

Spectral Properties and Ring Conformation of Some Novel 2,3-Dihydro-1*H*-1,4-diazepinium Cations

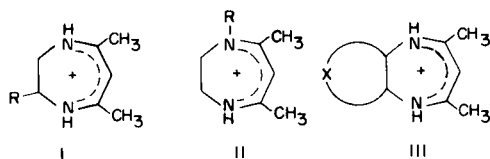
G. W. H. Potter (1), M. W. Coleman and A. M. Monro

Chemical Research Department, Pfizer Central Research, Pfizer Ltd., Sandwich, Kent CT13 9NJ, England

Received February 17, 1975

A series of 2,3-dihydro-1*H*-1,4-diazepinium salts, which includes fused ring systems of known ring-junction configuration, has been prepared. A study of the spectral properties indicates that this ring system is largely planar and is sufficiently flexible to permit *cis* and *trans* fusion at the 2,3-bond to 5- or 6-membered rings without significant distortion.

During a search for pharmacologically active compounds of novel structure, we prepared a series of 2,3-dihydro-1*H*-1,4-diazepinium cations (I, II and III). The only analogous derivatives of this ring system reported hitherto, were the 2-methyl, some *N,N'*-disubstituted and



the *trans*-fused cyclopentano- and cyclohexano- derivatives (2-4). As examination of models suggested that there was no reason, *a priori*, why *cis*-ring fusion should not be achieved, compounds containing this feature were included as synthetic targets. The spectral properties of the *cis*- and *trans*-fused rings were compared to provide evidence for the degree of ring strain or distortion caused by the two modes of fusion.

The title compounds (Table I) were prepared in satisfactory yields by condensing the corresponding 1,2-diamines with pentane-2,4-dione according to the procedure of Lloyd *et al.*, (2). With one exception the products were isolated as perchlorate salts; some were converted to hydrochlorides for characterisation.

Those diamines which were not commercially available were prepared by three methods. That of Minisci *et al.*, (5) involving the conversion of olefines to diazides and subsequent hydrogenolysis, gave the diamines required for the synthesis of I and the *trans*-isomers of III. The corresponding *cis*-diamines were obtained by a modification of the stereo-specific route of Swift and Swern (6); better yields were obtained with azidosylates as intermediates instead of azidomesylates as used by the original authors. The distinction between the physical properties of the

isomeric amines synthesised by the two routes, the latter providing unambiguous stereochemistry, established that the diazide route yielded *trans*-isomers. Diamines for II were prepared by reaction of 1,2-diaminoethane with the appropriate bromo compounds (7).









The ultraviolet spectra of the dihydro diazepinium cations fell into two groups. The absorption maxima for I and III were at *ca.* 324 nm (ϵ *ca.* 14×10^3), similar to that reported by Lloyd *et al.*, (2) for the parent compound. No significant differences were found between *cis*- and *trans*-fused rings. An alkyl substituent on N, however, induced a slight bathochromic shift, leading to λ max 329 nm (ϵ *ca.* 18×10^3). The *N*-phenyl derivative showed greater bathochromic and hyperchromic effects. These results are consistent with a large measure of planarity in the cation allowing delocalization of the 6 π electrons. In the *N*-phenyl derivative further conjugation is obtained, although molecular models suggest that the 5-methyl group will offer steric resistance to full coplanarity of the rings.

The proton magnetic resonance spectra were consistent with expectation based on that of the parent compound. The signal for the quasi-aromatic proton located between the two methyl groups lay between 4.77 and 5.08 τ , except in the *N*-phenyl derivative when it was at 4.55 τ .

The methyl resonances lay between 7.62 and 8.00 τ , and in compounds 1, 9, 10, 13 and 14 where molecular symmetry was present, the signal was a 6-proton singlet. The pmr signals for H₂ and H₃ protons in I constituted poorly resolved ABX systems (*ca.* 5-6.5 τ), with discernible coupling constants compatible with a large geminal coupling and two small vicinal couplings. In the *N*-substituted derivatives II and the fused systems III these protons gave, broad, incompletely resolved signals.

In order to test the hypothesis that these signals were broad because of rapid interconversion of conformers such

Table 1
Spectral Properties of Some 2,3-Dihydro-1*H*-1,4-diazepinium Salts

No.	R	R'	UV Absorption (a)		Proton magnetic resonance (in DMSO- <i>d</i> ₆) (b) of relevant protons (see text)				
			λ max (nm)	E × 10 ⁻³	2H	3H	6H	methyl protons	
1	H	H	323	16.6		6.48 (b)	5.08 (s)	7.88 (s)	
2	C ₆ H ₅	H	322	14.0	4.92 (b)	6.0 (q) J = 13 J' = 4	6.5 (q) J = 13 J'' = 1	4.90 (s) 7.7	7.95
3	C ₆ H ₅ OCH ₂	H	323	17.1	5.9 (o) (b)		6.4 (m)	4.95 (s)	
4	CO ₂ H	H	320	15.7	5.0 (o) (m)	5.75 (m) J = 14 J' = 4	6.7 (m) J = 14 J'' = 1	4.95 (o) 7.7	7.82
5	H	C ₆ H ₅	335	21.8		6.1 (m)	4.55 (s)	7.69	8.00
6	H	C ₆ H ₅ CH ₂	329	18.3		6.3 (m)	4.72 (s)	7.7	
7	H	C ₆ H ₅ CH ₂ CH ₂	330	14.5		6.5 (o) (m)	4.89 (s)	7.85	
8	H	C ₆ H ₅ OCH ₂ CH ₂	329	18.4		5.5 - 6.6 (o) (m)	4.77 (s)	7.62	7.79
ring junction protons									
9		<i>cis</i>	324	13.8		6.2 (b)	5.05 (s)	7.8	
10		<i>trans</i>	322	14.9		6.8 (b)	5.0 (s)	7.8	
11		<i>cis</i>	324	13.4	4.98 (b)		5.95 (b)	4.97 (s) 7.7	7.95
12		<i>trans</i>	324	13.4	5.53 (m)		6.42 (b)	4.83 (b)	7.76
13		<i>cis</i>	326	13.1		6.1 (b)	5.0 (s)	7.8	
14		<i>trans</i>	324	14.5		6.6 (b)	4.94 (b)	7.8	
15		<i>cis</i>	326	12.3	4.72 (m)		5.62 (b)	5.08 (s) 7.7	7.92
16		<i>trans</i>	323	12.0	5.4 (b)		6.5 (o)	4.83 (s) 7.7	7.75

(a) In 0.1 hydrochloric acid, (b) = broad, (s) = singlet, (q) = quartet, (m) = multiplet, (o) = overlap.

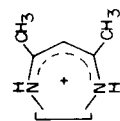
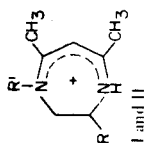


Table 2

Preparation of Compounds 2-16 (See Table 1) (a)

No.	Yield	Salt (b)	M.p. ^o	Found				Required			
				C	H	N	Cl	C	H	N	Cl
2	80	A	126-130	51.7	5.7	9.0	12.25	51.9	5.7	9.3	11.8
3	66	A	119-123	50.6	5.85	8.55	10.65	50.85	5.8	8.5	10.7
4	64	B	248 (dec)	47.0	6.45	13.7	17.15	46.9	6.4	13.7	17.3
5	45	A	112	51.9	5.8	9.25		51.9	5.7	9.3	
6	45	A	82-86	53.4	6.1	8.75	11.55	53.4	6.1	8.9	11.3
7	63	A	135-144	54.9	6.3	8.2		54.8	6.4	8.5	
8	41	A	76-80	52.5	6.4	8.0	10.3	52.25	6.1	8.1	10.3
9	84	A	168	(d)				47.4	6.8	10.05	12.75
10	49	B	> 300	61.3	8.8	12.95	16.5	61.5	8.9	13.05	16.5
11	54	A	154-157	55.1	5.85	8.5	11.0	55.1	5.85	8.6	10.85
12	63	B	> 300	68.3	7.4	10.5	13.7	68.55	7.3	10.7	13.5
13	70	A	147	45.2	6.6	10.4		45.4	6.5	10.6	
14	80	B	> 300	60.1	8.7	13.65	17.55	59.85	8.55	13.95	17.7
15	40	A	167-174 (c)	53.85	5.5	8.7	11.4	53.7	5.5	8.95	11.35
16	71	B	> 300	67.3	6.9	11.5	14.4	67.6	6.9	11.3	14.25

(a) Compound 1 (m.p. 139-140^o) was prepared as the perchlorate salt according to G. Swarzenbach and K. Lutz, *Helv. Chim. Acta*, 23, 1139 (1940). (b) A = ClO₄⁻ B = Cl⁻. (c) Lit. (8) m.p. 167^o. (d) No analytical data available; compound identity established by method of synthesis and uv, pmr and ir spectra being in accord with expectation based on that of analogues.

Table 3

Properties of 1,2-Diazides

	Yield (%) (a)	B.p. °C (mm Hg)	N _D ²⁵
<i>cis</i> -1,2-Diazidocyclopentane	27	47-50/0.5	1.5025
<i>trans</i> -1,2-Diazidocyclopentane	22	34-38/0.3	1.4911
<i>cis</i> -1,2-Diazidoindane	20	83-90/0.2	1.5775
<i>trans</i> -1,2-Diazidoindane	15	80-84/0.01	1.5714
<i>cis</i> -1,2-Diazido-1,2,3,4-tetrahydro naphthalene	24	96-98/0.1	1.5784
<i>trans</i> -1,2-Diazido-1,2,3,4-tetrahydro naphthalene	50	68-82/0.35	1.5796

(a) Overall yield from olefine.

as IV and V the pmr spectra of compounds 1 and 5 (Table 1) were recorded at low temperature.



The broad 4-proton singlet at 6.35 τ (deuteriochloroform, 30^o) in the spectrum of compound 1 changed as the temperature was lowered. At -10^o considerable broadening was observed, and at -20^o the band was resolved into two broad peaks at 6.0 and 6.8 τ . On lowering the temperature to -40^o, the two broad bands sharpened into multiplets centered at 5.85 and 6.90 τ with each band integrating for two protons. The high field multiplet approximated to a

broad doublet, the peaks of which were separated by *ca.* 16 Hz. However, the low field multiplet appeared as a very broad partially resolved doublet. Lowering the temperature to -60^o produced no further changes.

The spectral evidence suggests that the two multiplets centered at 5.85 and 6.90 τ represent protons in *pseudo*-equatorial and *pseudo*axial environments respectively, the low field signal being considerably broader than the high field signal owing to the larger predicted coupling to NH protons in the former case. Deuterium substitution of the NH protons at -40^o resulted in a sharpening of the low field signal (5.85 τ) into a broad doublet comparable to the size and shape of the high field signal (6.90 τ).

Similar behaviour was observed in the low temperature

spectrum of compound 5: at -10° the methylene resonances became very broad and at -30° they were resolved into two very broad multiplets centered at ca. 5.6 and 6.4 τ .

These results suggest that rapidly interconverting conformers are present at room temperature, while at low temperature the rate of interconversion is slow enough for the conformers to be distinguished.

A coalescence temperature of -15° was observed for the 2,3 protons of compound 1 and this represents a Free Energy of Activation (ΔG^{\ddagger}) of ca. 12.5 Kcals. per mole for the interconversion of conformers.

The spectral data reported here, and the similarity in ease of synthesis of the *cis*- and *trans*-fused systems, lead to the conclusion that the 2,3-dihydro-1*H*-1,4-diazepinium ring possesses a high degree of flexibility. This property is reflected in the conformational "flipping" of the monocyclic compounds, and the fact that 5 and 6-membered carbocyclic rings may be *cis*- or *trans*-fused without loss of conjugation.

EXPERIMENTAL

Melting points were obtained on a Kofler block. Infrared and ultraviolet spectra were recorded on Perkin Elmer Infracord 137 and Ultracord 137 instruments respectively. Proton magnetic resonance spectra were recorded on the Varian A60 and the Perkin Elmer R12B instruments.

Preparation of 2,3-Dihydro-1*H*-1,4-diazepinium Salts.

These were prepared from 1,2-diamines and 2,4-pentanedione at pH 4 according to the method of Lloyd *et al.*, (2). The products were isolated by dilution of the reaction mixture with water and treatment with excess 60% perchloric acid. The precipitated salts were crystallised from water or methanol-ether. The only exception was compound 4, which was prepared from DL-2,3-diaminopropionic acid hydrochloride, and following evaporation of the solvent, was isolated as the hydrochloride salt. Some perchlorates were converted to chlorides by ion exchange. Details are in Table 2.

Preparation of 1,2-Diazides.

a)

cis-Diazides were obtained from olefines *via* several intermediate steps using conventional procedures (see ref. 6 and above text). Most intermediates were purified sufficiently for characterisation (although not for analysis).

b)

trans-Diazides were prepared from olefines and sodium azide/potassium permanganate (5).

A small sample of each diazide was distilled (see Table 3); the remainder was decolorised by passage through alumina, if necessary. All the diazides showed infrared absorption peaks at ca. 2500 and 2100 cm^{-1} .

Preparation of 1,2-Diamines.

The above diazides were subjected to hydrogenolysis over platinum oxide in ethanol at 4 atmospheres for 24 hours. The products were distilled under reduced pressure and characterised generally as tosylate salts. Two novel diamines were obtained.

N-(2-Phenoxyethyl)ethane-1,2-diamine.

This compound had b.p. $100^{\circ}/0.05$ mm Hg; dihydrochloride, m.p. (sublimes).

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}$: C, 47.4; H, 7.15; N, 11.1. Found: C, 47.25; H, 7.0; N, 10.95.

cis-1,2-Diamino-1,2,3,4-tetrahydronaphthalene.

This compound had b.p. $97-105^{\circ}/0.4$ mm Hg; tosylate, m.p. $290-293^{\circ}$.

Anal. Calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_6\text{S}_2$: C, 56.9; H, 6.0; S, 12.7. Found: C, 56.9; H, 6.0; S, 12.7.

Acknowledgements.

The authors wish to thank Dr. M. Szelke for useful discussions on the synthesis of the diamines.

REFERENCES

- (1) Present address: Brunel Technical College, Bristol B57 9BU, England.
- (2) D. Lloyd, R. H. McDougall and D. R. Marshall, *J. Chem. Soc. (C)*, 780 (1966).
- (3) P. Bell and D. R. Marshall, *J. Chem. Soc.*, 2195 (1964).
- (4) C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd and D. R. Marshall, *J. Chem. Soc. (C)*, 93 (1966).
- (5) F. Minisci, M. Cecere and R. Galli, *Gazz. Chim. Ital.*, **94**, 1, 67 (1964).
- (6) G. Swift and D. Swern, *J. Org. Chem.*, **32**, 511 (1967).
- (7) A. E. Frost and A. A. Cowson, *ibid.*, **75**, 1581 (1959).
- (8) S. Veibel and J. I. Nielsen, *Kgl. Dan. Vidensk. Selsk., Mat.-Fys. Medd.*, **35**, (6) 32 (1966); *Chem. Abstr.*, **67**, 21898 x (1967) report an indanodiazepinium perchlorate of unspecified stereochemistry, but with m.p. 167° agreeing with our *cis*-isomer.