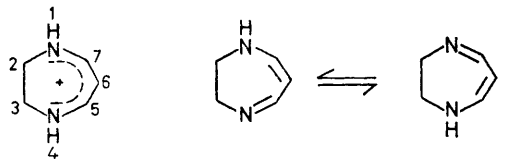
Diazepines. Part XVI.[1] Nuclear Magnetic Resonance Spectra of 2,3-Dihydro-1*H*-1,4-diazepinium Salts

By **Douglas Lloyd,* Raymond K. Mackie,** and **Hamish McNab,** Department of Chemistry, Purdie Building University of St. Andrews, St. Andrews, Fife
Donald R. Marshall, Department of Chemistry, University College of North Wales, Bangor, Caernarvonshire

The n.m.r. spectra of a number of 2,3-dihydro-1*H*-1,4-diazepinium perchlorates are discussed. They indicate that the dihydrodiazepinium cation has a half-chair shape which inverts rapidly at room temperature, but inversion is slow at lower temperatures. Variable temperature kinetic studies of the inversion show that it is facilitated by the presence of larger groups at the 6-position, but is independent of the electronic nature of these substituents. There appears to be complete delocalisation in the unsaturated portion of the molecule, and the 6-position has a greater electron density than the 5(7)-positions.

N.M.R. spectra of many 2,3-dihydro-1*H*-1,4-diazepinium salts (I) have been recorded, but they have not been discussed in detail. The spectra of some dihydrodiazepines (II) and their salts have been compared with those of pyrimidines and also of open-chain 1-amino-3-iminoprop-2-enes,[2] and the relation between the chemical shift of 6-hydrogen atoms in the dihydrodiazepinium salts and the calculated π-electron densities of the adjacent carbon atom has also been explored.[3] In the present paper salient factors concerning the n.m.r. spectra of dihydrodiazepinium salts are considered.



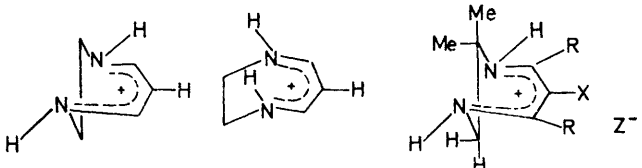
(I) (II)

The most striking feature of these spectra is the difference between the chemical shifts of protons at the 5(7)-positions (τ *ca.* 2·5) and the 6-positions (τ *ca.* 5·0), which can be correlated with the large difference in nucleophilicity of these sites, also exemplified by their enormous difference in reactivity and free energy of activation towards nucleophiles.[4] Phenyl groups at the 1,4-positions shift 6-H signals as well as 5,7-H signals to lower field. This must therefore be due to conjugative electron withdrawal; conjugative interaction with the dihydrodiazepinium ring is of necessity electron withdrawing at the 1,4,6-positions, and electron donating at the 5,7-positions.

U.v. spectra have indicated that vicinal methyl groups prevent coplanarity of 5(7)-phenyl groups with the dihydrodiazepinium ring.[5] This is also demonstrated by n.m.r. spectra for, whereas 5(7)-phenyl groups without flanking methyl groups give multiplet signals because of electronic interaction between the rings, dihydrodiazepinium salts with vicinal methyl and phenyl groups show sharp singlets for the phenyl groups, and their deshielding effect on the 6-H signal is diminished.

Coupling constants $J_{5,6(6,7)}$ and $J_{4,5(1,7)}$ are both *ca.* 8·0 Hz in a range of dihydrodiazepinium salts. The near identity of these two coupling constants provides conclusive evidence for the almost complete delocalisation of the electrons in the conjugated portion of the dihydrodiazepinium cations.

Coupling has also been observed between the NH and 6-CH groups ($J_{1,6}$ *ca.* 1·8 Hz). For coupling to take place through four bonds in simple systems a planar W shaped conformation of these bonds is normally required.[6] This coupling shows therefore that the whole delocalised portion of the molecule must be effectively coplanar. It also confirms the supposition [7] that the half-chair conformation (III) rather than the half-boat conformation (IV) represents the shape of the ring, since of these two forms only (III) has the N–H bonds coplanar with the 6-CH bonds. Supplementary evidence for the half-chair structure is provided by the fact that these salts have identical u.v. spectra to those of *trans*-2,3-dihydro-2,3-propano-1,4-diazepinium salts, which must have a zig-zag structure for C-1—C-4.[8]



(III) (IV) (V)

In neutral solvents the 2,3-methylene signals appear as a singlet, sometimes broad, but when these solutions are cooled the signal eventually appears as a complex multiplet. This indicates conformational mobility in the saturated part of the ring which is inhibited at lower temperatures.

In order to simplify the kinetic study of this inversion it was found convenient to use 2,2-dimethyldihydrodiazepinium salts (V). At −50°, a solution of (V;

[1] Part XV, H. P. Cleghorn, J. E. Gaskin, and D. Lloyd, *J. Chem. Soc.* (*B*), 1971, 1615.
[2] E. Daltrozzo and K. Feldmann, *Ber. Bunsengesellschaft Phys. Chem.*, 1968, **72**, 1140.
[3] H. P. Cleghorn, J. E. Gaskin, and D. Lloyd, *Rev. Latinoamer. Quim.*, 1971, **2**, 103.
[4] A. R. Butler, D. Lloyd, and D. R. Marshall, *J. Chem. Soc.* (*B*), 1971, 795; C. Barnett, D. R. Marshall, L. A. Mulligan, and D. Lloyd, *ibid.*, p. 1529.
[5] A. M. Gorringe, D. Lloyd, and D. R. Marshall, *J. Chem. Soc.* (*C*), 1969, 1081.
[6] R. J. Abraham, in ' Nuclear Magnetic Resonance for Organic Chemists,' ed. D. W. Mathieson, Academic Press, London, 1967, pp. 146*ff.*; S. Sternhell, *Quart. Rev.*, 1969, **23**, 259.
[7] C. Barnett, D. R. Marshall, and D. Lloyd, *J. Chem. Soc.* (*B*), 1968, 1536.
[8] D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 1958, 118.

R = Me, X = H, Z = ClO_4) gave a completely resolved spectrum. Since the ion is dissymmetric, separate peaks were observed for the two NH groups and also for the 5- and 7-methyl groups.

The 3-CH_2 group appeared as an AB system (J 13·6 Hz) with the downfield portion further split into two doublets (J 7·2 Hz) by coupling with the 4-NH group. From the relationship between coupling constants and dihedral angles the downfield portion must therefore represent the 'equatorial' proton. When the lower field signal of the two NH signals is irradiated the methylene signal collapses to a simple AB system; the lower field NH signal must therefore be ascribed to the 4-NH group. That the 1-NH signal appears at higher field than the 4-NH signal may be attributed to the inductive effects of the 2-methyl groups. The difference in chemical shift between the 'equatorial' and 'axial' methylene protons ($\Delta\delta$ 0·62 p.p.m.) could possibly be associated with a homo-homo-aromatic ring current which spanned the 1,4-gap but the n.m.r. spectrum of [$^2H_{11}$]cyclohexane [9] shows a similar difference between the axial and equatorial C–H signals ($\Delta\delta$ 0·48 p.p.m.) so that it is unnecessary in fact to invoke any such effect, for which there is in any case no other evidence.

The two NH signals are separated by *ca.* 30 Hz. The upfield (1-NH) signal is sharper than the 4-NH signal, the broadening of the latter presumably being due to coupling with the adjacent 3-CH signal and also possibly to its higher acidity (because of the inductive effects of the 2-methyl groups at the 1-position) which facilitates proton exchange.

The two signals for the 2-methyl groups are separated by 38·3 Hz. The upfield signal represents the 'axial' methyl group since it is sharpened by irradiating the upfield 'axial' 2-CH signal.

The 6-H signal appears as a triplet, presumably really a double doublet. When each NH signal is irradiated in turn, the 6-H signal is converted into a doublet. Coupling with the 1-NH (1·9 Hz) is greater than with the 4-NH (1·5 Hz).

The signals due to the 5- and 7-methyl groups are separated by 2·1 Hz. Irradiation of the 1-NH signal sharpens the upfield methyl signal showing that this represents the 7-substituent. The difference may again be associated with the different effects of the 2-CMe_2 and 3-CH_2 groups.

Studies of the n.m.r. spectra of various 2,2-dimethyldihydrodiazepinium salts (V) at varying temperatures have provided activation energies for their inversion; [10] enthalpies and entropies of activation have also been calculated (see Table). $\Delta G^{\ddagger}$* Is a value for the free energy of activation based on an empirical relationship,[11] $\Delta G^{\ddagger}* = 57{\cdot}3 + 0{\cdot}21T_c \pm 1{\cdot}9$ kJ mol^{-1} (T_c = coalescence temperature in °C). The agreement between $\Delta G^{\ddagger}$* and $\Delta G^{\ddagger}$ is noteworthy.

The electronic nature of the 6-substituent appears to have no effect on the ease of inversion since 6-nitro- and 6-methoxy-groups produce similar results. It does appear however that inversion is facilitated by the presence of larger groups at the 6-position. The reduction in $\Delta G^{\ddagger}$ with increasing size of the 6-substituent may be associated with steric repulsions between the groups present at the 5-, 6-, and 7-positions, which lead to a slight lengthening of the associated ring bonds, and which in turn would permit the methylene portion of the ring to invert more readily.* Alternatively interaction between vicinal substituent groups might cause slight buckling of the usually coplanar portion of the ring, thereby lowering the stabilisation energy and also permitting easier inversion. The effect might have had steric or ponderal origins, but a plot of mass of the group against coalescence temperature gave an irregular distribution, whereas a plot of van der Waals radii [12] of the monatomic substituents (H, Cl, Br, I) against coalescence temperature or against $\Delta G^{\ddagger}$ gave a straight line, with standard deviation in gradient of *ca.* 10%. Attempts by various methods to obtain the 6-fluoro-derivative, in order to provide an extra point, have hitherto been unsuccessful.

For the symmetrical polyatomic 6-methyl substituent the point did not lie on the straight line provided by the monatomic substituents, but rather the coalescence temperature was lower than 'expected' for its size, implying a more facile inversion.

Methyl groups substituted in cyclohexane rings have a

Activation parameters for ring-inversion in 2,2-dimethyldihydrodiazepinium salts (V)

Compound (V; Z = ClO_4)	T_c (°C)	$\Delta G^{\ddagger}$/kJ mol^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta G^{\ddagger}$*/kJ mol^{-1}
(R = Me, X = H)	4 ± 1	58·7 ± 0·6	57·2 ± 1·3	−5·3 ± 1·9	58·1 ± 1·9
(R = Me, X = NO_2)	−27 ± 1	51·8 ± 0·5	46·0 ± 0·7	−23·5 ± 1·2	51·6 ± 1·9
(R = Me, X = OMe)	−25 ± 1	52·0 ± 0·5	51·0 ± 2·5	−3·8 ± 3·0	52·0 ± 1·9
(R = Me, X = Cl)	−23 ± 1	52·6 ± 0·5	46·2 ± 1·5	−17·6 ± 2·0	52·5 ± 1·9
(R = Me, X = Br)	−25 ± 1	52·2 ± 0·5	50·5 ± 2·1	−7·0 ± 2·6	52·0 ± 1·9
(R = Me, X = I)	−32 ± 1	50·8 ± 0·5	46·7 ± 0·1	−16·8 ± 0·6	50·6 ± 1·9
(R = Me, X = Me)	−49 ± 1	47·1 ± 0·5	40·5 ± 1·0	−29·1 ± 1·5	47·0 ± 1·9
(R = Ph, X = H)	−2 ± 1	56·9 ± 0·6	54·5 ± 2·1	−9·3 ± 2·7	56·9 ± 1·9

[a] Calculated from empirical relationship.[11]

* This explanation was originally suggested to us by Professor J. H. Ridd, to whom we are grateful for a valuable discussion.

[9] F. A. L. Anet and A. J. R. Brown, *Proc. Chem. Soc.*, 1964, 145.

[10] A. Mannschreck, G. Rissmann, F. Vögtle and D. Wild, *Chem. Ber.*, 1967, **100**, 335; *cf.* I. O. Sutherland, *Ann. Rev. N.M.R. Spectroscopy*, 1971, **4**, 71.

[11] H. J. Berwin and S. Trippet, private communication.

[12] L. Pauling, 'The Nature of the Chemical Bond,' Cornell University Press, Ithaca, 3rd edn., 1960, p. 260.

greater tendency to take up equatorial positions than do bromine atoms,[13] although they have similar van der Waals radii. This has been attributed to the greater bonding radius of the bromine atom, wherefore it causes less crowding than does a methyl group. A similar interpretation would explain the present result.

Replacement of the 5(7)-methyl groups by phenyl groups leads to a small decrease in $\Delta G^{\ddagger}$. Since the u.v. spectra of such dihydrodiazepinium salts indicate that the phenyl groups are fairly coplanar with the seven-membered ring, steric effects, largely due to interaction between the 6-hydrogen atom and the *o*-hydrogen atoms of the phenyl groups, may well be responsible for this difference in $\Delta G^{\ddagger}$.

The effects of substituents at the 1—4-positions have not been investigated quantitatively, but it appears that increase in the size of substituents at these sites, especially at the 2(3)-position results in higher coalescence temperatures and $\Delta G^{\ddagger}$ values, as might be expected from simple ponderal effects.

The entropies of activation quoted in the Table are probably not quantitatively meaningful but they do indicate that the absolute values are small and negative in sign, which is consistent with a slight ordering effect which would be expected for the planar transition state of the inversion process.

EXPERIMENTAL

In the following preparative recipes, n.m.r. spectra were recorded at 100 MHz for 10% solutions in [$^2H_6$]acetone at ambient temperature. The positions of the NH signals were clarified by addition of trifluoroacetic acid (*ca.* 10%); the signals were too broad to provide consistent integrals. U.v. spectra were recorded for methanolic solutions and i.r. spectra for Nujol mulls.

2,3-*Dihydro*-2,2,5,7-*tetramethyl*-1H-1,4-*diazepinium Perchlorate*.—Prepared as described previously, this perchlorate, m.p. 118—120°, had τ 1·0br, 1·2br, 4·86 (1H, t, *J* 1·85 Hz), 6·60 (2H, s), 7·71 (6H, s), and 8·66 (6H, s).

6-*Bromo*-2,3-*dihydro*-2,2,5,7-*tetramethyl*-1H-1,4-*diazepinium Perchlorate*.—Bromine (9·6 g, 60 mmol) in methanol was added gradually to a solution of 2,3-dihydro-2,2,5,7-tetramethyl-1,4-diazepinium perchlorate (15·0 g, 60 mmol) in methanol. Addition of ether precipitated the bromodihydrodiazepinium salts as a red oil which slowly crystallised, and which was recrystallised from aqueous perchloric acid and from water to give the *bromo-derivative* (7·6 g, 38%), m.p. 134°, $\lambda_{max.}$ 261 and 347 nm (ε 700 and 13,100), $\nu_{max.}$ 3300, 1600, 1499, 1301, and 1100 cm^{-1}, τ 0·25br, 0·80br, 6·48 (2H, m), 7·38 (6H, s), and 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*.—The corresponding 6-bromo-compound (2·0 g, 6 mmol) was heated with sodium methoxide (from sodium; 1 g) in methanol (60 ml) at reflux temperature for 1·5 h. Methanol was evaporated, dilute aqueous sodium hydroxide was added, and the mixture was extracted four times with ether. This extract was dried and solvent was removed. The resultant methoxydihydrodiazepine was dissolved in ethanol (*ca.* 1 ml) and perchloric acid (60%, 0·8 g) was added, whereat an oil separated which after some time crystallised to give the *methoxy-derivative* (0·24 g, 11%), m.p. 122—123° [reprecipitated from isopropyl alcohol by light petroleum (b.p. 40—60°)], $\lambda_{max.}$ 347 nm (ε 13,800), $\nu_{max.}$ 3300, 1618, 1502, 1315, and 1100 cm^{-1}, τ 0·6br, 1·05br, 6·39 (3H, s), 6·64 (2H, m), 7·59 (6H, s), and 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*.—2,3-Dihydro-2,2,5,7-tetramethyldiazepinium perchlorate (2·5 g, 10 mmol) and *N*-chlorosuccinimide (1·3 g, 10 mmol) were heated in boiling chloroform (25 ml) for 1·5 h. Solvent was distilled off and the residue was recrystallised from water to give the *chloro-derivative* (1·85 g, 64%), m.p. 138—139° (from water), $\lambda_{max.}$ 344 nm (ε 11,800), $\nu_{max.}$ 3300, 1605, 1505, 1301, and 1100 cm^{-1}, τ 0·42br, 0·90br, 6·50 (2H, s), 7·47 (6H, s), and 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*.—Prepared as the 6-chloro-analogue but using *N*-iodosuccinimide in place of *N*-chlorosuccinimide, the *iododihydrodiazepinium perchlorate* (67%) had m.p. 98—100° [reprecipitated from isopropyl alcohol by light petroleum (b.p. 40—60°)], $\lambda_{max.}$ 307 and 354 nm (ε 2370 and 9040), $\nu_{max.}$ 3300, 1590, 1485, 1305, and 1100 cm^{-1}, τ 6·47 (2H, m), 7·22 (6H, s), and 8·62 (6H, s) (NH signals not detectable because compound is de-iodinated in acid) (Found: C, 28·15; 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*-2,2,5,7-*tetramethyl*-6-*nitro*-1H-1,4-*diazepinium Perchlorate*.—Fuming nitric acid (0·6 ml) was added slowly to a stirred solution of 2,3-dihydro-2,2,5,7-tetramethyldiazepinium perchlorate (2·5 g) in conc. sulphuric acid (8 ml) at 0°. The mixture was then heated at 35—40° for 1·5 h and poured onto crushed ice (10 g). Overnight the *nitrodihydrodiazepinium perchlorate* (0·7 g, 24%) crystallised out and had m.p. 177·5—178·5° [from ethanol–light petroleum (b.p. 40—60°)], $\lambda_{max.}$ 323 nm (ε 12,600), $\nu_{max.}$ 3300, 1620, 1515, 1340, and 1100 cm^{-1}, τ −0·05br, 0·35br, 6·35 (2H, s), 7·54 and 7·56 (2H, 2 × 5), and 8·53 (6H, s) (Found: C, 36·4; H, 5·65; N, 14·1. $C_9H_{16}ClN_3O_6$ requires C, 36·25; H, 5·4; N, 14·1%).

2,3-*Dihydro*-2,2,5,6,7-*pentamethyl*-1H-1,4-*diazepinium Perchlorate*.—3-Methylacetylacetone (1·14 g, 10 mmol) was added to a solution of 1,2-diamino-2-methylpropane (0·9 g, 10 mmol) in acetic acid (2 ml). The mixture was heated to *ca.* 120° for 15 min, cooled, and perchloric acid (60%; 2 g) was added. The *dihydrodiazepinium perchlorate* (0·8 g, 30%) separated as plates, m.p. 155·5—156° (from isopropyl alcohol), $\lambda_{max.}$ 340 nm (ε 13,500), $\nu_{max.}$ 3300, 1610, 1500, 1340, and 1100 cm^{-1}, τ 0·92br, 1·50br, 6·62 (2H, m), 7·64 (6H, 2s), 8·02 (3H, s), and 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%).

2,3-*Dihydro*-2,2-*dimethyl*-5,7-*diphenyl*-1H-1,4-*diazepinium Perchlorate*.—1,2-Diamino-2-methylpropane (3·6 g, 40 mmol), followed by dibenzoylmethane (2·24 g, 10 mmol), was added to cooled acetic acid (6·6 g). The mixture was then heated under reflux for 1·5 h, cooled, poured into water (20 ml), and extracted thrice with ether. Perchloric acid (60%, 10 ml), was added to the aqueous layer. A yellow oil separated which slowly solidified. This material

[13] See E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, pp. 42*ff*.

was finely ground and washed with water to remove impurities until its u.v. spectrum showed no peak in the region 220—240 nm. It was then recrystallised from isopropyl alcohol to give the *dihydrodiazepinium perchlorate* (1·4 g, 37%), m.p. 159·5—160·5°, $\lambda_{max.}$ 267 and 352 nm (ε 14,840 and 22,840), $\nu_{max.}$ 3300, 1585, 1565, 1330, and 1100 cm^{-1}, τ 0·5br, 0·95br, 2·0—2·6 (10H, complex), 4·26 (1H, s), 6·19 (2H, s), and 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%).

Determination of Variable Temperature N.m.r. Spectra.—Measurements were made at 60 MHz using 10% solutions in [$^2H_6$]acetone. The temperature was recorded directly by means of a copper–constantan thermocouple inserted in the probe. Linewidths were recorded as the average of three, run at the sweep width of 50 Hz, while the instrument resolution was kept constant by optimising the linewidth of the tetramethylsilane signal at each temperature. Activation parameters are typically reported for measurements in the range T_c (coalescence temperature) to $(T_c + 25)$. Activation energies are best fits to the log k *vs.* $1/T$ line, as calculated by the least squares method.

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