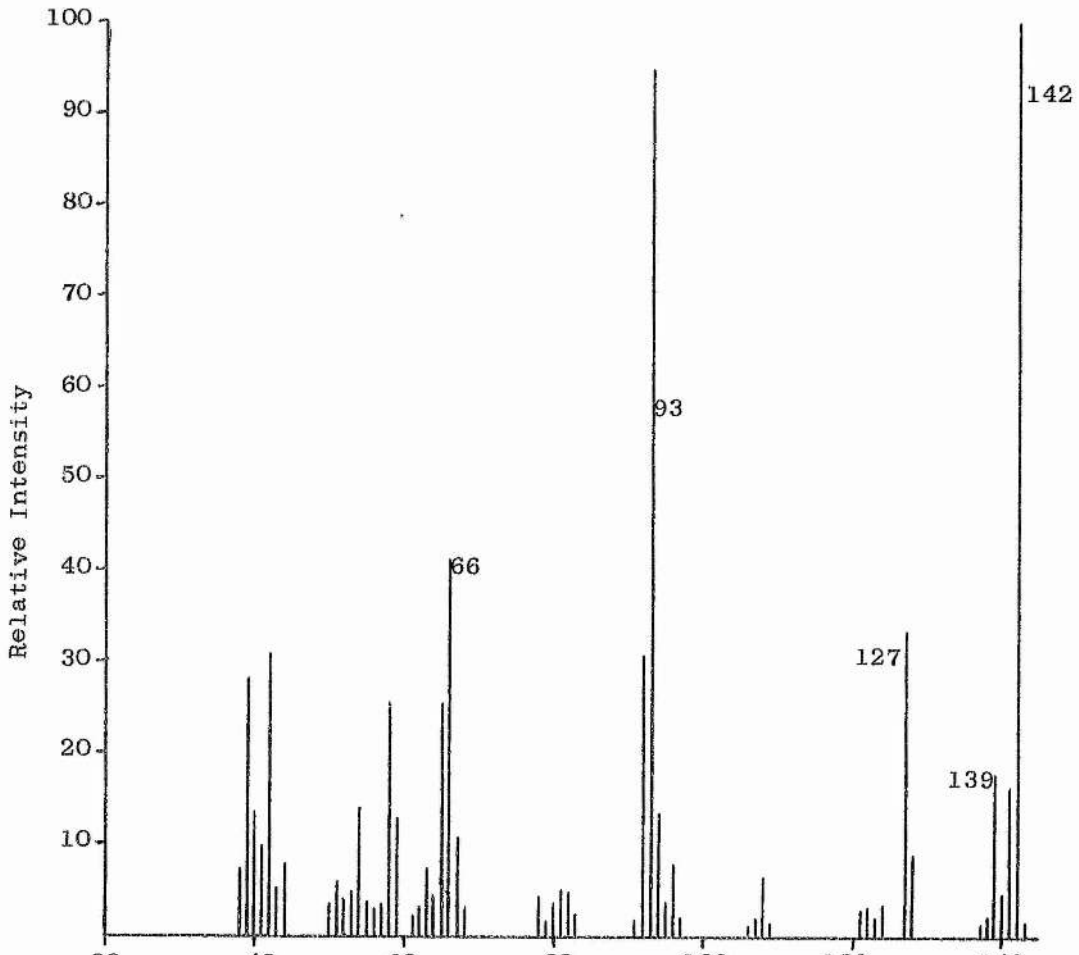
Atypical spectra are also shown by the 1,4(6)-methylated salts (62k) and (621) (Figure 8). The parent peak is characteristically at m/e 142 due to iodomethane (62k, Found, 141.928757; CH_3I requires 141.927946) or at 128 due to HI (62 1, Found, 127.912838; HI requires 127.912296), probably formed by thermal decomposition induced by the iodide counter-ion. The further decomposition of the heterocycles is also anomalous. Methylamine is eliminated, resulting in strong peaks at m/e 93 and m/e 79 in the spectra of (62k) and (62 1) respectively, which may be represented as pyridine derivatives (Scheme 4). (62k, Found, 93.057982, C_6H_7N requires 93.057846). Further evidence for this assignment is given by the direct loss of m/e 27 (HCN) from these species (62k, Found m^* 46.7; 93 ⟶ 66 requires m^* 46.8)[192].



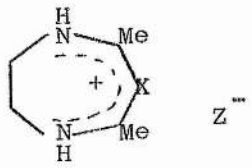
Scheme 4

The mass spectra of a selection of dihydrodiazepinium salts bearing electronegative substituents at the 6-position (70) were

Figure 8 Mass Spectrum of the 1,4,6-Trimethyldihydrodiazepinium Iodide (62k)



also recorded. The major breakdown process of these compounds



(70)

a, X = Cl, Z = I
b, X = Br, Z = Br
c, X = I, Z = I
d, X = NO_2, Z = I
e, X = OMe, Z = picrate

appears to be the loss of the 6-substituent, followed by the normal decomposition of the dihydrodiazepine nucleus. The spectrum of the 6-iodo derivative (70c) is exceptional (Figure 9). The only significant peaks are at m/e 250 (M_{base}, 100%), 128 (HI, 18%), 127 (I, 93%) and 63.5 (I^{2+}, 6%). It is probable that electron-impact in this case removes an electron from the iodo-substituent rather than from the dihydrodiazepine nucleus.

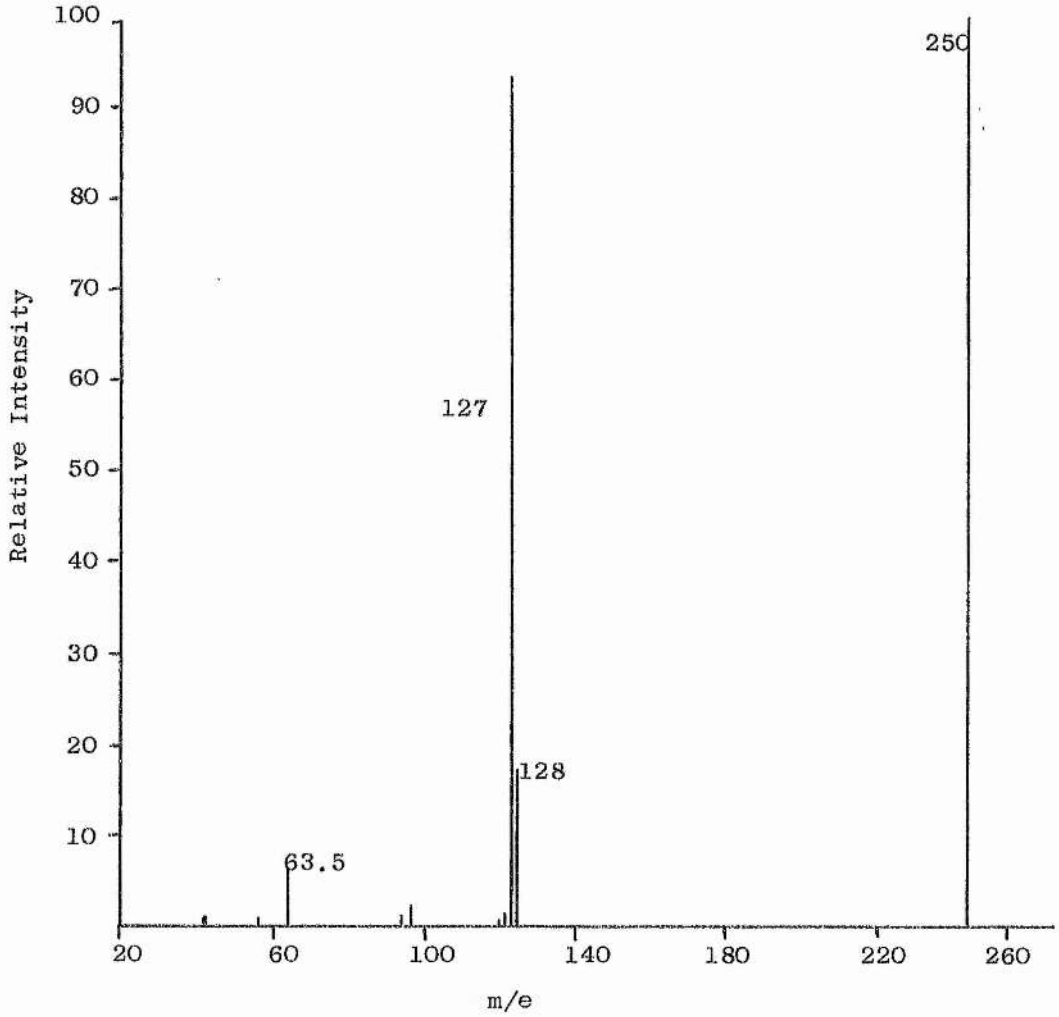


Figure 9 Mass Spectrum of the 6-Iododihydrodiazepinium Iodide (70c)

SECTION 3

STERIC EFFECTS IN THE BROMINATION OF DIHYDRODIAZEPINIUM SALTS[193]

Perhaps the most investigated meneidic reaction of dihydrodiazepinium cations is that of bromination[33,34]. The kinetics and mechanism of the substitution have been studied in detail for the 5,7-dimethyl-[31], 1,4,5,7-tetramethyl-[39] and 5-methyl-7-phenyl-[39] derivatives. In each case, second-order conditions in aqueous solution were used, and the rate of reaction monitored by the potentiometric method developed by Bell[194].

Under preparative conditions, however, bromination is usually accomplished in methanolic solution, and so the rate of reaction in this solvent is of interest. Further, the relatively high solubility of dihydrodiazepinium salts in methanol makes it possible to study a wide range of compounds under identical pseudo-first-order conditions. At these high concentrations the reactions are followed more conveniently by stopped flow techniques. Another advantage of methanol as a solvent for these studies is that its relatively low polarity (compared with water) increases the selectivity of the reagents, and hence increases the sensitivity of the technique as a method of determining small differences in the reactivity of different dihydrodiazepinium salts. Since the majority of known 6-unsubstituted dihydrodiazepines have relatively non-polar substituents, the rate of bromination in methanol is primarily a probe of the steric features adjacent to the reactive site of the heterocycle.

The stopped flow method is useful for reactions which are complete in 10 ms - 10 s. The principal features of the apparatus are outlined in Figure 10. The two reactant solutions are forced at the same rate, by means of syringes A and B, through the mixing chamber and via the spectrometer cell into the third syringe C.

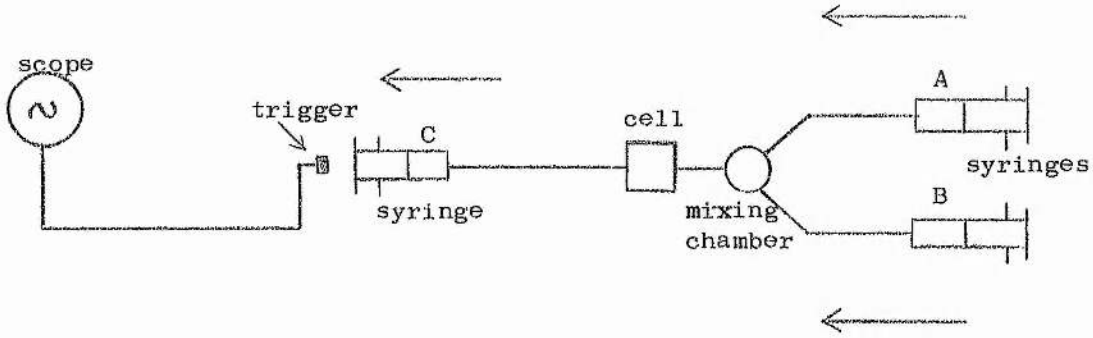


Figure 10

When this syringe becomes full, the flow of solutions is automatically stopped and simultaneously the oscilloscope is triggered. The trace follows the change in optical density at a fixed wavelength of the solution in the cell, as a function of the time of reaction. In the present studies, the decay of the bromine absorption at about 450 nm was monitored; reactions were first order in $[Br_2]$ (see experimental section) showing the presence of this species in the rate-determining step. Figure 11 shows a typical oscilloscope trace, and Figure 12 the corresponding first-order plot.

It should be emphasised that this investigation has little mechanistic significance. It is assumed that the bromine is used up solely by reaction with the dihydrodiazepinium cation at the 6-position. The rates of bromination of the dihydrodiazepines (71) are summarised in table 4.

Clearly the major steric influence on reaction at the 6-position will be the substituents at the neighbouring sites. Where these are large, the reaction rate should be reduced, and indeed the 5,7-diethyl derivative (71h) reacts more than ten times slower than its 5,7-dimethyl analogue (71a). Aryl groups at the 5- and 7-positions can interact conjugatively with the dihydrodiazepine ring only in an electron-donating manner[172] and so electronic effects would tend to increase reaction rate for these compounds. That the

Figure 11 Decay of Absorption at 420 nm by Reaction of the 2,2,5,7-Tetramethyldihydrodiazepinium Salt (71e) with Bromine

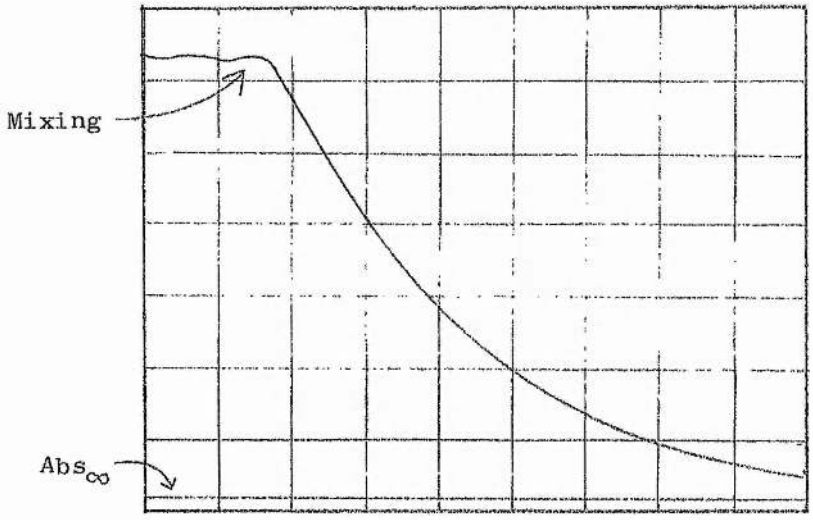
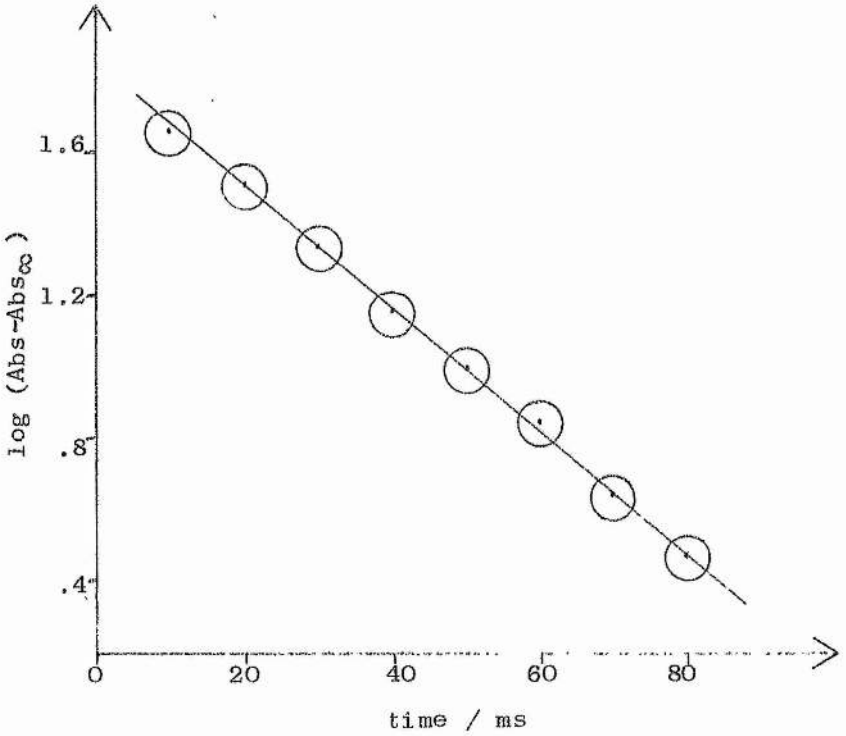
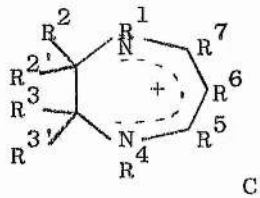


Figure 12 First-Order Plot for the Bromination Reaction of Figure 11





ClO_4^-

(71)

a, $R^5=R^7=Me$

b, 2,3-cyclohexano, $R^5=R^7=Me$

c, $R^1=R^5=R^7=Me$

d, $R^2=R^5=R^7=Me$

e, $R^2=R^{2'}=R^5=R^7=Me$

f, $R^1=R^4=Me$

g, $R^1=R^4=Ph, R^5=R^7=Me$

h, $R^5=R^7=Et$

i, $R^5=Me, R^7=Ph$

j, 2,3-cyclohexano, $R^5=Me, R^7=Ph$

k, $R^5=R^7=Ph$

l, $R^2=R^{2'}=Me, R^5=R^7=Ph$

m, $R^5=R^7=Me, R^6=Cl$

n, $R^5=R^7=Me, R^6=Br$

o, $R^5=R^7=Me, R^6=I$

p, $R^5=R^7=Me, R^6=NO_2$

(where unspecified, R = H)

Table 4 Rates of Reaction of the Dihydrodiazepines (61) with Bromine in Methanol

Compound	k/s^{-1}	Error %[v]	Rel. Rate[w]	Wavelength/nm
a	2600	4.5	1.00	420
b	3000	4.5	1.15	420
c	610	3	0.23	420
d	2300	3	0.88	420
e	750	2	0.29	420
g	1.4[x]	4.5	5.4×10^{-4}	450
h	210	1	0.081	420
i	53	2	0.020	420
j	48	3	0.018	420
k[y]	0.3	1	1.2×10^{-4}	450
l[y]	0.05	1	1.9×10^{-4}	450
m[y]	4.7×10^{-3}	3.2[z]	2×10^{-6}	450
n[y]	1.8×10^{-3}	1.6	7×10^{-7}	450

Notes
- v Estimated by the method of least squares
- w Rate relative to (71a) as standard
- x Absorption increased with time
- y Studied by conventional kinetic methods
- z Non-linear at start of reaction.

rate of the 5-methyl-7-phenyl compound (71i) is fifty times slower, and that for the 5,7-diphenyl derivative (71k) nearly ten thousand times slower than that for the corresponding 5,7-dimethyl-dihydrodiazepinium salt (71a), confirms the overwhelming steric

control of these reactions. The results also demonstrate the selectivity of the methanol as solvent. Bromination of (71i) in water is only 1.8 times slower than that of (71a)[39].

In contrast, aryl groups at the 1- and 4-positions of the dihydrodiazepine ring have necessarily an electron-withdrawing effect, and this may explain the low rate of reaction of the 1,4-diphenyl compound (71g). The product of the bromination of this salt under kinetic conditions (five times excess of dihydrodiazepine) was not identified; reaction can occur at the 6-position[17] and/or in the benzene ring[34].

The bromination of 1,4-dialkyldihydrodiazepines was more conventional. Although the reaction of the dimethyl compound (71f) was too rapid for quantitative work by stopped flow methods ($t_{\frac{1}{2}}$ ca. 5 ms, k ca. 4000 s^{-1}), bromination was readily accomplished preparatively. The dihydrodiazepinium cation is almost certainly the reactive species in this case, and since the rate is of the same order as that of related dihydrodiazepines [eg. (71a)], it is probable that bromination takes place *via* the cation in these instances as well.

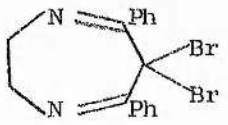
The buttressing effect[195] of groups at the 1- and 4-positions may also increase the crowding in the region of the 6-position. Molecular models suggest that there will be repulsion between the adjacent methyl groups in the 1,5,7-trimethyl compound (71c) tending to block access to the reactive centre. Indeed, a slight reduction in bromination rate is observed.

The normal ring inversion process of the dihydrodiazepinium system, discussed in section 1, is not possible in the case of 2,3-cyclohexano- derivatives, because the fused ring confers a rigidity on the system (cf. cyclohexane and *trans*-decalin). Internal motion, however, has little effect on reactivity, since compounds (71b) and (71j) consume bromine at similar rates to their 2,3-unsubstituted analogues, (71a) and (71i) respectively. Equally,

the fused ring is apparently too remote to exert any steric or electronic influence on the reaction.

More surprising is the slight, but reproduceable, rate reduction due to the presence of 2,2-dimethyl substituents especially since one 2-methyl group alone has little effect (table 4). If these results have a valid structural explanation, then the data for the 2,3-cyclohexano- derivatives imply that it must be the axial-methyl group which inhibits the reaction, possibly by acting as a barrier to incoming bromine molecules.

Dibromination of the 5,7-dimethyldihydrodiazepine (71a) has been observed kinetically in aqueous solution[31]. It was found that the rate of the second bromination step was about one hundredth that of the first. The reaction has also been carried out preparatively on the dihydrodiazepine base in non-polar media, and the 6,6-dibromodihydrodiazepine (72) was isolated[34]. Under the



(72)

present conditions, the 6-bromo derivative (71n) consumed further bromine, but the reaction was very slow indeed (table 4). It was nevertheless significantly faster than any reaction of bromine with the solvent[195a]. Once again, first-order kinetics were observed, but the mechanism of the reaction was not further investigated. The 6-chloro analogue (71m) reacted at a similar rate, but the 6-nitro derivative (71p) was apparently inert.

The reaction of the 6-iodo compound (71o) with bromine in methanol containing sodium bromide was anomalous. A comparatively rapid increase in absorption in the range 400-550 nm was observed, due to the formation of molecular iodine. Two mechanisms are possible (Scheme 5). The first involves the reverse of one method of preparation of 6-iododihydrodiazepines[34], followed by the oxidation

A 

$$2I^- + Br_2 \longrightarrow I_2 + 2Br^-$$

B 

$$2IBr \rightleftharpoons I_2 + Br_2$$

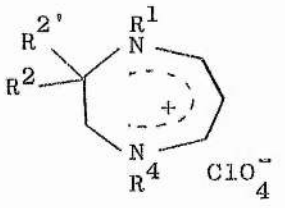
Scheme 5

of liberated iodide by bromine. The second involves nucleophilic attack by Br^- on the iodo-substituent [34,44], but requires no oxidising agent for the ultimate formation of I_2. Since the absorption increases only in the presence of bromine, it would appear that mechanism A predominates.

SECTION 4

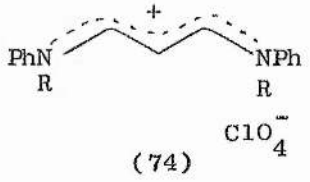
THE PREPARATION OF CYCLIC PRODUCTS BY REACTION OF 1,5-DIARYL-1,5-DIAZAPENTADIENIUM SALTS WITH DIAMINES

The general method of synthesis of dihydrodiazepines, by the acid-catalysed condensation of 1,2-diamines with β-dicarbonyl compounds, is generally inefficient for the preparation of 5,7-unsubstituted derivatives[17,18]. It has been suggested[13] that these compounds are kinetically unstable to hydrolysis under the conditions which thermodynamically favour their formation. Clearly a technique involving neutral conditions in preferably non-aqueous media is required. In one isolated report of such a reaction, the 1,4-dimethyldihydrodiazepine (73a) was made in good yield by the action of N,N'-dimethylethylenediamine on the 1,5-diazapentadienium salt (74a)[26]. Conditions of high dilution (ca. 0.003 M) in



a, $R^1=R^4=Me$
b, $R^1=Me$
c, $R^2=Me$
d, $R^1=R^4=CH_2Ph$
e, $R^n=H$

(73) (where unspecified, R=H)



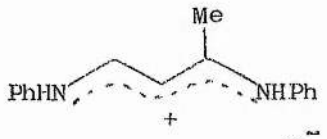
(74)

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

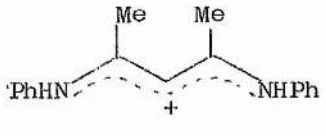
methanol were used in the synthesis. The success of the reaction depends upon the activity towards nucleophiles of the 2(4) positions of vinamidines (to which reference has already been made in the introduction) and also upon the leaving ability of amines (cf. ref. 73,74,75,97,101,112 etc). It is a special case of a transamination reaction. A transformation of this type represents another example of the meneidic character of these compounds, since the 1,5-diaza-pentadienium system as a whole is regenerated in the product.

In this study, the scope of the synthetic route was first explored before some mechanistic points were examined using mono-amine model compounds.

The open-chain salt (74a) is best made (rather inconveniently) from propynal by the standard route[65]. Some related derivatives including (74b)[47] and (74c) are much more readily prepared, however, by direct acid-catalysed condensation of the amine with 1,1,3,3-tetraethoxypropane. The 2-methyl derivative (75, Z = ClO_4, picrate) could be made in a similar manner; the dimethyl analogue (76) was synthesised from the mono-anil of acetylacetone by the method of Scheibe[64].



(75)



(76)

It proved possible to obtain 1,4-dimethyldihydrodiazepinium perchlorate (73a) from the readily available malondialdehyde dianil (74b). Under similar conditions, the 1-methyl (73b), 2-methyl (73c) and 1,4-dibenzyl (73d) analogues were also prepared. The isolation of the methyl derivatives (73b) and (73c) completes the series of possible mono-methyl dihydrodiazepines[18,22]. The preparation of the 1,4-dibenzyl compound (73d) is also of interest, since attempts to make it by condensation methods led to alternative products[17].

The synthesis is most useful, however, for the preparation of the unsubstituted dihydrodiazepinium perchlorate (73e)[27], which can be isolated in >70% yield from the salts (74b) or (74c). The latter precursor is preferred, since it gives a cleaner product. Excessively high dilution conditions are not required for this reaction; concentrations of up to 0.03 M give satisfactory results. The chemical properties of the dihydrodiazepine (73e), the parent member of the series, are discussed in section 5.

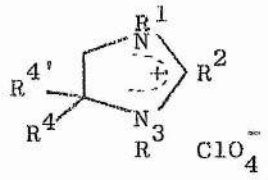
In general, the method is less efficient for the preparation of unsymmetrical derivatives, especially those with large substituents. Indeed, solid dihydrodiazepinium salts could not be isolated from the reaction of certain diamines with the dianils

(74) and (75) (cf. ref. 196). Thus, although from the nmr spectrum of the product, the seven-membered ring was formed by reaction of 1,2-diamino-2-methylpropane with the salts (74b) or (74c), the heterocycle could not be separated from contaminant and remained as a brown oil. Solvents other than methanol, including propan-2-ol, and acetonitrile gave similar results. To a certain extent, the crystallinity of the product may affect its isolation. 5-Methyldihydrodiazepine could not be obtained from (75, Z = ClO_4), but was readily isolated from the corresponding picrate. Conversely, 1,2-diaminocyclohexane did not give a dihydrodiazepine at all on reaction with the dianil (74c); the nmr spectrum of the resulting solid showed the continued presence of phenyl groups. From these and other negative results, it seems likely that the cyclisation is sensitive to small steric influences in the region of the reactive centres.

1,4-Diphenyldihydrodiazepinium salts are easily obtained in a crude state by standard methods[19], but purification of the product is difficult. By treating 1,2-dianilinoethane with the dianil (74c), the latter was recovered unchanged (38%) as the only ether-insoluble product; the lack of reactivity is probably due to the low nucleophilic character of the anilino-nitrogen atoms. We may therefore conclude that the success of these syntheses depends, at least in part, on the reactant diamine being a significantly better nucleophile than the arylamine leaving group. Thiourea was similarly unreactive.

In general, dihydrodiazepines with 5,7-methyl substituents are readily made directly from acetylacetone, but the 1,4,5,7-tetramethyl compound is an exception[17]. Since 5,7-dimethyldihydrodiazepinium perchlorate could be isolated by reaction of the dianil (76) with ethylenediamine, the corresponding reaction of N,N'dimethylethylenediamine was also studied. No diazepine was formed, but instead a compound with λ_{max} 235 nm was obtained in

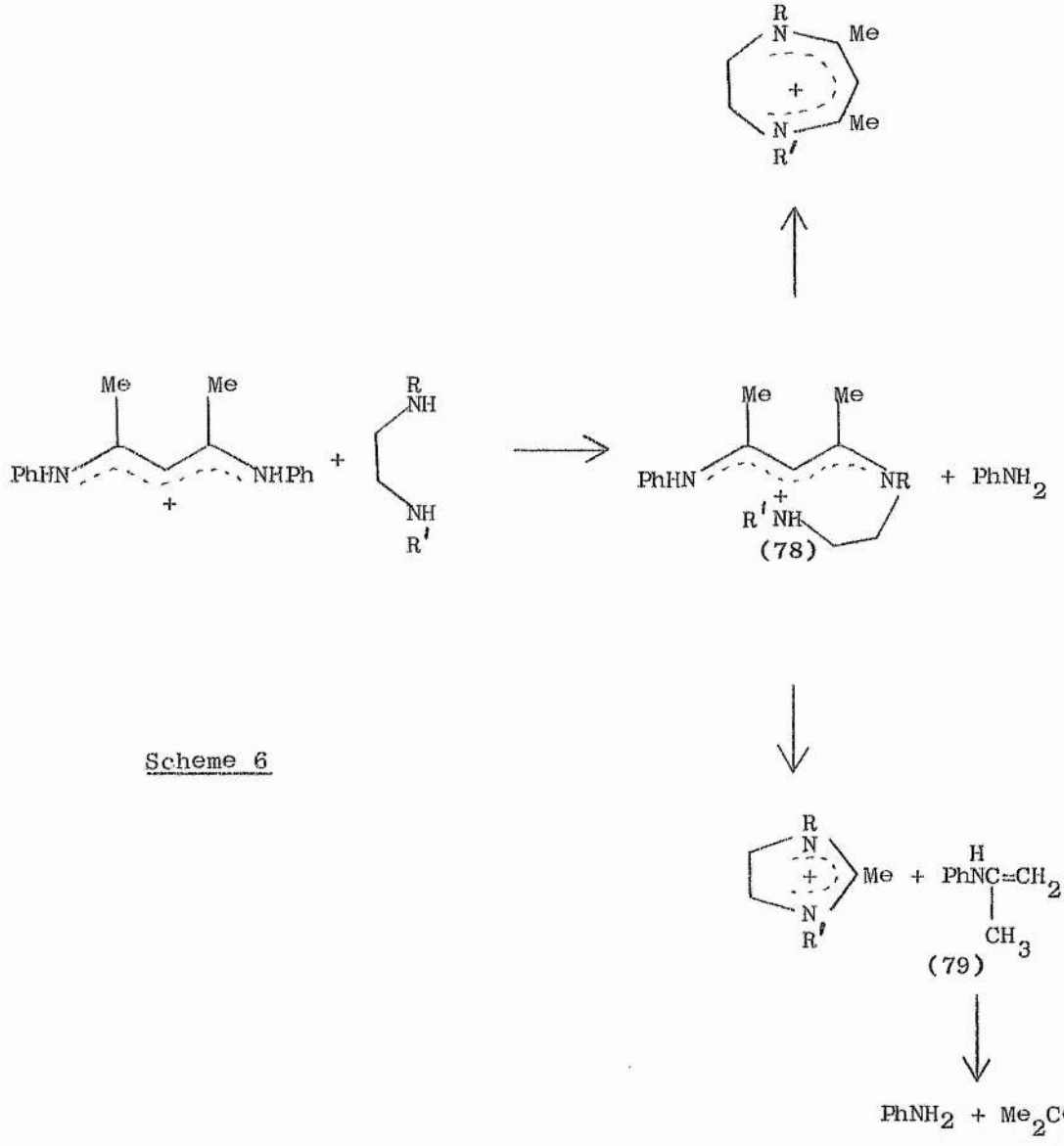
good yield. This was identified as the imidazolinium salt (77a) on the basis of its nmr and mass spectra, and its elemental analysis. Such species have been obtained previously in reactions expected to lead to dihydrodiazepines[17]. (See also page 107). Benzimidazoles are common side-products in 1,5-benzodiazepine formation[45].



(77)

a, $R^1 = R^2 = R^3 = Me$
b, $R^1 = R^2 = Me$
c, $R^2 = R^4 = R^{4'} = Me$
d, $R^2 = Me$

(where unspecified, R = H)



Scheme 6

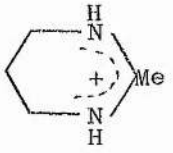
The probable mechanism of the reaction is outlined in Scheme 6. The free amine group (R'NH-) in the intermediate (78) may attack either the α-carbon (yielding an imidazolinium salt), or the γ-carbon (yielding a diazepinium salt). N-methylethylenediamine gave the imidazoline (77b) as the only isolable product, while the imidazoline (77c) was obtained from 1,2-diamino-2-methylpropane. In the latter case, the uv spectrum of the crude solid showed the presence of some dihydrodiazepine as a side-product. A dihydrodiazepine is also produced, albeit in low yield, by reaction of 1,2-diaminocyclohexane with the dianil (76). In this case, the formation of the five-membered ring is inhibited by the trans-stereochemistry of the fused rings in the product.

These results prompted a more detailed investigation of the reaction between ethylenediamine itself and the 1,5-diazapentadienium salt (76). The nmr spectrum of the crude product showed that its major constituent (70%) was the dihydrodiazepinium salt, but that the imidazoline (77d) was indeed also present (30%). The latter compound could not be isolated in a pure form from the mixture, and was characterised by mass spectrometry. The proportion of five-membered ring in the product could be increased to ca. 60% by the use of propan-2-ol instead of methanol as the solvent for the reaction. This may be due to simple temperature effects; a mixture containing only 40% imidazoline was formed when the propan-2-ol was kept at 59°. It is not unreasonable that bond fission to give the ring-contracted product is more favoured at high temperatures.

As might be expected, the pyrimidine (80) was formed by the reaction of the dianil (76) with 1,3-diaminopropane. Such tetrahydropyrimidines are commonly made by the reaction of 1,3-diamines with amidines[197], a further example of the use of amines as leaving groups.

It may be seen from Scheme 6 that the most likely product

to be formed along with the imidazoline by cleavage of the dianil (76), is the enamine (79), which would probably solvolyse under



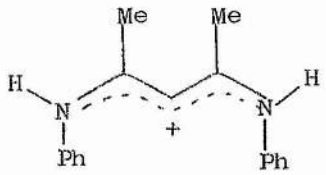
(80)

the reaction conditions to aniline and acetone. No attempt was made to isolate the latter product, but work-up of the ethereal mother-liquors yielded just two molar equivalents of aniline, consistent with the proposed mechanism.

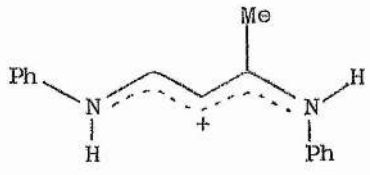
Before considering the reasons for the ready cleavage of the dianil (76), a reaction which is not observed in the chemistry of the 2,4-unsubstituted analogues (74), even under favourable conditions, it is necessary to make a digression to discuss the structure of these open-chain dianils. From the large CHCH and CHNH vicinal coupling constants (J ca. 12 Hz) in the nmr spectrum, the all-trans stereochemistry of the 1,5-diphenyl compound (74b) may be unambiguously assigned. The second N-phenyl groups in (74c) have little conjugative interaction with the vinamidinium system since the uv spectra of (74b) and (74c) are almost identical. That these groups are twisted out of plane is confirmed by the nmr spectrum of the tetraphenyl compound (74c). The 3-proton resonance occurs more than 1 ppm upfield of the corresponding signal in (74b), consistent with strong anisotropic shielding. The out-of-plane phenyl groups are therefore trans- to the 2- and 4-hydrogen atoms.

Anisotropic shielding effects are also evident in the spectrum of the dimethyl compound (76) when compared with that of (75). The value of the vicinal coupling constants (J_{34}, J_{45} ca. 12 Hz) in the latter compound confirms trans- geometry for the unsubstituted portion of the molecule. Further, the close correspondence of the methyl-group chemical shifts [(75), τ 7.24; (76), τ 7.29] suggests similar environments. That the methyl groups in (76) occur as a sharp singlet effectively eliminates the

possibility of a sickle-shape for these molecules. The 3-proton resonance of (75) is deshielded by 0.36 ppm relative to the corresponding signal in (76). Of the two possible all-trans structures for these molecules, this observation is consistent only with the N-phenyl group(s) being trans to the methyl and twisted out of plane, causing shielding effects on the 3-proton [structures (75A) and (76A)]. These effects are of comparable magnitude to



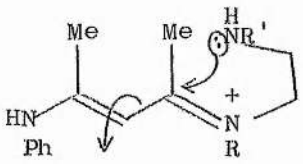
(76A)



(75A)

that discussed above in the spectra of the 2,4-unsubstituted compounds (74). The inefficient phenyl-vinamidine conjugative interaction is confirmed by the similarity in the uv spectra of the 1,5-diphenyl-2,4-dimethyl compound (76) (λ_{max} 346 nm), and its 1,1,2,4,6,6-hexamethyl analogue (λ_{max} 345 nm)[78].

The formation of 5-membered ring products, therefore, may be partially explained by the geometry of the molecule. γ-Attack (Scheme 6) by the free amino-group (-NHR') of the intermediate (78) is unfavourable because of the steric effects of the methyl groups and of the neighbouring phenyl group. An α-attack, to give the imidazoline, is substantially less hindered and moreover the formation of a linear S_Ni transition state (81) may be encouraged by the adjacent methyl group.



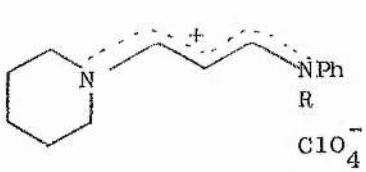
(81)

The nmr spectra of the imidazolinium salts closely resemble those of dihydrodiazepines. This electronic similarity has been used previously in bromination work, where the 2-position of the

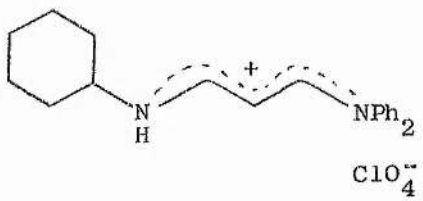
five-membered ring was taken as a model for the 5(7) positions in dihydrodiazepinium salts[36,39]. Parallels also exist in the mass spectral fragmentation of the heterocycles. The major breakdown pattern in the spectra of imidazolinium salts is again the loss of the (N^1-C^5) fragment. It is of interest that loss of $Me_2C{=}\dot{N}$ is preferred over that of $H_2C{=}N\cdot$ in the spectrum of the trimethyl derivative (77c), as found for dihydrodiazepinium salts.

A number of anomalies have arisen in the preparation of dihydrodiazepinium salts from 1,5-diazapentadienes. The necessity for high dilution conditions in the preparation of a seven-membered ring is curious, while the inefficiency of the syntheses for unsymmetrical compounds remains to be explained. In an attempt to answer these points, the reactions of the dianils (74b) and especially (74c) with monoamines were investigated. The substitution of two moles of N-methylaniline by piperidine from the dianil (74a) has been previously reported[66], while the replacement of only one mole could be achieved from 2-aryl-1,5-diazapentadienium salts[198]. This last result may be analogous to the low reactivity of carbonyl groups in aryl ketones.

It was therefore surprising to find that the treatment of the dianils (74b) and (74c) with two moles of piperidine under the same high dilution conditions used for dihydrodiazepine synthesis, led exclusively to the mono-substitution products (82a) and (82b) respectively. Similarly (83) was prepared by reaction of (74c)



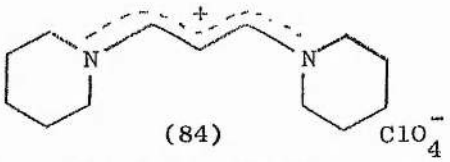
(82) a, R=H
b, R=Ph



(83)

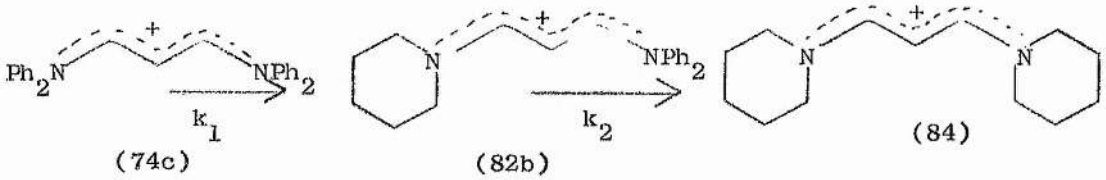
and cyclohexylamine. That high dilution conditions are not necessary for these reactions was demonstrated by the isolation of (82b) in high yield by direct reaction at ambient temperature.

Further substitution, yielding (84), could be effected by excess piperidine; attempts to prepare unsymmetrical N-alkyl-N'(alkyl)'-1,5-diazapentadienium salts were unsuccessful.



(84) ClO_4^-

The reactions of the diphenylamine derivatives (74c) and (82b) with piperidine were chosen for kinetic study since deprotonation of these salts is not possible. The stability of the mono-substitution product (82b), even in the presence of 100 times excess piperidine, is emphasised by the tight isosbestic point at 363 nm in the uv spectrum of the reacting solution (Figure 13). Quantitative experiments indicate that the initial substitution is 570 times faster than the second displacement (Scheme 7). The rate difference is probably due to the increase



(74c) (82b) (84)

Scheme 7

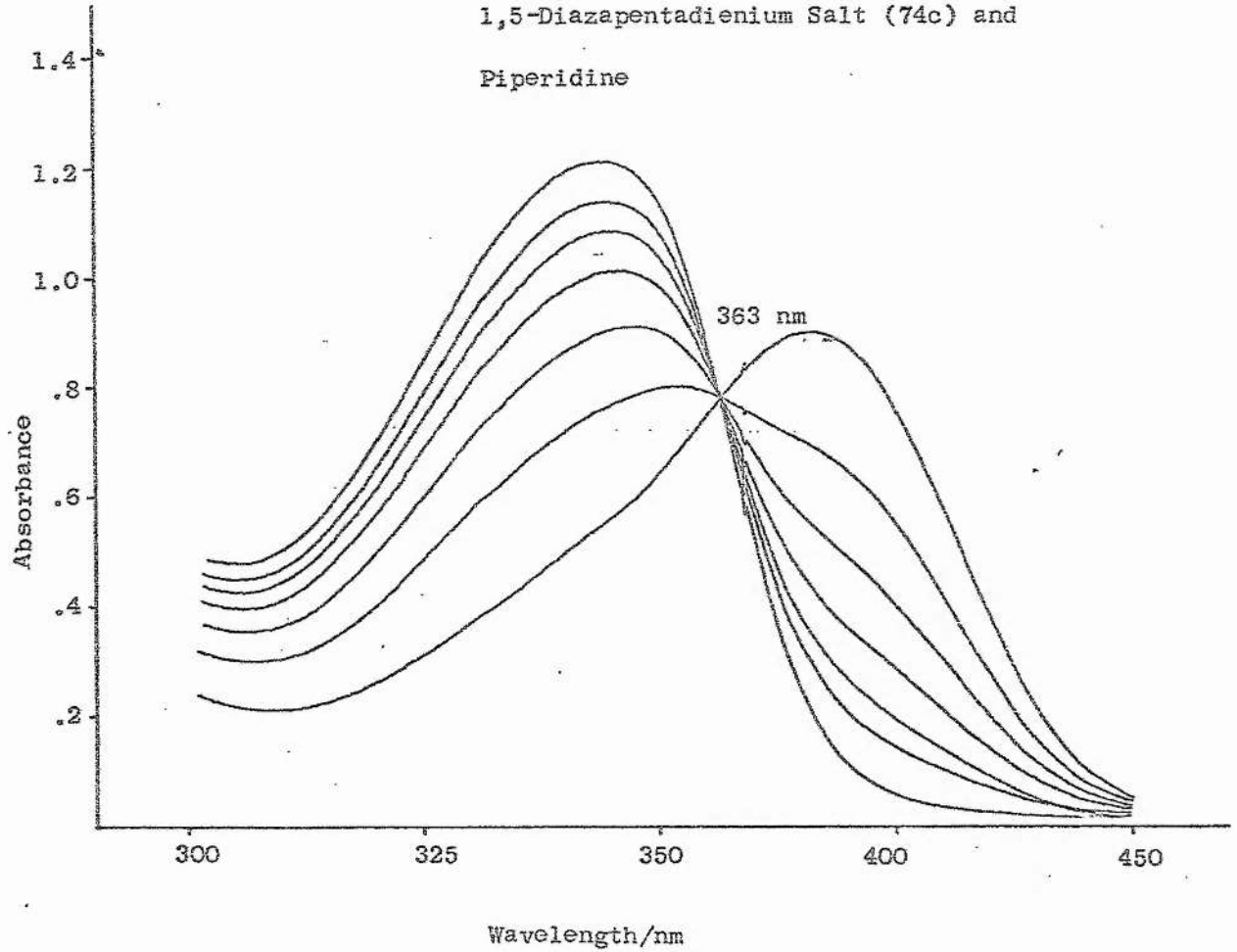
$k_1 = 1.86 \pm 0.02\ s^{-1}$

$k_2 = (3.26 \pm 0.08) \times 10^{-3}\ s^{-1}$

in electron density in the alkyl substituted compound (82b) as compared with the starting material (74c), thereby decreasing the electrophilicity of the reactive centres. This result explains the need for high dilution conditions in the dihydrodiazepine synthesis. When both reactants are present in high concentration, polymerisation rather than cyclisation is kinetically favoured.

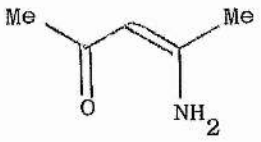
The reaction rate is also affected by small steric changes in the neighbourhood of the reactive site. Thus 2-methylpiperidine reacts with (74c) at ca. one fifteenth the rate of piperidine itself ($k = 0.120 \pm 0.002\ s^{-1}$). In the case of unsymmetrical

Figure 13 UV Spectra of Reacting Solution of the 1,5-Diazapentadienium Salt (74c) and Piperidine



diamines, such rate differences may determine whether clean cyclisation or polymerisation occurs predominantly. Cyclisation in these cases may be favoured by the use of a more polar solvent, such as acetonitrile or acetic acid, but this aspect of the reactions was not investigated.

Dihydrodiazepines may also be obtained by reaction of oxo-enamines with diamines. Thus the 5,7-dimethyl derivative was formed in good yield by reaction of ethylenediamine with (85) or (86) in acetic acid.



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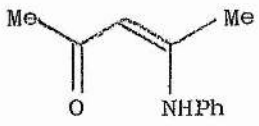
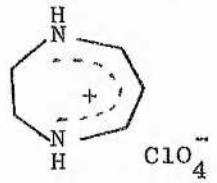


(86)

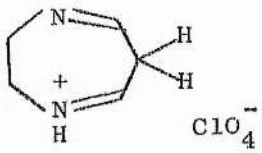
SECTION 5

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

Although the unsubstituted dihydrodiazepinium salt (87) has been reported previously[18], a systematic investigation of its properties has awaited an efficient synthetic route. The ready availability of this compound by the high dilution procedure[27] (section 4) has now made this study feasible.



(87)

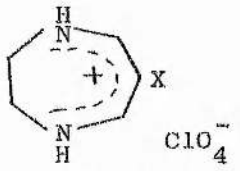


(87A)

The melting-point of (87) has been earlier reported as 79-80°[18]. The much higher values now found (ca. 250°) presumably reflect the previous trouble in the isolation and purification of the compound. Its uv spectrum is also of interest since it has formed the basis of empirical rules for calculating the spectral parameters of substituted dihydrodiazepines[18]. The reported extinction coefficient of 11200 is rather lower than the calculated value (13500); measurements on a carefully recrystallised sample show that the coefficient is more probably 14300 ± 200. This high value may reflect an increase in planarity of the totally unsubstituted ring as compared with its substituted analogues, or perhaps may be due to the very low concentration of the non-absorbing bis-imine tautomer (87A) in this case.

The nmr spectrum of the dihydrodiazepine (87), when recorded in [^{2}H]TFA solution, shows no signals corresponding to the 1,4 or 6-protons, due to their rapid exchange with the medium. After 9 days in solution no decomposition had occurred, and the ratio of the 5,7-proton integral to that of the methylene protons was unchanged, demonstrating once more the vanishingly low activity of these positions towards electrophiles[30,39].

As with other dihydrodiazepinium cations, (87) is active towards electrophiles at the 6-position. As well as exchanging in deuteriated acid, it may be brominated by molecular bromine in methanol to give the 6-bromo derivative (88b). The 6-chloro- and 6-iodo compounds (88a) and (88c) are obtained in excellent yield by heating the parent compound (87) briefly with the appropriate N-halogenosuccinimide in acetic acid. Attempts to



(88)

a, X = Cl
b, X = Br
c, X = I

make a 6-nitro derivative by the methods used for other dihydrodiazepines[35] have hitherto been unsuccessful. In contrast to other dihydrodiazepines, the parent compound (87) is apparently decomposed irreversibly by strong acids.

The 6-halogeno derivatives (88) show similar spectroscopic properties. The high-wavelength maximum in the uv spectrum of the bromo compound (88b) is at 360 nm, a bathochromic shift of 29 nm relative to the 6-unsubstituted compound. The corresponding shift in the 5,7-dimethyldihydrodiazepine series is 24 nm. The 6-bromo and 6-iodo compounds (88b) and (88c) also have subsidiary low-wavelength maxima, as do their 5,7-substituted analogues. The chemical shift of the 5,7-protons in the nmr spectra of the halogeno derivatives (88) is apparently independent of the identity of the halogen; the vicinal coupling constant J_{17} is about 8.2 Hz, and is observable only in the presence of acid.

As found with 6-iodo-5,7-dimethyldihydrodiazepinium salts[199], the iodo-compound (88c) is slowly protodeiodinated in acid solution; this is shown by the appearance of the 6-proton signal in the nmr spectrum of the solution.

Characteristically, 6-unsubstituted dihydrodiazepines are inert towards nucleophiles. The parent compound (87), however, reacts readily with excess piperidine to give the open-chain

compound (84), thereby demonstrating unequivocably the electrophilicity of the 5- and 7-positions of the ring in the absence of other effects. A kinetic study of this reaction in methanol showed isosbestic points at 265 nm and 334 nm (Figure 14); hence there can be no stable intermediate in the reaction. The 5,7-dimethyldihydrodiazepinium perchlorate was apparently completely inert to piperidine under similar conditions. In any event, after extended reaction times, the absorption maximum due to this dihydrodiazepinium salt had changed by $< 5\%$. The methyl groups, therefore, inhibit the reaction by a factor of at least 20000; the effect is probably of a steric nature, but electronic influences may also be involved.

As a further example of activity towards nucleophiles, the dihydrodiazepinium salt (87) was heated with an excess of N,N'-dimethylethylenediamine, and the 1,4-dimethyldihydrodiazepinium salt was obtained in reasonable yield. This 'transdiazepination' reaction is not, however, of general synthetic utility; an attempt to prepare the elusive 2,2-dimethyl derivative from 1,2-diamino-2-methylpropane and the salt (87) was unsuccessful.

The reactions of the 6-halogeno compounds (88) with nucleophiles were also anomalous. Whereas the 6-bromo-5,7-dimethyl derivative reacts rapidly with methoxide ion to give the substitution product[33], the 6-bromo compound (88b) was recovered unchanged after 30 min under reflux. Spectroscopic techniques confirm that the only reaction to take place in the alkoxide solution is the conversion of the dihydrodiazepinium salt to the free base.

The lack of reactivity towards nucleophiles of the 6-position in the compounds (88) may be rationalised by the proposed mechanism of these reactions (Scheme 1, page 5), which is thought to involve the bis-imine tautomer of the heterocycle. Since this tautomer, if present, would be highly reactive, its formation must be suppressed in the absence of substituents on the 5- and 7-positions.

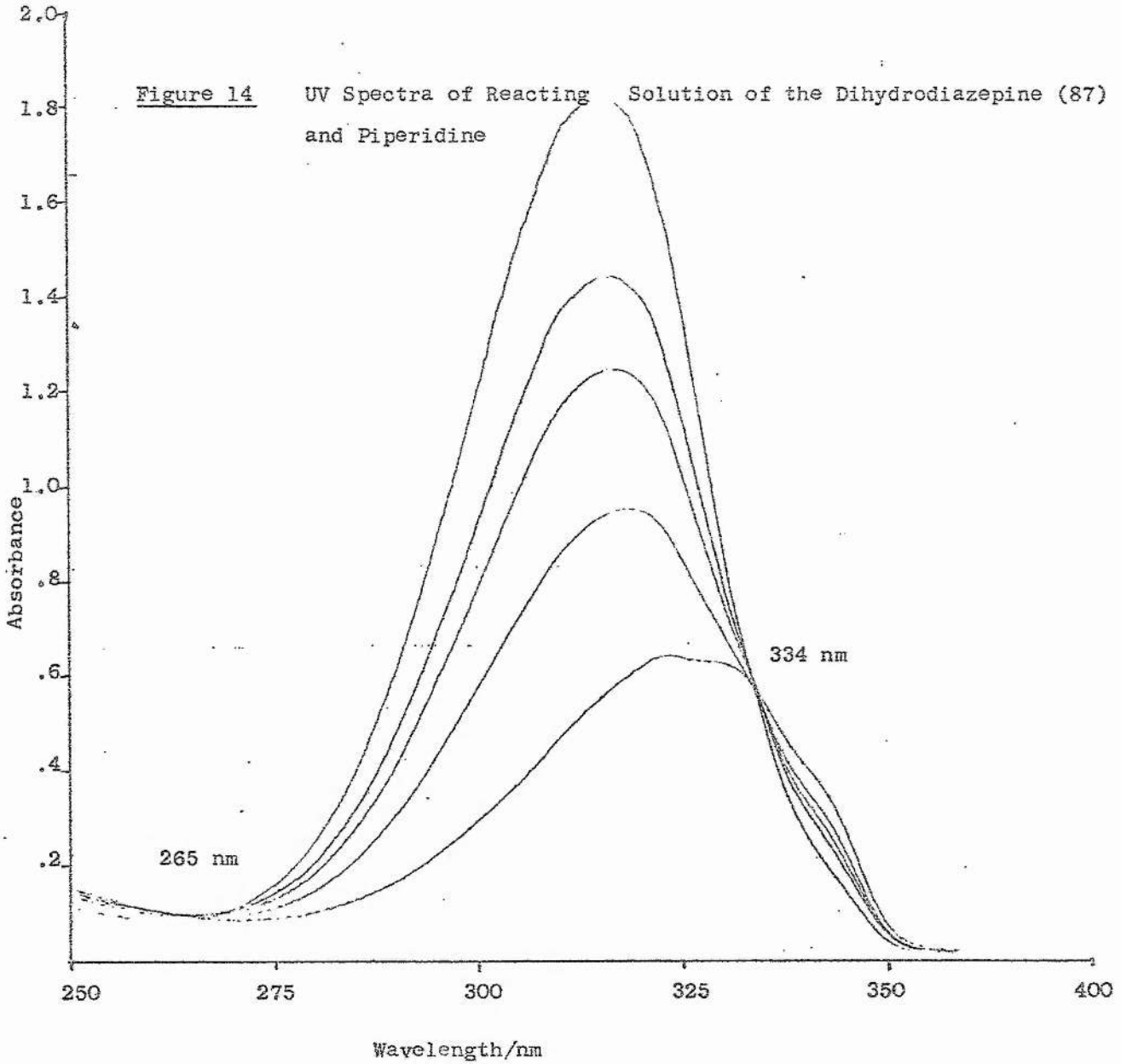


Figure 14 UV Spectra of Reacting Solution of the Dihydrodiazepine (87) and Piperidine

That the bis-imine is relatively favoured in the presence of these substituents is not surprising on steric grounds, because of the relief of two coplanar vicinal interactions. A low concentration of bis-imine was proposed earlier to account for the high extinction coefficient of the dihydrodiazepine (87).

The action of thiourea on the 6-halogeno compounds (88b) and (88c) was also briefly investigated. It is known[44] that the 5,7-dimethyl analogues of these dihydrodiazepines react by 'abnormal' substitution to give the 6-unsubstituted compound (Scheme 1). Not surprisingly, the bromo-derivative (88b) was recovered unchanged after 23 h under reflux with thiourea in ethanol. Under similar conditions the iodo-compound (88c) did undergo protodeiodination, but the same result was obtained in the absence of the nucleophile, suggesting that the reaction is in fact a slow thermal decomposition.

Hence two anomalous properties of dihydrodiazepines in general, the reactivity of the 6-position and unreactivity of the 5(7) positions towards nucleophiles, are not inherent properties of the ring system itself, but rather a consequence of the importance of substituent effects in the chemistry of these compounds.

DISCUSSION

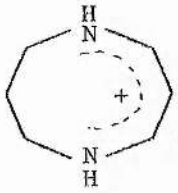
PART 2

DIHYDROPYRIMIDINES

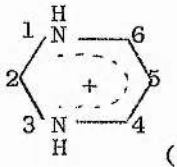
SECTION 1

1,2-DIHYDROPYRIMIDINES

In view of the interesting properties shown by dihydrodiazepinium salts, it is of interest to speculate on the importance of the well-defined geometry of the seven-membered ring in these reactions. The 1,5-diazapentadienium system, held in a planar configuration, represents the active part of the molecule and so the groups merely preserving this geometry should be chemically irrelevant. Hence



(89)

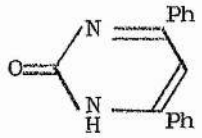


(90)

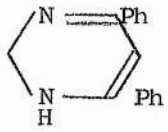
replacement of the methylene carbons at positions 2 and 3 in the dihydrodiazepine with a one- or a three-methylene bridge may little affect the characteristic properties of the compounds, unless the diazapentadienium system is distorted thereby. Thus the tetrahydrodiazocinium ion (89), probably cannot comply with the planarity requirements of the system, and so 1,2-dihydropyrimidinium salts (90) were chosen as possible examples of 'nor-dihydrodiazepines'.

1,2-Dihydropyrimidines have never been studied in detail, and only two rather specialised synthetic routes are available. Reduction of the 2-oxopyrimidine (91) with lithium aluminium hydride is reported to yield the dihydropyrimidine (92) (isolated as its picrate), which could be oxidised to 4,6-diphenylpyrimidine by potassium permanganate[200]. Pyrimidines without the 2-oxo substituent show variable reactivity towards the reducing agent, but 1,2-dihydropyrimidines are not obtained[201,202].

The second route to these compounds involves the 'curious'[203] reaction of a ketoacetal and a ketone with ammonia in the presence of ammonium nitrate[52,53]. This was first reported by Hoffmann and Schulze for the 'self'-condensation of 2-oxobutyraldehyde-dimethylacetal[52] (Scheme 8, R = Me, R' = $CH_2CH(OMe)_2$), but later

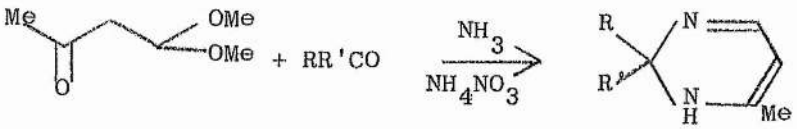


(91)



(92)

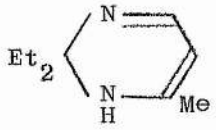
work showed that pyrimidines with more conventional 2-substituents could be made by the addition of excess ketone to the reaction mixture[53] (eg. Scheme 8, R = R' = Et). The mechanism of this reaction remains uninvestigated.



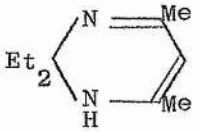
Scheme 8

In this study, the dihydropyrimidines were made by the method of Hoffmann[53]. Salts were isolated, their spectroscopic properties discussed and their activity towards electrophiles and nucleophiles reported.

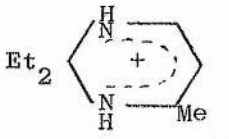
Of the various 2,2-substituted derivatives prepared by Hoffmann and Muehle[53], the 2,2-diethyl-4-methyl compound (93) was chosen. Also, because the 5,7-dimethyldihydrodiazepine has been the most fully studied member of that series, the corresponding 2,2-diethyl-4,6-dimethyldihydropyrimidine (94) was prepared. In this case, the action of ammonia on a mixture of diethyl ketone and a monoketal of acetylacetone in the presence of ammonium nitrate gave the dihydropyrimidine as a semi-solid mass in 63% yield. Both the dihydropyrimidine bases were unstable at room temperature, even when stored in anhydrous conditions, but could be conveniently kept for long periods in a deep-freeze, or under dry-ice. Because of high solubility, the perchlorate salts (95) and (96) (Z = ClO_4) were unfortunately not obtained. The halides (95a) and (95b), however, were readily made by the action of the appropriate gaseous hydrogen halide on an ether solution of the base. Under similar conditions, the dimethyl compound (94) yielded only oils; both



(93)

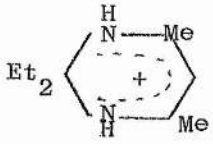


(94)



a, Z=Cl
b, Z=Br
c, Z=picrate

(95)

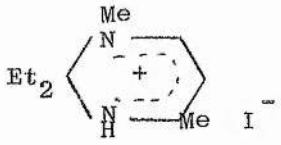


Z=picrate

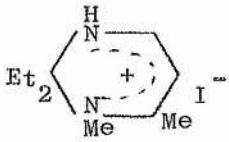
(96)

dihydropyrimidines (93) and (94) gave stable crystalline picrates.

The bases (93) and (94) reacted with excess iodomethane to give N-methyl derivatives. The isomers (97) and (98) are possible products from the methylation of (93), but the first was formed exclusively. This assignment is possible from the nmr spectrum of



(97)

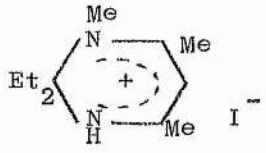


(98)

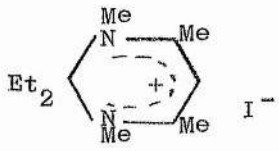
the product which shows a double-doublet for the 5-proton (J 6.4 Hz, 2.0 Hz), showing coupling to the 6-proton and to the N-H. The 6-proton, however, appears as a sharp doublet due to coupling to the 5-proton only, and so must be adjacent to the N-methyl group. The formation of the isomer (97) is not unexpected on steric grounds. The nmr spectrum of this compound, when recorded in TFA solution, shows a complex multiplet for the methylene protons of the ethyl groups and not a simple quartet. INDOR experiments confirm that this is due to non-equivalence of these protons caused by the pseudo-asymmetry of the 2-carbon atom of the ring.

Methylation of the dimethyldihydropyrimidine (94) gave a 3:1 mixture of the tri- and tetra-methyl derivatives (99) and (100), which were not separated. The trimethyl salt formed initially must

equilibrate with unreacted base to give some of the base corresponding to (99), which may then be further methylated to give (100). The



(99)



(100)

production of this overcrowded tetramethyl derivative is surprising in view of the difficulties encountered in preparing a 1,4,5,7-tetramethyldihydrodiazepine[17]. It may reflect reduced substituent interaction due to the smaller bond-angles of the six-membered ring.

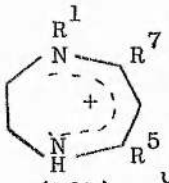
Since these dihydropyrimidinium salts show similar structural features to dihydrodiazepinium ions, it is of interest to compare their spectral properties. Unfortunately, direct comparisons are not possible since information is seldom available for species with corresponding counter-ions and solvent. Nevertheless, the remarkable electronic similarity of the two systems is clear from tables 5 and 6, which list nmr data for dihydropyrimidinium and dihydrodiazepinium ions respectively. The protons at positions α- to the nitrogen atoms resonate at τ 2.3-2.6, while the electron-rich meso-positions show signals between τ 4.95 and 5.05. Methyl groups attached to the α-position or to the nitrogen also have similar chemical shifts whether in a seven or a six-membered ring environment.

The major differences which are apparent from tables 5 and 6 lie in the values of the vicinal coupling constants. The relevance of these to the shape of the ring has been discussed in part 1, where it was found that dihydrodiazepinium cations show a typically 'six-membered ring' geometry around the conjugated portion. The rather smaller coupling constants observed for the dihydropyrimidinium ions are consistent with a more constrained system, with bond angles intermediate between those of typical five- and six-membered rings.

Table 5 Chemical Shifts and Coupling Constants for Dihydropyrimidinium Salts.

Compound	Solvent	τ[4,(6)]	τ(5)	τ(1-Me)	τ(4-Me)	J_{56} /Hz	J_{16} /Hz	J_{15} /Hz	Anion
95a	$[^2H_6]$DMSO	2.35	4.95	-	7.82	5.8	6.8	1.3	Cl^-
95a	$C[^2H]Cl_3$	2.63	5.11	-	7.71				Cl^-
95c	$[^2H_6]$DMSO	2.31	4.87	-	7.85				picrate
96	$C[^2H]Cl_3$	-	5.01	-	7.80	-	-	1.8	picrate
97	$C[^2H]Cl_3$	2.31	5.12	6.75	7.62	6.4	-	2.0	I^-
99	$C[^2H]Cl_3$	-	5.13	6.87	?	-	-		I^-

Table 6 Chemical Shifts and Coupling Constants for the Dihydrodiazepinium Salts (101)



(101)

a, R^5=Me
b, R_1=R^7=Me
c, R^1=R^5=Me
d, R^1=R^5=R^7=Me
(where unspecified, R=H)

Compound	Solvent	τ[5,(7)]	τ(6)	τ(1-Me)	τ(5-Me)	J_{67} /Hz	J_{17} /Hz	J_{16} /Hz	Anion
101a	$[^2H_6]$DMSO	2.57	5.06	-	7.80	8.2	7.8	1.7	picrate
101a[22]	$[^2H_6]$DMSO	2.60	5.10	-	7.82	8			picrate
101b	$[^2H_6]$DMSO	-	5.08	-	7.83	-	-	1.8	ClO_4^-
101c	$[^2H_6]$DMSO	2.53	5.13	6.67	7.82	8.3	-	2.1	picrate
101d	$[^2H_6]$DMSO /TFA	-	4.96	6.73	7.84 7.78	-	-	1.7	ClO_4^-

Table 7 UV Spectra of Dihydropyrimidines

Compound	Anion	λ_{max}/nm	ε
95a	Cl^-	356	4600
93	base	349	-
96	Cl^- x	350	-
94	base	345	-
97	I^-	374	5100

x, not isolated

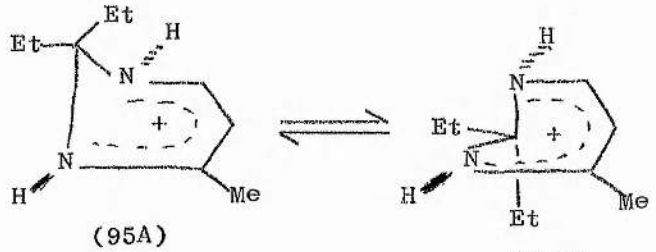
Table 8 UV Spectra of Dihydrodiazepinium Salts

Compound	Anion	λ_{max}/nm	ε
101a	Br^- x	323	-
101b[18]	ClO_4^-	323	15900
101d	ClO_4^-	331	18500

x, not isolated

It is of interest that 1,5-diazapentadiene bases, which adopt an all-cis chelate structure in non-polar solvents, show vicinal coupling constants of similar magnitude[72] (J 5.5-6.0 Hz). The complete delocalisation of electrons in dihydropyrimidinium ions is suggested by the similarity in the magnitude of J_{56} and J_{16} for the 4-methyl derivative (95).

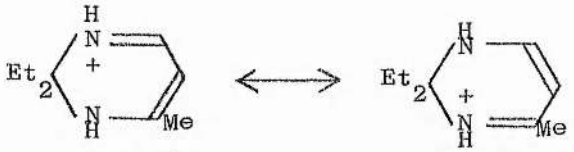
The observation of small 'meta' coupling from the NH to the 5-position establishes the approximate planarity of this portion of the ring. The possibility of exchange processes involving the groups at the 2-position was investigated, but there was no change in the spectrum of (95a) at -60°. The system may either be rigid or equilibrating rapidly between the two possible forms (95A) and (95B). Similar results were found by Olah[150] for the 4-methylbenzenium ion, which is superficially related to these compounds.



(95A) (95B)

The NH protons of the 4-methyl derivative (95) occur as a broad singlet and a broad doublet at τ -0.36 and τ -0.10 respectively when the solvent is $C[^2H]Cl_3$. Spin decoupling of the 6-proton causes the doublet to reduce to a singlet, and so the NH adjacent to the 4-methyl group is apparently the downfield one despite the inductive effect of the latter. A similar effect was found in the

spectrum of the 5-bromo analogue of (95). It is possible that of the two canonical forms (95C) $\longleftrightarrow$ (95D), the latter is more important because of the electron-donating properties of the methyl group. Hence the 3-NH, the more positive centre, resonates at lower field.

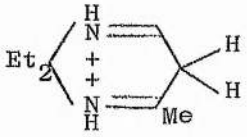


(95C) (95D)

The uv spectra of methanolic solutions of the dihydropyrimidines and related dihydrodiazepines are given in tables 7 and 8; the spectra of picrate salts are not discussed because of the large absorption due to the counter-ion. The dihydropyrimidines show pronounced bathochromic shifts compared with the dihydrodiazepines and the extinction coefficients of the former are rather low. It is possible that this last observation may be explained by an increased strain on the 1,5-diazapentadienium system reducing the efficiency of conjugation; the extinction coefficients of dihydrodiazepines themselves are markedly lower than those of strain-free all-trans vinamidinium salts.

A feature of the uv spectra of dihydrodiazepinium salts is the regular effect of substituents on the value of λ_{max}. The empirical rules derived for these compounds[18] cannot be aplied directly to the dihydropyrimidine series, although the trends are similar. For example an N-methyl group causes a bathochromic shift of 6 nm in the spectrum of a dihydrodiazepine; in the case of dihydropyrimidines, a shift of 18 nm is observed.

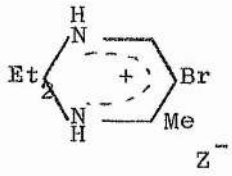
Dihydrodiazepinium ions are reversibly protonated in concentrated sulphuric acid and similar behaviour is found for the 4-methyl derivative (95). The dication, presumably (102), had weak absorption maxima at 335 nm and 262 nm; dilution with water regenerated the monocation (λ_{max} 356 nm). The same reversible behaviour was shown, even after the sulphuric acid solution had been set aside for 10 days.



(102)

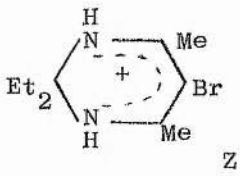
Whereas protonation of dihydrodiazepinium ions occurs only under conditions of high acidity[16], dihydropyrimidinium dications are apparently formed in relatively weak acids. In TFA solution, for example, the 5-proton signal of (95) occurs as a broad singlet, probably due to the exchange reaction (95) + $H^+ \rightleftharpoons$ (102). The 6-proton signal is also broad under these conditions, since coupling with the N-H and with the 5-proton is affected. It therefore appears that the dihydropyrimidine monocation is stable over a more restricted pH range than the corresponding dihydrodiazepine; pK_a data for dihydropyrimidines are not available, but would be of considerable interest.

As might be expected on the basis of dihydrodiazepine chemistry, dihydropyrimidines are active towards electrophiles at the 5-(meso)-position, and substitution products are normally isolated. Thus compounds (95), (96) and (97) show deuterium exchange in [^{2}H]TFA, and 5-bromo derivatives of the 4-methyl and 4,6-dimethyldihydropyrimidines (95) and (96) may be prepared by reaction with bromine in methanol. In the case of the picrate (96), the bromide salt (104a) is exclusively formed, the counter



a, Z=Cl
b, Z=Br

(103)

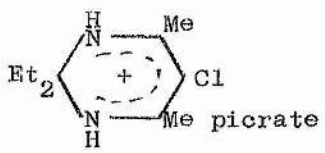


a, Z=Br
b, Z=picrate

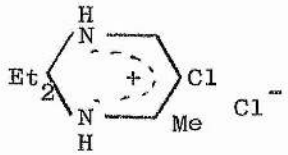
(104)

ions acting as a buffer for the liberated hydrogen ions. Reaction of the bromide (95b) with bromine yields the 5-bromo bromide (103b), but the chloride salt (103a) may be prepared by the action of N-bromosuccinimide on (95a). N-Halogenosuccinimides also react with the picrate (96) to give the picrates(104b) and (105); the chloro

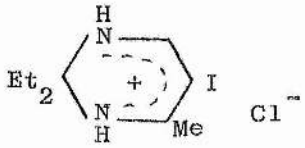
and iodo derivatives (106) and (107) are obtained similarly. The



(105)



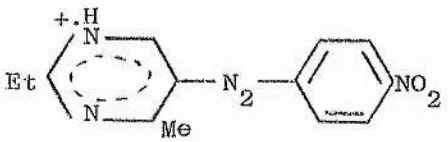
(106)



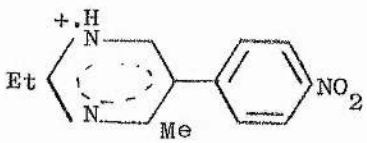
(107)

5-chloro chloride (106) could not be isolated reproduceably as a solid, and was characterised by mass spectrometry. Reaction of the bromide (95b) with N-chlorosuccinimide in an attempt to prepare a 5-chlorodihydropyrimidinium bromide gave instead the bromo-compound (103a). This is thought to involve the chlorination of the bromide counter-ion (by either an electrophilic or a radical mechanism) to give a species which will act preferentially as a brominating agent.

Attempts were made to nitrate the dihydropyrimidines (95) and (96), using a variety of conditions, but none were successful. Similarly, preliminary diazo-coupling experiments using compound (95) and p-nitrophenyldiazonium tetrafluoroborate gave complex mixtures of products. However, the mass spectrum of the crude product tentatively indicated that coupling and Gomberg-arylation could have taken place, the ions possibly corresponding to breakdown fragments (108) and (109) being identified by high resolution (Found, 272.114207;



(108)



(109)

(108) requires 272.114743. Found, 244.109428; (109) requires 244.108597).

The observation of electrophilic substitution reactions in dihydropyrimidines is by no means surprising when considered in the light of dihydrodiazepine chemistry. Nevertheless, simple, fully 'aromatic' pyrimidines are notably resistant to electrophiles, and

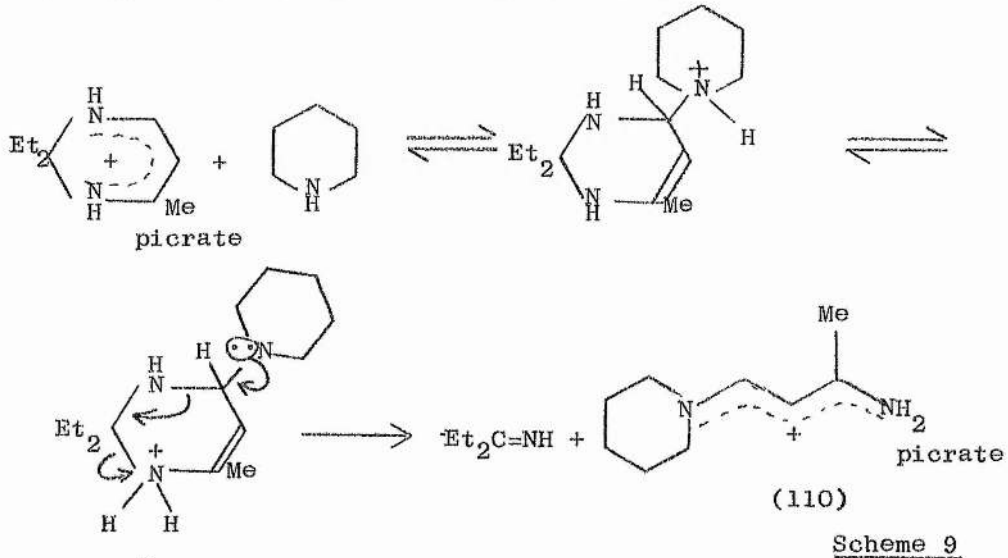
so we have a remarkable example of a series of reduced aromatic compounds showing classical aromatic reactivity to a much higher degree than the parent system.

The nmr spectra of the 5-halogeno-derivatives show the expected downfield shift of the signals due to the groups at the 4- and 6-positions, as compared with the 5-unsubstituted compounds. The total absence of the 5-proton signal confirms that this is the position of substitution. When recorded in [^{2}H]-chloroform, the 4-methyldihydropyrimidines show coupling between the 6-proton and the 1-NH. (J_{16} (103b) 7.4 Hz, J_{16} (106) 7.6 Hz, J_{16} (107) 6.6 Hz). The coupling constants are rather higher than for the meso-unsubstituted compound; the same situation obtains for dihydrodiazepines. In the uv spectra, the 5-halogeno substituent causes a bathochromic effect of 20-25 nm, which is quantitatively similar to that found in the dihydrodiazepine series. As before, the extinction coefficients are lower than might be expected.

As discussed in Part 1, dihydrodiazepinium salts without substituents at the 5- and 7-positions react readily with N-nucleophiles, while those with blocking groups at these positions are inert. The dihydropyrimidine (95) has a free 6-position and might therefore be active towards nucleophiles. That the bromide (95b) indeed reacted with piperidine was clear from the uv spectrum of the reactant solution, although no pure product could be isolated. Use of the picrate (95c) under similar conditons, however, gave the mono-replacement product (110) as a yellow solid. This result emphasises again the dominating effect of methyl groups on the control of these nucleophilic reactions. A probable mechanism is given in Scheme 9; after the initial attack of piperidine, the driving force is probably the formation of diethyl-ketimine, with concomitant regeneration of the vinamidinium system. No such mechanism can be drawn for the reaction of the 5-methyldihydro-diazepinium ion (111) with piperidine, and indeed it was recovered

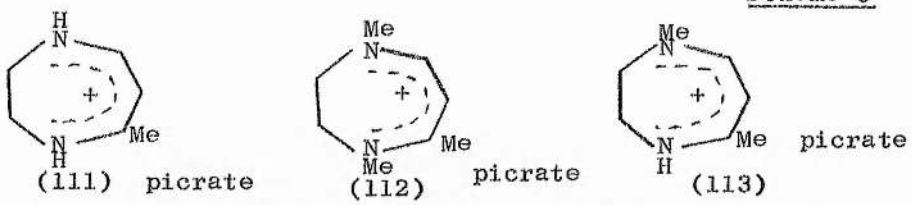
unchanged, even after extended reaction times.

The attack of a nucleophile at the 4-position of the dihydropyrimidine (95) can be induced when such a reaction leads to



(110)

Scheme 9



(111) (112) (113)

dihydrodiazepinium salts. Thus the compounds (111)-(113) were prepared by the action of the appropriate ethylenediamine on the picrate (95c). The exclusive formation of (113) rather than its 1,7-dimethyl isomer, is clear from its nmr spectrum in [$^2H_6$]DMSO/TFA, which shows a double-doublet at τ 5.13 due to the 6-proton coupling to the 7-proton (J_{67} 8.4 Hz) and the N-H (J_{46} 2.1 Hz). The 7-proton resonates as a sharp doublet at τ 2.53, and so is adjacent to the nitrogen carrying the methyl group. Two factors combine to favour the production of (113). The initial attack of the -NHMe group on the unsubstituted 6-position is consistent with its high nucleophilicity, while the subsequent attack of the $-NH_2$ group on the 4-position is favourable on steric grounds.

There was no change in the uv spectrum of the mixture when the 4,6-dimethyl derivative (96) was treated with piperidine. Attempted work-up was complicated by the isolation of piperidinium picrate, but some unreacted dihydropyrimidine was recovered.

6-Halogenodihydrodiazepines show variable reactivity towards nucleophiles, with substitution and protodehalogenation being competing reactions. The latter usually predominates only in sterically hindered situations, and so it is surprising that the 5-bromo-4-methyldihydropyrimidine (103) is smoothly debrominated by thiourea. Analogous experiments with the 4,6-dimethyl compound (104a) were inconclusive, although debromination is strongly suspected from the uv spectrum of the reactant solution. Whereas 6-chloro-5,7-dimethyldihydrodiazepinium perchlorate gives an S-isothiuronium salt with thiourea[44], the dihydropyrimidinium salt (105) was recovered unchanged despite long reaction times. Clearly such reactions are as complex as those of the dihydrodiazepine series and a more detailed study is necessary before any conclusions can be drawn.

In the mass spectra of the dihydropyrimidinium salts studied, the major breakdown pathway is the loss of one 2-ethyl group from the base to give a pyrimidinium cation (114) (Scheme 10). (For

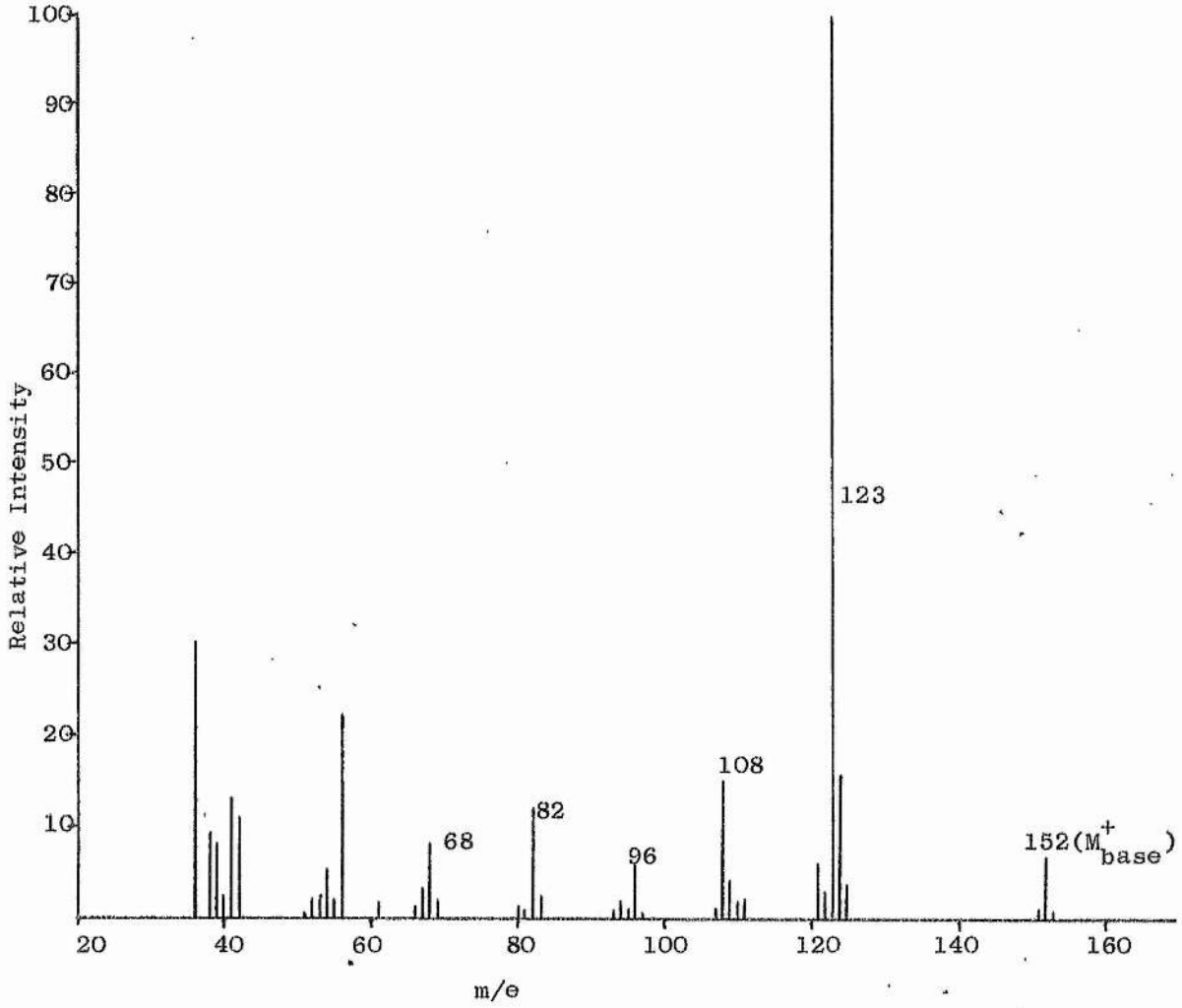
Scheme 10 (114)

example, (96): Found, 137.107372. $C_8H_{12}N_2$ requires 137.107868. Found m^* 113; 166 ⟶ 137 requires m^* 113.0). This facile decomposition is important even for the 5-halogeno compounds; loss of the 5-substituent is a subsequent process. The importance of this breakdown confirms that 'aromatic reactivity' does not necessarily parallel 'aromatic stability' since the dihydropyrimidines show this strong tendency to revert to the fully conjugated pyrimidine structure.

The further decomposition of the pyrimidinium cation (114) gives rise to peaks of relatively low intensity (Figure 15), and that due to the trivial loss of a methyl group is probably the

most important. (For example (96); Found m^* 108.7; 137 $\longrightarrow$ 122 requires m^* 108.6). The breakdown of the ring itself characteristically involves the loss of cyanide molecules. Thus peaks at m/e 68, 82 and 96 in the spectrum of 4-methyldihydropyrimidinium chloride (Figure 15) correspond to the cleavage of EtCN, MeCN and HCN molecules respectively.

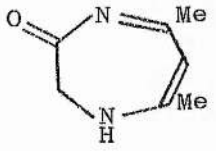
Figure 15 Mass Spectrum of the 4-Methyldihydropyrimidinium Chloride (95a)



SECTION 2

1,2-DIHYDRO-2-OXO- and 1,2-DIHYDRO-2-THIOPYRIMIDINES

In the previous section, the chemistry of the vinamidinium system was studied in a geometrical environment different from that found in dihydrodiazepines. In contrast, it is of interest to vary the electronic nature of the substituents adjacent to the system and investigate the changes in properties. To accomplish this end, attempts have been made to produce 2,3-dihydro-2-oxo-1,4-diazepines (115) by condensation of glycinamide with acetylacetone,

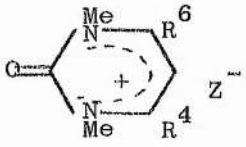


(115)

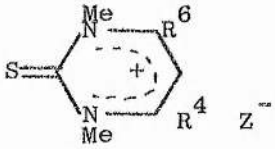
(116) (117)

but no cyclic products were obtained[16]. More recently, one such dihydrodiazepine has been synthesised, but its properties were not studied[204]. However, six-membered ring analogues, which are 1,2-dihydro-2-oxopyrimidines (or 2-pyrimidinones) (116) are readily made by the condensation of a urea with a β-dicarbonyl compound.

These oxopyrimidines exist in equilibrium with the hydroxy tautomer (117), and so it is clearly imperative to lock the compounds in the oxo-form so that the properties of the 1,5-diazapentadienium system may be unambiguously studied. Hence a series of 1,3-dimethyl derivatives (118), (119) and (120) were prepared; the effect of the 2-substituent was further investigated by the synthesis of the corresponding 2-thio compounds (121), (122) and (123).

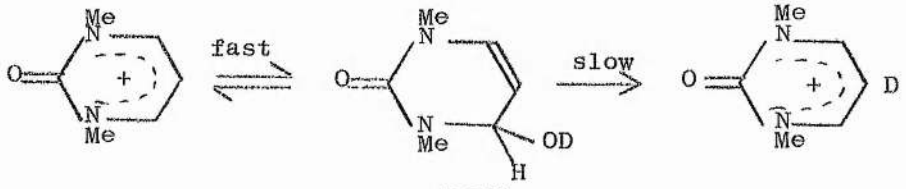


(118), $R^4=R^6=H$
(119), $R^4=Me, R^6=H$
(120), $R^4=R^6=Me$



(121) $R^4=R^6=H$
(122) $R^4=Me, R^6=H$
(123) $R^4=R^6=Me$

Although these latter compounds were previously unknown, the 2-pyrimidinones have been previously studied. Hopkins and co-workers[205] assigned the structure (118) (Z=I) to a compound prepared by exhaustive methylation of the sodium salt of 2-hydroxypyrimidine. The properties of the dimethyl compound (118) have been included in a series of investigations by Katritzky and co-workers on the kinetics and mechanism of electrophilic substitution of heteroaromatic compounds[206,207,208]. It may be deuteriated at the 5-(meso-)position in acid solution[206,207], but in contrast to deuteriation of unperturbed vinamidines, the reaction is extremely slow. ($k = 1.5 \times 10^{-2} h^{-1}$ at pH 1.25, 107°) Nevertheless, the exchange was faster than expected on the basis of the deactivating effect of a ring nitrogen atom, since the rate was 10^4 times greater than that for the 3- or 5-positions in 2-oxopyridine. From this anomalous rate, and from further kinetic evidence, the mechanism cannot proceed by a simple electrophilic substitution, and the sequence shown in Scheme 11 was proposed. The covalent hydrate (124) was observed spectroscopically in basic solution[207]. The



(124)

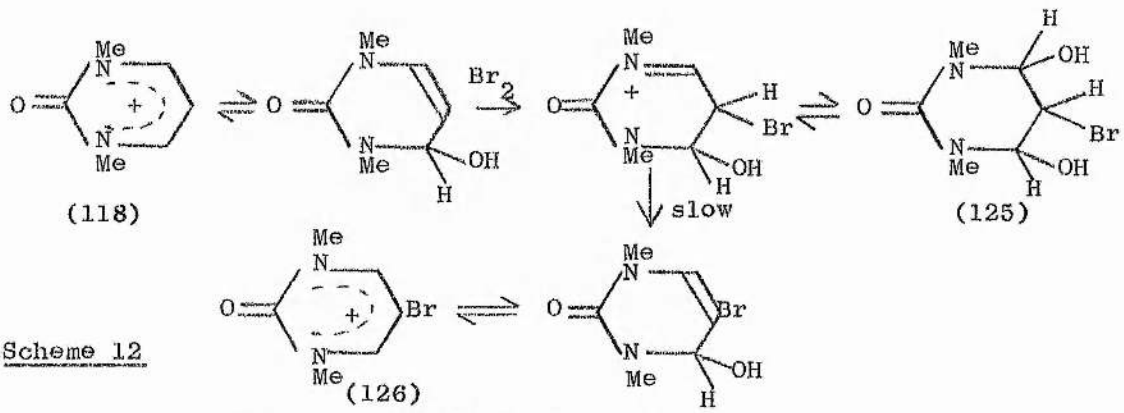
Scheme 11

un-methylated and mono-N-methylpyrimidinones followed similar kinetics, hence the mechanism for these derivatives is also that of Scheme 11.

This reaction may at once be contrasted with dihydrodiazepine chemistry. The observed pyrimidinone exchange is slower by a factor of ca. 10^{10} than that reported for 5,7-dimethyldihydrodiazepine, and hence any reaction by a 'simple' mechanism must be slower still. The stability of the pseudobase (124) is also different; as reported in Part 1, there is no stable intermediate in the reaction of

dihydrodiazepinium salts with piperidine to give open-chain 1,5-diazapentadienium salts.

While this present work was being carried out, Tee and Banerjee reported the bromination of the pyrimidinone (118) at the 5-position, and proposed the pseudo-base mechanism (Scheme 12) to account for the observed spectroscopic changes during the reaction[209,210]. The decomposition of the intermediate (125) was studied kinetically; the results were complicated by the formation



Scheme 12

of a dibromo compound (127)(R=H), which could also be isolated. Again

the contrast with dihydrodiazepines is apparent.

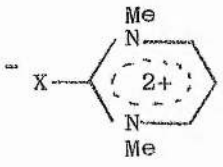
The tendency of 2-pyrimidinone cations to lose their charge - as in the ready formation of the pseudo-base (124) - is also found in the reactions of the 4- and 6-methylated derivatives (119) and (120). Treatment of the salts with mild base gives the exo-methylene compounds (128), (R=H, R=Me)[211]; the activity of these methyl groups is further exemplified by their ability to couple with diazonium salts, and to form condensation products with aromatic aldehydes[211]. Such reactivity of 5(7)-methyl groups is without precedent in the studies of dihydrodiazepines or dihydropyrimidines.

In general, the chemistry of these 2-oxo- and 2-thiopyrimidines may be rationalised as a competition between two meneidic systems

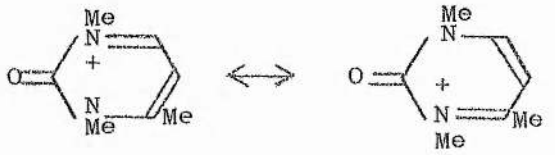
in the molecule (viz. the 1,5-diazapentadienium, and the urea) for the nitrogen lone pair. This may alternatively be visualised as a competition between the 'Y-aromaticity'[212] of the urea, and the 'quasi-aromaticity'[3] of the remainder of the molecule. In this study, the properties of the pyrimidines (118)-(123) are discussed with reference to the chemistry of unperturbed vinamidinium salts. The reactions of the salts with electrophiles and nucleophiles are reported, along with the chemical and spectroscopic properties of the products.

The 2-oxo- and 2-thiopyrimidines (118)-(123) ($Z=HSO_4$) were all readily prepared by the condensation of N,N'-dimethylurea or N,N'-dimethylthiourea with the appropriate β-carbonyl compound (or its acetal precursor) in the presence of excess sulphuric acid (cf. reference 211). Bromide or perchlorate salts could be made similarly; iodide salts were conveniently prepared from the perchlorates by reaction with methanolic potassium iodide. The salts are stable, crystalline hygroscopic solids; the 2-oxo compounds are colourless while the 2-thio-derivatives are yellow, due to the tail of an ultraviolet absorption at about 370 nm.

The nmr spectra of the compounds (118) -(123) ($Z=HSO_4$) are reported in table 9. Table 10 lists the appropriate data for dihydrodiazepinium salts (129). It is clear that the peaks due to the six-membered ring compounds occur at significantly lower field than those of the dihydrodiazepines, consistent both with an inductive deshielding, and with a mesomeric deshielding due to the resonance structure (130). That the protons in the 2-pyrimidinthiones resonate at lower field than those of the 2-pyrimidinones



(130)



(119A) (119B)

confirms that the major deshielding mechanism is conjugative. The presence of a 4-methyl group has little effect on the chemical shift of the 5-proton, although the 6-proton resonance is shifted upfield by more than 0.2 ppm. As found for dihydropyrimidines, this may reflect the increased importance of the resonance structure eg. (119B) due to the inductive effective of the methyl group. The coincidence of the N-methyl resonances in this compound is a case of accidental degeneracy, since two distinct peaks are found in the ^{13}C nmr spectrum. The vicinal coupling constants for the pyrimidine derivatives shown in table 9 are of the same magnitude as those for dihydropyrimidines reported in section 1.

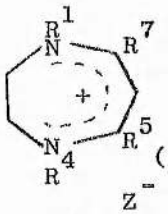
The pyrimidines (118)-(123) ($Z=HSO_4$) generally show two maxima in the uv spectrum (Table 11). Those at high wavelength are characteristic of the 1,5-diazapentadienium system, while the high energy absorptions are presumably due to the urea chromophore. That these are more intense for the 2-pyrimidinthiones is consistent both with the known high absorption of thiourea itself[213], and with

Table 9 Chemical Shifts and Coupling Constants for the Pyrimidines (118)-(123)

Compound	Solvent	τ[4,(6)]	τ(5)	τ(1,3-Me)	τ(4(6)-Me)	J_{45}/Hz	Anion
118	[$^2H_6$]DMSO	0.89	2.97	6.29	-	6.4	HSO_4^-
121	[$^2H_6$]DMSO	0.64	2.58	5.99	-	6.3	HSO_4^-
119	[$^2H_6$]DMSO	1.11	2.96	6.34	7.28	6.5	HSO_4^-
122	[$^2H_6$]DMSO	0.86	2.56	5.95,6.02	7.17	6.6	HSO_4^-
120	[$^2H_6$]DMSO	-	2.94	6.38	7.36	-	HSO_4^-
123	[$^2H_6$]DMSO	-	2.51	5.98	7.24	-	HSO_4^-

the greater tendency of these derivatives to the urea-like resonance structure (130) (X=S). 4(6)-Methyl groups cause hypsochromic shifts of 3 nm and 7 nm in the maxima of the oxo- and thio- compounds respectively, and also effect an increase in extinction coefficient.

Table 10 Chemical Shifts and Coupling Constants for the Dihydrodiazepines (129)



a, $R^1=R^4=Me$
b, $R^1=R^4=R^5=Me$
c, $R^1=R^4=R^5=R^7=Me$
(where unspecified R=H)

(129)

Compound	Solvent	τ[5,(7)]	τ(6)	τ(1,4-Me)	τ(5(7)-Me)	J_{56}/Hz	Anion
129a	[$^2H_6$]acetone	2.35	5.00	6.49	-	7.8	ClO_4^-
129b	[$^2H_6$]acetone	2.58	4.93	6.55	7.66	8.8	picrate
129c[40]	TFA	-	not apparent	6.5	7.55	-	ClO_4^-

Table 11 UV Spectra of the Pyrimidines (118)-(123)

Compound	λ_{max}/nm	ε
118	322 ca. 235	7000 -
119	318 ca. 240	9300 -
120	316 -	11100 -
121	379 280	1400 18800
122	372 281	2200 21200
123	366 283	2900 21100

Similar results are found for 5(7)-methyl groups in the spectra of dihydrodiazepines[18]. The spectra of (118) and the corresponding 1,3-dimethylpyrimidinthione (121) were substantially unaltered when recorded with concentrated sulphuric acid as solvent. This reluctance to form a 5-protonated structure supports the kinetic evidence for an alternative deuteriation mechanism[206,207].

Whereas the nmr spectra of these pyrimidinones and pyrimidinthiones were interpreted in terms of the perturbation of the vinamidinium system by the urea, it is of interest to consider the ir spectra conversely. Thus the (thio)-carbonyl bands in the

heterocycle occur approximately 100 cm^{-1} higher than in the free urea, consistent with a reduction in importance of the resonance structure (130) (X=O,S) compared with the free urea, due to the competition of the remainder of the molecule for the lone pairs of the nitrogen atoms.

In [^{2}H]TFA solution, vinamidinium salts characteristically show rapid exchange at the meso-position, but no detectable reaction was found with any of the 1,2-dihydro-2-oxo- or 2-thio-pyrimidines studied. Under the conditions of strong aqueous acid and of high temperature which were used previously[206,207] deuteriation at the 5-position was observed for the pyrimidinthione (121); a competitive experiment suggested that the reaction proceeds at about the same rate as that for the corresponding pyrimidinone. This remains the only unambiguous electrophilic 'substitution' on the 2-thiopyrimidinium nucleus.

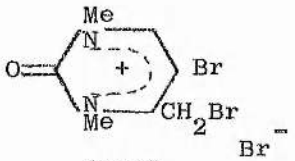
Deuteriation also occurs at the 4(6)-methyl groups of the pyrimidines (119), (120), (122) and (123) in neutral or mildly acidic media; the mechanism probably involves the exomethylene bases eg. (128) (cf. reference 214). The reactions of the 4-methyl derivatives (119) and (122) with [^{2}H]$_2$O under ambient conditions of temperature and p[^{2}H] followed first-order kinetics (k (119) = (7.5 $\pm$ 0.2) x 10^{-6} s^{-1}; k (122) = (11.6 $\pm$ 0.3) x 10^{-6} s^{-1}).

The preparation of the 5-bromo pyrimidine (126) from its 5-unsubstituted analogue (118) may be effected in excellent yield by bromine in methanol. The reaction of (118) with two moles of bromine gave the dimethoxy compound (127) (R=Me), which itself reverted to the bromo derivative (126) on treatment with aqueous hydrobromic acid. Tee and Banerjee[209,210] presented no evidence for the covalent hydrate (124) as an intermediate in the bromination (Scheme 12). This assumption was confirmed by stopped flow experiments which showed that the uptake of bromine followed zero-order kinetics, consistent with a slow step not involving the

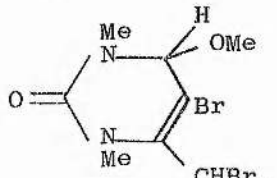
electrophile.

Surprisingly, the reaction of the thio compound (121) with excess bromine in methanol, gave the 5-bromo-2-oxo derivative (126) in good yield. When the experiment was carried out with one equivalent of bromine only, the nmr spectrum of the crude product showed it to be a mixture of starting material, the corresponding 2-oxo compound (118), and the bromo-compound (126). This indicates that the reaction sequence is dethionation followed by bromination. The ultimate fate of the sulphur atom in this process remains unknown, although it is certainly not present as sulphide or as elemental sulphur; it is probably oxidised under the reaction conditions.

Bromination of the 1,3,4-trimethyl compound (119) yields the dibromopyrimidine (131) as the only isolable salt, even when excess



(131)

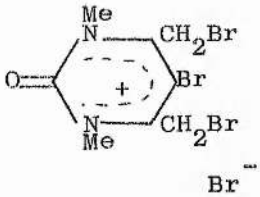


(132)

bromine and extended reaction times are employed. One mole of bromine is taken up rapidly, followed by a slow consumption of the remainder. The reaction does not follow simple kinetics, but is overall about fifty times slower than that for its 4-unsubstituted analogue. Preparative experiments using three equivalents of bromine yield, from chloroform extracts, an impure yellow oil, ν_{max} 1650 cm^{-1}, λ_{max} 272 nm (Found, M = 405.834320; $C_8H_{11}{}^{81}Br^{79}Br_2N_2O_2$ requires 405.834990), whose spectra are consistent with the tribromo pyrimidine (132) or its 4-methoxy isomer. Reaction of this compound with dilute hydrobromic acid readily gives the dibromo derivative (131). Clearly the mechanism of bromination of 4-methyl-2-pyrimidinones is complex, and does not proceed by the sequence of Scheme 12.

Reaction of the thio-compound (122) with excess bromine again results in desulphurisation, and the oxo-derivative (131) was the only isolated product.

The bromination of the tetramethylpyrimidine (120) is complicated by the formation of a stable complex which precipitates from solution. Its uv spectrum shows a weak shoulder at 380 nm consistent with the presence of molecular bromine, while there is no peak at 270 nm corresponding to the tribromide anion. Reaction of the complex with acetone regenerates the pyrimidine as its bromide salt. The elemental analysis of the complex suggests that four atoms of bromine are associated with each pyrimidinium cation, of which one is presumably the bromide anion. The strength of the binding forces in the complex may be judged by the fact that the analytical sample was dried overnight at a pressure of 10^{-1} torr. Such complexing is well known in hydroxy-pyrimidine chemistry[215]. The only isolable brominated product of



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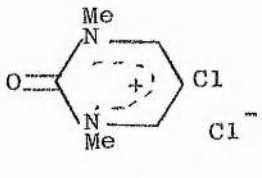

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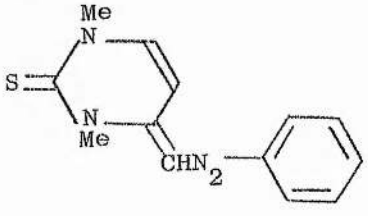


(135)

the reaction was the tribromo derivative (133), obtained in very low yield. A related reaction, also involving side-chain and nuclear bromination, is shown by 2-amino-4,6-dimethylpyrimidine[216].

The 5-chloro compound (134) was formed by the reaction of methanolic chlorine with the pyrimidinone (118). Under identical conditions, dihydrodiazepinium salts are solvolysed.

The nmr and uv spectra of these halogenated pyrimidinones are summarised in Tables 12 and 13. The general tendency of the nmr signals to occur at lower field on increased substitution is consistent with the electron-withdrawing nature of the halogen. The relatively high field resonance of the 4(6)-protons in the 5-chloro-derivative (134) is anomalous, however. In the uv spectra,

Table 12 Chemical Shifts for Halogenated 2-Pyrimidinones

Compound	Solvent	τ(1,3-Me)	τ[4,(6)]	τ(CH_2Br)	Other	Anion
126	TFA	6.05	0.95	-	-	Br^-
131	TFA	5.95,6.02	0.91	5.22	-	Br^-
133	TFA	5.92	-	5.12	-	Br^-
127 R=Me	$C[^2H]Cl_3$	6.98	5.37	-	methoxy 6.32	-
134	TFA	6.03	1.03	-	-	Cl^-

Table 13 UV Spectra of Halogenated 2-Pyrimidinones

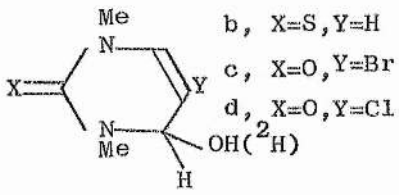
Compound	λ_{max}/nm	ε
126	351 253	1300 7500
131	356 261	500 6200
133	ca.360(sh) 282	- 5300
134	348 252	600 7500

the high wavelength maximum is shifted to longer wavelength than in the unsubstituted compounds, but the marked reduction in absorbance is unexpected. The further decrease in extinction coefficient on increased substitution is consistent with deformation of the ring.

The effect of other electrophiles on the pyrimidinone (118) was examined, in relation to the reactions of dihydrodiazepines. It was inert to N-chlorosuccinimide in boiling acetic acid, even after 24 h reaction time, inert to nitrating media[208], and to diazonium salts under neutral or acidic conditions. The reaction of the 4(6)-methylpyrimidinones(119) and (120) with diazonium salts to give 4-(arylazomethylene) derivatives has been reported[211], and was confirmed for the thio compound (122) which yielded (135) after basic workup. This material was identified as its hydrochloride;

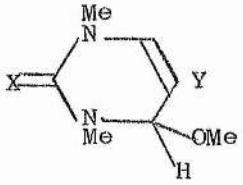
the position of protonation was not determined.

The activity of 4(6)-methyl groups has already been noted in the reaction of the pyrimidines (119) and (120) with bases, to give the exo-methylene compounds (128)[211]. Alternatively, the expected reactivity of the 4(6) positions themselves towards nucleophiles is exemplified by the observation of the pseudobase (124) in solution[206,207]. This effect is quite general, and the adducts (136)-(139) were formed quantitatively in solution in the presence of about a twofold excess of the base. Attempts to isolate the adduct (136a) were unsuccessful, but the methoxy compounds (137) could be obtained as crude viscous oils, and were characterised by mass spectrometry. The remarkable stability of these pseudobases must again be emphasised. Only after three days in ca. 1 M sodium deuteroxide solution did decomposition peaks in the nmr spectrum of (136a) become comparable in intensity to those of the simple adduct,



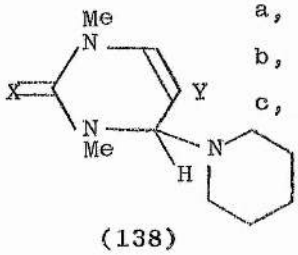
a, X=O, Y=H
b, X=S, Y=H
c, X=O, Y=Br
d, X=O, Y=Cl

(136)



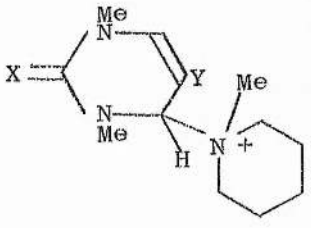
a, X=O, Y=H
b, X=S, Y=H
c, X=O, Y=Br

(137)



a, X=O, Y=H
b, X=S, Y=H
c, X=O, Y=Br

(138)



a, X=O, Y=H
b, X=S, Y=H
c, X=O, Y=Br

(139)

while the piperidine pseudobase (138b) was effectively unchanged after a similar period in [$^2H_6$]DMSO. Clearly the meneidic properties of the 1,5-diazapentadienium system are much reduced in these series of compounds. The formation of stable adducts with base is analogous to the production of Meisenheimer-type complexes

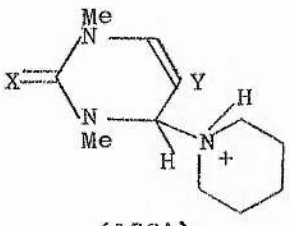
in the chemistry of dinitrobenzenes[217].

There was no evidence of nucleophilic substitution products in any of these reactions involving 5-halogeno-2-pyrimidinones.

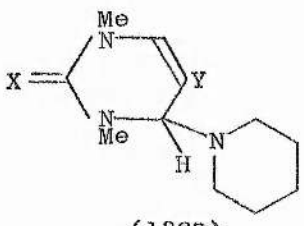
The covalent hydrate (136a) is thought to be the intermediate in the reactions of the pyrimidinone (118) with electrophiles (Schemes 11 and 12). The isolation of the methoxy-adducts (137) has enabled such reactions to be observed directly. Indeed, treatment of the 2-oxo compound (137a) with bromine gives the 5-bromo derivative (126); this product (as its chloride salt) is also obtained by the action of N-bromosuccinimide on (137a), followed by work-up with dry methanolic hydrogen chloride. Attempts were made to prepare the elusive 2-thio analogue of (126) by this method, but no stable products could be isolated.

The formation of the base adducts (137) is reversible. The salts (118) and (121) could be regenerated by addition of acid to a solution of the pseudobases (137a) and (137b) respectively.

The nmr spectra of the adducts (136)-(139) are summarised in Table 14. As observed for the salts, the pyrimidinthione resonances are consistently at lower field than those of their oxo-analogues. For the methoxy-compounds (137), the assignment of the high-field signals as O-Me and N-Me was made by analogy with the hydroxy and piperidine adducts, but is not unambiguous. One further ambiguity in the structure of these compounds concerns the piperidine adducts (138), which may exist in a protonated or unprotonated form, (138A) and (138B) respectively. The difficulty was resolved by the



(138A)



(138B)

preparation of the N-methylpiperidine derivatives (139); the similarity of the chemical shifts of protons 4-6 in compounds (138a) and (139a) confirm that the former was protonated under the

Table 14 Chemical Shifts and Coupling Constants for Pseudobases (136)-(139)[x]

Compound	τ(4)	τ(5)	τ(6)	τ(1,3-Me)	Δτ(1,3-Me) /Hz	J_{45} /Hz	J_{56} /Hz	J_{46} /Hz	Other
136a	4.65	4.95	3.84	6.97,7.03	6.4	4.4	7.7	0.5	-
136b	4.57	4.70	3.70	6.59,6.63	3.8	4.3	7.3	0.6	-
136c	4.69	-	3.62	6.99,7.09	9.8	-	-	1.2	-
136d	4.72	-	3.66	6.98,7.07	8.6	-	-	1.2	-
137a	4.69	5.26	3.42	7.06,7.13	7.3	4.4	7.8	ca.0	τ(OMe) 7.00
137b	4.52	4.93	3.18	6.59,6.69	10.3	4.6	7.8	ca.0	7.05
137c	4.58	-	2.93	7.01,7.11	10.2	-	-	0.6	6.96
138a	4.77	5.12	3.66	7.00,7.09	9.2	4.3	7.9	ca.0	-
138b	4.63 5.20	4.84 5.00	3.45 3.44	6.61,6.67, 6.72	5.7	4.7	7.6	ca.0	-
138c	5.31	-	3.18	7.06,7.16	10.3	-	-	ca.0	-
139a	4.79	5.12	3.69						
139b	4.61	4.81	3.42						
139c	4.80	-	3.23						

x. For conditions, see experimental section

Table 15 UV Spectra of Pseudobases (136)- (138)[x]

Compound	λ_{max}/nm	ε
136a	240	5600
136b	272 254(sh)	11400 9300
136c	252	7700
136d	250	6300
137a	239	5200
137b	276 250(sh)	14400 5200
137c	252	7200
138a	240(sh)	ca.7500
138b	272 254(sh)	12200 ca.9500
138c	248(sh)	ca.8300

conditions of the experiment. The bromo-compound (138c) was unprotonated, while the thio-derivative (138b) existed in both forms (Table 14).

Attempts were made to deduce the geometry of these adducts using equations derived by Garbisch relating coupling constants to dihedral angles for allylic systems[218]. A symmetrical structure with a dihedral angle of 50 $\pm$ 5° at the 4-position was deduced from the magnitude of J_{45} and J_{46}. The relative signs of these coupling constants [(136a) and (136b), J_{45}, J_{56} and J_{46} all positive] as determined by the INDOR technique are, however, inconsistent with this assignment. The equations probably cannot be directly applied to such systems with electronegative substituents.

The nmr spectrum of the methoxy adduct (137c) is of interest. The 6-proton resonance occurs as a doublet (J_{46} 0.6 Hz) shown by double resonance to be due to allylic coupling with the 4-proton. The 4-proton resonance, however, appears as a broad singlet, which is resolved into a doublet (J_{46} 0.6 Hz) on irradiation of the N-methyl signals. Conversely, irradiation of the 4-proton signal causes greatest enhancement in the size of the central methyl peak (τ 7.01), which is therefore the 3-methyl group.

The uv spectra of all the pseudobases were measured *in situ*, in the presence of excess base (Table 15). The low-wavelength peaks are presumably due to the (modified) enamine system, while for the sulphur-containing compounds, the maximum at around 270 nm is clearly caused by the thiourea chromophore. The presence of a 5-halogeno-substituent causes a bathochromic shift in the maxima; the nature of the 4-substituent has little effect.

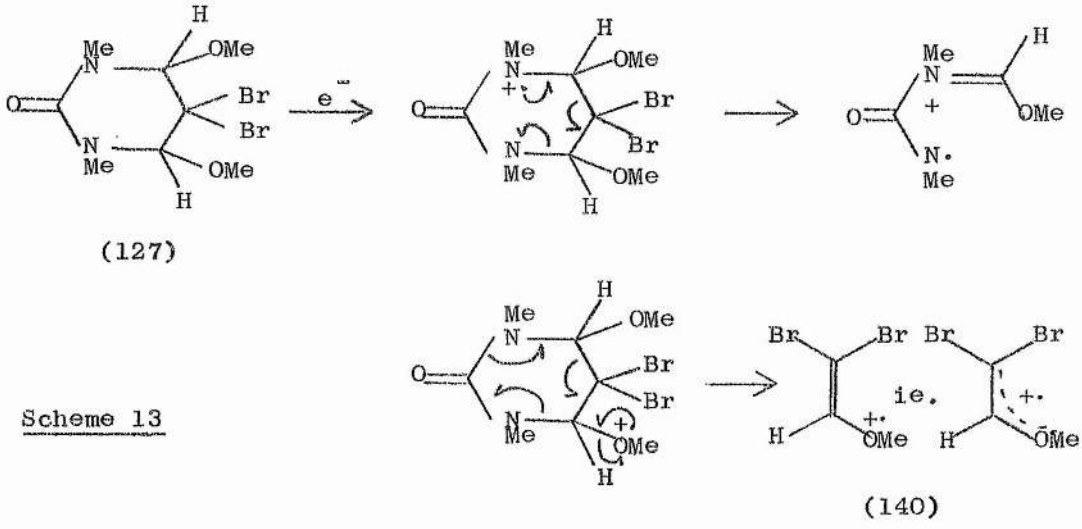
In the ir spectra of the methoxy adducts (137a) and (137c) the carbonyl bands at 1660-1670 cm^{-1} are intermediate between those of the salts (eg. (118), 1715 cm^{-1}) and N,N'-dimethylurea itself (1610 cm^{-1}), consistent with an intermediate delocalisation of electrons through the carbonyl group. The corresponding C=S stretch in the thio-compound (137b) may occur at 1120 cm^{-1}.

All of the 2-pyrimidinones and 2-pyrimidinthiones studied gave consistent mass spectra. Bromide salts show characteristic

clusters at m/e 79-82 (Br^+ and HBr^+), while the hydrogen sulphates have intense peaks at m/e 48 and 64 (SO^+ and SO_2^+). The 1,3-dimethyl derivatives (118) and (121) show the molecular ions of the cations as the base peak, whereas the parent peak for the 4(6) methyl compounds (119), (120), (122) and (123) is at (M_{cation}-1). In the former case, therefore, vaporisation must occur by some charge-transfer mechanism (cf. page 37). Further breakdown of the latter compounds is by the loss of the 2-carbon and its substituent; whereas the 2-oxo derivatives (119) and (120) lose CO itself [(119) Found, m^* 87.7, 138 ⟶ 110 requires m^* 87.7: (120) Found m^* 101, 152 ⟶ 124 requires m^* 101.0], the major peaks in the spectra of the 2-thio compounds (122) and (123) are due to M-45 and M-46. This loss of HCS and H_2CS presumably reflects the relative stability of CO and CS.

As found for 6-halogenodihydrodiazepines, the cleavage of the halogen substituent in the 5-halogeno pyrimidinones (126) and (134) is the major breakdown mechanism, although the molecular ion of the cation is found in both spectra. The polybrominated species (131) and (133), however, have peaks at (M(cation-1) and show intense loss of halogen, probably from the 4(6)-bromomethyl group. The 5,5-dibromo derivative (127) (R=Me) shows a more curious spectrum. The major breakdown from the molecular ion (m/e 344, 346, 348) is apparently the formation of the olefin (140) (m/e 214, 216, 218) which is the base peak of the spectrum. (Found, 213.863810; $C_3H_4{}^{79}Br_2O$ requires 213.862869) A peak at m/e 130 (relative intensity 50%) is also present, which may represent the nitrogenous residue of the molecule (Found, 130.074926; $C_5H_{10}N_2O_2$ requires 130.074222) (Scheme 13).

The cation radical derived from the diazo-coupled product (135) can decompose by two routes. The simple cleavage of the phenylazo group causes the base peak at m/e 153 (Found m^* 90.8, 258⟶ 153 requires m^* 90.7), while an intense peak at m/e 185



(127)

Scheme 13

(140)

(relative intensity 83%) is due to the loss of MeNCS (Found m^* 132.8, 258 ⟶ 185 requires m^* 132.6).

In the mass spectra of the methoxy adducts (137), the molecular ions are of low intensity, and the base peak in each case is due to the loss of m/e 31 (=OMe), a process which regenerates the 1,5-diazapentadienium system.

DISCUSSION

PART 3

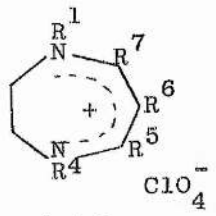
CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTRA

Although ^{13}C nmr (cmr) signals have been recognised since 1957[219], it has only been recently that the potential of the technique as a routine tool in organic chemistry has been realised. The development of 'third-generation' spectrometers, operating in the Fourier Transform mode, has largely overcome the major problem of sensitivity, and satisfactory spectra can now be obtained from solutions of similar concentration to that required for proton nmr. Because the signal intensity is also enhanced by noise decoupling of the proton resonances, the only parameter available from a routine cmr spectrum is that of chemical shift (δ), measured in ppm downfield from TMS.

The factors influencing the chemical shift are as yet incompletely understood[220]. In the absence of steric, strain, or substituent effects, however, it seems to relate to the charge density at the carbon atom[221,222]. The chemical shift is apparently little affected by the presence of a ring current, but is more sensitive to stereochemical factors[223].

In the present work, the cmr chemical shifts of the dihydrodiazepinium salts (141), dihydropyrimidinium salts (142) and (143) and open-chain 1,5-diazapentadienium salts (144) (Tables 16-18 respectively) are assigned and compared. Where possible, attempts are made to correlate this parameter with the charge distribution in the system; substituent effects are reported empirically and compared with those of benzene derivatives. The spectra were all recorded at 25.2 MHz for 10% solutions in $[^2H_6]$DMSO, and the counter-ion was generally perchlorate. That the effects of the counter-ion are small, was demonstrated by the spectra of [(142), Z = Br, picrate] (Table 17).

The most striking feature of the spectra of these compounds is the spectacular chemical shift difference between the meso carbons (δ *ca.* 90 ppm), and those α- to the nitrogens (δ *ca.* 160 ppm), which clearly reflects the electron distribution in the



(141)

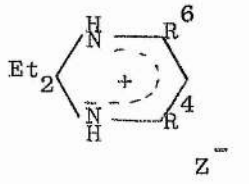
a, R^n=H
b, R^1=Me
c, R^1=R^4=Me
d, R^5=R^7=Me
e, R^5=R^7=Ph
f, R^1=Me, R^5=R^7=Ph
g, R^1=R^4=Ph
h, R^1=R^4=Ph, R^5=R^7=Me
i, R^5=R^7=Me, R^6=Br
j, R^5=R^7=Me, R^6=NO_2
k, R^5=R^7=Me, R^6=OMe (picrate anion)

(Where unspecified, R^n = H)

Table 16 Cmr Spectra of Dihydrodiazepinium Salts (141)

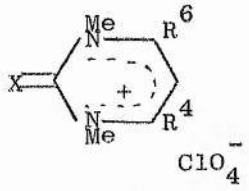
Compound	δ(6)	δ(5,7)	δ(2,3)	δ(other)
141a	88.01	157.31	48.81	-
141b	87.43	158.53 156.06	47.64 47.07	1-Me, 56.47
141c	87.04	157.21	46.71	1,4-Me, 55.20
141d	91.39	166.96	47.87	5,7-Me, 23.67
141e	90.64	166.33	49.34	5,7-Ph, 136.54, 132.43 129.46, 128.63
141f	93.52	168.00 163.92	48.72 45.37	1-Me, 57.06; 5,7-Ph, 136.74, 136.21, 131.59, 130.75, 128.85, 128.36, 127.94
141g	92.64	155.40	55.84	1,4-Ph, 144.97, 129.73, 128.29, 122.62
141h	96.34	165.45	58.67	5,7-Me, 25.14; 1,4-Ph, 144.73, 130.06, 129.07, 125.70
141i	84.53	166.65	48.20	5,7-Me, 28.40
141j	126.65	162.52	47.55	5,7-Me, 21.29
141 k	124.75	164.31	47.75	5,7-Me, 19.48; O-Me, 61.31; picrate, 125.22

vinamidinium cation. The electronic similarity between both the 'U'-systems and the 'W'-system is also emphasised. Application of an empirical relation quoted by Stothers[224] gives an estimation of the π-electron density at the meso-positions as ca. 1.3 electrons, while that at the α-positions is only 0.8 electrons. Hence the majority of the charge in the system must remain on the nitrogen atoms (ca. 1.6 electrons each). The paradox of the



(142)

a, R^4=Me, R^6 = H, Z = Br,
Z = picrate
b, R^4=R^6=Me, Z = picrate



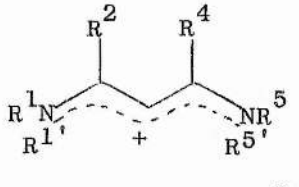
(143)

a, R^4=R^6=H, X = O
b, R^4=R^6=H, X = S
c, R^4=Me, R^6=H, X = O
d, R^4=Me, R^6=H, X = S

Table 17 Cmr Spectra of Dihydropyrimidinium Salts (142) and (143)

Compound	δ(5)	δ(4,6)	δ(2)	δ(other)
142a (Z=Br)	90.42	166.55 152.87	73.86	4-Me, 19.72; 2,2-Et, 30.56, 7.63
142a (Z=picrate)	90.30	166.31 152.90	73.34	4-Me, 19.54; picrate, 125.25; 2,2-Et, 30.21, 7.21
142b	90.95	164.56	73.75	4,6-Me, 19.29; picrate, 125.20; 2,2-Et, 30.47, 7.23
143a	103.28	159.99	147.73	1,3-Me, 40.32
143b	107.05	158.02	171.93	1,3-Me, 48.13
143c	105.52	172.71 156.19	148.41	1-Me, 40.10; 3-Me, 34.74; 4-Me, 21.72
143d	110.07	170.78 154.50	173.37	1-Me, 48.45; 3-Me, 42.51; 4-Me, 23.20

vinamidinium cation being electron-rich is further demonstrated by the spectrum of the isoelectronic pentadienide anion which has been reported recently[225]. The chemical shift of the 3-position in this species (86.9 ppm) is very close to that of the meso-position of 1,5-diazapentadienium salts. It is also of interest that this meso-carbon resonance is at much higher field than normally found for nitrogen heterocycles[226], but approaches that of the meso-position in porphyrins[227], and that of the methine carbon in the enol-form of β-diketones[228].



(144) ClO_4^-

a, R^1-$R^{1'}$=R^5-$R^{5'}$=pentamethylene
b, R^1=Ph, R^5-$R^{5'}$=pentamethylene
c, R^1=R^5=Ph
d, R^1=R^5=Ph, R^2=R^4=Me

(Where unspecified, R^n=H)

Table 18 Cmr Spectra of 1,5-Diazapentadienium Salts (144)

Compound	δ(3)	δ(2,4)	δ(other)
144a	88.51	160.78	pentamethylene, 55.48, 46.70, 26.27, 24.98, 22.91
144b	94.07	162.58 156.91	Ph, 139.31, 130.28, 125.63, 117.36; pentamethylene, 56.86, 48.00, 26.68, 25.56, 23.17
144c	98.89	158.60	1,5-Ph, 138.72, 130.39, 126.64, 117.98
144d	ca. 93.2 (br)	ca. 170.8 (br)	1,5-Ph, 137.02, 129.96, 127.97, 125.57; 2,4-Me, 22.25

The signals of each carbon atom in the 2-oxo- and especially the 2-thiopyrimidinium salts (143) occur at lower field than in the corresponding dihydropyrimidinium or dihydrodiazepinium salt. The only exception to this general rule is the resonances of the N-methyl groups. The peak due to the 2-carbon is at higher field than in the spectrum of the corresponding tetramethyl(thio)urea; an empirical relation between carbonyl and thiocarbonyl cmr chemical shifts[229] gives poor correlation in this case.

A methyl group in the position α- to the nitrogens causes a downfield shift of ca. 10 ppm in the signal of that carbon. This effect is quantitatively similar to that observed for benzene derivatives[230]. 5,7-Phenyl groups in dihydrodiazepines cause deshielding of the same order, whereas the resonance of the 1-carbon in biphenyl is 13 ppm downfield of benzene. A substituent in the α-position also causes a downfield shift in the signal due to the meso-carbon, while in the dihydrodiazepine series, each N-methyl group causes an upfield shift of ca. 0.5 ppm in this resonance.

In contrast, the 5(7)-carbon signals in the spectra of the 1,4-dimethyldihydrodiazepinium salt (141c) and its unsubstituted analogue (141a) show similar chemical shifts, while in the 1-methyl compound (141b) these signals are symmetrically split by 2.5 ppm.

The qualitative effects of electronegative substituents also parallel those found in the spectra of aryl derivatives. Pronounced downfield shifts are observed for the 6-carbon resonance in the 6-nitro and 6-methoxy compounds(141j) and (141k), whereas the 6-bromo derivative (141i) shows a significant upfield shift.

The effects of substituents are also shown by the signals due to the methyl carbon atoms. The N-methyl groups in the 1,3,4-trimethyl-2-oxo- and 2-thiopyrimidinium cations (143c) and (143d) give signals separated by ca. 6 ppm; that due to the 3-methyl group is probably the more upfield. Similarly 6-nitro and 6-methoxy substituents in dihydrodiazepines cause an upfield shift in the peaks due to adjacent methyl groups, an effect which appears to be general in the spectra of benzenoid compounds also[231]. The downfield shift of the methyl resonance in the spectrum of the 6-bromo derivative (141i) is anomalous (cf. reference 232).

The spectra of the phenyl-substituted vinamidines are of interest, since they demonstrate the conjugative interaction between the two systems. It has already been noted that N-phenyl groups can interact with the 1,5-diazapentadienium system only by electron-withdrawal, whereas α-phenyl groups can only donate electrons[172]. The first of these processes is well exemplified by the spectra of the diphenyldihydrodiazepinium salt (141g) and of the open-chain compound (144c), in which the meso-carbon signal occurs at lower field than in their N-alkyl analogues. That the effect is greater for the open-chain derivatives is consistent with more efficient conjugation in the vinamidinium system of the dihydrodiazepinium ring due to it being held in a very rigid geometry. Surprisingly, the chemical shift of the meso carbon in

the 5,7-dimethyl-1,4-diphenyldihydrodiazepinium salt (141h) shows only the additive effect of the four substituents; the probable twisting of the phenyl groups out of the plane of the ring appears to have little effect. It is known for related systems, however, that quite substantial deformation has little influence on the conjugation[233]. In contrast, the meso carbon resonance of the 1-methyl-5,7-diphenyldihydrodiazepine (141f) is almost 3 ppm downfield of the signal due to the 6-carbon in its N-unsubstituted analogue (141e). This effect cannot be due to the N-methyl group, which normally exerts an upfield influence, but is consistent with reduced conjugation.

The effects of N-phenyl substitution are also reflected by the spectra of the open-chain compounds (144). Whereas the successive replacement of alkyl substituents with aryl causes a regular shift in the meso-carbon signal, the α-carbons in the unsymmetrical compound (144b) are split to extremes of field by more than 5 ppm. The rigidity of the vinamidinium system in these compounds is demonstrated by the five distinct peaks due to the pentamethylene carbon atoms in the spectra of (144a) and (144b). The spectrum of the 2,4-dimethyl compound (144d) is anomalous because the 2,3- and 4-carbons give rise to unaccountably broad signals, but in any event the inefficiency of conjugation between the aryl groups and the vinamidinium system is again demonstrated (cf. page 56).

One major advantage of the absence of coupling in routine cmr spectra is that peaks may be readily assigned to each position in aryl groups. The assignments reported in Table 19 were made assuming that the most downfield peak was that due to the 1-carbon, and that the p-carbon gave rise to the other peak of low intensity. In general, the o-carbon peak was adjacent to that of the p-carbon,

Table 19 Cmr Chemical Shifts of the Phenyl Groups in the Aryl-substituted 1,5-Diazapentadienium Salts (141) and (144)

Compound	δ(para)	δ(meta)	δ(ortho)	δ(1)	|δ(m)-δ(p)|
141e	132.43	129.46	128.63	136.54	2.97
141f	131.59 130.75	128.85	128.36 127.94	136.74 136.21	2.74,1.90
141g	128.29	129.73	122.62	144.97	1.44
141h	129.01	130.01	125.70	144.73	1.00
144b	125.63	130.28	117.36	139.31	4.65
144c	126.64	130.39	117.98	138.72	3.75
144d	127.97	129.96	125.57	137.02	1.99

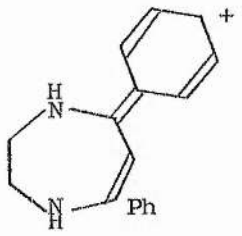
but in cases of doubt, the signal at 129.5 ± 1 ppm was considered to be due to the m-carbon. The carbon atoms in benzene itself resonate at 128.5 ppm downfield of TMS and the m-carbon atoms in its derivatives would be expected to show the least deviation from that norm.

Clearly the electronic effects evident from the vinamidinium signals in the spectrum can also be deduced from the chemical shifts of the p-carbon atom. The electron-donating ability of 5(7)-phenyl groups in dihydrodiazepines is apparent from the low-field p-carbon resonance, while the opposite effect is shown by the corresponding signals of N-phenyl groups.

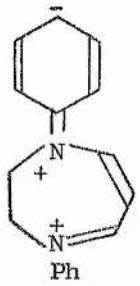
Since the chemical shift of the m-carbon atom is virtually independent of electronic effects, the quantity δ(m)-δ(p) should give an indication of the efficiency of the conjugation (Table 19). The reduced interaction for the compounds in which methyl groups are vicinal to the phenyl, is clear from the table. It is also apparent that 5(7)-phenyl groups in dihydrodiazepines show better conjugation than 1(4)-phenyl substituents. This presumably

reflects the relative stability of the canonical forms (141eA) and (141gA) which result from such delocalisation.

The cmr chemical shift of para-carbon atoms has been correlated



(141eA)



(141gA)

with Hammett-type σ^{-}_{+} parameters[234], and from this relation, it is possible to make an estimate of the parameter for 1,5-diazapentadienium groups. The 5-(7-phenyldihydrodiazepinium) system, considered as a substituent of benzene, has σ^{-}_{+} ca. 0.57, and is therefore comparable in electron-withdrawing ability to the $-COCH_3$ group. The slight electron-donating tendency of the N-(N'-phenyl-1,5-diazapentadienium) group is reflected when the vinamidinium system is all-trans (σ^{-}_{+} ca. -0.1), but not when it has the 'U'-configuration (σ^{-}_{+} ca. 0.0).

EXPERIMENTAL

Materials and Apparatus

Light petroleum had boiling range 40-60°.

Melting points were determined in open capillaries, and are uncorrected.

Unless otherwise stated, ultraviolet spectra are quoted for methanolic solutions; analytical samples were used.

Infrared spectra were recorded for nujol mulls.

Nmr spectra were recorded at 100 MHz for 10% solutions, with tetramethylsilane as internal reference. Sodium trimethylsilylpropanesulphonate was used as internal reference when deuterium oxide was the solvent. Coupling constants were measured at a sweep width of 100 Hz.

Abbreviations

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

br: broad

(d): (after melting point): with decomposition

DMSO: dimethylsulphoxide

TFA: trifluoroacetic acid

TMS: tetramethylsilane

PART 1

N-Methyl Dihydrodiazepinium Salts

2,3-Dihydro-1,5,7-trimethyl-1H-1,4-diazepinium perchlorate - 1-(2-Acetyl-1-methylvinylamino)-2-methylaminoethane perchlorate[21] (6.3 g) was heated under reflux in acetic acid (25 ml) for 1 h. Evaporation of the solvent in vacuo gave the perchlorate (5.3 g, 91%) as a waxy solid which could be recrystallised from methanol at -78°. It had mp 53.5-54.5°, λ_{max} 331 nm (ε 18500), ν_{max} 3300, 1610, 1530, 1320, 1100 cm^{-1}, τ([$^2H_6$]acetone) 1.4 (br), 4.83 (1H, s), 6.19 (4H, s), 6.58 (3H, s), 7.67 (3H, s), 7.74 (3H, s), $J_{4,6}$ ([$^2H_6$]DMSO/TFA) 1.7 Hz. (Found: C, 39.95; H, 6.4; N, 11.5. $C_8H_{15}ClN_2O_4$ requires C, 40.15; H, 6.3; N, 11.7%).

2,3-Dihydro-1-methyl-5,7-diphenyl-1H-1,4-diazepinium perchlorate - N-Methylethylenediamine (1.48 g, 20 mmoles) followed by dibenzoylmethane (2.24 g, 10 mmoles) was added to cooled acetic acid (3.3 g) and the mixture was heated under reflux for 1.5 h. When cooled, the solution was mixed with water (25 ml) and extracted three times with ether. Perchloric acid (60%, 3.5 ml) was added to the aqueous layer, and the dihydrodiazepinium perchlorate crystallised overnight (1.93 g, 53%). This means of preparation is substantially more efficient than that previously reported[21]. τ([$^2H_6$]DMSO/TFA) -0.24 (br.s), 2.2-2.6 (complex), 4.71 (d, $J_{4,6}$ 1.8 Hz), 6.06 (br.s), 6.79 (s).

2,2-Dimethyldihydrodiazepinium Salts (59) and (60)

2,3-Dihydro-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate (59a) - Prepared by the standard method as described previously[16], from acetylacetone and 1,2-diamino-2-methylpropane in acetic acid, the perchlorate had mp 118-120°, τ([$^2H_6$]acetone) 1.0 (br), 1.2 (br), 4.86 (1H, t, $J_{1(4),6}$ 1.8 Hz), 6.60 (2H, s), 7.71 (6H, s), 8.66 (6H, s).

2,3-Dihydro-2,2,5,7-tetramethyl-6-nitro-1H-1,4-diazepinium perchlorate (59b) - Fuming nitric acid (0.6 ml) was added slowly to a cooled solution of the 6-unsubstituted dihydrodiazepinium perchlorate (59a) (2.5 g, 10 mmoles) in concentrated sulphuric acid (8 ml). The mixture was heated at 35-40° for 1.5 h and poured onto crushed ice (10 g). The perchlorate (0.7 g, 24%) which crystallised overnight had mp 177.5-178.5° (reprecipitated by light petroleum, from ethanol) λ_{max} 323 nm (ε 12600), ν_{max} 3300, 1620, 1520, 1340, 1100 cm^{-1}, τ([$^2H_6$]acetone) - 0.05 (br), 0.35 (br), 6.35 (2H, s), 7.54 and 7.56 (6H, 2s), 8.53 (6H, s). (Found: C, 36.4; H, 5.65; N, 14.1. $C_9H_{16}ClN_3O_5$ requires C, 36.25; H, 5.4, N, 14.1%).

6-Bromo-2,3-dihydro-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate (59e) - Bromine (9.6 g, 60 mmoles) in methanol was added to a methanolic solution of the 6-unsubstituted dihydrodiazepinium perchlorate (59a) (15.0 g, 60 mmoles), and the 6-bromo dihydrodiazepinium salt (7.6 g) was precipitated by ether as a red oil which slowly crystallised. Recrystallisation, first from aqueous perchloric acid, and then from water, gave the perchlorate (7.6 g, 38%), mp 134°, λ_{max} 347 and 261 nm (ε 13000 and 700), ν_{max} 3300, 1600, 1500, 1300, 1100 cm^{-1}, τ([$^2H_6$]acetone) 0.25 (br), 0.8 (br), 6.48 (2H, m), 7.38 (6H, s), 8.62 (6H, s). (Found: C, 32.3; H, 5.0; N, 8.4. $C_9H_{16}BrClN_2O_4$ requires C, 32.4; H, 4.8; N. 8.4%)

2,3-Dihydro-6-methoxy-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate (59c) - The corresponding 6-bromo compound (59e) (2.0 g, 6 mmoles) was heated under reflux for 1.5 h in methanol (60 ml) containing sodium methoxide (from sodium 1.0 g). The solvent was evaporated, water was added, and the mixture was extracted four times with ether. The combined ether extracts were dried (Na_2SO_4) and the ether was evaporated. The residual oil was dissolved in ethanol (ca. 1 ml) and perchloric acid (60%, 0.8 g) was added. The

6-methoxydihydrodiazepinium perchlorate (0.24 g, 11%), which slowly crystallised, had mp 122-123° (reprecipitated by light petroleum, from propan-2-ol), λ_{max} 347 nm (ε 13800), ν_{max} 3300, 1620, 1500, 1320, 1100 cm^{-1}, τ ([$^2H_6$]acetone) 0.6 (br), 1.05 (br), 6.39 (3H, s), 6.64 (2H, m), 7.59 (6H, s), 8.68 (6H, s). (Found: C, 42.6; H, 7.0; N, 9.9. $C_{10}H_{19}ClN_2O_5$ requires C, 42.4; H, 6.7; N, 9.9%).

6-Chloro-2,3-dihydro-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate (59d) - The corresponding 6-unsubstituted compound (59a) (2.5 g, 10 mmoles) and N-chlorosuccinimide (1.3 g, 10 mmoles) were heated under reflux in chloroform (25 ml) for 1.5 h. Evaporation of the solvent in vacuo, followed by recrystallisation of the residue from water, gave the perchlorate (1.85 g, 64%), mp 138-139° (from water) λ_{max} 344 nm (ε 11800), ν_{max} 3300, 1610, 1500, 1300, 1100 cm^{-1} τ([$^2H_6$]acetone) 0.42 (br), 0.90 (br), 6.50 (2H, s), 7.47 (6H, s), 8.62 (6H, s). (Found: C, 37.65; H, 5.75; N, 9.5. $C_9H_{16}Cl_2N_2O_4$ requires C, 37.5; H, 5.55; N, 9.7%).

2,3-Dihydro-6-iodo-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate (59f) - Prepared by the same method as the 6-chloro analogue, but using N-iodosuccinimide in place of N-chlorosuccinimide, the 6-iodo-dihydrodiazepinium perchlorate (67%) had mp 98-100°, (reprecipitated by light petroleum, from propan-2-ol), λ_{max} 358 and 307 nm (ε 9000, and 2400), ν_{max} 3300, 1590, 1490, 1310, 1100 cm^{-1}, τ([$^2H_6$]acetone) 6.47 (2H, m), 7.22 (6H, s), 8.62 (6H, s), (the NH signals could not be detected due to deiodination in the presence acid). (Found: C, 28.1; H, 4.45; N, 7.35. $C_9H_{16}ClIN_2O_4$ requires C, 28.5; H, 4.2; N, 7.4%).

2,3-Dihydro-2,2,5,6,7-pentamethyl-1H-1,4-diazepinium perchlorate (59g) - 3-Methylacetylacetone (1.14 g, 10 mmoles) was added to a solution of 1,2-diamino-2-methylpropane (0.9 g, 10 mmoles) in acetic acid (2 ml), and the mixture was heated to ca. 120° for 15 minutes.

Perchloric acid (60%, 2 g) was added to the cooled solution and the dihydrodiazepinium perchlorate (0.8 g, 30%) separated as colourless crystalline plates, mp 155.5-156° (from propan-2-ol), λ_{max} 340 nm (ε 13500), ν_{max} 3300, 1610, 1500, 1340, 1100 cm^{-1}, τ([$^2H_6$]acetone) 0.92 (br), 1.50 (br), 6.62 (2H, m), 7.64 (6H, 2s), 8.02 (3H, s), 8.68 (6H, s). (Found: C, 44.85; H, 7.4; N, 10.65. $C_{10}H_{19}ClN_2O_4$ requires C, 44.95; H, 7.1; N, 10.5%). Previous attempts to prepare 6-methyldihydrodiazepines by this method were unsuccessful[16].

2,3-Dihydro-2,2-dimethyl-5,7-diphenyl-1H-1,4-diazepinium perchlorate (60) - 1,2-Diamino-2-methylpropane (3.6 g, 40 mmoles) followed by dibenzoylmethane (2.24 g, 10 mmoles) was added to cooled acetic acid (6.6 g) and the mixture was heated under reflux for 1.5 h. The cooled solution was poured into water (20 ml) and extracted three times with ether. An excess of perchloric acid (60%, 10 ml) was added to the aqueous layer and a yellow oil separated which slowly solidified. This material was ground to a fine powder and was washed with water to remove a side product (see below) until the uv spectrum of the solid showed no peaks in the range 220-240 nm. Recrystallisation from propan-2-ol gave the dihydrodiazepinium perchlorate (1.4 g, 37%), mp 159.5-160.5°, λ_{max} 354 and 267 nm (ε 22800 and 14800), ν_{max} 3300, 1590, 1570, 1330, 1100 cm^{-1}, τ([$^2H_6$]acetone) 0.5 (br), 0.95 (br), 2.0-2.6 (10H, complex), 4.26 (1H, s), 6.19 (2H, s), 8.44 (6H, s). (Found: C, 60.85; H, 5.9; N, 7.5. $C_{19}H_{21}ClN_2O_4$ requires C, 60.45; H, 5.55; N, 7.4%).

The side-product from this reaction could be obtained pure by repeated recrystallisation of the crude solid from ethanol. It was identified as 4,4-dimethyl-2-phenylimidazolinium perchlorate on the basis of its spectra and elemental analysis. It had mp 167-169°, λ_{max} 238 and ca 269 (sh) nm (ε 15300 and 3400), ν_{max} 3300, 1620, 1560, 1100, 790 cm^{-1}, τ([$^2H_6$]acetone) 1.95-2.5 (5H, complex), 6.00 (2H, s), 8.37 (6H, s). The NH signals were not apparent. (Found: C, 48.05; H, 5.7; N, 10.2. M^+ 174.

$C_{11}H_{15}ClN_2O_4$ requires C, 48.1; H, 5.45; N, 10.2%. M^+_{base} requires 174).

Variable Temperature Nmr Spectra - Quantitative kinetic measurements were made at 60 MHz for 10% solutions in [$^2H_6$]acetone. The temperature was measured directly by means of a copper-constantan thermocouple inserted in the probe. Linewidths were recorded as the average of three, run at a sweep width of 50 Hz, while the instrument resolution was kept constant by optimising the linewidth of the TMS signal at each temperature. Activation parameters are typically reported for measurements in the range T_c to T_c+25^o: activation energies are best fits to the log k vs 1/T line, as calculated by the method of least squares. The errors in E_a were computed as standard deviations.

Dihydrodiazepinium iodides

2,3-Dihydro-5,7-dimethyl-1H-1,4-diazepinium iodide (62a) - The corresponding perchlorate[15] (0.45 g, 2 mmoles) was dissolved in the minimum quantity of methanol, and a solution of potassium iodide (0.34 g, 2 mmoles) in methanol was added. The precipitated potassium perchlorate was filtered and the methanol evaporated in vacuo. Addition of ether promoted the crystallisation of the dihydrodiazepinium iodide in essentially quantitative yield. It was recrystallised from water to remove traces of inorganic material, and finally from propan-2-ol. It had mp 238-240°(d).(Found: C, 33.15; H, 5.45; N, 10.9. $C_7H_{13}IN_2$ requires C, 33.35; H, 5.15; N, 11.1%). The iodides listed in table 20 were made analogously.

2,3-Cyclohexano-2,3-dihydro-5,7-diphenyl-1H-1,4-diazepinium perchlorate - Dibenzoylmethane (2.24 g, 10 mmoles) was added to a cooled solution of 1,2-diaminocyclohexane (2.28 g, 20 mmoles) in acetic acid (3.3 g) and the mixture was heated under reflux for 75 min. The cooled mixture was poured into water (50 ml) and extracted three times with ether to remove unchanged diketone. Addition of perchloric acid (60%, 3.4 ml) to the aqueous layer caused the crystallisation of the perchlorate (2.9 g, 72%), mp 258.5-260°(d) (from nitromethane), λ_{max} 358 and 267 nm (ε 21700 and 15500), ν_{max} 3300, 1570, 1490, 1300, 1100 cm^{-1}, τ([$^2H_6$]DMSO/TFA) 0.46 (2H, s), 2.0-2.6 (10H, complex), 4.66 (1H, s), 6.52 (2H, br), 8.0-8.8 (8H, br complex). (Found: C, 62.6; H, 5.9; N, 6.95. $C_{21}H_{23}ClN_2O_4$ requires C, 62.55; H, 5.7; N, 6.95%).

Table 20 Dihydrodiazepinium Iodides

Compound	M.p.	Recryst. Solvent	ANALYSIS FOUND %C	%H	%N	THEORETICAL %C	%H	%N	Ref.
62b	170.5-171.5°	water, then propan-2-ol	38.6	6.25	9.9	38.55	6.05	10.0	16
62c	198-198.5°	water, then propan-2-ol	54.5	4.2	7.45	54.25	4.5	7.45	21
62d	236-239°	water, then reppt ex methanol by ether	56.5	5.35	7.15	56.45	5.2	6.95	x
62e	206.5-208°(d)	propan-2-ol	35.95	5.55	10.45	36.1	5.65	10.55	18
62f	139-141°	reppt ex methanol by ether	35.85	5.85	10.65	36.1	5.65	10.55	21,x
62g	161-162°	water, then propan-2-ol	45.8	5.0	8.75	45.85	4.8	8.9	20
62h	208-210°	water, then propan-2-ol	57.0	5.4	7.0	56.5	5.2	6.9	17
62i	194.5-195.5°	water, then propan-2-ol	42.95	6.25	9.2	43.15	6.2	9.15	16
62j	300-302°(d)	nitro-methane	58.0	5.4	6.4	58.6	5.35	6.5	x
62k	144.5-145°	propan-2-ol	36.0	5.85	10.35	36.1	5.65	10.55	17
62l	104.5-105°	propan-2-ol	33.35	5.4	11.4	33.35	5.15	11.1	17
70a	185-186°(d)	water	29.2	4.4	9.9	29.3	4.2	9.75	x
70c	185-186°(d)	water	22.05	3.4	7.55	22.2	3.15	7.4	34
70d	253-253.5° (d)	water	28.35	4.2	14.45	28.3	4.05	14.15	35

x: this work

Dihydrodiazepinium Salts for Bromination Rate Studies

The preparation of the following dihydrodiazepinium perchlorates has been described; 2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71a), mp 140-142° (lit[15] 138-141.5°), 2,3-cyclohexano-2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71b), mp 189-192° (lit[16] 188-190°), 2,3-dihydro-1,5,7-trimethyl-1H-1,4-diazepinium perchlorate (71c), mp 54.5-55.5° (this work, p.104), 2,3-dihydro-2,5,7-trimethyl-1H-1,4-diazepinium perchlorate (71d), mp 105-106.5° (lit[16] 105-106.5), 2,3-dihydro-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate (71e), mp 118-120° (lit[16] 117-119°), 2,3-dihydro-1,4-dimethyl-1H-1,4-diazepinium perchlorate (71f), mp 95-97° (lit[17] 98-99°), 2,3-dihydro-1,4-diphenyl-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71g) mp 180-182° (lit[17] 176°), 2,3-dihydro-5-methyl-7-phenyl-1H-1,4-diazepinium perchlorate (71i), mp 127-129° (lit[20] 123-124.5°), 2,3-dihydro-5,7-diphenyl-1H-1,4-diazepinium perchlorate (71k) mp 157-158° (lit[21] 154-156°), 2,3-dihydro-2,2-dimethyl-5,7-diphenyl-1H-1,4-diazepinium perchlorate (71 l), mp 157-159° (lit[172] 159.5-160.5°), 6-bromo-2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71n), mp 156-157° (lit[33] 160-162°), 6-iodo-2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71o), mp 166-168° (lit[34] 168-170°), 2,3-dihydro-6-nitro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71p), mp 228-231°(d) [lit[35] 235°(d)].

5,7-Diethyl-2,3-dihydro-1H-1,4-diazepinium perchlorate (71h) - Heptane-3,5-dione (1.28 g, 10 mmoles) was added to a solution of ethylenediamine (0.6 g, 10 mmoles) in acetic acid (1 ml) and the mixture was heated to 120-130° for 15 min. Addition of perchloric acid (60%, 2 ml) to the cooled solution caused the dihydrodiazepinium perchlorate (0.84 g, 33%) to crystallise slowly. It had mp 130-131° (from propan-2-ol), λ_{max} 326 nm (ε 16400), ν_{max} 3300, 1610, 1550, 1330, 1250, 1100, 840 cm^{-1}, τ([$^2H_6$]acetone) 1.20 (2H, br), 4.81 (1H, t, $J_{1(4),6}$ 2.0 Hz), 6.22 (4H, m), 7.45 (4H, q), 8.74 (6H, t). (Found: C,42.6;

H, 7.05; N, 10.8. $C_9H_{17}ClN_2O_4$ requires C, 42.75; H, 6.75, N, 11.1%).

2,3-Cyclohexano-2,3-dihydro-5-methyl-7-phenyl-1H-1,4-diazepinium perchlorate (71j) - Benzoylacetone (8.1 g, 50 mmole) was added to a solution of 1,2-diaminocyclohexane (5.7 g, 50 mmole) in acetic acid (50 ml), and the mixture was heated under reflux for 1 h. Water (350 ml) was added to the cooled solution and it was extracted three times with ether. Addition of perchloric acid (70%, 22 ml) to the aqueous layer caused the crystallisation of the perchlorate (11.0 g, 65%), mp 169-170° (from ethanol), λ_{max} 341 and 258 nm (ε 17600 and 9300), ν_{max} 3300, 1610, 1510, 1100, 810, 780, 720 cm^{-1}, τ([$^2H_6$]DMSO) 0.57 (1H, s), 0.88 (1H, s), 2.40 (5H, complex), 4.81 (1H, s), 6.72 (2H, m), 7.70 (3H, s), 8.0-8.8 (8H, complex). (Found: C, 56.65; H, 6.15; N, 8.25. $C_{16}H_{21}ClN_2O_4$ requires C, 56.4; H, 6.15; N, 8.2%).

6-Chloro-2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (71m) - Prepared as its 2,2,5,7-tetramethyl analogue (page 106) from 2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (2.25 g, 10 mmoles) and N-chlorosuccinimide (1.3 g, 10 mmoles) in chloroform (25 ml), this perchlorate had mp 135-137° (from propan-2-ol), λ_{max} 346 nm (ε 12600), ν_{max} 3300, 1620, 1510, 1430, 1320, 1100, 900, 700 cm^{-1}, τ([$^2H_6$]acetone) 0.60 (2H, br), 6.19 (4H, s), 7.49 (6H, s). (Found: C, 32.4; H, 4.85; N, 10.8. $C_7H_{12}ClN_2O_4$ requires C, 32.45; H, 4.65; N, 10.8%).

6-Bromo-2,3-dihydro-1,4-dimethyl-1H-1,4-diazepinium perchlorate - Bromine (0.16 g, 1 mmole) in methanol (3 ml) was added dropwise to a solution of the dihydrodiazepinium perchlorate (71f) (0.23 g, 1 mmole) in methanol (5 ml). Addition of ether completed the precipitation of the 6-bromo compound (0.22 g, ca. 70%), presumably with a mixture of bromide and perchlorate anions. Recrystallisation from ethanolic perchloric acid gave the perchlorate, (0.18 g, 59%), mp 180-181° (from ethanol), λ_{max} 372 and 268 nm (ε 12600 and 480), ν_{max} 1640, 1580, 1340, 1260, 1160, 1100, 630 cm^{-1}, τ(saturated

solution in [$^2H_6$]acetone) 1.90 (2H, s), 6.00 (4H, s), 6.41 (6H, s). (Found: C, 26.7; H, 4.05; N, 9.05. $C_7H_{12}BrClN_2O_4$ requires C, 27.7; H, 3.95; N, 9.25%).

Kinetic Studies - These were carried out at 25°C on solutions in methanol (AR grade). The dihydrodiazepinium perchlorate concentrations were fixed at 0.1 M, while the bromine solutions were 0.02 M, and also 0.02 M in sodium bromide. The fast reactions were observed by stopped-flow methods, and the remainder by conventional spectrometric techniques. In all cases, the decay of the bromine absorption was followed, either at 420 or 450 nm. Unless stated otherwise, the reactions obeyed first-order kinetics for at least three half-lives; the errors were computed by the method of least squares. Results are shown in table 4 (page 46).

N,N'-Diarylliminoenamines

1,5-Diaza-1,5-diphenyl-1H-pentadienium perchlorate (74b) (cf. reference 47) - Addition of perchloric acid (60%, 10 ml) to a solution of 1,1,3,3-tetraethoxypropane (11 g, 50 mmoles) and aniline (9.3 g, 100 mmoles) in ethanol (5 ml) caused the crystallisation of the perchlorate (12.5 g, 75%). It had mp 220-221°(d) (from ethanol), λ_{max} 380 and 242 nm (ε 45100 and 12400), ν_{max} 3200, 1630, 1590, 1340, 1200, 1100, 1020 cm^{-1}, τ([$^2H_6$]DMSO) - 1.94 (2H, br), 1.24 (2H, br), 2.3-2.8 (10H, complex), 3.76 (1H, t). (Found: C, 56.0; H, 4.85; N, 8.6. $C_{15}H_{15}ClN_2O_4$ requires C, 55.8; H, 4.65; N, 8.7%).

1,5-Diaza-1,1,5,5-tetraphenyl-1H-pentadienium perchlorate (74c) - Perchloric acid (60%, 10 ml) was added to a solution of 1,1,3,3-tetraethoxypropane (5.5 g, 2·5 mmoles) and aniline (8.5 g, 50 mmoles) in ethanol (10 ml) and the solution was heated to ca. 80° for 30 min. Addition of ether to the cooled solution promoted the crystallisation of the perchlorate (8.4 g, 71%), mp 208-209.5° (from ethanol), λ_{max} 386 and 241 nm (ε 46100 and 19300), ν_{max} 1610, 1560, 1490, 1240, 1100, 770, 700 cm^{-1}, τ(TFA) 1.47 (2H, d), 2.3-2.9 (20H, complex), 4.51 (1H, t). (Found: C, 68.05; H, 4.7; N, 5.85. $C_{27}H_{23}ClN_2O_4$ requires C, 68.3; H, 4.85; N, 5.9%).

1,5-Diaza-2-methyl-1,5-diphenyl-1H-pentadienium salts (75) - Perchloric acid (60%, 20 ml) was added to a solution of 2-oxobutyraldehyde-dimethylacetal (13 g, 0.1 mole) and aniline (18.8 g, 0.2 mole) in methanol (10 ml), and the solution was heated to ca. 60° for 1 h. Addition of ether to the cooled solution caused the perchlorate salt to crystallise (19.5 g, 58%). It had mp 185-187° (from propan-2-ol), λ_{max} 367 and 238 nm (ε 37700 and 9400), ν_{max} 3300, 1640, 1560, 1490, 1330, 1260, 1100, 770 cm^{-1}, τ([$^2H_6$]acetone) -0.46 (br, d), 1.28 (1H, q), 2.4-2.8 (10H, complex), 3.90 (1H, d), 7.24 (3H, s). (Found:

C, 56.9; H, 5.05; N, 8.4. $C_{16}H_{17}ClN_2O_4$ requires C, 57.05; H, 5.05; N, 8.3%).

The use of picric acid (wet, ca. 60 g) in place of perchloric acid, and of ethanol (100 ml) and acetone (100 ml) as solvent in the above recipe gave the corresponding picrate (67%), mp 149-150° (from ethanol). (Found: C, 56.55; H, 4.2; N, 14.75. $C_{22}H_{19}N_5O_7$ requires C, 56.75; H, 4.1; N, 15.05%).

1,5-Diaza-2,4-dimethyl-1,5-diphenyl-1H-pentadienium perchlorate (76) - This perchlorate was made by the method described by Scheibe[64] for the chloride salt, from 4-anilinopent-3-ene-2-one[235] and anilinium perchlorate. Recrystallised from ethanol, it had mp 166.5-167.5°, λ_{max} 346 and 231 nm (ε 22700 and 10000), ν_{max} 3300, 1600, 1530, 1300, 1100, 1040, 700 cm^{-1}, τ([$^2H_6$]acetone) 0.10 (br), 2.6-2.8 (complex), 4.26 (s), 7.29 (s). (Found: C, 58.35; H, 5.65, N, 7.9. $C_{17}H_{19}ClN_2O_4$ requires C, 58.2; H, 5.4; N, 8.0%).

Reactions with 1,2-diamines

Typical recipe:

2,3-Dihydro-1H-1,4-diazepinium perchlorate[27] (73e) (cf. reference 26) - Ethylenediamine (0.18 g, 3 mmoles) in methanol (100 ml) and the pentadienium perchlorate (74b) (0.97 g, 3 mmoles) in methanol (100 ml) were added over a period of ca. 3h to boiling methanol (500 ml). Evaporation of the solvent in vacuo and addition of ether promoted the crystallisation of the dihydrodiazepinium perchlorate (0.41 g, 69%), mp 310-312°(d) (from ethanol), λ_{max} 331 nm (ε 12600), ν_{max} 3300, 1640, 1570, 1320, 1240, 1100 cm^{-1}, τ([$^2H_6$]acetone) 0.7 (br), 2.20 (2H, br.m), 4.76 (1H, t), 6.10 (4H, s). (Found: C, 30.9; H, 4.85; N, 14.25. $C_5H_9ClN_2O_4$ requires C, 30.55; H, 4.6; N, 14.25%).

Use of the tetraphenylpentadienium perchlorate (74c) in place of its diphenyl analogue in the above recipe also gave the

dihydrodiazepine in similar yield, but the quality of the product was improved. This compound had identical spectra to those above (however, λ_{331} 14300 ± 200 in the uv spectrum), but decomposed violently at ca. 250°. The synthesis may be carried out on a larger scale (eg. 12 mmole) with the same volume of methanol reservoir.

By the same method, the following dihydrodiazepinium salts were prepared:

2,3-Dihydro-1,4-dimethyl-1H-1,4-diazepinium perchlorate (73a) - Prepared from the diphenylpentadienium perchlorate (74b) (0.97 g, 3 mmole) and N,N'-dimethylethylenediamine (0.27 g, 3 mmoles), this salt (0.54 g, 80%) had mp 95-97° (from ethanol), mixed mp 95-96° (lit[17] 98-99°).

2,3-Dihydro-1-methyl-1H-1,4-diazepinium perchlorate (73b) - Prepared from the diphenylpentadienium perchlorate (74b) (0.97 g, 3 mmoles)and N-methylethylenediamine(0.22 g, 3 mmoles), this salt (0.3 g, 48%) had mp 102-103° (from ethanol), λ_{max} 336 nm (ε 15000), ν_{max} 3340, 1640, 1570, 1330, 1100, 800 cm^{-1}, τ([$^2H_6$]acetone), 2.25 (2H, complex), 4.87 (1H, t), 6.10 (4H, s), 6.45 (3H, s). (NH signals not apparent). (Found: C, 34.25; H, 5.4; N, 13.25. $C_6H_{11}ClN_2O_4$ requires C, 34.2; H, 5.25; N, 13.3%).

2,3-Dihydro-2-methyl-1H-1,4-diazepinium perchlorate (73c) - Obtained in very low yield (ca. 100 mg) from the diphenylpentadienium perchlorate (74b) (0.97 g, 3 mmoles) and 1,2-diaminopropane (0.22 g, 3 mmoles), this perchlorate had mp 182-184° (carefully reprecipitated by ether from methanol), λ_{max} 330 nm (ε 13400), ν_{max} 3300, 1640, 1570, 1320, 1100, 740 cm^{-1}, τ([$^2H_6$]acetone) 0.6 (br), 2.14 and 2.27 (2H, triplets), 4.72 (1H, t), 5.80 (1H, br), 6.26 (2H, s), 8.66 (3H, d). (Found: C, 34.25; H, 5.30; N, 13.1. $C_6H_{11}ClN_2O_4$ requires C, 34.2; H, 5.25; N, 13.3%).

1,4-Dibenzyl-2,3-dihydro-1H-1,4-diazepinium perchlorate (73d) - This salt (0.54 g, 48%) was obtained as an oil which solidified on trituration with a little methanol, from the diphenylpentadienium perchlorate (74b) (0.97 g, 3mmoles) and N,N'-dibenzylethylenediamine (0.72 g, 3 mmoles). It had mp 107.5-108.5° (from ethanol), λ_{max} 347 nm (ε 22800), ν_{max} 1640, 1570, 1240, 1100, 760, 710 cm^{-1}, τ([$^2H_6$]acetone) 2.02 (2H, d), 2.63 (10H, s), 4.74 (1H, t), 5.10 (4H, s, benzyl methylenes), 6.33 (4H, br.s, ring methylenes). (Found: C, 60.45; H, 5.4; N, 7.45. $C_{19}H_{21}ClN_2O_4$ requies C, 60.55; H, 5.6; N, 7.45%).

2,3-Dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate - Obtained from the 2,4-dimethylpentadienium perchlorate (76) (0.7 g, 2 mmoles) and ethylenediamine (0.12 g, 2 mmoles), this salt (0.24 g, 53%) had mp 136-138° (from ethanol), mixed mp 137-139° (lit[15] 139-141°). Its ir and uv spectra were identical with those of a genuine sample.

2,3-Cyclohexano-2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate - Prepared from the dimethylpentadienium perchlorate (76) (1.05 g, 3 mmoles) and 1,2-diaminocyclohexane (0.34 g, 3 mmoles), this perchlorate (0.28 g, 33%) had mp 189-190° (from propan-2-ol, after washing with water), mixed mp 188-189° (lit[16] 188-190°). The nmr spectrum of the crude product was identical with that of an authentic sample, but its uv spectrum suggests contamination by a compound with λ_{max} 232 nm.

2,3-Dihydro-5-methyl-1H-1,4-diazepinium picrate - Prepared as a crude solid (0.31 g, 46%) from the methylpentadienium picrate (75, Z = picrate) (0.94 g, 2 mmoles) and ethylenediamine (0.12 g, 2 mmoles), this picrate was purified by reprecipitation from hot ethanol by ether. It had mp 141-142° (from ethanol), mixed mp 142-144° (lit[22] 146-147°).

The following imidazolinium and tetrahydropyrimidinium salts were also prepared by means of the typical recipe:

1,2,3-Trimethyl-1H-imidazolinium perchlorate (77a) - This salt (1.45 g, 68%) was obtained from the dimethylpentadienium perchlorate (76) (3.51 g, 10mmoles) and N,N'-dimethylethylenediamine (0.9 g, 10 mmoles), and had mp 242-244° (from ethanol), λ_{max} 235 nm (ε 7500), ν_{max} 1640, 1310, 1100, 625 cm^{-1}, $\tau([^2H_2]O)$ 6.21 (4H, s), 6.96 (6H, s), 7.84 (3H, s). (Found: C, 34.0; H, 6.5; N, 13.05. $C_6H_{13}ClN_2O_4$ requires C, 33.9; H, 6.1; N, 13.2%).

1,2-Dimethyl-1H-imidazolinium perchlorate (77b) - This perchlorate (0.32 g, 53%) prepared from the dimethylpentadienium perchlorate (76) (1.05 g, 3 mmoles), and N-methylethylenediamine (0.22 g, 3 mmoles), had mp 135.5-136.5° (from propan-2-ol), λ_{max} 226 nm (ε 5400), ν_{max} 3350, 1650, 1600, 1300, 1100, 625 cm^{-1}, $\tau([^2H_2]O)$ 6.17 (4H, s), 6.96 (3H, s), 7.83 (3H, s). (Found: C, 30.1; H, 5.85; N, 14.25. $C_5H_{11}ClN_2O_4$ requires C, 30.25; H, 5.55; N, 14.1%).

2,4,4-Trimethyl-1H-imidazolinium perchlorate (77c) - Prepared from the dimethylpentadienium perchlorate (76) (1.05 g, 3 mmoles) and 1,2-diamino-2-methylpropane(0.27g, 3 mmoles), this salt(0.51g,ca.80%) had mp 119-119.5° (from propan-2-ol), λ_{max} 216 nm (ε 6700), ν_{max} 3300, 1610, 1340, 1100, 670 cm^{-1}, $\tau([^2H_2]O)$ 6.36 (2H, s), 7.82 (3H, s), 8.61 (6H, s). (Found: C, 33.9; H, 6.2; N, 12.95. $C_6H_{13}ClN_2O_4$ requires C, 33.9; H, 6.1; N, 13.2%). The uv spectrum of the crude product also shows a small peak at 325 nm, consistent with the formation of some 2,3-dihydro-2,2,5,7-tetramethyl-1H-1,4-diazepinium perchlorate.

Reactions between Ethylenediamine and 1,5-Diaza-2,4-dimethyl-1,5-diphenyl-1H-pentadienium perchlorate -

1. In Methanol - The dianil (76) (0.35 g, 1 mmole), in methanol (50 ml), and ethylenediamine (0.06 g, 1 mmole) in methanol (25 ml), were added over a period of 40 min to boiling methanol (200 ml), and the solution was heated under reflux for a further 10 min. The solvent

was evaporated in vacuo, leaving a residue of solution (6 ml) to which ether (200 ml) was added. The solid product (0.1 g) was filtered after 16 hr at 0°. Its nmr spectrum ([$^2H_6$]acetone) showed dihydrodiazepinium salt: imidazolinium salt in the proportion 70:30 [τ(imidazolinium salt) 5.93 (4H, s), 7.64 (3H, s)].

2. In Refluxing Propan-2-ol - This experiment was carried out under identical conditions to the above, with propan-2-ol replacing methanol. The nmr spectrum ([$^2H_6$]acetone) of the product (0.1 g) showed dihydrodiazepinium salt: imidazolinium salt = 40:60. The 2-methyl imidazolinium perchlorate (77d) had λ_{max} 219 nm, ν_{max} 3350, 1610, 1300, 1100, 710 cm^{-1}, τ([$^2H_2$]O) 6.12 (4H, s), 7.81 (3H, s), but could not be isolated in sufficient purity for analysis. (Found: M^+ 84.069221; M^+(cation-1) requires 84.068745).

3. In Propan-2-ol at 59° - The recipe was the same as (2) above, except that the temperature of the solution was maintained at 59° by means of a thermostatically controlled water-bath. The product (0.1 g) had dihydrodiazepinium salt: imidazolinium salt in the ratio 60:40, from its nmr spectrum ([$^2H_6$]acetone).

3,4,5,6-Tetrahydro-2-methyl-1H-pyrimidinium perchlorate (80) - Prepared from the dimethylpentadienium perchlorate (76) (1.05 g, 3 mmoles) and 1,3-diaminopropane (0.22 g, 3 mmoles), this compound (0.22 g, 37%) crystallised only with difficulty when cooled to -78°. It had mp 78-79° (from methanol/ether at -78°), λ_{max} ca. 208 nm (ε ca 5200), ν_{max} 3340, 1670, 1630, 1320, 1100 cm^{-1}, τ([$^2H_2$]O) 6.63 (4H, t), 7.87 (3H, s), 8.06 (2H, m). (Found: C, 30.45; H, 5.65; N, 13.6; M^+ 98.083824; $C_5H_{11}ClN_2O_4$ requires C, 30.25; H, 5.55; N, 14.1%, M^+(cation-1) requires 98.084394).

Identification of Side Product in Reactions leading to Imidazolinium Salts - The ethereal mother liquors from the reaction between N-methylethylenediamine and the 2,4-dimethylpentadienium salt (76) described

above, were evaporated in vacuo. The residual oil (0.59 g) had an ir spectrum identical with that of aniline, with a superimposed peak at 1100 cm^{-1} due to some remaining perchlorate ions (theoretical yield for 2 equivalents of aniline is 0.56 g). The constitution of the oil was further proved by the formation of N-benzylideneaniline [0.34 g, 87%, mp 50-51°, mixed mp 49-50° (lit 54°)], from benzaldehyde (0.2 g) and the oil (0.2 g).

Reactions with Monoamines

These preparations were carried out using the experimental conditions of the diamine reactions above, and the same work-up technique was used. Later experiments [eg. the improved procedure for (82b)] indicate that the compounds may be more easily obtained.

1,5-Diaza-5,5-pentamethylene-1-phenyl-1H-pentadienium perchlorate (82a) - Prepared from the diphenylpentadienium perchlorate (74b) (0.97 g, 3 mmoles) and piperidine (0.51 g, 6 mmoles), this salt (0.44 g, 47%) had mp 186-187° (from ethanol), λ_{max} 348 and 234 nm (ε 43200 and 7600), ν_{max} 3300, 1630, 1590, 1250, 1100, 1030, 850, 770 cm^{-1}, τ(TFA) 1.10 (1H, brd), 1.94 (1H, t), 2.31 (1H, d), 2.5-2.9 (5H, complex), 4.04 (1H, t), 6.35 (4H, br), 8.18 (6H, br.s). (Found: C, 53.45; H, 5.95; N, 8.8. $C_{14}H_{19}ClN_2O_4$ requires C, 53.4; H, 6.05; N, 8.9%).

1,5-Diaza-5,5-pentamethylene-1,1-diphenyl-1H-pentadienium perchlorate (82b) - Prepared from the tetraphenylpentadienium perchlorate (74c) (1.43 g, 3 mmoles) and piperidine (0.51 g, 6 mmoles), this salt (1.0 g, 86%) had mp 207-208° (from ethanol), λ_{max} 344 and 230 nm (ε 44800 and 11700), ν_{max} 1630, 1570, 1250, 1100, 1010, 780, 710 cm^{-1}, τ(TFA) 1.80 (1H, d), 2.18 (1H, d), 2.4-2.9 (10H, complex) 4.51 (1H, t), 6.28 and 6.56 (4H, br. singlets), 8.22 (6H, br.s). (Found: C, 58.6; H, 5.85; N, 6.7. $C_{20}H_{23}ClN_2O_4 \cdot H_2O$ requires C, 58.75; H, 6.10; N, 6.85%).

This compound may be prepared more conveniently without recourse to high dilution techniques . A solution of piperidine (0.51 g, 6 mmoles) in methanol (20 ml) was added to a solution of the dianil (74c) (1.43 g, 3 mmoles) in methanol (100 ml), and the solvent was evaporated. The perchlorate (1.1 g, 95%), which crystallised on addition of ether, had mp 204-205°, mixed mp 205-206°, and identical ir and uv spectra to those of the authentic compound.

1,5-Diaza-5-cyclohexyl-1,1-diphenyl-1H-pentadienium perchlorate (83) - Obtained from the tetraphenylpentadienium perchlorate (74c) (1.43 g, 3 mmoles) and cyclohexylamine (0.6 g, 6 mmoles), this salt (0.94 g, 80%) had mp 217-219° (from propan-2-ol), λ_{max} 342 and 230 nm (ε 58800 and 16200), ν_{max} 3200, 1650, 1620, 1580, 1490, 1250, 1220, 1100, 710 cm^{-1}, τ(TFA) 1.81 (1H, m), 2.11 (1H, d), 2.2-2.9 (10H, complex), 4.43 (1H, t), 6.52 (1H, br.s), 7.8-8.8 (10H, br. complex). (Found: C, 62.1; H, 6.2; N, 6.7. $C_{21}H_{25}ClN_2O_4$ requires C, 62.3; H, 6.2; N, 6.9%).

1,5-Diaza-1,1,5,5-bispentamethylene-1H-pentadienium perchlorate (84) - A solution of 1,5-diaza-5,5-pentamethylene-1,1-diphenyl-1H-pentadienium perchlorate (82b) (0.2 g, 0.5 mmole) and piperidine (0.25 g, 3 mmoles, 6 x excess) in methanol (10 ml) was heated under reflux for 20 min. Evaporation of the solvent, followed by addition of ether, caused the crystallisation of the perchlorate (0.14 g, 92%), mp 131-132.5° (from ethanol) (lit[66] 130-131°), λ_{max} 315 nm (ε 60900), ν_{max} 1630, 1620, 1250, 1100, 1030, 820 cm^{-1}, τ[$^2H_6$]acetone) 2.21 (2H, d), 4.21 (1H, t), 6.34 (8H, br.s), 8.27 (12H, br.d). (Found: C, 50.9; H, 7.65, N, 9.05. $C_{13}H_{23}ClN_2O_4$ requires C, 50.9; H, 7.5; N, 9.15%).

Use of only one equivalent of piperidine caused incomplete conversion to the symmetrical iminoenamine, even after 1 h under reflux. The progress of the reaction was monitored conveniently by uv spectroscopy.

Attempt to Prepare Unsymmetrical Dialkyl 1,5-Diazapentadienium Salt - A solution of 1,5-diaza-5-cyclohexyl-1,1-diphenyl-1H-pentadienium perchlorate (83) (0.2 g, 0.5 mmole) and piperidine (0.25 g, 3 mmoles , 6 x excess) was heated under reflux for 30 min. Evaporation of the solvent and addition of ether gave a solid (0.13 g), mp and mixed mp 130-131°, whose ir and uv spectra were identical with those of 1,5-diaza-1,1,5,5-bispentamethylene-1H-pentadienium perchlorate (84), therefore obtained in 85% yield.

Kinetic Studies - These were carried out at 25°C on solutions in methanol (AR grade). The reactions of the tetraphenyl compound (74c) were followed at 390 nm; the solution was 2.1×10^{-5} M in the pentadienium salt, and was 2.5×10^{-3} M, and 0.02 M in piperidine and 2-methylpiperidine respectively. The reaction of the diphenyl derivative (82b) was followed at 340 nm; the solution was 2.4×10^{-5} M in the perchlorate and 0.25 M in piperidine. The reactions obeyed first order kinetics for at least three half-lives; the errors were computed by the method of least squares.

Dihydrodiazepines from Oxo-enamines

1. From 4-aminopent-3-ene-2-one - A solution of ethylenediamine (1.2 g, 20 mmoles) and the oxoenamine[236] (2.04 g, 20 mmoles) in acetic acid (2 ml) was heated to ca. 120° for 15 min. Addition of perchloric acid (60%, 4 ml) to the cooled solution yielded 2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium perchlorate (2.65 g, 59%) as a white solid. It had mp and mixed mp 141-142° (lit[15] 139-141°), and had ir and uv spectra identical with those of a genuine sample.

2. From 4-anilinopent-3-ene-2-one - Similarly, a solution of ethylene-diamine (0.6 g, 10 mmoles) and the oxoenamine[235] (1.75 g, 10 mmoles) in acetic acid (1 ml) were heated to ca. 120° for 15 min. Addition of perchloric acid (60%, 2 ml) to the cooled solution gave the

5,7-dimethyldihydrodiazepinium perchlorate (1.53 g, 68%) mp 140-142°, mixed mp 141-142° (lit[15] 139-141°), whose ir and uv spectra were identical with those of an authentic sample.

Reactions of 2,3-Dihydro-1H-1,4-diazepinium perchlorate

6-Bromo-2,3-dihydro-1H-1,4-diazepinium perchlorate (88b) - Bromine (0.16 g, 1 mmole) in methanol (3 ml) was added dropwise to a solution of the corresponding 6-unsubstituted compound (0.2 g, 1 mmole) in methanol (10 ml). Addition of ether provided the 6-bromo compound (0.2 g, ca.72%), which, when recrystallised from ethanolic perchloric acid gave the perchlorate, mp 154-155°, λ_{max} 360 and 268 nm (ε 10200 and 3000), ν_{max} 3300, 1630, 1540, 1330, 1250, 1100, 920 cm^{-1}, τ([$^2H_6$]DMSO) -0.4 (br), 1.95 (2H, s), 6.36 (4H, s), J_{17}([$^2H_6$]DMSO/TFA) 7.8 Hz. (Found: C, 22.05; H, 3.1; N, 10.1. $C_5H_8BrClN_2O_4$ requires C, 21.8; H, 2.9; N, 10.15%).

6-Chloro-2,3-dihydro-1H-1,4-diazepinium perchlorate (88a) - A solution of the 6-unsubstituted dihydrodiazepinium perchlorate (0.4 g, 2 mmoles) and N-chlorosuccinimide (0.27 g, 2 mmoles) in acetic acid (8 ml) was heated under reflux for 2 min. Addition of ether to the cooled solution precipitated the chloro compound (0.38 g, 83%), mp 121-121.5° (from ethanol), λ_{max} 359 nm (ε 9800), ν_{max} 3300, 1640, 1550, 1320, 1240, 1100, 930 cm^{-1}, τ([$^2H_6$]DMSO) -0.42 (br), 1.96 (2H, s), 6.34 (4H, s), J_{17}([$^2H_6$]DMSO/TFA) 8.2Hz. (Found: C, 26.15; H, 3.45; N, 12.4. $C_5H_8Cl_2N_2O_4$ requires C, 25.95; H, 3.45; N, 12.1%).

2,3-Dihydro-6-iodo-1H-1,4-diazepinium perchlorate (88c) - The use of N-iodosuccinimide (0.45 g, 2 mmole) in place of N-chlorosuccinimide in the above recipe gave the 6-iodo compound (0.58 g, 90%), mp 234-235°(d) (from ethanol), λ_{max} 369 and 314 nm (ε 7700 and 1400), ν_{max} 3300, 1630, 1550, 1330, 1100, 930 cm^{-1}, τ([$^2H_6$]DMSO) -0.25 (br), 1.98 (2H, s), 6.34 (4H, s), J([$^2H_6$]DMSO/TFA) 8.4 Hz. (Found: C, 18.65; H, 2.6; N, 8.8. $C_5H_8ClIN_2O_4$ requires C, 18.6; H, 2.5; N, 8.7%).

Reaction of Piperidine with 2,3-Dihydro-1H-1,4-diazepinium perchlorate - A solution of the dihydrodiazepinium perchlorate (0.2 g, 1 mmole)

and piperidine (0.86 g, 10 mmole, 5 x excess) in methanol (12 ml) was heated under reflux for 20 min. The solvent was removed *in vacuo*, whereupon addition of ether caused the crystallisation of 1,5-diaza-1,1,5,5-bispentamethylene-1*H*-pentadienium perchlorate (84) (0.25 g, 82%), mp 129-131°, mixed mp 129-130° (lit[66] 130-131°). The product also had uv, ir and nmr spectra identical with those of an authentic sample.

In a parallel experiment, 2,3-dihydro-5,7-dimethyl-1*H*-1,4-diazepinium perchlorate (0.23 g, 1 mmole) was treated with piperidine under the above conditions. After 12 h under reflux, the dihydrodiazepinium salt was recovered unchanged [mp 140-141.5° (lit[15] 139-141°)] (0.19 g, 83%).

Kinetic Studies - These were carried out at 25°C on solutions in methanol (AR grade). The solutions were *ca.* 1.5-2.0 M in piperidine; the concentration of 2,3-dihydro-1*H*-1,4-diazepinium perchlorate was 5.1×10^{-3} M and the reaction was followed over one half-life at 295 nm. It obeyed first-order kinetics, ($k = (2.55 \pm 0.09) \times 10^{-3}$ min^{-1}). The concentration of the 5,7-dimethyl derivative was 0.25 M, and no reaction was apparent over a period of 7 days. The dihydrodiazepinium salt (mp 139-141°, mixed mp 139-140°) was recovered unchanged.

Reaction of 1,2-Diamines with 2,3-Dihydro-1H-1,4-diazepinium perchlorate - A solution of the dihydrodiazepinium perchlorate (0.2 g, 1 mmole) and *N,N'*-dimethylethylenediamine (0.45 g, 5 mmole) in methanol (15 ml) was heated under reflux for 1 h. Evaporation of the solvent and addition of ether gave an oil which crystallised from hot ethanol yielding 2,3-dihydro-1,4-dimethyl-1*H*-1,4-diazepinium perchlorate (0.15 g, 67%) as a white solid. It had mp and mixed mp 95-96° (lit[17] 98-99°) and ir and uv spectra identical with those of a genuine sample.

In contrast, reaction of 1,2-diamino-2-methylpropane with the

dihydrodiazepinium salt under the above conditions gave an oil whose uv spectrum (λ_{max} 310 nm) confirmed that an alternative reaction had taken place.

Action of Nucleophiles on the 6-Halogeno Compounds (88) -

1. Sodium Methoxide - 6-Bromo-2,3-dihydro-1H-1,4-diazepinium salt (88b) (0.14 g, ca. 0.5 mmole) was dissolved in a solution of sodium methoxide [from sodium (0.13 g)] in methanol. The uv spectrum of the solution showed a shift in absorption maximum to 337 nm. No further change was observed on heating under reflux for 30 min. The methanol was evaporated in vacuo, water (5 ml) was added, the solution was extracted with ether (3 x 10 ml) and the combined organic layers were dried (Na_2SO_4). On evaporation of the ether, perchloric acid (70%, 0.1 ml) was added, and a solid (0.05 g) crystallised slowly. This material had mp 148-150° (from ethanol), mixed mp 149-151°, and ir and uv spectra identical with those of the initial 6-bromodihydrodiazepinium salt, (88b), recovered, therefore, in 36% yield. (The low recovery is probably due to the necessarily harsh work-up conditions.)

The compound with λ_{max} 337 nm was identified as the bromo-dihydrodiazepine base by its nmr spectrum, taken in situ in $C[^2H_3]O[^2H]/NaOC[^2H_3]$: τ 2.57 (2H, s), 6.40 (4H, s). The equivalence of the protons at the 5- and 7-positions excludes any possibility of nucleophilic attack at these sites.

2. Thiourea - The 6-bromo compound (88b) (0.14g, 0.5 mmole) and thiourea (0.04 g, 0.5 mmole) were heated under reflux in ethanol (5 ml) for 23 h. The uv spectrum of the mixture showed that no reaction had taken place. Addition of ether to the cooled solution precipitated the unchanged 6-bromo derivative (88b) (0.1 g, 72%), mp 146-149° (from ethanol), mixed mp 148-150°, whose ir and uv

spectra were also identical with those of a genuine sample. (The low melting-point is presumably due to some thiourea contaminant, since it has similar solubility properties.)

A repeat of this experiment with the 6-iododihydrodiazepinium perchlorate (88c) (0.16 g, 0.5 mmole), gave, after 24 h under reflux, the 6-unsubstituted compound (0.07 g, 70%), identical by ir and uv spectra with an authentic sample. Similar deiodination occurred, however, in the absence of thiourea.

PART 2

1,2-Dihydropyrimidines

2,2-Diethyl-1,2-dihydro-4-methylpyrimidinium salts (95) - The base was made by the method of Hoffmann and Mühle[53]. Gaseous ammonia was passed for 8 h through a stirred solution of 2-oxobutyraldehyde-dimethylacetal (33 g) and diethylketone (50 g) containing ammonium nitrate (10 g). Sodium hydroxide (60 g) in water (60 ml) was then added slowly. The crude dihydropyrimidine (93) separated as an oil and was purified by distillation. The fraction of bp 80-90° (1-2 mm) [lit[53] 85-87° (1.5 mm)] solidified in the receiver, and was sufficiently pure for the isolation of the salts (yield 11.2 g, 30%).

Gaseous hydrogen bromide was passed through a solution of the base (5.3 g) in ether, and the bromide (95b) immediately separated as yellow crystals (7.4 g, 91%). It had mp 184.5-185° (from nitromethane). (Found: C, 46.25; H, 7.4; N, 12.0. $C_9H_{17}BrN_2$ requires C, 46.35; H, 7.3; N, 12.0%).

The chloride salt (95a) which was made by a similar method, had mp 180-180.5° (from nitromethane), λ_{max} 356 nm (ε 4550), ν_{max} 3100, 1630, 1570, 1540, 1260, 1160, 820 cm^{-1}, τ($C[^2H]Cl_3$) -0.36 (br.s), -0.10 (br.d), 2.63 (1H, double d), 5.11 (1H, d), 7.71 (3H, s), 8.01 (4H, q), 8.93 (6H, t). (Found: C, 57.6; H, 9.5; N, 14.75. $C_9H_{17}ClN_2$ requires C, 57.3; H, 9.0; N, 14.85%). This salt could be made more conveniently but in slightly poorer yield from the base and methanolic hydrogen chloride.

Addition of a saturated solution of picric acid (wet, ca. 2.5 g) in acetone to a solution of the base (93) (1.53 g, 10 mmoles) in ether caused the crystallisation of the picrate (95c) (2.5 g, 66%), mp 123-125° (from ethanol). (Found: C, 47.25; H, 5.0; N, 18.35. $C_{15}H_{19}N_5O_7$ requires C, 47.2; H, 5.0; N, 18.2%).

2,2-Diethyl-1,2-dihydro-1,4-dimethylpyrimidinium iodide (97) - 2,2-Diethyl-1,2-dihydro-4-methylpyrimidine (93) (0.77 g, 5 mmoles) was dissolved in ether (20 ml) and methyl iodide (6.3 g, 9.5 times excess) was added. The solution became cloudy in a few minutes, and was left overnight at room temperature, whereafter the iodide (97) crystallised (0.8 g, 55%) on trituration with a little acetone. It had mp 153-154° (from propan-2-ol), λ_{max} 374 nm (ε 5100), ν_{max} 3200, 1630, 1570, 1510, 1300, 1160, 1030, 780 cm^{-1}, $\tau(C[^2H]Cl_3)$ 0.74 (1H, br), 2.31 (1H, d), 5.12 (1H, double d), 6.75 (3H, s), 7.62 (3H, s), 7.89 (4H, m), 8.85 (6H, t). (Found: C, 40.75; H, 6.65; N, 9.7. $C_{10}H_{19}IN_2$ requires C, 40.8; H, 6.45; N, 9.5%).

2,2-Diethyl-1,2-dihydro-4,6-dimethylpyrimidinium picrate (96) - A monoketal of acetylacetone was first made by the method of Dorman[62]. Acetylacetone (100 g, 1 mole) and ethylene glycol (62 g, 1 mole) were heated under reflux in benzene (500 ml) containing p-toluenesulphonic acid (0.2 g) under conditions for the azeotropic removal of water. After water (18 ml, 1 mole) had been collected, the solvent was removed, and the residue was distilled at reduced pressure. The fraction of bp 96-100° (22 mm) (60 g, 42%), was used for the next stage.

The cyclisation to give the pyrimidine was effected by the same method as for the 4-methyl analogue, except that the acetylacetone monoketal (38 g) was used in place of the keto acetal. The pyrimidine base (94) (25.9 g, 63%) so obtained had bp 60° (0.5 mm) and solidified in the receiver flask.

Treatment of the base with gaseous hydrogen halides yielded only oils. However, the reaction of the base (4.15 g, 25 mmoles) in ether with picric acid (wet with ethanol, 6.5 g) in acetone gave a stable picrate (96) (6.75 g, 68%) after evaporation of the solvent and addition of ether. The salt had mp 138-140°(d) (from propan-2-ol), λ_{max} 352 nm (ε 19800), ν_{max} 3300, 1640, 1560, 1320, 1270, 1170 cm^{-1},

τ(C[^{2}H]Cl$_3$, saturated solution) 1.15 (2H, s), 1.68 (br), 5.01 (1H, s), 7.80 (6H, s), 8.08 (4H, q), 9.01 (6H, t). (Found: C, 48.65; H, 5.3; N, 17.85. $C_{16}H_{21}N_5O_7$ requires C, 48.6; H, 5.3; N, 17.7%).

Reaction of 2,2-diethyl-1,2-dihydro-4,6-dimethylpyrimidine (94) with methyl iodide - Reaction of the 4,6-dimethylpyrimidine base (94) (1.66 g, 10 mmoles) in ether (10 ml) with methyl iodide (12.0 g, 9 times excess) under the same conditions as for the 4-methyl analogue, gave a yellow solid (1.89 g) mp 162-164° (from propan-2-ol), λ_{max} 366 nm. Its nmr spectrum showed it to be a 3:1 mixture of 2,2-diethyl-1,2-dihydro-1,4,6-trimethylpyrimidinium iodide (99) [τ(C[^{2}H]Cl$_3$) 0.90 (br), 5.13 (1H, s), 6.87 (3H, s), 7.88 (q) and 8.90 (t)], and 2,2-diethyl-1,2-dihydro-1,3,4,6-tetramethylpyrimidinium iodide (100) [τ(C[^{2}H]Cl$_3$) 5.05 (1H, s), 6.79 (6H, s), 7.88 (q) and 8.85 (t). The 4- and 6-methyl groups of the two compounds gave signals at τ 7.67, 7.71 and 7.74, but could not be further assigned.] (Found: C, 43.35; H, 7.1; N, 8.8. The proposed mixture requires C, 43.3; H, 6.9; N, 9.0%).

Reactions with Electrophiles

5-Bromo-2,2-diethyl-1,2-dihydro-4-methylpyrimidinium salts (103) -

Method 1 - Bromine (0.70 g, 4.4 mmoles) in methanol (3 ml) was added dropwise to a solution of the 5-unsubstituted dihydropyrimidinium bromide (95b) (0.92 g, 4 mmoles) in methanol (3 ml). Addition of ether precipitated the bromo-compound (103 b) (0.92 g, 75%), mp 114-116° (reprecipitated from propan-2-ol by ether), λ_{max} 379 nm (ε 3800), ν_{max} 3100, 1610, 1520, 1260, 1160 cm^{-1}, τ(C[^{2}H]Cl$_3$) -0.14 (br), 0.13 (br), 2.42 (1H, d), 7.51 (3H, s), 7.96 (4H, m), 8.92 (6H, t). (Found: C, 34.45; H, 5.45; N, 9.1. $C_9H_{16}Br_2N_2$ requires C, 34.6; H, 5.15; N, 8.95%).

Method 2 - N-Bromosuccinimide (0.36 g, 2 mmoles) and the 5-unsubstituted dihydropyrimidinium chloride (95a) (0.38 g, 2 mmoles) were shaken

together in chloroform (5 ml), until all the solid had dissolved. The solvent was evaporated and the residue was taken up in a little methanol. When the solution was cooled to -78° it caused crystallisation of succinimide, which was filtered off. Addition of ether to the concentrated filtrate promoted crystallisation of the chloride (103a), (0.4 g, 76%), mp 109-110° (reprecipitated from propan-2-ol by ether), (Found: C, 39.3; H, 6.1; N, 9.95. $C_9H_{16}BrClN_2 \cdot \frac{1}{2}H_2O$ requires C, 39.05; H, 6.15; N, 10.15%).

5-Bromo-2,2-diethyl-1,2-dihydro-4,6-dimethylpyrimidinium salts (104)

Method 1 - Reaction of bromine (0.16 g, 1 mmole) in methanol (2 ml) with the 5-unsubstituted dihydropyrimidinium picrate (96) (0.4 g, 1 mmole) in methanol (3 ml) as above, yielded, on evaporation of the solvent and addition of ether, the bromide (104a) (0.29 g, 89%). It had mp 127-129° (from propan-2-ol), λ_{max} 368 nm (ε 4400), ν_{max} 3100, 1610, 1560, 1290, 1170, 1100, 1040, 750 cm^{-1}, τ(C[^{2}H]Cl_3) 0.12 (2H, br), 7.53 (6H, s), 7.96 (4H, q), 8.94 (6H, t). (Found: C, 36.65; H, 5.45; N, 8.6. $C_{10}H_{18}Br_2N_2$ requires C, 36.8; H, 5.5; N, 8.6%).

Method 2 - The 5-bromodihydropyrimidinium picrate (104b) (0.66 g, 70%) was obtained as above from N-bromosuccinimide (0.36 g, 2 mmoles) and the 5-unsubstituted dihydropyrimidine (96) (0.8 g, 2 mmoles) in chloroform (10 ml). In this case, work-up at -78° yielded the pyrimidine directly, which was recrystallised from propan-2-ol. It had mp 155-156°. (Found: C, 40.7; H, 4.35; N, 14.85. $C_{16}H_{20}BrN_5O_7$ requires C, 40.5; H, 4.2; N, 14.75%).

Reaction of 2,2-diethyl-1,2-dihydro-4-methylpyrimidinium salts (95) with N-chlorosuccinimide -

1. Chloride - Reaction of the 5-unsubstituted dihydropyrimidinium chloride (95a) (0.76 g, 4 mmoles) with N-chlorosuccinimide (0.52 g, 4 mmoles) in chloroform (10 ml) by the same method as described for

bromination, gave, on work-up, the chloro compound (106) as an oil which could not be crystallised reproduceably. It had λ_{max} 374 nm, $\tau(C[^2H]Cl_3)$ 2.51 (1H, d), 7.56 (3H, s), 7.99 (4H, q), 8.93 (6H, t). (Found M^+ 186.092705. $C_9H_{15}{}^{35}ClN_2$ [= M(cation-1)] requires 186.092370). The mass spectrum also showed an intense peak at m/e 99 corresponding to succinimide

2. Bromide - Reaction of the corresponding bromide (95b) (0.46 g, 2 mmoles) with N-chlorosuccinimide (0.26 g, 2 mmoles) in chloroform (5 ml) yielded 5-bromo-2,2-diethyl-1,2-dihydro-4-methylpyrimidinium chloride (103a) (0.38 g, 71%), mp 110-111° (reprecipitated from propan-2-ol by ether), λ_{max} 378 nm (ε 3600), M^+ 229, 231. (Found: C, 39.2; H, 6.1; N, 9.9; Cl^- (as AgCl) 13.75. $C_9H_{16}BrClN_2 \cdot \frac{1}{2}H_2O$ requires C, 39.05; H, 6.15; N, 10.15; Cl^- 12.85%).

5-Chloro-2,2-diethyl-1,2-dihydro-4,6-dimethylpyrimidinium picrate (105) - Prepared as for its 5-bromo analogue, from the 5-unsubstituted dihydropyrimidinium picrate (96) (0.8 g, 2 mmoles) and N-chloro-succinimide (0.26 g, 2 mmoles) in chloroform (10 ml), the 5-chloro compound (105) (0.32 g, 36%) so obtained had mp 153.5-154.5° (from propan-2-ol), ν_{max} 3300, 1620, 1550, 1300, 1170, 1090, 1040, 730 cm^{-1}, $\tau(C[^2H]Cl_3$, saturated solution) 1.13 (2H, s), 7.63 (6H, s), 8.03 (4H, q), 9.01 (6H, t). (The NH signal was not apparent.) (Found: C, 44.95; H, 4.7; N, 16.25. $C_{16}H_{20}ClN_5O_7$ requires C, 44.7; H, 4.65; N, 16.3%).

2,2-Diethyl-1,2-dihydro-5-iodo-4-methylpyrimidinium chloride (107) - The use of N-iodosuccinimide (0.5 g, 2 mmoles) in place of N-bromo-succinimide in the above recipe gave the 5-iodo compound (107) (0.45 g, 66%), mp 96-96.5°(d) (reprecipitated from methanol by ether), λ_{max} 384 nm (ε 3500), ν_{max} 3100, 1610, 1530, 1270, 1160, 770 cm^{-1}, $\tau(C[^2H]Cl_3)$ -0.80 (br), -0.47 (br), 2.41 (1H, d), 7.53 (3H, s), 8.02 (4H, q), 8.93 (6H, t). (Found: C, 34.05; H, 5.05; N, 8.8. $C_9H_{16}ClIN_2$ requires C, 34.35; H, 5.1; N, 8.9%).

Reaction of 2,2-diethyl-1,2-dihydro-4-methylpyrimidinium chloride (95a) with p-nitrophenyldiazonium salts - The pyrimidine (95a) (0.38 g, 2 mmoles) and p-nitrophenyldiazonium fluoroborate (0.54 g, slight excess) were suspended in water (10 ml) and kept overnight. The red solid which precipitated was thoroughly washed with benzene and ether. Its mass spectrum suggested that the coupled product and the Gomberg arylated product may be present in the mixture (see Discussion).

Reactions with Nucleophiles

Reactions of 2,2-Diethyl-1,2-dihydro-4-methylpyrimidinium salts (95) with nucleophiles -

1. Piperidine - A solution of the dihydropyrimidinium picrate (95c) (0.38 g, 1 mmole) and piperidine (0.86 g, 10 mmoles) in methanol (10 ml) was heated under reflux for 20 min. The solvent was removed in vacuo, and addition of ether gave a red oil which crystallised (0.18 g) on scratching the walls of the flask, mp 142-142.5° (from ethanol), λ_{max} 315 nm (ε 52100), ν_{max} 3400, 3100, 1620, 1570, 1350, 1290, 1170, 1090, 760 cm^{-1}, $\tau([^2H_6]DMSO)$ 1.16 (br), 1.40 (2H, s), 2.10 (1H, d), 4.59 (1H, d), 6.42 and 6.60 (4H, br. singlets), 7.77 (3H, s), 8.37 (6H, br.s). (Found: C, 47.05; H, 5.3; N, 18.05. $C_{20}H_{27}N_5O_7$ requires C, 47.25; H, 5.0; N, 18.35%). It had M^+ 152, and was identified as 1,5-diaza-5,5-pentamethylene-2-methyl-1H-pentadienium picrate, therefore obtained in 47% yield. The spectroscopic evidence does not exclude the possibility of this being the 4-methyl isomer. An analogous reaction with the bromide (95b) gave a product contaminated with piperidinium bromide.

2. Ethylenediamine Derivatives - The dihydropyrimidinium picrate (95c) (1.90 g, 5 mmoles) and ethylenediamine (1.5 g, 25 mmoles) were heated under reflux in methanol (10 ml) for 20 min. The methanol was evaporated in vacuo, and addition of ether gave a crude red-brown solid (1.68 g). Recrystallisation from ethanol produced

2,3-dihydro-5-methyl-1H-1,4-diazepinium picrate (111), (0.9 g, 53%), mp 127-128°, λ_{max} 330 nm (ε 26100), ν_{max} 3300, 1640, 1560, 1330, 1270, 800 cm^{-1}, τ([$^2H_6$]DMSO) ca. 0.5 (v.br), 1.40 (2H, s), 2.57 (1H, d), 5.06 (1H, d), 6.40 (4H, br.s), 7.80 (3H, s). (Found: C, 42.25; H, 3.7; N, 20.85. $C_{12}H_{13}N_5O_7$ requires C, 42.5; H, 3.85; N, 20.65%). The melting-point (lit[22] 146-147°) could not be raised by recrystallisation; samples prepared at a later date showed the reported melting-point, which was not diminished on mixing with this material.

By the same method, 2,3-dihydro-1,4,5-trimethyl-1H-1,4-diazepinium picrate (112) (0.16 g, 43%) was prepared from the picrate (95c) (0.38 g, 1 mmole) and N,N'-dimethylethylenediamine (0.45 g, 5 mmole). It had mp 118-119° (from ethanol), λ_{max} 343 nm (ε 28700), ν_{max} 1640, 1570, 1340, 1270, 800 cm^{-1}, τ([$^2H_6$]acetone) 1.37 (2H, s), 2.58 (1H, d), 4.93 (1H, d), 6.07 (4H, br.s), 6.55 (6H, s), 7.67 (3H, s). (Found: C, 45.6; H, 4.85; N, 19.2. $C_{14}H_{17}N_5O_7$ requires C, 45.8; H, 4.65; N, 19.05%).

Similarly, 2,3-dihydro-1,5-dimethyl-1H-1,4-diazepinium picrate (113) was prepared in 70% yield from the picrate (95c) (0.38 g, 1 mmole) and N-methylethylenediamine (0.37 g, 5 mmole). It had mp 141-142° (from ethanol), λ_{max} 338 nm (ε 28100), ν_{max} 3200, 1640, 1620, 1530, 1340, 1170, 1090, 720 cm^{-1}, τ([$^2H_6$]DMSO) 1.39 (2H, s), 2.53 (1H, d), 5.13 (1H, d), 6.37 (4H, complex), 6.67 (3H, s), 7.82 (3H, s), the NH signal was not apparent. (Found: C, 43.85; H, 4.3; N, 19.7. $C_{13}H_{15}N_5O_7$ requires C, 44.2; H, 4.25; N, 19.85%).

Reaction of Piperidine with 2,3-Dihydro-5-methyl-1H-1,4-diazepinium picrate (111) - The dihydrodiazepinium salt (111) (0.15 g) and piperidine (0.43 g) were heated under reflux in methanol (5 ml) for 8.5 h, during which time there was no change in the uv spectrum of the mixture. Evaporation of the solvent in vacuo and addition of ether gave the unchanged picrate (111) (0.13 g, 87% recovery), mp

and mixed mp 142-144°.

Reaction of Piperidine with 2,2-Diethyl-1,2-dihydro-4,6-dimethylpyrimidinium picrate (96) - The picrate (96) (0.4 g, 1 mmole) was heated under reflux with piperidine (0.86 g, 10 mmoles) in methanol (10 ml) for 5 h, during which time there was little change in the uv spectrum of the solution. Evaporation of the solvent followed by addition of ether and light petroleum gave a solid (0.23 g) whose nmr spectrum was consistent with piperidinium picrate. A small amount of dihydropyrimidinium picrate (96), mp 140-141°, mixed mp 139-140° was recovered by swamping the mother liquors with ether.

Reaction of 5-bromo-2,2-diethyl-1,2-dihydro-4-methylpyrimidinium bromide (103b) with thiourea - A solution of the dihydropyrimidinium salt (103b) (0.16 g, 0.5 mmole) and thiourea (0.04 g, 0.5 mmole) in ethanol (5 ml) was heated under reflux for 20 min. Addition of ether to the cooled solution provided a solid (0.09 g) whose ir spectrum was identical with that of the corresponding 5-unsubstituted dihydropyrimidine (95b). Recrystallised from propan-2-ol, it had mp 182-183°, mixed mp 180-181°, and was therefore obtained in 77% yield.

In a control experiment, the uv spectrum of the 5-bromo compound was unchanged after 100 min under reflux in ethanol.

Reaction of 5-bromo-2,2-diethyl-1,2-dihydro-4,6-dimethylpyrimidinium bromide (104a) with thiourea - A solution of the dihydropyrimidine (104a) (0.32 g, 1 mmole) and thiourea (0.08 g, 1 mmole) in ethanol (10 ml) was heated under reflux for 2 h. The uv spectrum of the solution had λ_{max} 350 nm, consistent with the 5-unsubstituted compound. Evaporation of the solvent and addition of ether gave an oil, whose nmr and mass spectra also suggested that protodebromination had taken place.

Action of thiourea on 5-chloro-2,2-diethyl-1,2-dihydro-4,6-dimethyl-pyrimidinium picrate (105) - The dibromopyrimidine (105) (0.21 g, 0.5 mmole) and thiourea (0.04 g, 0.5 mmole) were heated under reflux in ethanol (5 ml) for 5 h. The uv spectra of the solution recorded at intervals during the reaction showed no relative change in the pyrimidine/picrate absorption at 358 nm, and the thiourea absorption at 240 nm. Addition of ether, and light petroleum to the cooled solution gave a solid (0.16 g) whose ir spectrum was identical to that of the 5-chlorodihydropyrimidine (105) but whose uv spectrum showed the continued presence of thiourea, even after recrystallisation from propan-2-ol. The mass spectrum of the product showed an intense peak at m/e 76 corresponding to thiourea, and peaks at 202 and 200 (intensity ratio 1:3) confirming the presence of unreacted starting material.

2-Pyrimidinones and 2-Pyrimidinthiones

1,2-Dihydro-1,3-dimethyl-2-oxopyrimidinium salts (118) - (cf. reference 211). N,N'-Dimethylurea (4.4 g, 50 mmoles) and 1,1,3,3-tetraethoxypropane (11.0 g, 50 mmoles) were dissolved in ethanol (25 ml) and the mixture was cooled in ice. Sulphuric acid (concentrated, 3.5 ml, ca. 1.3 times excess) was added, and the solution was set aside overnight, when the hydrogen sulphate (118) (Z = HSO_4) crystallised as colourless needles (7.4 g, 64%). It had mp 203-205° (from methanol) (lit[207] 200-205°), λ_{max} 322 nm (ε 7000), ν_{max} 1720, 1600, 1320, 1200, 870, 780 cm^{-1}, τ([$^2H_6$]DMSO) 0.89 (2H, d), 2.97 (1H, t), 6.29 (6H, s). (Found: C, 32.35; H, 4.7; N, 12.45. $C_6H_{10}N_2O_5S$ requires C, 32.45; H, 4.5; N, 12.6%).

The use of hydrobromic acid in place of sulphuric acid gave the bromide (118) (Z=Br), mp 267.5-268°(d) (from methanol). (Found: C, 35.3; H, 4.6; N, 14.0. $C_6H_9BrN_2O$ requires C, 35.1; H, 4.4; N, 13.65%), while the use of perchloric acid gave the perchlorate (118) (Z=ClO_4), mp 200-200.5° (from methanol). (Found: C,32.25; H, 4.25; N, 12.7. $C_6H_9ClN_2O_5$ requires C, 32.0; H, 4.0; N, 12.45%).

The iodide salt, previously made by exhaustive methylation[205,207] can be obtained more conveniently via the perchlorate (cf. page 109) in 92% yield. It had mp 232-234° (lit[207] 237-239°), τ([$^2H_2$]O, 60 MHz) 1.06 (2H, d), 3.02 (1H, t), 6.28 (6H, s).

1,2-Dihydro-1,3,4-trimethyl-2-oxopyrimidinium salts (119) and 1,2-Dihydro-1,3,4,6-tetramethyl-2-oxopyrimidinium salts (120) - These salts were made in 91% and 50% yield respectively by the method of Seefelder[211]. The trimethyl hydrogen sulphate salt (119) (Z=HSO_4) had mp 158.5-159.5° (from methanol), λ_{max} 318 nm (ε 9300), ν_{max} 1710, 1620, 1580, 1200, 1050, 880, 770 cm^{-1}, τ([$^2H_6$]DMSO) 1.11 (1H, d), 2.96 (1H, d), 6.34 (6H, s), 7.28 (3H, s). (Found: C, 33.4; H, 5.75; N, 11.0. $C_7H_{12}N_2O_5S \cdot H_2O$ requires C, 33.05; H, 5.5; N, 11.0%), while the corresponding perchlorate (119) (Z=ClO_4) had mp 127-128°.

(Found: C, 35.15; H, 4.5; N, 11.65. $C_7H_{11}ClN_2O_5$ requires C, 35.2; H, 4.6; N, 11.75%). The tetramethyl hydrogen sulphate salt (120) (Z=HSO_4) had mp 146-147° (variable, due to hydration) (from ethanol), λ_{max} 316 nm (ε 11100), ν_{max} 1700, 1620, 1570, 1200, 1040, 860, 770 cm^{-1}, τ([$^2H_6$]DMSO) 2.94 (1H, s), 6.38 (6H, s), 7.36 (6H, s). (Found: C, 38.05; H, 6.0; N, 10.95. $C_8H_{14}N_2O_5S$ requires C, 38.4; H, 5.6; N, 11.2% . A repeat analysis gave: Found: C, 35.45; H, 6.3; N, 10.05. $C_8H_{14}N_2O_5S \cdot H_2O$ requires C, 35.8; H, 5.95; N, 10.45%).

1,2-Dihydro-1,3-dimethyl-2-thiopyrimidinium salts (121) - N,N'-Dimethylthiourea (2.6 g, 25 mmoles) was dissolved in ethanol (10 ml) and mixed with a solution of 1,1,3,3-tetraethoxypropane (5.5 g, 25 mmoles) in ethanol (5 ml). The mixture was cooled in ice while sulphuric acid (concentrated, 1.8 ml, ca. 1.3 times excess) was added. After being kept overnight at room temperature, addition of ether (ca. 10 ml) caused the crystallisation of the hydrogen sulphate (121) (Z=HSO_4) (3.0 g, 50%), mp 153.5-154° (from methanol at -78°), λ_{max} 379 and 280 nm (ε 1400 and 18800), ν_{max} 1610, 1580, 1300, 1200, 1020, 850, 700 cm^{-1}, τ([$^2H_6$]DMSO) 0.64 (2H, d), 2.58 (1H, t), 5.99 (6H, s). (Found: C, 29.95; H, 4.5; N, 11.5. $C_6H_{10}N_2O_4S_2$ requires C, 30.25; H, 4.2; N, 11.75%).

The use of hydrobromic acid in place of sulphuric acid gave the bromide (121) (Z=Br) in 63% yield. It had mp 201-201.5°(d), (reprecipitated from methanol by ether) (Found: C, 32.95; H, 4.4; N, 13.05. $C_6H_9BrN_2S$ requires C, 32.6; H, 4.05; N, 12.65%). The perchlorate (121) (Z=ClO_4) mp 157-158°, was made similarly. (Found: C, 29.8; H, 3.9; N, 11.65. $C_6H_9ClN_2O_4S$ requires C, 29.95; H, 3.75; N, 11.65%).

1,2-Dihydro-1,3,4-trimethyl-2-thiopyrimidinium salts (122) - The hydrogen sulphate (122) (Z=HSO_4) was prepared in 88% yield, by the same method as above, using 3-oxobutyraldehydedimethylacetal (3.4 g, 25 mmoles) in place of the tetraethoxypropane. It had mp 156-156.5°

(from methanol at -78°), λ_{max} 372 and 281 nm (ε 2200 and 21200), ν_{max} 1610, 1570, 1200, 1110, 1030, 870 cm^{-1}, τ([$^2H_6$]DMSO) 0.86 (1H, d), 2.56 (1H, d), 5.95 (3H, s), 6.02 (3H, s), 7.17 (3H,s). (Found: C, 31.15; H, 5.55; N, 10.25. $C_7H_{12}N_2O_4S_2 \cdot H_2O$ requires C, 31.1; H, 5.2; N, 10.35%). The perchlorate had mp 90.5-91.5°. (Found: C, 32.85; H, 4.45; N, 10.95. $C_7H_{11}ClN_2O_4S$ requires C, 33.0; H, 4.3; N, 11.0%).

1,2-Dihydro-1,3,4,6-tetramethyl-2-thiopyrimidinium hydrogen sulphate (123) (Z=HSO_4) - This salt was prepared in 50% yield in the same manner as its 1,3-dimethyl analogue, using acetylacetone (2.25 g, 25 mmoles) in place of the tetraethoxypropane. It had mp 198-198.5° (d) (from methanol at -78°), λ_{max} 366 and 283 nm (ε 2900 and 21100), ν_{max} 1610, 1550, 1270, 1200, 1100, 1050, 1020, 860 cm^{-1}, τ([$^2H_6$]DMSO) 2.51 (1H, s), 5.98 (6H, s), 7.24 (6H, s). (Found: C, 35.9; H, 5.7; N, 10.25. $C_8H_{14}N_2O_4S_2$ requires C, 36.1; H, 5.25; N, 10.55%).

Deuterium Exchange Measurements - The rates of deuterium exchange at the 4-methyl groups of the 1,3,4-trimethyl derivatives (119) and (122) were measured in unbuffered [$^2H_2$]O at ambient temperature in the nmr probe (ca. 34°). The peak areas were measured relative to those of the 1,3-dimethyl peak(s), which remained constant over the period of measurement (ca. 3h). The errors were computed by the method of least squares.

The deuterium exchange at the 5-position of the dimethyl derivatives (118) and (121) was measured competitively. A mixture of the two compounds (ca. 50 mg of each) was dissolved in 10% [^2H]Cl solution (0.5 ml). After 6 days at temperatures in the range 95-100°, the appearance of singlets at the centre of the 4(6) proton doublets at τ 0.90 and 1.05 (60 MHz) confirmed the exchange of the 5-proton in the thio- and oxo-compounds respectively.

Reactions with Halogens

5-Bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium bromide (126) - A solution of bromine (0.9 g, 5.6 mmoles) in methanol (10 ml) was added dropwise with stirring over a period of ca. 30 min to a methanolic solution of the 5-unsubstituted oxopyrimidinium bromide (118) (Z=Br) (1.03 g, 5 mmoles). Evaporation of the solvent, followed by trituration with acetone (10 ml) of the resultant orange solid, gave the 5-bromo derivative (126), (1.25 g, 88%) as light yellow needles, mp 274-275°(d) (from methanolic hydrobromic acid) [lit[210] 267-268°(d)], λ_{max} 351 and 253 nm (ε 1300 and 7500), ν_{max} 1720, 1570, 1310, 1080, 1050, 970, 950, 770 cm^{-1}, τ([$^2H_2$]O) 0.82 (2H, s), 6.19 (6H, s). (Found: C, 25.25; H, 3.0; N, 9.8. $C_6H_8Br_2N_2O$ requires C, 25.35; H, 2.8; N, 9.85%).

5,5-Dibromohexahydro-4,6-dimethoxy-1,3-dimethyl-2-oxopyrimidine (127), (R=Me) - The 5-unsubstituted oxopyrimidinium hydrogen sulphate (118) ($Z=HSO_4$) (1.2 g, 5 mmoles) was dissolved in methanol (70 ml) and added to a solution of bromine (2.0 g, 12.5 mmoles) in methanol (20 ml). The mixture was left overnight, poured into water (50 ml) and extracted four times with chloroform. The combined extracts were washed with dilute sodium hydroxide solution and then with water, and dried (Na_2SO_4). The solvent was evaporated, and the oily residue crystallised on addition of ether. The colourless pyrimidine (127) (R=Me) (0.53 g, 31%) had mp 132-133° (from carbon tetrachloride), λ_{max} ca. 232 nm, ν_{max} 1640, 1490, 1400, 1270, 1150, 1100, 1060, 760, 750, 720 cm^{-1}, τ(C[^{2}H]Cl_3) 5.37 (2H, s), 6.32 (6H, s), 6.98 (6H, s): the N-methyl signals are probably the more upfield. (Found: C, 27.5; H, 4.25; N, 8.2. $C_8H_{14}Br_2N_2O_3$ requires C, 27.75; H, 4.05; N, 8.1%).

Reaction of the 5,5-Dibromo Compound (127) (R=Me) with Acid - The dibromo compound (127) (R=Me) (0.1 g) was dissolved in acetone (3 ml) and aqueous hydrobromic acid (50%, 0.1 ml) was added, whereupon

a solid (0.07 g) immediately crystallised. It had mp 277-278°(d) and was identical by ir, nmr and uv spectroscopy with the 5-bromo compound (126), obtained in 86% yield.

Reaction of 1,2-Dihydro-1,3-dimethyl-2-thiopyrimidinium salts (121) with Bromine - The thiopyrimidinium bromide (121) (Z=Br) (1.1 g, 5 mmoles) was dissolved in methanol (15 ml) and bromine in methanol was added slowly with stirring until its colour persisted (ca. 3.6 g, 20 mmoles of bromine required). The precipitated solid (0.2 g) was filtered and washed with acetone; the filtrate was concentrated and triturated with acetone giving a yellow solid (0.85 g). Recrystallisation of both solids from methanolic hydrobromic acid gave identical materials, whose nmr, mass, ir and uv spectra showed them to be the 5-bromo-2-oxo derivative (126), mp 275-277°(d), obtained in 74% yield.

Use of only one molar equivalent of bromine in the above reaction gave a mixture whose nmr spectrum ($[^2H_2]O$) indicated the presence of both the reactant and product pyrimidinium salts, and also the unbrominated 2-oxo derivative (118). [peaks at τ 1.1 (d), 3.0 (t) and 6.2 (s)].

Tests for sulphide ion in the reaction mixture using sodium nitroprusside solution proved negative.

In an attempt to detect elemental sulphur in the reaction mixture, the hydrogen sulphate (121) ($Z=HSO_4$) (0.96 g, 4 mmoles), dissolved in the minimum volume of methanol was treated with bromine (3 g, > 16 mmoles) in methanol and the solution was stirred for 15 min. It was then poured into water (50 ml), and extracted four times with carbon disulphide. The organic extracts were washed with sodium hydroxide solution, and then with water, and finally dried (Na_2SO_4). The solvent was removed by distillation at atmospheric pressure, yielding a white solid (0.41 g), whose nmr, mass and ir spectra were consistent with those of the 5,5-dibromo compound (127) (R=Me), mp 126-128°, mixed mp 127-129°, obtained in

32% yield.

5-Bromo-4-bromomethyl-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium bromide (131) - Bromine (5.1 g, 32 mmoles) in methanol (20 ml) was added slowly, with stirring, to a solution of the trimethyloxopyrimidinium hydrogen sulphate (119) ($Z=HSO_4$) (2.4 g, 10 mmoles) in methanol (20 ml). After the addition was complete, the mixture was stirred for 1 h, and the solvent was removed *in vacuo*. On trituration of the residue with acetone (20 ml), the 5-bromo-4-bromomethyl derivative (131) crystallised (0.54 g). A reaction time of 10 min gave the same product in low yield (0.18 g), whereas extended reaction times of *ca.* 24 h gave a much higher yield (1.75 g, 45%) of an identical compound. It had mp 204.5-205°(d) (variable, depending on length of time the sample was heated) (from propan-2-ol/hydrobromic acid), λ_{max} 356 and 261 nm (ϵ 500 and 6200), ν_{max} 1720, 1600, 1540, 1280, 1050, 770 cm^{-1}, τ(TFA) 0.91 (1H, s), 5.22 (2H, s), 5.95 (3H, s), 6.02 (3H, s). ($\Delta\tau$(*N*,*N*'-diMe) 8.0 Hz at 100 MHz) (Found: C, 22.55; H, 2.7; N, 7.6. $C_7H_9Br_3N_2O$ requires C, 22.3; H, 2.4; N, 7.45%).

In another experiment, instead of the normal work-up by evaporation of methanol, the mixture was poured into water and extracted four times with chloroform. Evaporation of the dried (Na_2SO_4) combined organic extracts gave an impure yellow oil (3.78 g) which could not be crystallised. This material may be 5-bromo-4-(dibromomethyl)-1,2,5,6-tetrahydro-6-methoxy-1,3-dimethyl-2-oxopyrimidine (132) (Found: M^+ 405.834320; $C_8H_{11}{}^{81}Br^{79}Br_2N_2O_2$ requires M^+ 405.834990).

Reaction of this tetrahydropyrimidine (1.44 g) in acetone (15 ml) with aqueous hydrobromic acid (50%, 1 ml) gave the 5-bromo-4-bromomethyl derivative (131) (0.58 g, 43%), identical by ir, nmr, and uv spectroscopy with an authentic sample.

Reaction of 1,2-Dihydro-1,3-dimethyl-2-thiopyrimidinium hydrogen sulphate (122) ($Z=HSO_4$) with Bromine - Bromine (2.0 g, ca. 12 mmoles) in methanol (10 ml) was added slowly to a solution of the hydrogen sulphate (122) ($Z=HSO_4$) (0.51 g, 2 mmoles) in methanol (5 ml), and the mixture was kept overnight. The methanol was removed in vacuo, and acetone (2-3 ml) was added. Crystallisation was promoted by the addition of ether, and by cooling, thereby yielding a yellow product (0.18 g), identical by uv, ir, and nmr spectroscopy with the 5-bromo-4-bromomethyl-2-oxo derivative (131), obtained in 23% yield.

Reaction of 1,2-Dihydro-1,3,4,6-tetramethyl-2-oxopyrimidinium hydrogen sulphate (120) ($Z=HSO_4$) with Bromine - Bromine (1.6 g, 10 mmoles) in methanol (10 ml) was added slowly, with stirring, to a solution of the oxopyrimidinium salt (120) ($Z=HSO_4$) (1.26 g, 5 mmoles) in methanol (5 ml). The mixture was stirred for a further 30 min, and the yellow precipitate (1.55 g) was collected. It was dried overnight at 10^{-1} torr, and analysed without further purification. (Found: C, 20.65; H, 3.05; N, 6.2. $C_8H_{13}Br_4N_2O$ requires C, 20.25; H, 2.75; N, 5.9%), mp 143.5-144°, λ_{max} 316 nm (ε 9400). These results are consistent with a complex of unreacted oxopyrimidinium cation with molecular bromine, probably with bromide as counter-ion, which was obtained in 66% yield.

The complex (1.55 g) could be decomposed with acetone (5 ml) yielding the unchanged oxopyrimidinium bromide (120) (Z=Br), mp 206-208°(d) (from ethanol), τ(TFA, 60 MHz) 3.14 (1H, s), 6.16 (6H, s), 7.23 (6H, s). (Found: C, 39.85; H, 6.0; N, 11.6. $C_8H_{13}BrN_2O \cdot \frac{1}{2}H_2O$ requires C, 39.65; H, 5.8; N, 11.55%: Hydrogen sulphate counter-ion requires C, 38.4; H, 5.6; N, 11.2%), ν_{max} 3500 cm^{-1} (H_2O).

After the complex was filtered in the initial reaction between the oxopyrimidinium salt and bromine, the methanol mother liquors were concentrated and triturated with acetone (1-2 ml). When the flask was cooled and its walls were scratched, it induced the

crystallisation of 5-bromo-4,6-bis(bromomethyl)-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium bromide (0.15 g, 5%) as an orange powder, which was recrystallised from methanol/hydrobromic acid. It did not melt below 330°, but decomposed extensively, beginning at ca. 190°, λ_{max} 282 nm (ε 5300), ν_{max} 1700, 1550, 1060, 1010, 880, 760 cm^{-1}, τ(TFA) 5.12 (4H, s), 5.92 (6H, s). (Found: C, 20.4; H, 2.2; N, 6.05. $C_8H_{10}Br_4N_2O$ requires C, 20.45; H, 2.15; N, 5.95%).

Extended reaction times of up to 16 days did not substantially affect the yield of either product, which were the only compounds isolated.

Kinetic Studies - The reactions of the 2-oxopyrimidinium salts (118) and (119) with bromine were studied at 25° for aqueous solutions. The bromine solutions also contained potassium bromide. Reactions were performed under first-order conditions, with the pyrimidine present in 10-100 times excess. The progress of the reaction was followed by the decay in the bromine absorption at 380 nm.

5-Chloro-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium chloride (134) - A freshly made[237] solution of chlorine in methanol (containing ca. 2 mmoles of chlorine) was added in one portion to a solution of the 5-unsubstituted pyrimidinium hydrogen sulphate (118) (Z=HSO_4) (0.45 g, 2 mmoles) in methanol (50 ml). The methanol was evaporated in vacuo, and ether was added to the residue, whereupon the 5-chloro derivative (134) (0.46 g, ca. 90%) crystallised. Reprecipitation of the product twice from dry methanolic hydrogen chloride (ca. 1 M) with ether, followed by recrystallisation from methanol, gave the chloride salt (134), mp 243.5-244°(d), λ_{max} 348 and 252 nm (ε 600 and 7500), ν_{max} 1730, 1580, 1310, 1080, 1050, 960, 760 cm^{-1}, τ(TFA) 1.03 (2H, s), 6.03 (6H, s). (Found: C, 36.8; H, 4.25; N, 14.4. $C_6H_8Cl_2N_2$ requires C, 36.9; H, 4.1; N, 14.35%).

Analogous experiments with the trimethyl salt (119) failed to yield solid products, while 2,3-dihydro-5,7-dimethyl-1H-1,4-diazepinium

perchlorate gave a white, water soluble solid. Its nmr spectrum was consistent with that of a disalt of ethylenediamine, formed by solvolysis of the heterocycle.

1,2,3,4-Tetrahydro-1,3-dimethyl-4-(phenylazomethylene)-2-thiopyrimidine (135) -(cf. reference 211). Aniline (0.38 g, 4 mmoles) was dissolved in a mixture of hydrochloric acid (1.4 g) and water (1.4 ml); sodium nitrite (0.3 g) in water (1 ml) was added slowly, with cooling, in ice. This solution was added slowly, with cooling to a solution of the trimethyl thiopyrimidinium salt (122) ($Z=HSO_4$) (1.16 g, 4 mmoles) in water (10 ml), and the mixture was kept overnight at 0^o. The precipitated solid was discarded, and when an excess of sodium acetate solution was added to the filtrate, a bright red gelatinous precipitate (135) (0.6 g, 58%) separated out. Recrystallisation from aqueous hydrochloric acid gave the pyrimidine (135) as its hydrochloride, mp 221.5-223.5^o(d) (from dimethylformamide), λ_{max} 453 and 278 nm (ϵ 27000 and 19700), ν_{max} 1650, 1610, 1320, 1100, 910, 770 cm^{-1}, τ([$^2H_6$]DMSO, saturated solution), 1.51 (d, 6-CH), 1.82 (s, methine CH), 2.22 (d, 5-CH), 2.3-2.8 (complex, Ph group), 5.89 and 6.10 (both s, N,N'-methyl groups). The solution was too weak for a consistent integral to be recorded. (Found: C, 49.9; H, 5.6; N, 18.15. $C_{13}H_{15}ClN_4S\cdot H_2O$ requires C, 49.9; H, 5.45; N, 17.9%).

Reactions with Bases . (The spectra of the products are reported in the Discussion).

1,2,3,4-Tetrahydro-4-hydroxy-1,3-dimethyl-2-oxopyrimidine (126a) - The dimethyl oxopyrimidinium hydrogen sulphate (118) ($Z=HSO_4$) (50 mg) was dissolved in ca. 1 M sodium deuteroxide solution, and the nmr spectrum of the solution was characteristic of the 4-deuterioxy adduct (126a). The adduct was formed quantitatively only in the presence of excess base. It could not be isolated by extraction of

the mixture with ether, or by work-up of an attempted metathetic reaction using the hydrogen sulphate (118) ($Z=HSO_4$) and barium hydroxide.

Solutions of 1,2,3,4-tetrahydro-4-hydroxy-1,3-dimethyl-2-thiopyrimidine (136b), 5-bromo-1,2,3,4-tetrahydro-4-hydroxy-1,3-dimethyl-2-oxpyrimidine (136c) and 5-chloro-1,2,3,4-tetrahydro-4-hydroxy-1,3-dimethyl-2-oxopyrimidine (136d) were investigated in a similar manner. The uv spectra of the adducts (136) were recorded *in situ* for aqueous solutions, *ca.* 2×10^{-2} M in sodium hydroxide.

1,2,3,4-Tetrahydro-1,3-dimethyl-4-(N-piperidinyl)-2-oxopyrimidine (138a), 1,2,3,4-Tetrahydro-1,3-dimethyl-4-(N-piperidinyl)-2-thiopyrimidine (138b), 5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-4-(N-piperidinyl)-2-oxopyrimidine (138c) and their N-methylpiperidinyl analogues (139) - The pyrimidinium salt (118), (120) or (126) (50 mg) was dissolved in [$^2H_6$]DMSO (0.5 ml), and piperidine (50 mg) was added. In some cases, especially in the case of N-methylpiperidine, the addition of [$^2H_2$]O (to *ca.* 5%) improved the solubility of the product and the quality of the nmr spectrum, which was characteristic of the adduct. The uv spectra were recorded for aqueous solutions, *ca.* 2×10^{-2} M in piperidine; the quoted extinction coefficients are approximate, since the maxima were merely shoulders on the low-wavelength piperidine peak.

1,2,3,4-Tetrahydro-4-methoxy-1,3-dimethyl-2-oxopyrimidine (137a) - A solution of the 1,3-dimethyl-2-oxopyrimidinium hydrogen sulphate (118) ($Z=HSO_4$) (2.2 g, 10 mmoles) in methanol (120 ml) was mixed with a solution of sodium methoxide [from sodium (0.23 g, 10 mmoles)] in methanol (20 ml). The solvent was evaporated, and the resultant semi-solid mass was washed thoroughly with ether. The inorganic residue was filtered off and the ether was evaporated, leaving the crude 4-methoxy adduct (0.86 g, 56%) as an oil. Attempted

distillation at 0.3 torr resulted in decomposition of the sample. It had ν_{max} (liquid film) 1650, 1580, 1340, 1260, 1040, 880, 740 cm^{-1}. (Found: M^+ 156.089020; $C_7H_{12}N_2O_2$ requires M^+ 156.089872).

The uv spectra of the 4-methoxy adducts (137) were recorded in situ in methanol. The solutions were ca. 2×10^{-2} M in sodium methoxide. Their nmr spectra were recorded for solutions in [$^2H_6$]DMSO.

1,2,3,4-Tetrahydro-4-methoxy-1,3-dimethyl-2-thiopyrimidine (137b) - This pyrimidine was prepared in the same way as its oxo analogue, from the corresponding thiopyrimidinium hydrogen sulphate (120) (Z=HSO_4) (2.4 g, 10 mmoles) in methanol (30 ml), and sodium methoxide [from sodium (0.23 g, 10 mmoles)] in methanol (20 ml). It was obtained in 45% yield and had ν_{max} (liquid film) 1670, 1470, 1340, 1290, 1230, 1120, 1030, 910 cm^{-1}. (Found: M^+ 172.067458 $C_7H_{12}N_2OS$ requires M^+ 172.067032).

5-Bromo-1,2,3,4-tetramethyl-4-methoxy-1,3-dimethyl-2-oxopyrimidine (137c) - This pyrimidine was prepared in 90% yield, by the same method as above, using the corresponding 5-bromopyrimidinium bromide (126) (0.26 g, 1 mmole) in methanol, and sodium methoxide [from sodium (0.025 g, 1 mmole)] in methanol (5 ml). It had ν_{max} (liquid film) 1670, 1470, 1340, 1250, 1040, 780, 760 cm^{-1}. (Found M^+ 235.999163; $C_7H_{11}{}^{81}BrN_2O_2$ requires M^+ 235.998324).

Reactions of 1,2,3,4-Tetrahydro-4-methoxy-1,3-dimethyl-2-oxo-pyrimidine (137a) with electrophiles -

1. Acid - The 4-methoxy adduct (137a) (0.05 g) was dissolved in acetone (2 ml) and perchloric acid (60%, 2 drops) was added. Addition of ether precipitated 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium perchlorate (118) (Z=ClO_4) (0.045 g, 63%), mp and mixed mp 192-194°. Its uv spectrum was also identical to that of an authentic sample.

2. Bromine - A solution of bromine (0.16 g, 1 mmole) in chloroform (5 ml) was added in one portion to a solution of the 4-methoxy adduct (137a) (0.16 g, 1 mmole) in chloroform (5 ml). After 5 minutes the precipitated complex was filtered and decomposed with acetone: further product was obtained by addition of acetone to the filtrate. The product (0.1 g, 35%) had mp 279-282°(d) (from methanolic hydrobromic acid), and was identical by uv, ir and nmr spectroscopy with the 5-bromo pyrimidinium bromide (126).

3. N-Bromosuccinimide - N-Bromosuccinimide (0.18 g, 1 mmole) was added to a solution of the 4-methoxy adduct (137a) (0.16 g, 1 mmole) in chloroform (5 ml) and the mixture was shaken until all the solid had dissolved. The solvent was evaporated in vacuo, and the addition of ether, followed by dry methanolic hydrogen chloride (containing HCl, 1 mmole) caused the crystallisation of 5-bromo-1,2-dihydro-1,3-dimethyl, -2-oxopyrimidinium chloride (0.07 g, 25%), mp 255-257°(d), τ([$^2H_2$]O, 60 MHz), 0.78 (2H, s), 6.20 (6H, s). (Found: C, 29.85; H, 3.5; N, 12.05. $C_6H_8BrClN_2O$ requires C, 30.05; H, 3.35; N, 11.7%).

Reactions of 1,2,3,4-Tetrahydro-4-methoxy-1,3-dimethyl-2-thiopyrimidine (137b) with electrophiles -

1. Acid - The 4-methoxy adduct (137c) (0.1 g) was dissolved in acetone (2 ml) and aqueous hydrobromic acid (50%, 2 drops) was added. The yellow product (0.09 g), which was precipitated by ether, had mp 197-198°(d) (reprecipitated by ether from methanol), and was identical by uv and nmr spectroscopy with 1,2-dihydro-1,3-dimethyl-2-thio-pyrimidinium bromide, obtained in 70% yield.

2. N-Bromosuccinimide - No identifiable product was obtained when this reaction was carried out under the same conditions used for its oxo analogue (137a) above. Some reaction had nevertheless taken place as shown by the shift in the uv maxima of the reaction mixture.

APPENDIX

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