The Application of Proton Magnetic Resonance Spectra to the Determination of Configuration and Conformation of 1,2,3,4,4a,9a-Hexahydrocarbazoles

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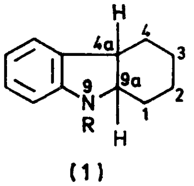
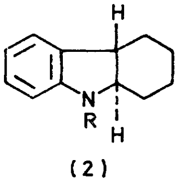
Proton magnetic resonance spectra, recorded at 60, 100, and 220 MHz, are used to assign configurations and preferred conformations to *cis*- and *trans*-1,2,3,4,4a,9a-hexahydrocarbazoles and their acyl derivatives.

RECENT papers[1-3] have emphasised the difficulties encountered in interpreting the spectra of *cis*- (1) and *trans*-1,2,3,4,4a,9a-hexahydrocarbazoles (2) in terms of configuration. We now publish our own conclusions, based on ^{1}H n.m.r. spectra at 60, 100, and 220 MHz.



(1)



(2)

Chemical shifts are reported in Table 1. The line separations given in Table 2 (*trans*-compounds) are close to the actual coupling constants, owing to the relatively large chemical shift differences between the coupled protons involved. In the spectra of the *cis*-compounds, only 9a-H and 4a-H are seen to be well-shifted. Consequently, although the separation of outer lines (' bandwidth ') for 4a- and 9a-H signals can be equated with the *sum* of the appropriate coupling constants, the only individual coupling constant which can be deduced is $J_{4a,9a}$ (Table 3).

TABLE 1

Proton shifts (τ) in spectra of hexahydrocarbazoles ($CDCl_3$)

Compound	9a-H	4a-H	1*eq*-H	1*ax*-H	4*eq*-H	4*ax*-H	Others
(2; R = H)[a]	6·92	7·48	7·95	8·6	7·68	8·36	8·14,[b] 8·6[c]
(2; R = Ac)[a]	6·51	7·27	7·09		7·65	8·29	7·67[d]
(2; R = Bz)	6·38	7·20[e]	7·32		7·67		
(1; R = H)[a]	6·29	6·91					
(1; R = Ac)[f]	5·60	6·50					7·74
(1; R = Bz)[a]	5·55	6·47	7·71				
(8)[a,g]	6·61						8·71[d]

[a] 220 MHz (probe temperature +13°). [b] 2*eq*, 3*eq* protons. [c] 2*ax*, 3*ax* protons. [d] Me. [e] Assignment by decoupling. [f] At 60 MHz and +90°, to allow rapid rotation about the N–C(=O) bond. [g] *cis*- 1,2,3,4,4a,9a-Hexahydro-4a-methylcarbazole.

TABLE 2

Coupling constants (Hz) for *trans*-hexahydrocarbazoles

Compound	$J_{9a,4a}$	$J_{9aax,1ax}$	$J_{9aax,1eq}$	$J_{4a,4ax}$	$J_{4a,4eq}$	$J_{1eq,1ax}$	$J_{4eq,4ax}$	$J_{4ax,3ax}$	$J_{4ax,3eq}$
(2; R = H)	11·8	11·8	3·0	11·0	*a*	11·0	12·0	11·5	2·5
(2; R = Ac)	11·5	11·5	2·5	11·0	*a*	15·0	11·5	11·5	3·0
(2; R = Bz)	11·0	11·0	3·0	*a*	*a*	*a*	*a*	*a*	*a*

[a] Not seen clearly.

TABLE 3

Band widths, line separations, and coupling constants (Hz) for *cis*-hexahydrocarbazoles

	Band widths and line separations *		Coupling constants		
Compound	9a-H	4a-H	$J_{4a,9a}$	$J_{9a,1ax} + J_{9a,1eq}$	$J_{4a,4ax} + J_{4a,4eq}$
(1; R = H)	18(q, sepns. *ca.* 6)	19·5(q, sepns. *ca.* 6·5)	6	12	13
(1; R = Ac)	23(q, sepns. *ca.* 7·5)	14·5(t, sepns. *ca.* 7)	7	16	7·5
(1; R = Bz)	22·5(q, sepns. *ca.* 7·5)	14·0(t, sepns. *ca.* 7)	7	15·5	7
(8)	8·3(t, sepns. *ca.* 4·15)			8·3	

* q = 1 : 3 : 3 : 1 Quartet; t = 1 : 2 : 1 triplet.

The 220 MHz spectrum of *trans*-hexahydrocarbazole, m.p. 124—126° (2; R = H), allows confident assignment of seven of the ten cyclohexyl protons, and an interpretation of the J values in terms of conformation (3) is straight-forward. In particular, 9a-H gives a well-resolved triplet ($J_{4a,9a} \simeq J_{9a,1ax} = 11{\cdot}8$ Hz), each portion being a well-resolved doublet ($J_{9a,1eq}$3 Hz); also 4a-H gives a triplet ($J_{4a,9a} \simeq J_{4a,4ax} \simeq 11$ Hz), each portion being broadened by the coupling with H_{4eq}. The low-field triplet was assigned to 9a-H because the deshielding effect of N-acylation was more marked for this signal than for the high-field triplet. Further,

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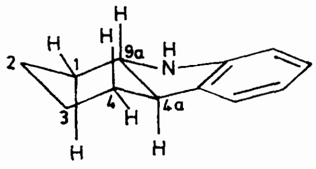
[1] A. Smith and J. H. P. Utley, *J. Chem. Soc.* (*C*), 1970, 1.

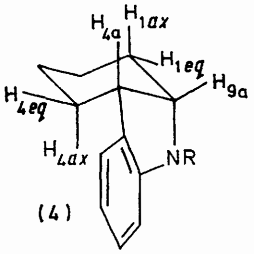
[2] D. Shaw, A. Smith, and J. H. P. Utley, *J. Chem. Soc.* (*B*), 1970, 1161.

[3] S. McLean, U. O. Trotz, K. S. Dichmann, J. K. Fawcett, and S. C. Nyberg, *Tetrahedron Letters*, 1970, 4561.

assignment of a quartet (J 11·5—12 Hz), with approximate intensity ratios 1 : 3 : 3 : 1 [each portion a doublet, (J *ca.* 2·5 Hz)], to 4*ax*-H (rather than 1*ax*-H) is based on the observation that the position of this signal is virtually unaltered after the free base (2; R = H) has been converted to its *N*-acetyl derivative (2; R = Ac). A similar argument allows assignment of the doublet (J *ca.* 12 Hz) at τ 7·68 to 4*eq*-H rather than 1*eq*-H. Conformation (3) has a slightly strained cyclohexane chair, fused to a five-membered ring in an envelope conformation, C-9a being the extraplanar atom. Additional support comes from the spectral parameters for the derived *N*-acetyl and *N*-benzoyl compounds (Tables 1 and 2).



(3)



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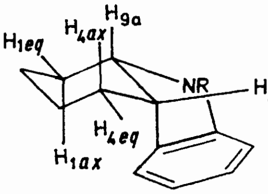

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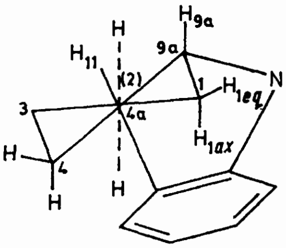

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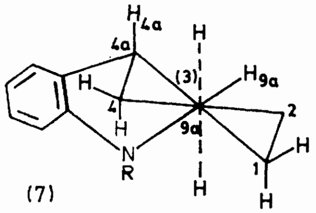

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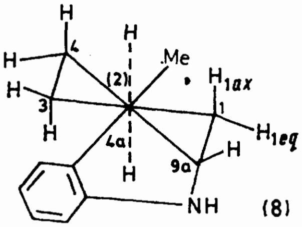

(8)

The isomeric hexahydrocarbazole, m.p. 98—99°, must therefore have the *cis*-configuration, although the spectra of the base and its acyl derivatives yield for $J_{4a,9a}$ a value (6—7 Hz) which is not immediately diagnostic of a *cis*-ring fusion (see later). Nevertheless, the assignment of configuration originally made by Gurney *et al.*[4] is clearly confirmed. Our conclusion also agrees with the recent findings of Smith and Utley,[1] although we consider their arguments to be of questionable validity. Thus, these workers assume in the first place that the five-membered ring is planar. Now the energy barriers between stable conformations of five-membered rings are generally less than those for six-membered rings, and therefore one might expect the strain involved in a six–five fusion to find relief *less* easily in a conformational distortion of the six-membered ring, than in a conformational change of the five-membered ring. In addition, the precise conformation of *cis*-octahydro-*N*-methylindole methiodide is not known with certainty, and therefore the comparison [1] of *N*-methyl shift differences in this compound with those in hexahydro-9-methylcarbazole methiodide, is of doubtful value.

In the 220 MHz spectrum of *cis*-hexahydrocarbazole (1; R = H), 4a- and 9a-H appear as well-resolved 1 : 3 : 3 : 1 quartets, but the approximately equal band widths (18 Hz for 9a-H and 19·5 Hz for 4a-H) are not consistent with conformation (4) (expected: 10—11 Hz for 9a-H and 18—19 Hz for 4a-H), *nor* with conformation (5) (expected: 18—19 Hz for 9a-H and 10—11 Hz for 4a-H). However, a mixture of conformations (4) (mole fraction x) and (5) [mole fraction $(1 - x)$] in rapid equilibration, has to be considered. Now the *average* couplings experienced by 9a-H in such a mixture are given by expressions (1)—(3).

$$J_{4a,9a} = xJ_{eq,ax} + (1 - x)J_{ax,eq} \qquad (1)$$

$$J_{9a,1} = xJ_{eq,eq} + (1 - x)J_{ax,ax} \qquad (2)$$

$$J_{9a,1'} = xJ_{eq,ax} + (1 - x)J_{ax,eq} \qquad (3)$$

Assuming $J_{eq,ax} = J_{ax,eq}$, the band width of the 9a-H signal is given by $(J_{4a,9a} + J_{9a,1} + J_{9a,1'})$, that is, $2J_{ax,eq} + J_{ax,ax} - x(J_{ax,ax} - J_{eq,eq})$. A similar procedure gives the band width of the 4a-H signal as $2J_{ax,eq} + J_{eq,eq} + x(J_{ax,ax} - J_{eq,eq})$.

Interestingly, the *sum* of these band widths is $(4J_{ax,eq} + J_{ax,ax} + J_{eq,eq})$ and is independent of the value of x. Taking realistic values of 11·5 and 2·5 Hz for $J_{ax,ax}$ and $J_{eq,eq}$, respectively, it is seen that band widths of 18 and 19·5 Hz for 9a-H and 4a-H respectively require the average of all $J_{ax,eq}$ values to be about 6 Hz. Since this value is well outside the normal range for cyclohexanes (2·5—4·5 Hz), the possibility of a mixture of (4) and (5) in rapid equilibration can be dismissed. On the other hand, the twist conformations (6) and (7) offer distinct advantages in terms of reduced repulsive interactions. Models of (6) and (7) are interconvertible through a boat conformation which does not appear to offer a particularly high energy barrier. The twist conformation (6) involves dihedral angles for 9a-H of *ca.* 33° (4a-H), 71° (1*eq*-H), and 169° (1*ax*-H). The corresponding coupling constants are expected to be about 7, 1·5, and 11 Hz, respectively. In the twist conformation (7) the dihedral angles for 9a-H of *ca.* 33° (4a-H), 33° (1*eq*-H), and 153° (1*ax*-H) lead to predicted coupling constants of *ca.* 7 Hz in all three cases. The

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[4] J. Gurney, W. H. Perkin, jun., and S. G. P. Plant, *J. Chem. Soc.*, 1927, 2676.

averaged coupling constants for 9a-H with adjacent protons in the equilibrium (6) $\rightleftharpoons$ (7) (equal proportions) are therefore calculated to be 7 (4a-H), 4·3 (1*eq*-H), and 9 Hz (1*ax*-H). Now the observation of *equal* ' couplings ' of about 6—6·5 Hz for 9a-H with adjacent protons in the equilibrium (6) $\rightleftharpoons$ (7) is only possible if the two protons at C-1 have approximately the same shift, leading to a ' deceptively simple ' spectrum in which 9a-H appears to be equally coupled to 1*ax*- and 1*eq*-H by a ' coupling constant ' equal to the average of the two J values (the average of 4·3 and 9 being 6·65). The 4a-proton in the equilibrium (6) $\rightleftharpoons$ (7) can be considered in an analogous manner, and the averaged coupling constants for 4a-H with adjacent protons are calculated to be 7, 4·3, and 9 Hz. Again, therefore, the observed spectrum is only possible if the two protons at C-4 have approximately the same chemical shifts. Unfortunately, the 220 MHz spectrum of *cis*-hexahydrocarbazole (1; R = H) is not interpretable in the high-field region, and we have been unable to determine the shifts of 1*ax*- and 1*eq*-H, and of 4*ax*- and 4*eq*-H. Nevertheless, we believe that the evidence at present available is best explained by assuming that *cis*-hexahydrocarbazole (1; R = H) exists as a mixture, in equal proportions, of the rapidly interconverting twist conformations (6) and (7).

The situation is completely different for the *cis*-*N*-acetyl and *cis*-*N*-benzoyl derivatives, the spectra of which display a comparatively *large* band width for 9a-H and a comparatively *small* one for 4a-H. Conformations (4) and (7) are now disfavoured by interactions between the *N*-substituent and 1*eq*-H and the molecule prefers conformation (5), with the cyclohexane ring slightly flattened in the region of C-9a, C-4a, and C-4. Conformation (5) accounts well for the observed band widths and, interestingly, is similar to that adopted by *cis*-*N*-acetyl-4a-ethylhexahydrocarbazole in the crystalline state.[3]

In the 220 MHz spectrum of 1,2,3,4,4a,9a-hexahydro-4a-methylcarbazole,[5] the high-field region is uninterpretable; however, the well-shifted signal at τ 6·61, due to 9a-H, is a well-resolved symmetrical triplet, and the separations of *ca.* 4·15 Hz are only consistent with a *cis*-fusion of five- and six-membered rings. The value of 8·30 Hz for $(J_{9a,1ax} + J_{9a,1eq})$ suggests a preference for conformation (8), in which the dihedral angles for 9a-H are approximately 49 (1*eq*-H) and 71° (1*ax*-H). This is a surprising conclusion, since models suggest that conformation (5) involves the least interactions amongst the three most likely conformations (5), (6), and (8). The merit of conformation (8), as against (5) and (6), is that it gives a situation in which the 4a-methyl group suffers the minimum repulsive interactions.

From these results, we conclude that molecules in which five- and six-membered rings are *cis*-fused show considerable variability of conformation, in spite of possible constraints imposed by the attachment of a benzene ring to the five-membered ring.

EXPERIMENTAL

Compounds were prepared as described.[4-7] Spectra were measured on Perkin-Elmer R10, Varian HA-100, and Varian HR-220 spectrometers. We are indebted to Imperial Chemical Industries, Ltd. (Petrochemical and Polymer Laboratory) for spectra at 220 MHz.

[1/830 *Received*, 24*th May*, 1971]

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[5] H. Booth, F. E. King, and J. Parrick, *J. Chem. Soc.*, 1958, 2302.

[6] J. Gurney and S. G. P. Plant, *J. Chem. Soc.*, 1927, 1314.

[7] C. Graebe and B. von Adlerskron, *Annalen*, 1880, **202**, 25.