# 2, 3-DIHYDRO-1, 4-DIAZEPINES 1973-1977

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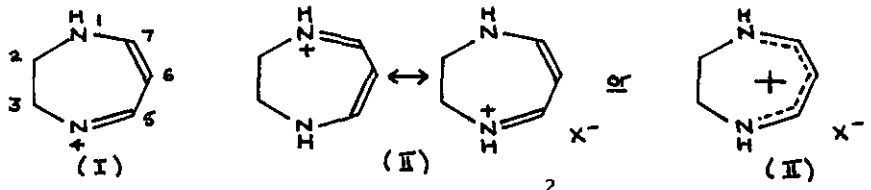
The chemistry of 2, 3-dihydro-1, 4-diazepines and their salts as recorded in the literature 1973-1977 (with a few references from 1978) is discussed under the headings:

Introduction
Preparation of Dihydrodiazepines
Structure and Spectra
Reactions with Electrophiles
Reactions with Nucleophiles
Rearrangement Reactions
Electrochemical Reduction

It was a pleasure and honour to be invited to contribute an article in celebration of Professor Tetsuo Nozoe's "Kiju". This article is dedicated to him with high personal as well as chemical regard and carries the authors' greetings and best wishes.

## Introduction

2, 3-Dihydro-1, 4-diazepines (I) and the related monocations (II) have been known since 1940.[1] Throughout this article the terms "dihydrodiazepine" and "dihydrodiazepinium salt" refer solely to this particular class of



(I) (II) (III)

diazepines. The chemistry of the vinamidinium[2] portion of these molecules (atoms 4-7, 1) has been of particular interest because of similarities to that of benzene. The dihydrodiazepines, and especially their monocations, are very stable species, for example the cations have a resonance energy of about 19 kcal $mol^{-1}$.[3]

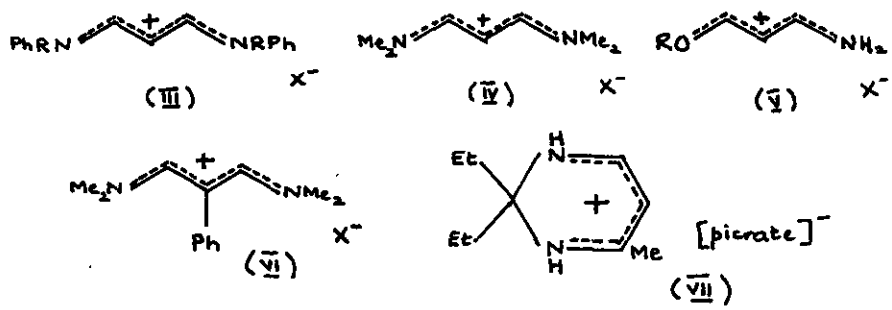
A comprehensive review of their chemistry as reported to the end of 1972 has been published,[4] and readers are referred to this review for earlier work. The present article deals with further work which has appeared in the literature in the five years 1973-1977, with a few references to work published in 1978.

## Preparation of Dihydrodiazepines

The commonest method for the preparation of dihydrodiazepines has been by the condensation reactions between 1, 2-diamines and 1, 3-dicarbonyl compounds, in solutions of appropriate pH. A number of new dihydrodiazepines has been prepared by this method;[5-11] of interest are the preparation of 6-fluoro,[6] 6-dimethylamino[9] and 6-arylazo[7,12] derivatives prepared from the corresponding malonaldehyde derivatives. 2, 3-Cyclopropanodihydrodiazepines, which have been used as substrates for the study of Cope type rearrangements, as discussed later in this article, were also made in this way from cis-1, 2-diaminocyclopropane dihydrochloride and the sodium salt of malonaldehyde.[10] Reaction between C, C'-tetramethylethylenediamine and acetylacetone had been earlier reported[13] to give only the acetylacetonate salt of the diamine, but the dihydrodiazepine is obtained[11] under the preferred conditions.[4]

Use of derivatives of dicarbonyl compounds such as diazapentadienium or vinamidinium salts e. g. (III, IV) and azaoxapentadienium salts

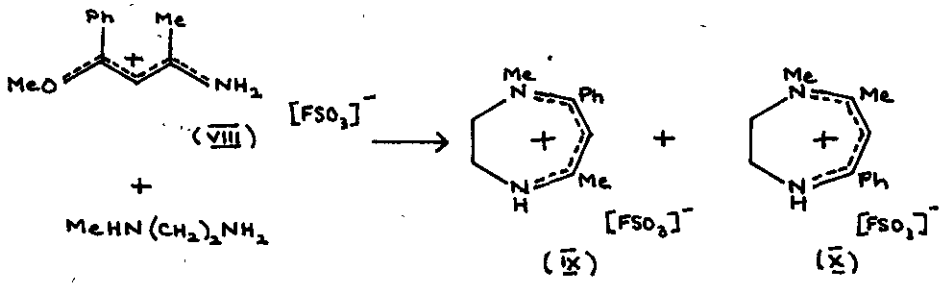
e. g. (V) may offer advantages over the use of the related dicarbonyl compounds themselves.




Thus the completely unsubstituted dihydrodiazepinium salt (II) is easily prepared from the vinamidinium salt (III, R=H or Ph).[14,15] A variety of substituted dihydrodiazepinium salts has been made from the salts (III) or from substituted analogues thereof, including dihydrodiazepines which have not been readily obtained otherwise.[15,16] An attempted preparation of a 2,3-cyclopropanodihydrodiazepinium salt from (III, R=H) gave instead a fourteen-membered ring.[10] Sometimes, when C-substituted vinamidinium salts were used, imidazolinium salts were formed instead of or as well as dihydrodiazepinium salts;[15] it appears that steric factors may be responsible. High dilution conditions are normally required in the direct reactions of the salts (III) with diamines, because there is a considerable difference in the rates of replacement of the first and second arylamine groups.[15] This may be overcome by first of all passing ammonia through a solution of (III) before adding the diamine, and this modification provides the most convenient method for the preparation of the unsubstituted dihydrodiazepinium salt (II), and also has been used to prepare derivatives hitherto unobtainable by reaction of amines with either the dicarbonyl compound or directly with the vinamidinium salts.[15] The vinamidinium salts (III, IV) are prepared from propynal[17] or, more simply, from 1,1,3,3-tetraethoxypropane.[14] C-substituted derivatives may be made similarly from dicarbonyl compounds, and from β-chlorovinylaldehydes, and the 3-phenyl derivative (VI) is readily obtained from phenylacetic acid.[18]

Dihydrodiazepinium salts have also been obtained by the action of 1,2-diamines on the dihydropyrimidinium salt (VII), which is itself a cyclic vinamidinium salt.[19]

The azaoxapentadienium salts (V) are prepared from oxoenamines which in turn are obtained from β-diketones and amines. They too react with diamines to give dihydrodiazepinium salts.[15] Sometimes this may provide a regioselective synthesis of a dihydrodiazepine which is only formed as a minor product from a diketone.[15] Thus N-methylethylenediamine reacts with the azaoxapentadienium salt (VIII) to give the 1,5-dimethyl-7-phenyldihydrodiazepinium salt (IX) as the main product, whereas with benzoylacetone the alternative isomer (X) is the predominant product.[15]




The earlier reported[20] conversion of bisanils of 1,2-diaminocyclopropanes into 2,3-dihydrodiazepines has been investigated further.[16] Reaction of the cis-diamine with several arylaldehydes provided only the dihydrodiazepine as the isolated product and the intermediate bisimine was not detectable on the n.m.r. time scale. With trimethylacetaldehyde, however, an intermediate bisimine was isolable, which only rearranged slowly at 100°, presumably because of the steric hindrance in the resultant 2,3-di-t-butyldihydrodiazepine. In the case of the trans-diamine both arylaldehydes and trimethylacetaldehyde provided bisimines; the arylimines, but not the t-butylimine, were converted into dihydrodiazepines when heated in vacuo.

Structure and Spectra

All spectroscopic evidence has suggested that dihydrodiazepines

take up a half-chair conformation with atoms N(4)-C(7), N(1) coplanar and atoms C(2, 3) staggered. An X-ray examination of a substituted dihydrodiazepinium cation nicely confirms this supposition.[21] The delocalisation of electrons in the vinamidinium moiety is also evident, with CN and CC bond lengths respectively of 1.33 and 1.40Å.

Electronic and infra-red spectra had been the subject of study before 1973 ;[4] more recent spectroscopic studies have largely dealt with $^{1}H$ [5, 16, 22, 23] and $^{13}C$ [24, 25] n. m. r. spectra, and also with mass spectra.[26]

In a detailed study[22] of the proton n. m. r. of a number of dihydrodiazepinium salts the magnitude of the coupling between the N-H and 6-C-H confirms both that the unsaturated portion of the molecule is planar and that the methylene groups must take up a half-chair conformation, since in a half-boat conformation these hydrogen atoms would not be coplanar. The coupling constants $J_{5,6,(6,7)}$ and $J_{4,5(1,7)}$, which are both $\sim$ 8.0 Hz, also provide evidence for the almost complete delocalisation of electrons over the conjugated chain. Dihydrodiazepinium salts which do not have large substituents on the 2, 3-positions undergo rapid ring inversion at room temperature,[5, 22] but cis-2, 3-diaryl derivatives show coalescence temperatures for 2, 3-H $\geqslant 50^{\circ}$,[16] while the spectrum of the cis-2, 3-di-t-butyldihydrodiazepinium cation is unchanged up to $100^{\circ}$.[16] In contrast crowding in the conjugated part of the ring appears to lower the activation energy for ring inversion.[22] This effect, which is apparently steric rather than ponderal* or electronic, may be due to slight distortion of the ring brought about by steric interaction of the vicinal groups. Further evidence for such vicinal crowding is shown in the spectra of phenyl groups attached to the conjugated part of the ring; in the absence of adjacent substituent groups they provide multiplet signals, but appear as singlets when vicinal methyl groups are present.[22]

A detailed study of the $^{13}C$-n. m. r. spectra of a variety of dihydrodiazepinium salts has been made,[25] and in a separate study the effect of a range of 6-substituents on spectra of 1, 4-diphenyldihydrodiazepinium salts

has been recorded.[24] The spectra emphasise the alternating polarity along the conjugated chain, the signals for 6-C appearing at $\delta \sim 90$ ppm and those for 5,7-C at $\delta \sim 160$ ppm. It is intriguing to note that the 6-C signal appears at a very similar position to that of the 3-C of the isoelectronic pentadienide anion, thus nicely demonstrating the ironical fact that the dihydrodiazepinium cation is an electron-rich cation. The application of an empirical relationship[27] provides an estimated electron density of $\sim 1.3$ electrons at C(6) and $\sim 0.8$ electrons at C(5,7), suggesting that the $\pi$-electrons are predominantly associated with the nitrogen atoms ($\sim 1.6$ electrons each).

Variable temperature studies again show the ring inversion.[25] They also indicate that a 2-methyl group shows equal preference for the quasi-equatorial or quasi-axial positions, presumably because there are no other axial substituents, resulting in an absence of 1,3-diaxial interactions.

The chemical shifts caused by different substituent groups closely resemble those observed for benzene derivatives.[24,25] As with proton n.m.r. the effect of vicinal groups on the conjugation between the vinamidinium system and substituent phenyl groups is clearly evident.

The mass spectra of a wide range of dihydrodiazepinium iodides have also been investigated.[26] In the case of 1,4-unsubstituted compounds a molecular ion peak for the cation is not observed, and thermal dissociation of the salt appeared to precede electron bombardment, but where the 1,4 and 6-positions were substituted the molecular ion was sometimes observable.

The chief fragmentation process is usually elimination of the C(2)-N(1) fragment, leaving a charged moiety which then breaks down further. Another less favoured breakdown involves ejection of the N(1)-C(7) fragment. Atypical spectra were observed for the 1,4-dimethyl and 1,4,6-trimethyl derivatives. For these compounds the iodide counter-ion removes a methyl group, and this is followed by loss of methylamine to generate a pyridine radical ion. When electronegative substituents are present at C(6), the major breakdown appears to be loss of the 6-substituent

followed by normal breakdown, but a 6-iodo derivative was anomalous in that electron impact appears to remove an electron from the iodo substituent rather than from the dihydrodiazepine nucleus.

Reactions with Electrophiles

Electrophiles characteristically attack dihydrodiazepinium cations at the 6-position to give 6-substituted derivatives; thus many 6-unsubstituted cations can be deuteriated, halogenated or nitrated, some of these reactions involving the interesting feature of electrophilic attack by one cation (e. g. $NO_2^+$) on another cation. (cf. ref. 4). Further examples of halogenation by bromine or by N-bromo or N-chlorosuccinimide have been reported.[8] A study of the protodehalogenation of a series of 6-halogeno-5, 7-dimethyl- or -diphenyl-dihydrodiazepinium salts in strong acid showed that the reaction proceeds more readily for iodo-derivatives than for bromo-derivatives and that chloroderivatives are the least reactive.[28] In addition to the relative ease of formation of the different halonium cations, steric factors also seem to be involved since reaction is more rapid for the 5, 7-diphenyl derivatives than for the 5, 7-dimethyl analogues,[28] while the 5, 7-unsubstituted-6-iodo derivative reacts yet more slowly.[29]

Like the 5, 7-substituted derivatives which had been studied earlier the unsubstituted cation (II) is easily halogenated, but, unlike these 5,7-substituted derivatives, it cannot be nitrated by nitric acid, for it appears to be decomposed irreversibly by mineral acids.[29]

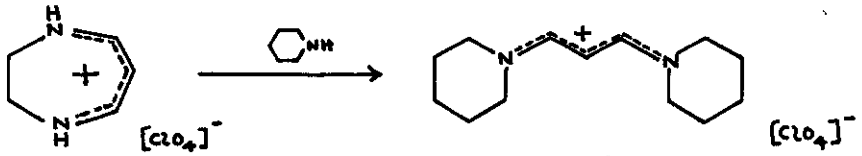
Deuteriation studies on this cation using deuteriotrifluoroacetic acid confirm the unreactivity of the 5, 7-positions towards electrophiles, for, while the 1, 4, 6-protons are exchanged very rapidly, no exchange of the 5, 7-protons had occurred after 9 days.[29]

6-Bromo- and 6-methyl-substituted dihydrodiazepinium cations are further attacked at the 6-position by bromine in aqueous solution but not in non-aqueous conditions. The kinetics of these reactions, which provide hydrolysis products, have been studied, and a reaction scheme has been elucidated.[30] 6-Phenyldihydrodiazepinium cations undergo electrophilic

substitution at the p-position of the phenyl ring, the normal reactivity of the 6-position being transmitted through the phenyl ring.[11]

Reactions with Nucleophiles

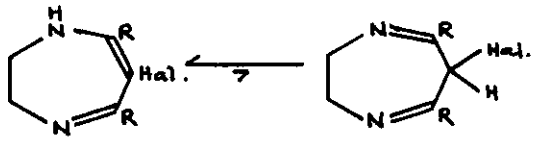
It had been thought earlier that dihydrodiazepinium salts, contrary to expectations, were rather inert to nucleophilic attack at the 5,7-positions. However, studies of 5,7-unsubstituted derivatives show that the unreactivity hitherto noted is due to the inhibiting effect of 5,7-substituents.[29] Thus the parent unsubstituted compound reacts readily with piperidine to give the vinamidinium salt (XI) in high yield.[29] By contrast the 5,7-dimethyl




(II) (XI)

derivative of (II) was effectively unchanged after being kept in a methanolic solution of piperidine for a week.[29] In some cases transdiazepination reactions ensue with 1,2-diamines, for example (II) reacts with N,N'-dimethylethylenediamine to give a 1,4-dimethyldihydrodiazepinium salt.[29]

6-Halogenodihydrodiazepines react with nucleophiles either by direct nucleophilic substitution or to give protodehalogenated products, the latter pathway being generally favoured by increasing size of the nucleophile and/or of neighbouring substituent groups. (cf. ref. 4). Because of the general similarity of dihydrodiazepines and their salts to aryl derivatives this susceptibility to nucleophilic displacement of halogen was surprising, as also was the ready nucleophilic attack at C(6) since this site is electron-rich and subject to ready electrophilic attack. It was suggested that both nucleophilic substitution and nucleophilic protodehalogenation proceeded via a small amount of the tautomer (XII) present, the first type of reaction involving nucleophilic attack at C(6) and the latter at the halogen atom. (see ref. 4).



(XIII) (XII)

Hal. = halogen atom

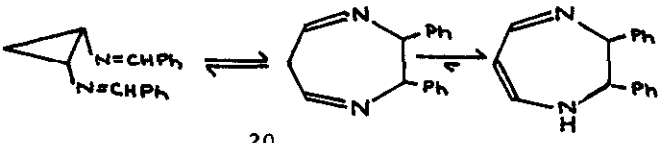
Protodehalogenation is favoured over nucleophilic substitution as the halogen atom varies from chlorine to bromine to iodine,[28] as might be expected on both steric grounds and from the ease of formation of a halonium ion.

Since nucleophilic substitution had been shown to be favoured by decrease in the size of adjacent substituent groups at the 5,7-positions it was expected that the 6-bromo derivative of the otherwise unsubstituted compound (II) would undergo rapid conversion into a 6-methoxy compound on treatment with methoxide ion, but in fact the bromo compound was recovered unchanged after being heated with sodium methoxide in methanol for 30 min.[29] Spectroscopic examination showed that the only product formed was the corresponding 6-bromodihydrodiazepine base.[29] This has been rationalised as follows.[29] If attack of nucleophiles on 6-halogeno compounds involves the bisimine form (XII) this must none the less be present only in very small amount, for its presence has not been demonstrated spectroscopically. Formation of the bisimine tautomer will be disfavoured because of the loss of the conjugation, with its considerable stabilisation energy. However there will be some slight compensating energetic gain if the substituents R are large, since in the conjugated tautomer these substituents and the 6-halogen atom must be distorted from coplanarity by overcrowding, but this crowding is relieved when position 6 becomes tetrahedral in the bisimine tautomer. In the case where R=H there will be no crowding in the conjugated form, and hence no compensation in forming the bisimine tautomer. Thus there may be a vanishingly small contribution from the bisimine form which would explain the unreactivity of the 6-bromo derivative of (II) (i. e. XIII, R=H) towards nucleophilic substitution.[29]

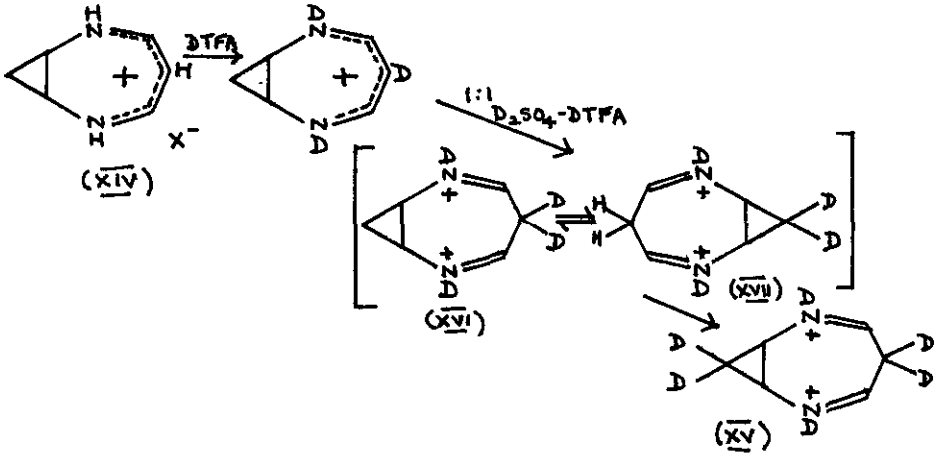
Thus the surprising reactivity towards nucleophiles at position 6 is shown to be not an inherent property of the 2, 3-dihydro-1, 4-diazepine system but rather a consequence of a substituent effect.

Rearrangement Reactions

Dihydrodiazepines obtained from bisanils of 1, 2-dicyclopropane are formed via a Cope rearrangement.[13, 16, 20] It was suggested that the final tautomerism controls the overall equilibrium.[20]




A very interesting example of a degenerate Cope rearrangement involving a dihydrodiazepine has been reported recently.[10] When a 2, 3-cyclopropanodihydrodiazepinium salt (XIV) was dissolved in deuteriotrifluoroacetic acid, deuterium exchange of the 1, 4, 6-hydrogen atoms occurred at once. On addition of deuteriosulphuric acid to the solution the hydrogen atoms of the methylene group of the cyclopropane ring were also replaced and the hexadeuteriodication (XV) was formed. Formation of the dication



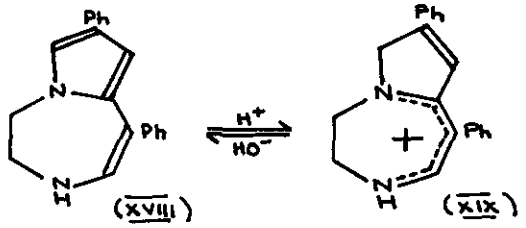

(XVI) provides a species which undergoes a Cope rearrangement to form (XVII), which is then further deuteriated, finally resulting in the observed

hexadeuteriated product (XV). In trifluoromethylsulphonic acid protonated species analogous to (XVI) and (XVII) are formed and the rearrangement reaction is detectable by $^{1}$H-n. m. r. spectroscopy. At room temperature the cyclopropane signals appear as an $ABX_2$ system but when the temperature is raised the structure of this system disappears. At $\sim 110^{\circ}$ the signals for the 2, 3- and 5, 7-hydrogen atoms coalesce. $\Delta G^{\ddagger}$ for the rearrangement is $73 \pm 2$ KJ mol$^{-1}$. Methyl groups at the 5, 7-positions would be expected to hinder such a Cope rearrangement and this is found to be so.

Another novel type of rearrangement which has been reported is the decomposition of 2, 3-diphenyldihydrodiazepine above its melting point giving ammonia and 2, 3-diphenylpyridine.[16] As noted in a previous section similar breakdowns sometimes take place in the mass spectrometer.[26]

Electrochemical Reduction

Electrochemical reduction of the 6-phenyldihydrodiazepinium cation in dimethylformamide at a mercury or a platinum electrode provided in high yield the unexpected product (XVIII).[31] A plausible explanation for its formation involves dimerisation of an initially formed radical followed by intramolecular displacement of ethylenediamine.




(XVIII) (XIX)

The base is converted by acid, reversibly, into a yellow cation (XIX).[31] This acid-base equilibrium is interesting in that it represents the interconversion of two distinct stabilised delocalised systems, a pyrrole and a dihydrodiazepinium cation, each of which have very similar resonance energies ($\sim$ 80-85 KJ mol$^{-1}$).[3] A similar product to (XVIII), but with an N-methyl group, is obtained from the reduction of the 1-methyl-6-phenyldihydrodiazepinium cation.[31]

The chemistry of 2, 3-dihydro-1, 4-diazepines has consistently provided unexpected results (see ref. 4). This has continued to be the case in the more recent work reported here, and there is every hope that these compounds will continue to produce interesting new features.

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