Diazepines. Part XX.[1] The Properties of 2,3-Dihydro-1,4-diazepinium Perchlorate

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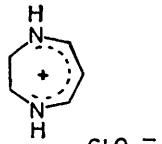
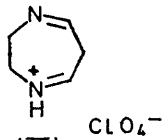
The unsubstituted 2,3-dihydro-1,4-diazepinium ion shows a number of differences from the substituted derivatives studied hitherto. Although it undergoes halogenation at position 6, it cannot be nitrated by nitric acid and is decomposed by mineral acids. The ring is also opened by the action of nucleophiles at the 5- and 7-positions. A transdiazepination reaction occurs with *NN'*-dimethylethylenediamine to give the *NN'*-dimethyldihydrodiazepinium salt. 6-Halogeno-derivatives do not react at the 6-position with nucleophiles.

THE properties of 2,3-dihydro-1,4-diazepinium salts have been studied extensively [2] but the chemistry of the parent salt (I) has hitherto been uninvestigated, principally because the standard method of preparation, from a 1,2-diamine and a 1,3-dicarbonyl compound gave only a very low yield.[3] An alternative mode of preparation,[4]


(I)


(II)

which provides this salt in good yield, has made it possible to study its properties, which differ in a number of respects from those of its substituted derivatives, probably for steric reasons.

The m.p. of compound (I) had earlier been reported [3] as 79—80°; the much higher value now found (*ca.* 250°, with violent decomp.) presumably reflects the difficulties involved in isolation and purification by the older method.

The earlier reported value for the u.v. extinction coefficient at $\lambda_{max.}$ 331 nm (ε 11,200) [5] is lower than the value calculated empirically (ε 13,500) from the values for other substituted dihydrodiazepinium salts,[3] but measurements on a carefully purified sample now indicate a value of 14,300 ± 200. This high value may reflect the absence of distortion of the π-system caused by substituents (for which there is spectroscopic evidence [6,7]) and/or an extremely low concentration of the non-absorbing bisimine tautomer (II); a small contribution from this form may arise in the case of substituted dihydrodiazepinium salts because some relief of crowding by substituents at the 5-, 6-, and 7-positions is introduced, although at the expense of the loss of the conjugated system.

The n.m.r. spectrum of the salt (I) in [$^2H_6$]acetone [7] presents the 5- and 7-H signals as a broad multiplet, but addition of a small quantity of trifluoroacetic acid provides sharp signals. Coupling constants $J_{5,6(6,7)}$ and $J_{4,5(1,7)}$ are respectively 7·8 and 7·2 Hz; their near identity is evidence of the almost complete delocalisation of the electrons in the conjugated portion of the cation. There is also a small *meta*-coupling, $J_{1(4),6}$ 1·5 Hz. The methylene groups appear as a singlet at room temperature, indicating fast inversion of this portion of the ring (*cf.* ref. 7).

Dihydrodiazepinium salts undergo electrophilic substitution at position 6,[8-10] and the ratio of the reactivities of positions 6 and 5(7) towards deuteriation in deuterioacids has been shown [11] to be at least 10^9 : 1. This result was obtained from the study of salts in which both positions 5 and 7 or position 6 were unsubstituted, but no comparison of these sites in the same molecule has hitherto been recorded. When the salt (I) was dissolved in trifluoroacetic [^{2}H] acid, no signals due to the 1-, 4-, or 6-protons were seen, owing to their rapid exchange with the solvent, but after 9 days in this solution no decomposition had occurred and the ratio of the 5- and 7-H integral to that of the methylene 2- and 3-protons was unchanged, demonstrating again the low reactivity of the 5- and 7-positions towards electrophiles.

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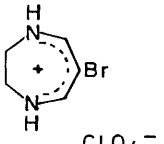
[11] A. R. Butler, D. Lloyd, and D. R. Marshall, *J. Chem. Soc.* (*B*), 1971, 795.

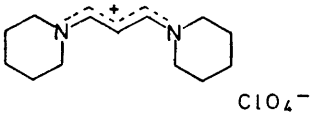
Like other dihydrodiazepinium salts without 6-substituents the salt (I) is readily brominated at the 6-position by bromine in methanol. 6-Chloro- and 6-iodo-derivatives of (I) were also obtained in excellent yield by the action, respectively, of *N*-chloro- and *N*-iodo-succinimide. Like other 6-brominated dihydrodiazepinium salts, (III) shows a bathochromic shift in its principal absorption maximum but the shift is greater in this case (29 nm; *cf.* 24 nm for the 5,7-dimethyl derivative, 16 nm for the 5,7-diphenyl derivative).

The 6-iodo-derivative of (I) resembles other 6-iodo-dihydrodiazepinium salts in being protodeiodinated in solution in acid; in accord with the trend for protodehalogenation to take place more readily with increase in size of 5- and 7-substituents,[12] the present iodo-compound is protodeiodinated much more slowly than its 5,7-dimethyl or 5,7-diphenyl derivative.

Whereas 5,7-disubstituted dihydrodiazepinium salts are readily nitrated by nitric acid to give 6-nitro-derivatives,[10] attempts failed to prepare the 6-nitro-derivative of (I) under analogous conditions. In contrast to the substituted salts, the parent salt (I) is apparently decomposed irreversibly by mineral acids.



(III)



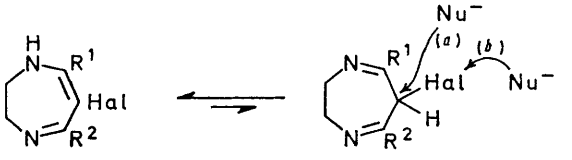
(IV)

The 6-unsubstituted dihydrodiazepines studied hitherto are inert towards nucleophiles. The parent compound (I) reacts readily with piperidine, however, to give the dipiperidinopropenylium salt (IV) [13] in high yield. A kinetic study of this reaction showed two isosbestic points, indicating that there is no stable intermediate. This reaction indicates clearly the reactivity of the 5- and 7-positions towards nucleophiles, which is not generally observed in the cases of 5,7-substituted derivatives. For example, 5,7-dimethyldihydrodiazepinium perchlorate was 83% unchanged when heated with piperidine under reflux for 12 h, and when a solution of this dihydrodiazepinium salt and piperidine in methanol was kept for 7 days at 25 °C the u.v. spectrum showed that >95% of the salt remained. The methyl groups thus have a strong inhibiting effect, presumably mainly steric, on the reactivity of the 5- and 7-positions, and kinetic studies showed that they lower the reactivity by a factor of at least 20,000. 1,4-Dimethyldihydrodiazepinium perchlorate, also lacking 5- and 7-blocking substituents, reacted similarly with piperidine in [$^2H_6$]acetone solution to give the product (IV).

1,4-Dimethyldihydrodiazepinium perchlorate was itself prepared by the reaction of compound (I) with a nucleophile, *NN'*-dimethylethylenediamine, but unfortunately this transdiazepination reaction was not of general application; for example reaction of (I) with 2-methylpropane-1,2-diamine did not, as judged from spectra, provide any dihydrodiazepine.

6-Halogenodihydrodiazepines react readily with nucleophiles, either (*a*) by normal substitution, or else (*b*) to give the protodehalogenated product, the latter course being favoured by increasing size of the nucleophile and of 5- and 7-substituents.[8,9,12] It was expected, therefore, that the bromo-compound (III) would rapidly form the 6-methoxy-derivative on exposure to methoxide ion, but in fact it was unchanged after being heated with sodium methoxide in refluxing methanol for 30 min. Spectroscopic examination (u.v., n.m.r.) of the resultant solution showed that the only product was the corresponding 6-bromodihydrodiazepine base; in particular the n.m.r. spectrum confirmed that there had been no attack by the nucleophile at the 5- or 7-position.

Since the 6-position in dihydrodiazepines is itself nucleophilic, the reactions of other 6-halogenodihydrodiazepines (V) with nucleophiles have been rationalised in terms of the presence of a small amount of the bis-imine tautomer (VI), which would be expected to be highly reactive towards nucleophiles.[9,12] As discussed above formation of the tautomer (VI) is disfavoured because the conjugation of form (V) is thereby lost; indeed tautomer (VI) must be present in only a small amount in any simple dihydrodiazepine since it is not observed spectroscopically. However there will be some slight compensating energetic gain if R^1 and R^2 are large, since in form (V) R^1, R^2, and Hal must be distorted from coplanarity owing to crowding, but this crowding is relieved when position 6 becomes tetrahedral as in tautomer (VI). In the



(V) (VI)

Hal = halogen, Nu = nucleophile

case where $R^1 = R^2 = H$ there will be no crowding in (V) and hence no compensation in forming the tautomer (VI). Thus there may be a vanishingly small contribution from the bis-imine form which would explain the unreactivity of the bromo-compound (III) towards nucleophilic substitution.

Likewise, whereas 6-bromo-5,7-dimethyldihydrodiazepinium bromide underwent protodebromination when heated in ethanolic thiourea, compound (III) was unchanged after 23 h under the same conditions.

The 6-iodo-analogue of (III) was however converted into (I) when heated with ethanolic thiourea or ethanol alone.

5,7-Disubstituted 6-bromodihydrodiazepine bases react with neat piperidine to give either the 6-piperidino- or 6-unsubstituted analogues,[9] but the bromo-compound (III) reacted with piperidine in methanol with destruction

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of the seven-membered ring. No tractable products were isolated save piperidinium bromide.

Thus two surprising properties of the dihydrodiazepines described previously, namely their ready reactivity towards nucleophiles at position 6 but not at positions 5 and 7, are shown not to be inherent properties of the 2,3-dihydro-1,4-diazepine system itself, but rather a consequence of substituent effects.

EXPERIMENTAL

Electronic spectra were recorded for methanolic solutions, and i.r. spectra for Nujol mulls.

2,3-Dihydro-1,4-diazepinium perchlorate (I) was prepared as previously described.[4]

6-Bromo-2,3-dihydro-1,4-diazepinium Perchlorate (III).—Bromine (0·16 g, 1 mmol) in methanol (3 ml) was added dropwise to compound (I) (0·2 g, 1 mmol) in methanol (10 ml). Addition of ether precipitated the bromo-compound (0·12 g, *ca.* 72%), which was recrystallised from ethanolic perchloric acid to give the *perchlorate*, m.p. 154—155°, $\lambda_{max.}$ 360 and 268 nm (ε 10,200 and 3000), $\nu_{max.}$ 3300, 1630, 1540, 1330, 1250, 1100, and 920 cm^{-1}, τ [$(CD_3)_2SO$] —0·4br, 1·95 (2H, s), and 6·36 (4H, s), $J_{1,7}$ [$(CD_3)_2SO$–CF_3·CO_2H] 7·8 Hz (Found: C, 22·05; H, 3·1; N, 10·1. $C_5H_3BrClN_2O_4$ requires C, 21·8; H, 2·9; N, 10·15%).

6-Chloro-2,3-dihydro-1,4-diazepinium Perchlorate.—A solution of the unsubstituted dihydrodiazepinium salt (I) (0·4 g, 2 mmol) and *N*-chlorosuccinimide (0·27 g, 2 mmol) in acetic acid (8 ml) was heated under reflux for 2 min. Addition of ether to the cooled solution precipitated the *chlorodihydrodiazepinium perchlorate* (0·38 g, 83%), m.p. 121—121·5° (from ethanol), $\lambda_{max.}$ 359 nm (ε 9800), $\nu_{max.}$ 3300, 1640, 1550, 1320, 1240, 1100, and 930 cm^{-1}, τ [$(CD_3)_2SO$] —0·42br, 1·96 (2H, s), and 6·34 (4H, s), $J_{1,7}$ [$(CD_3)_2SO$–CF_3·CO_2H] 8·4 Hz (Found: C, 26·15; H. 3·45; N, 12·4. $C_5H_3Cl_2N_2O_4$ requires C, 25·95; H, 3·45; N, 12·1%).

2,3-Dihydro-6-iodo-1,4-diazepinium Perchlorate.—A solution of the unsubstituted dihydrodiazepinium salt (I) (0·4 g, 2 mmol) and *N*-iodosuccinimide (0·45 g, 2 mmol) in acetic acid (8 ml) was heated under reflux for 2 min. When the solution was cooled the *iodo-compound* separated (0·58 g, 90%), m.p. 234—235° (from ethanol), $\lambda_{max.}$ 369 and 314 nm (ε 7700 and 1350), $\nu_{max.}$ 3300, 1630, 1550, 1330, 1100, and 930 cm^{-1}, τ [$(CD_3)_2SO$] —0·25br, 1·98 (2H, s), and 6·34 (4H, s), $J_{1,7}$ [$(CD_3)_2SO$–CF_3·CO_2H] 8·4 Hz (Found: C, 18·65; H, 2·6; N, 8·8. $C_5H_3ClIN_2O_4$ requires C, 18·6; H, 2·5; N, 8·7%).

Reaction of the Dihydrodiazepinium Salt (I) *with Piperidine.*—A solution of the salt (I) (0·2 g, 1 mmol) and piperidine (0·45 g, 10 mmol) in methanol (12 ml) was heated under reflux for 20 min. Solvent was evaporated *in vacuo*, and addition of ether to the residue caused crystallisation of 1,3-dipiperidinopropenylium perchlorate (IV) (0·25 g, 82%), m.p. 129—131° (lit.,[13] 130—131°), mixed m.p. 129—130°, u.v., i.r., and n.m.r. spectra identical with those of an authentic sample.

Attempted Reaction of 2,3-Dihydro-5,7-dimethyl-1,4-diazepinium Perchlorate with Piperidine. The dihydrodiazepinium salt (0·23 g, 1 mmol) and piperidine (0·45 g, 10 mmol) in methanol (12 ml) were heated under reflux for 12 h. After evaporation of solvent and addition of ether the diazepinium salt was recovered (0·19 g, 83%), m.p. 140—141·5°.

Kinetic Studies of the Reactions with Piperidine.—Studies were carried out in solutions in methanol (reagent grade) at 25 °C, and the reaction was followed over 1 half-life at 295 nm. Piperidine concentration was *ca.* 1·5—2·0 mol l^{-1}. The dihydrodiazepinium salt (I) concentration was 5·1 × 10^{-3} mol l^{-1}, and the reaction in this case followed first-order kinetics [k (2·55 ± 0·09) × 10^{-3} min^{-1}]. In the case of the 5,7-dimethyl analogue of (I) (0·25 mol l^{-1}), no reaction was observed in 7 days, and the salt was unchanged (mixed m.p.).

2,3-Dihydro-1,4-dimethyl-1,4-diazepinium Perchlorate.—A solution of the dihydrodiazepinium salt (I) (0·2 g, 1 mmol) and *NN'*-dimethylethylenediamine (0·45 g, 5 mmol) in ethanol (15 ml) was heated under reflux for 1 h. Solvent was removed and ether was added to give an oil which after dissolution in ethanol, followed by cooling of this solution, gave the 1,4-dimethyldihydrodiazepinium perchlorate (0·15 g, 67%), m.p. and mixed m.p. 95—96°, i.r. and u.v. spectra identical with those of an authentic sample,[5] τ (CF_3·CO_2H) 2·6 (2H, d), 4·95 (1H, t), 6·15 (4H, s), and 6·5 (6H, s), $J_{5(7),6}$ 7·8 Hz.

Attempted Reaction of 6-Bromo-2,3-dihydro-1,4-diazepinium Perchlorate (III) *with Sodium Methoxide.*—The bromo-compound (III) (0·14 g, *ca.* 0·5 mmol) was dissolved in a solution of sodium methoxide [from sodium (0·13 g)] in methanol. The u.v. absorption shifted to $\lambda_{max.}$ 337 nm and did not change after the solution had been heated under reflux for 30 min. The solvent was then evaporated off *in vacuo*, water (5 ml) was added, and the solution was extracted with ether (3 × 10 ml). The extract was dried (Na_2SO_4) and evaporated. Addition of perchloric acid (70%; 0·1 ml) caused the slow crystallisation of the bromo-compound (III) (0·05 g, 36%), m.p. 148—150° (from ethanol), mixed m.p. 149—151°, u.v. and i.r. spectra identical with those of an authentic sample. The low recovery was probably due to the necessarily harsh work-up procedure. The product of $\lambda_{max.}$ 337 nm was identified as the dihydrodiazepine base by dissolving the bromo-compound (III) in [$^2H_4$]methanol containing sodium [$^2H_3$]methoxide in an n.m.r. tube [τ 2·57 (2H, s) and 6·40 (4H, s)].

Attempted Reaction of the Bromo-compound (III) *with Thiourea.*—A solution of the bromo-compound (III) (0·14 g, 0·5 mmol) and thiourea (0·04 g, 0·5 mmol) in ethanol (5 ml) was heated under reflux for 23 h; the u.v. spectrum indicated that no reaction had taken place. Ether was added to the cooled solution and precipitated starting material (III) (0·1 g, 72%), m.p. 146—149°, mixed m.p. 148—150°, identical i.r. and u.v. spectra. (The low m.p. was due to a small quantity of thiourea which was not separated by recrystallisation.)

Reaction of 6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium Bromide with Thiourea.—A solution of the dihydrodiazepinium bromide (0·85 g, 3 mmol) and thiourea (0·21 g, 3 mmol) in ethanol (15 ml) was heated under reflux for 3 h. Addition of ether to the cooled solution gave 2,3-dihydro-5,7-dimethyl-1,4-diazepinium bromide (0·58 g, 95%), identified by mixed m.p. and spectra.

Protodeiodination of 2,3-Dihydro-6-iodo-1,4-diazepinium Perchlorate.—A solution of this iodo-compound (0·16 g, 0·5 mmol) and thiourea (0·04 g, 0·5 mmol) in ethanol (5 ml) was heated under reflux for 24 h. Addition of ether to the cooled solution precipitated 2,3-dihydro-1,4-diazepinium perchlorate (I) (0·07 g, 70%), identical (i.r. and u.v. spectra) with an authentic specimen. The same result was obtained when a methanolic solution of the iodo-compound alone was heated under reflux.

Reaction of 6-Bromo-2,3-dihydro-1,4-diazepinium Salt with

Piperidine.—A solution of an unpurified sample of brominated dihydrodiazepinium salt (anion for the most part bromide but some perchlorate) (0·28 g, *ca.* 1 mmol) and piperidine (0·86 g, 10 mmol) in methanol (15 ml) was heated under reflux for 20 min. After solvent had been evaporated off, addition of ether to the residue gave a solid (0·18 g) whose m.p. and i.r. spectrum showed it to be piperidinium bromide, m.p. (of a sample purified by solution in chloroform and reprecipitation by ether) 237—239°, mixed m.p. 237—238°.

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