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Preface

Seven-membered rings are featured in three of the chapters of the present volume, namely, the benzazepines (S. Kasparek), 1,5-benzodiazepines (D. M. G. Lloyd and H. P. Cleghorn), and 2,3-dihydro-1,4-diazepines (D. M. G. Lloyd, H. P. Cleghorn, and D. R. Marshall). Recent advances in oxazole chemistry are described by R. Lakhan and B. Ternai, and H.-J. Timpe surveys the heteroaromatic *N*-imines. The final chapter is a review of aromaticity (M. J. Cook, A. R. Katritzky, and P. Linda), and it concentrates on the heterocyclic aspects of this controversial subject.

A. R. KATRITZKY
A. J. BOULTON

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2,3-Dihydro-1,4-diazepines

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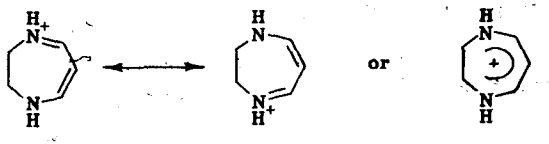
I. Introduction

Diazepines were reviewed in a previous volume in this series in 1967,[1] in a chapter which dealt with the whole range of diazepines. The present chapter and the succeeding one in this volume deal with two particular classes of diazepines, the 2,3-dihydro- and 2,3-benzo-1,4-diazepines. The literature is covered to the end of 1972, with some later references.

The first example of a 2,3-dihydro-1,4-diazepine was prepared in 1940,[2] although a compound had been described[3] previously as a dihydrodiazepine but, from its melting point, now appears to have been an alternative acyclic product. In recent years their chemistry has been studied extensively, particularly because of their chemical resemblance to benzenoid compounds and their quasi-aromatic[4] or meneidic[5,6] character. Throughout this chapter the terms "dihydrodiazepine" and "dihydrodiazepinium" are used solely to refer to 2,3-dihydro-1,4-diazepines (1) and their monocations (2), respectively. Spectroscopic data show that dihydrodiazepines



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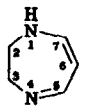

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(3)

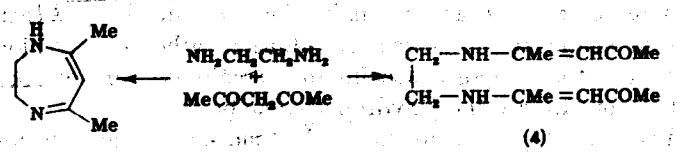
normally exist in the conjugated form (1) rather than in the tautomeric bisimino form (3).

II. Preparation of Dihydrodiazepines

The first diazepine to be prepared, namely the 5,7-dimethyl derivative, was obtained by condensation of acetylacetone with ethylenediamine,[2]

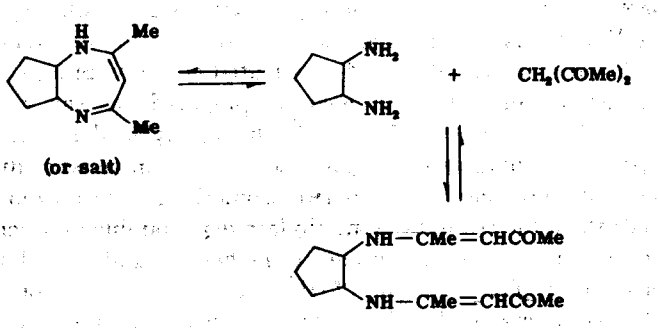
[1] F. D. Popp and A. C. Noble, *Advan. Heterocycl. Chem.* **8**, 21 (1967).
[2] G. Schwarzenbach and K. Lütz, *Helv. Chim. Acta* **23**, 1139 (1940).
[3] M. A. Rosanova, *J. Russ. Phys. Chem.* **47**, 611 (1915).
[4] D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 1760 (1964).
[5] D. Lloyd and D. R. Marshall, *in* "Aromaticity, Pseudo-aromaticity, Anti-aromaticity" (E. D. Bergmann and B. Pullman, eds.), p. 85. Israel Acad. Sci. Humanities, Jerusalem, 1971.
[6] D. Lloyd and D. R. Marshall, *Angew. Chem.* **84**, 447 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 404 (1972).

and the reaction between β-dicarbonyl compounds and 1,2-diamines has remained the commonest method for the preparation of these compounds. The original workers[6] had shown that under different conditions an alternative product, the bisoxoenamine 4, was formed. Indeed some earlier workers[7] had described the formation of only the bisoxoenamine from these reactants, while other workers[8] had reported the preparation of the diazepine but quoted physical constants which are those of the bisoxoenamine. The structures of these alternative open-chain products, e.g., 4, as bisoxoenamines rather than as tautomeric diimines, was later confirmed by NMR spectroscopy.[8,9] A detailed examination of the reactions



(4)

between acetylacetone and *trans*-1,2-diaminocyclopentane in aqueous solution[10] showed that at room temperature a bisoxoenamine was the major product in neutral and mildly alkaline conditions, whereas the dihydrodiazepine (or its salt) was the sole product at pH values less than 6 or greater than 10. The results are dependent on the (simplified) equilibria shown in Eq. (1). Dihydrodiazepines are extremely stable



(1)

compounds over a very wide range of pH and their hydrolysis may be ignored save at high alkalinity. Bisoxoenamines, on the other hand, are readily hydrolyzed and at all but moderately alkaline pH the hydrolysis

[7] A. Combes, *C. R. Acad. Sci.* **108**, 1252 (1889); A. Combes and C. Combes, *Bull. Soc. Chim. Fr.* **7**, 788 (1892); L. Rügheimer, *Ber.* **47**, 2759 (1914).
[8] H. A. Staab and F. Vögtle, *Chem. Ber.* **98**, 2681 (1965).
[9] D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc. C*, 780 (1966).

equilibrium is such that this condensation is effectively suppressed, leaving formation of the dihydrodiazepine to proceed without competition. At moderately alkaline pH, however, the bisoxoenamine is stable and furthermore precipitates from solution. Thus its formation competes successfully with the alternative reaction and it is the predominant product. At higher temperatures the yields of bisoxoenamine drop sharply even at the most favored pH values.[10] Almost identical results were found in reactions of other alicyclic or aliphatic diamines with acetylacetone.[11]

In general the preferred method of preparation for most bisoxoenamines is by mixing the reactants in methanol or ethanol at room temperature,[9] while dihydrodiazepines are normally best obtained by heating the reactants in acetic acid followed by addition either of perchloric acid to precipitate the dihydrodiazepinium perchlorate or of potassium hydroxide to precipitate the dihydrodiazepine base.[9]

Sometimes slight variations in these conditions result in improved yields for individual dihydrodiazepines.[12] In particular, when aryl diketones are used as reactants, somewhat different reaction conditions may be required.[13,14] Thus in the reaction of benzoylacetone with ethylenediamine a bisoxoenamine is the main product over a much wider pH range, while in alkaline solution yet another product was formed, namely the bisimine derived from ethylenediamine and acetophenone, this ketone resulting from hydrolytic cleavage of the diketone.[13] Amended conditions were thus required to obtain the best yields of dihydrodiazepine in this case[13] and also from other aryl diketones,[14] the differences being due to the lower reactivities of aryl-substituted carbonyl groups.

Dihydrodiazepinium salts can also be prepared by the reaction of *N*-alkyl-,[14] *N*,*N*′-dialkyl-,[12,14,15] or *N*,*N*′-diarylethylenediamines[15,16] with β-dialdehydes or β-diketones. When both the diamine and dicarbonyl compounds used are unsymmetric, two isomeric dihydrodiazepines may be obtained; thus, for example, *N*-methylethylenediamine and benzoylacetone give a mixture of 1,5-dimethyl-7-phenyl- and 1,7-dimethyl-5-phenyldiazepines.[14] The acid salt of the bis(*N*-methylanil) of malondialdehyde also reacts with *N*,*N*′-dimethylethylenediamine to give a

[10] D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 2597 (1956).
[11] A. M. Gorringe, D. Lloyd, and D. R. Marshall, unpublished results.
[12] C. Barnett, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. B*, 1536 (1968).
[13] A. M. Gorringe, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 2340 (1967).
[14] A. M. Gorringe, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 1081 (1969).
[15] C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 93 (1966).
[16] B. Eistert and F. Haupter, *Chem. Ber.* **93**, 264 (1960).

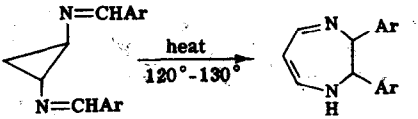
dihydrodiazepinium salt,[16a] while the parent dihydrodiazepinium cation may best be prepared by the reaction of the bisanil or, preferably, the bis(*N*-phenylanil) of malondialdehyde with ethylenediamine.[16b]

When condensation of acetylacetone with *C*,*C'*-tetramethylethylenediamine was attempted, the only product isolated, in high yield, was the acetylacetonate salt of the diamine.[8]

Dihydrodiazepines have also been prepared by methods not involving the use of condensation reactions.

In the first of these methods, the addition of ethylenediamine to buta-1,3-diyne gave a high yield of 5-methyldihydrodiazepine.[17]

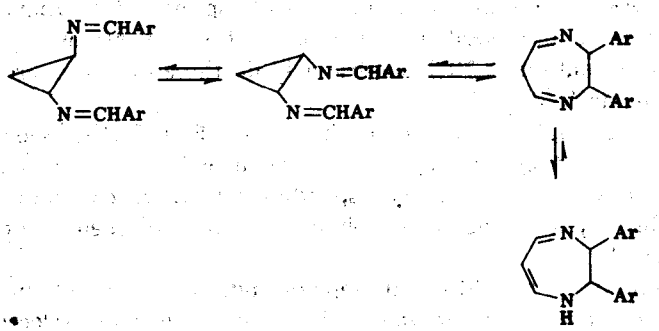
In the second method the bisanils of 1,2-diaminocyclopropanes were shown to undergo a Cope rearrangement when heated, forming thereby 2,3-diaryldihydrodiazepines,[18–20] e.g., as in Eq. (2).



(2)

Ar = Ph, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, α-naphthyl

The reaction sequence in Eq. (3) was proposed.[20] It was further suggested



(3)

that the overall equilibrium is controlled by the equilibrium of the last

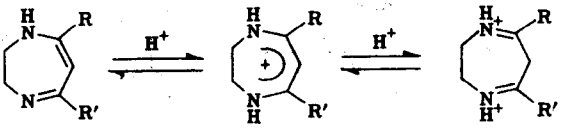
[16a] G. Scheibe, J. Heiss, and K. Feldmann, *Angew. Chem.* 77, 545 (1965); *Angew. Chem. Int. Ed. Engl.* 4, 525 (1965).
[16b] D. Lloyd, H. McNab and D. R. Marshall, *Synthesis*, 791 (1973).
[17] W. W. Paudler and A. G. Zeiler, *J. Org. Chem.* 34, 999 (1969).
[18] H. A. Staab and F. Vögtle, *Tetrahedron Lett.* 51 (1965).
[19] H. A. Staab and F. Vögtle, *Chem. Ber.* 98, 2691 (1965).
[20] H. A. Staab and F. Vögtle, *Chem. Ber.* 98, 2701 (1965).

step, which is shown by all work on dihydrodiazepines to be almost entirely on the side of the conjugated form. In support of this it was shown[20] that the bisanil of *trans*-2,3-diamino-1,1-diphenylcyclopropane does not rearrange thermally to a dihydrodiazepine. In this case the last step is prevented by the presence of two phenyl groups at the 6-position.

1-Methyl-2-oxodihydrodiazepines have been obtained by dehydrogenation of 2,3,6,7-tetrahydrodiazepines with benzoyl peroxide and *N*-bromosuccinimide.[20a]

III. General Stability of Dihydrodiazepines

The dihydrodiazepinium monocations (6) are extremely stable. This is



(5) (6) (7)

demonstrated by the enormous pH range over which the monocation is the predominant species. The pK_a values for the equilibria with the related bases (5) are about 13–14,[9,21] while spectra of solutions indicate the absence of any notable contribution of the dications (7) in 40% sulfuric acid; only in >70% sulfuric acid do these dications predominate over the monocations.[9,11]

The base strength of the dihydrodiazepines (5) is further shown by the fact that when they are kept in solution in chloroform for some hours they are converted into the corresponding dihydrodiazepinium chlorides, presumably by bringing about elimination of hydrogen chloride from the solvent.[9]

The stability of the dihydrodiazepines and, even more, of the dihydrodiazepinium salts, is due to their delocalized systems of π-electrons; this is especially marked in the monocations where the system is symmetrical. Calculations based on pK data suggest a resonance energy of about 19 kcal mole^{-1} for these cations.[22] A similar calculation suggests that dihydrodiazepine bases have 8 kcal mole^{-1} less resonance energy than the cor-

[20a] C. M. Hoffmann and S. R. Safir, *J. Med. Chem.* **12**, 914 (1969); *Chem. Abstr.* 71, 79386 (1969).

[21] G. Schwarzenbach and K. Lütz, *Helv. Chim. Acta* **23**, 1162 (1940).

[22] D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 335 (1972).

responding cations (in accord with the asymmetry of the conjugated system in the bases). This, however, still leaves a resonance energy of perhaps 10–12 kcal mole^{-1} for the conjugated base structure **1**, accounting for the preference of this structure over the nonconjugated bisimine structure (**3**).

This stability is also reflected in their chemical behavior. The electronic system resists breakdown and, to use Armit and Robinson's classic phrase,[23] shows a great tendency to retain the type. This is particularly reflected in the way that these compounds undergo substitution rather than additive or destructive reactions and is discussed further in Section VIII.

Attempts have been made to dehydrogenate dihydrodiazepines or their salts using a variety of methods, but the dihydrodiazepines (or their salts) were recovered unchanged.[9,24]

Solutions containing only the dihydrodiazepinium monocations (**6**) are unaffected by aqueous permanganate, even after several days, but solutions in either strong acid or alkali, which contain appreciable concentrations of, respectively, the dications or free bases, decolorize permanganate solutions fairly rapidly.

Catalytic reduction of a dihydrodiazepine over a prereduced platinum oxide catalyst in aqueous acetic acid has been reported.[17]

N,*N*′-Unsubstituted dihydrodiazepines and their salts resist hydrolytic cleavage over a wide range of pH values and are normally only hydrolyzed at very high or very low pH.[10] With aqueous sodium hydroxide and benzoyl chloride cleavage ensues and dibenzoylethylenediamine is formed.[9] The presence of a substituent group at the 6-position seems to make hydrolysis take place more easily. For example, 6-methyl-substituted dihydrodiazepinium salts are slowly hydrolyzed when kept in dilute sulfuric acid for some days[25] and 6-bromo-substituted salts are hydrolyzed quite readily under the same conditions.[26,27] Similarly, it is not possible to isolate the base forms of 6-nitro- and 6-aminodihydrodiazepines from the respective dihydrodiazepinium cations which are, however, themselves resistant to hydrolysis in the absence of alkali.[28]

N,*N*′-Disubstituted dihydrodiazepinium salts are stable in acid but decompose in alkali.[15,16] In this case it is not possible to obtain any corresponding dihydrodiazepine bases and the only available course of

[23] J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).
[24] S. Veibel and J. I. Nielsen, *Mat. Fys. Medd. Dan. Vid. Selsk.* **35**, No. 6 (1966).
[25] A. R. Butler, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. B*, 795 (1971).
[26] D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 118 (1958).
[27] C. Barnett, D. Lloyd, D. R. Marshall and L. A. Mulligan, *J. Chem. Soc. B*, 1529 (1971).
[28] A. M. Gorringe, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 617 (1970).

reaction with alkali inevitably entails ring-opening. Usually the N,N'-disubstituted amines are the isolated products, but when 5,7-dimethyl-1,4-diphenyldihydrodiazepinium perchlorate was heated for a short time in aqueous sodium hydroxide the monooxoenamine (8) was isolated.[14]

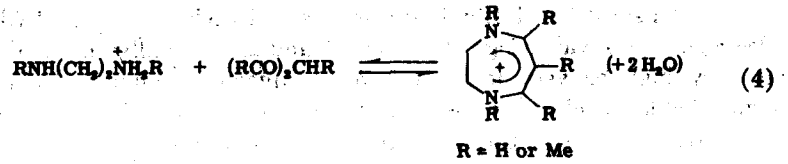
$$MeCOCH{=}CMe{-}NPhCH_2CH_2NHPh$$

(8)

This is the only example of the isolation of this type of product from hydrolysis of a dihydrodiazepine.

IV. Stability Constants of Dihydrodiazepines and Hydrolysis Equilibria

The marked chemical stability of dihydrodiazepines and their ready formation in aqueous solution are reflected in the stability constants for their formation. These were measured[12] for a range of methyl-substituted diazepines and referred to the equilibrium of Eq. (4).



(4)

The equilibrium constants for 25°C, ignoring the water formed, are tabulated in approximate order of stability in Table I.

When few methyl groups are present, stability is high, with values exceeding 10^9. (Inclusion of water concentration would raise this to 10^{13}.) The 5,7-dimethyl compound, on which much experimental work has been based, is not in fact the most stable. The most striking values, however, are those for the highly substituted compounds. The last two compounds listed have never been isolated and are formed in no more than very small amounts even at the most favorable pH values. Their stability constants are very rough values based only on observed UV absorption spectra. Clearly this ring system is made less stable by crowding of substituents. This is presumably caused by distortion of the ring, though this simple explanation is not wholly satisfactory; it is not clear, for example, why (ix) should be so much less stable than (vii) or (viii).

The parent compound (I) is very difficult to prepare by the standard method from malondialdehyde and ethylenediamine,[12] although it is one

TABLE I

STABILITY CONSTANTS OF DIHYDRODIAZEPINIUM CATIONS

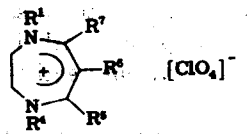
Compound No.	Methyl substituent positions					K
	4	5	6	7	1	
(i)	—	—	—	—	—	2.5×10^9
(ii)	Me	—	—	—	Me	3.2×10^8
(iii)	Me	—	Me	—	Me	7×10^6
(iv)	—	—	Me	—	—	1.3×10^8
(v)	—	Me	—	Me	—	3.4×10^8
(vi)	Me	Me	—	Me	Me	1.5×10^6
(vii)	—	Me	Me	Me	—	$\leqslant 10^6$
(viii)	—	Me	Me	—	—	1.0×10^8
(ix)	Me	Me	Me	—	Me	$\sim 10^{-3}$?
(x)	Me	Me	Me	Me	Me	$\sim 10^{-5}$?

of the most stable, but can be prepared readily from anils of malondialdehyde and ethylenediamine in non-aqueous conditions.[16b] This is apparently because it is hydrolyzed relatively quickly under conditions which favor equilibrium instability. (Thus chromatographic separations, successful with most dihydrodiazepines, can result in progressive loss of material.) In contrast, derivatives substituted at positions 5 and 7 are hydrolyzed very slowly, nucleophilic attack at these positions being inhibited.

V. Theoretical Considerations

A. MODEL

A Hückel molecular orbital (HMO) model has been used to explain some of the characteristic properties of dihydrodiazepines.[29] The authors assumed that there was conjugative interaction between positions 4, 5, 6, 7, and 1 on the dihydrodiazepine ring but no N,N' lone pair interaction. The results obtained by this model are given in Table II.



(9)

[29] H. P. Cleghorn, J. E. Gaskin and D. Lloyd, *Rev. Latinoamer. Quim.* 2, 103 (1971).

TABLE II

HMO DATA AND WAVENUMBERS FOR LONG-WAVELENGTH TRANSITIONS OF SOME DIHYDRODIAZEPINIUM PERCHLORATES, AND CHEMICAL SHIFT PARAMETERS

Salt	R^4	R^5	R^6	R^7	R^1	$-\Delta m$[a]	$\bar{\nu}$ (cm^{-1})	δ_H[b]	ρ_C[a]
(9a)	H	Me	H	Me	H	1.24	30960	4.9	1.120
(9b)	H	Me	H	Ph	H	1.065	29290	4.5	1.110
(9c)	H	Ph	H	Ph	H	0.94	27930	4.05	1.096
(9d)	Ph	H	H	H	Ph	0.975	26320	4.25	1.098
(9e)	Ph	Me	H	Me	Ph	0.995	28820	4.25	1.112
(9f)	H	H	H	H	H	1.275	30300	—	—
(9g)	Me	H	H	H	Me	1.17	29400	—	—
(9h)	Me	H	Me	H	Me	1.095	27730	—	—
(9i)	Me	Me	H	Me	Me	1.16	29580	—	—
(9j)	Me	Me	Me	Me	Me	1.08	27780	—	—

[a] For explanation of terms, see text.
[b] δ_H measured in trifluoroacetic acid.

In calculating HMO data, β_{CN} (resonance integral) is taken to be $0.84\beta_{CC}$ instead of $1.076\beta_{CC}$ as stated in Cleghorn *et al.*[28]

B. ABSORPTION SPECTRA

Dihydrodiazepinium salts are characterized by intense absorption bands (ϵ = 15,000–25,000) lying between 300 and 360 nm.[9,13–15] These high absorption values are indicative of π–π^* transitions, and this is substantiated in some cases by the presence of n–π^* transitions on their long-wavelength side.[30,31]

The relationship between the wavenumbers ($\bar{\nu}$) of these transitions and Δm, the difference between the parameters of the lowest unoccupied MO, m_{m+1}, and the highest filled MO, m_m, have been tested.[29] A plot of $\bar{\nu}$ against Δm for some ten dihydrodiazepinium perchlorates illustrates the essential distinction in compound type between these salts depending on whether there are exocyclic phenyl groups or methyl groups at position 5(7), presumably because of conjugative interaction in the case of the 5(7)-phenyl substituents.

The same authors also investigated the use of the semiempirical equation

[30] E. Daltrozzo and K. Feldmann, *Ber. Bunsenges. Phys. Chem.* **72**, 1140 (1968).
[31] K. Feldmann, E. Daltrozzo, and G. Scheibe, *Z. Naturforsch. B.* **22**, 722 (1967).