627. *Proton Magnetic Resonance in Some Substituted Epimeric Piperidin-4-ols*

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Proton magnetic resonance spectra are recorded for a number of substituted epimeric piperidin-4-ols and are discussed in terms of preferred configurations and conformations. In all cases studied, the piperidine rings exist predominantly in chair forms, as expected from conformational analysis. Reduction of 2,2,6,6-tetramethyl-4-piperidine to give only a single product by different methods indicates that this six-membered hetero-ring cannot be rigid. The "boat–chair" equilibrium in α-1,3,5-trimethyl-2,6-diphenylpiperidin-4-ol, m. p. 134—135°, has been re-examined, the conclusion being that the contribution from the boat conformer is less than 16%. In several cases, spectra of free bases have been taken in different solvents, such as benzene, deuteriochloroform, and carbon disulphide; no indication of interactions between deuteriochloroform and solute has been found. The C-2 protons in the β-epimers are deshielded by the axial 4-hydroxy-groups; this can be attributed to 1,3-diaxial spatial proximity.

It is generally accepted [1] that, owing to the similarities in bond lengths as well as bond angles, the conformational analysis of six-membered heterocyclic compounds having nitrogen, oxygen, or sulphur in the ring should not be very different from that of cyclohexane derivatives. Extensive studies on alkaloids,[2-7] have established that the piperidine ring mostly prefers the chair conformation. However, conformational studies on simple piperidine derivatives have been limited, and only recently has the stereochemistry of certain piperidin-4-ols been investigated systematically by chemical means.[8] This Paper reports the proton magnetic resonance (p.m.r.) spectra of some compounds in the series just named; it proceeds to show that such data can provide (a) direct physical evidence on the preferred configurations and conformations adopted by these molecules as solutes, and (b) indirect confirmation of the stereochemical courses taken by various methods of reduction applied to the corresponding piperidones.

Experimental

P.m.r. spectra were recorded, on a Varian A-60 spectrometer operating at 40° with tetramethylsilane (TMS) as internal standard, for 5—7% w/v solutions. With the exception of

[1] D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 1956, **10**, 44.
[2] A. F. Thomas, H. J. Vipond, and L. Marion, *Canad. J. Chem.*, 1955, **33**, 1290, and references therein.
[3] J. B. Stenlake, *J.*, 1955, 1626.
[4] E. J. Gabe and W. H. Barnes, *Acta Cryst.*, 1963, **16**, 796.
[5] F. R. Ahmed and W. H. Barnes, *Acta Cryst.*, 1963, **16**, 1249.
[6] F. R. Ahmed, W. H. Barnes, and L. di Marco Masironi, *Acta Cryst.*, 1963, **16**, 2373.
[7] A. R. Pinder, *Chem. Rev.*, 1964, **64**, 551, and references therein.
[8] M. Balasubramanian and N. Padma, *Tetrahedron*, 1963, **19**, 2135.

2,2,6,6-tetramethylpiperidin-4-ol and its *N*-methyl derivative, the preparation of the compounds followed that of Balasubramanian and Padma; [8] 2,2,6,6-tetramethylpiperidin-4-ol was prepared by reducing the parent ketone, m. p. 37—38°,[9] with lithium aluminium hydride; the recrystallised product (from benzene) had m. p. 127—128°, and was seemingly identical with

TABLE 1

Piperidin-4-ols and their melting points

Compound	Substituents		M. p.
(I)	2,2,6,6-Tetramethyl-		127—128°
(II)	1,2,2,6,6-Pentamethyl-		143—144
(III)	2,6-Diphenyl-	α-form *	123—124
(IV)	,,	β-form	138—139
(V)	1-Methyl-2,6-diphenyl-	α-form	164—165
(VI)	,, ,,	β-form †	155—156
(VII)	3,5-Dimethyl-2,6-diphenyl-	α-form	132—133
(VIII)	,, ,,	β-form	110—111
(IX)	1,3,5-Trimethyl-2,6-diphenyl-	α-form	134—135
(X)	,, ,,	β-form	98—99

* The α-forms are epimers obtained predominantly from Na–Bu^{n}OH and $LiAlH_4$ reductions, whilst the β-forms are those prepared from the Meerwein–Ponndorf–Verley reduction; cf. ref. 8. † This compound was prepared from the methylation of the β-isomer of 2,6-diphenylpiperidin-4-ol; recrystallisation from benzene–light petroleum afforded the product.

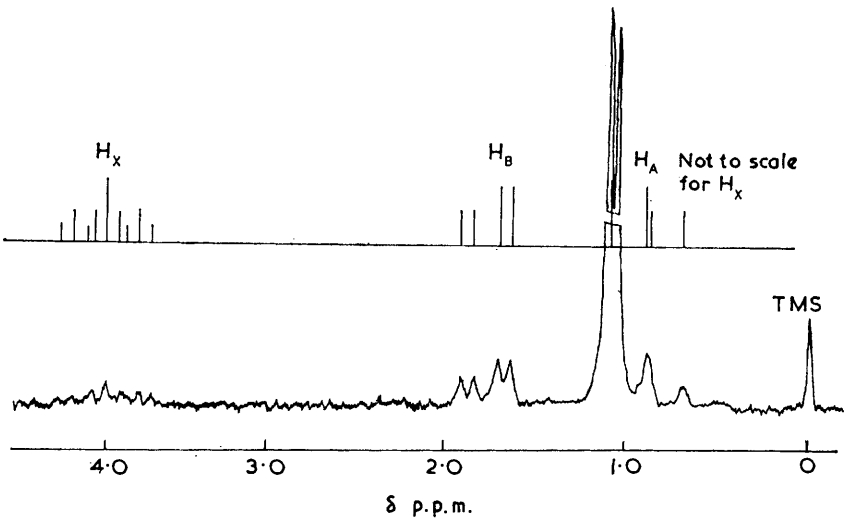
that obtained [10] by the hydrogenation of the ketone in ethanol with platinum as catalyst. 1,2,2,6,6-Pentamethylpiperidin-4-ol, obtained by reduction of 1,2,2,6,6-pentamethyl-4-piperidone with lithium aluminium hydride, had m. p. 143—144° (from light petroleum–ether) (lit.,[11] 145°, from ethanol or chloroform). The melting points of the samples used are given in Table 1.

DISCUSSION

Configurations and Conformations of 2,2,6,6-*Tetramethylpiperidin*-4-*ol* (I) *and* 1,2,2,6,6-*Pentamethylpiperidin*-4-*ol* (II).—Hitherto, only a single product (I) had been obtained from the reduction of 2,2,6,6-tetramethyl-4-piperidone regardless of whether sodium amalgam in alcohol,[12] hydrogen with platinum in ethanol, or lithium aluminium hydride was used. In their review of the stereochemistry of nucleophilic additions to the carbonyl group of cyclic ketones, Kamernitzky and Akhrem [13] pointed out that, for structurally rigid tetrasubstituted cyclohexanones having geminal substitution in the 3- and 5-positions, all methods of reduction, except reduction with sodium and alcohol, form alcohols with the hydroxyl group mainly or exclusively axially arranged. In the case of 7-oxotetrahydroalantolic acid, probably owing to the polar influence of the carboxyl group, reduction with sodium and isopropyl alcohol gives the corresponding axial alcohol in 75% yield. These facts are rather difficult to reconcile with the reduction of 2,2,6,6-tetramethyl-4-piperidone. Moreover, the p.m.r. spectrum (Figure) of 2,2,6,6-tetramethylpiperidin-4-ol (I) obtained from reduction with lithium aluminium hydride shows unambiguously that the molecule has the six-membered ring in a chair form with the hydroxyl group equatorial. As expected, the tertiary C-4 proton gives rise to an X-part of two ABX systems. Analysis of the spectrum [14,15] reveals that $J_{AX} = 11{\cdot}2$, $J_{BX} = 3{\cdot}9$, and $J_{AB} = 12{\cdot}4$ c./sec. (all coupling constants reported in this Paper are absolute values) which requires the configuration of (I) to be either (A) or (B). The configuration (B) can be eliminated owing to the unfavourable interactions involved which would tend to force the ring into a " twisted " or " flexible "

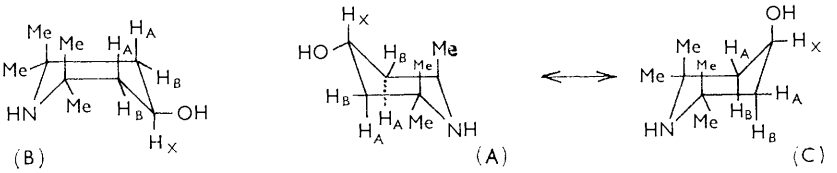
[9] H. K. Hall, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 5444.
[10] E. A. Mailey and A. R. Day, *J. Org. Chem.*, 1957, **22**, 1061.
[11] Beilstein's Handbuch, Vol. XXI, p. 12.
[12] E. Fischer, *Ber.*, 1884, **17**, 1789.
[13] A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, 1962, **18**, 728, and references therein.
[14] F. A. L. Anet, *J. Amer. Chem. Soc.*, 1962, **84**, 1054.
[15] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1964, **86**, 2742.

form; [16-19] this would be incompatible with the coupling constants observed. Furthermore, the observed J_{AX} and J_{BX}, when compared with corresponding data from *trans*-4-t-butyl-3,3,4,5,5-pentadeuteriocyclohexanol,[14] suggest strongly that in compound (I) molecules with conformations as (A) predominate; however, these cannot be rigid but must invert between the two extreme chair forms, (A) ⟷ (C), as shown by the fact that only



The proton magnetic resonance spectrum of 2,2,6,6-tetramethylpiperidin-4-ol (I) in deuteriochloroform after deuterium oxide exchange

one product has ever been obtained by various methods of reduction of 2,2,6,6-tetramethyl-4-piperidone. Such inversion of the ring would yield a single product irrespective of whether the initial attack on the carbonyl group of the parent ketone is equatorial (hindered approach as in the reductions with lithium aluminium hydride, or hydrogen with platinum in ethanol) or axial (unhindered approach as in the case of reductions with sodium in alcohols). Nevertheless, the contribution from the conformer (C) in the ground state of (I must be very small [seemingly less than 2—3%, if we compare the J_{aa} in compound (I) with that in *trans*-4-t-butyl-3,3,4,5,5-pentadeuteriocyclohexanol (J_{aa} = 11·07 c./sec) [14]].



An accurate estimate cannot be made owing to the possible geometric differences between the six-membered ring in the last-named compound and that in compound (I). It is interesting to note, that, although in cyclohexanol no less than 16% of the molecules have the hydroxyl group axial,[14,20,21] those in 2,2,6,6-tetramethylpiperidin-4-ol (I) exist almost exclusively as in conformation (A). Such a contrast may be attributed, at least partly, to steric factors. Constrction of a Leybold model reveals that the interactions between

[16] H. Sachse, *Ber.*, 1890, **23**, 1363; *Z. phys. Chem.*, 1892, **10**, 203.
[17] W. A. Wightman, *J.*, 1925, **127**, 1421.
[18] P. Hazebroek and L. J. Oosterhoff, *Discuss. Faraday Soc.*, 1951, **10**, 87.
[19] W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, 1961, **83**, 606.
[20] W. Masschelein, *J. Mol. Spectroscopy*, 1963, **10**, 161.
[21] P. Neelakantan, *Proc. Indian Acad. Sci.*, 1963, **57**, *A*, 94.

an axial 4-hydroxyl and the C-2 and C-6 axial hydrogens are relatively small yet become very much enhanced when these hydrogens are replaced by methyl groups; on the other hand, there seems to be no analogous congestion between the axial C-4 hydrogen and either C-2 and C-6 axial methyl groups or C-2 and C-6 axial hydrogens. Since compound (II) is obtainable [11] from *N*-methylation of compound (I), and such a reaction is not expected to cause any change in the skeleton of (I), we expected that 1,2,2,6,6-pentamethylpiperidin-4-ol (II) would also have the configuration and conformation of (A), with a methyl group replacing the imino hydrogen. The p.m.r. spectrum of (II) [$J_{AX} = 11{\cdot}3$, $J_{BX} = 4{\cdot}3$, and $J_{AB} = 12{\cdot}4$ c./sec., with, in τ units, H_X 5·95, H_B 8·08, and H_A 8·98 p.p.m. (partially obscured by the methyl signals)] is compatible with such an assignment.

Configurations and Conformations of the Epimeric 2,6-*Diphenylpiperidin*-4-*ols*.—The p.m.r. spectra of the epimeric 2,6-diphenylpiperidin-4-ols [compounds (III)—(X)] are summarised in Table 2. Since we are concerned with the configurations and conformations

TABLE 2

Chemical shift data (τ values) for the epimeric 2,6-diphenylpiperidin-4-ols (splitting J in c./sec.)

Compound [a]	Solvent [b]	2,6-Protons	4-Proton	*N*-Me
(III)	2	6·51 [c] (J = 2·6, 11·1)	6·40 [d] (J = 5·1, 11·1)	—
(IV)	2	5·80 [e] (J = 5·7, 9·0)	6·14 [f] (J = 3·0, base width 16·4 c./sec.)	—
(V)	1	6·81 [c] (J = 2·9, 11·2)	6·17 [d] (J = 4·4, 10·8)	8·25
(VI)	1	6·39 [g] (J = 7·90)	5·80 [h] (base width 16·0 c./s.)	8·20
(VII)	1	6·60 [i] (J = 9·9)	6·97 [g] (J = 9·7)	—
(VIII)	2	6·20 [i] (J = 10·3)	6·60 [g] (J = 2·6)	—
(IX)	1	7·18 [i] (J = 10·1)	6·77 [g] (J = 9·7)	8·40
(X)	1	6·76 [i] (J = 10·6)	6·25 [g] (J = 2·5)	8·45

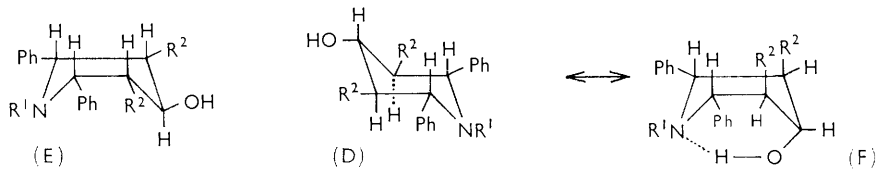
[a] The numbering of the compounds follows that of Table 1. [b] Solvents: 1, deuteriochloroform ($CDCl_3$); 2, benzene. The solvents used are those minimising the overlap of 4-proton signals. [c] Centre of quartet. [d] Centre of the highest peak (9 lines). [e] Centre of quartet; J's are separations between lines 1 and 3, and 3 and 4. [f] Centre of pseudo-quintet. [g] Centre of 1 : 2 : 1 triplet. [h] Centre of broad, unresolved signal. [i] Centre of AB doublet.

of the six-membered heterocyclic rings, the aromatic protons are not recorded. However, from the splitting and broadness of the aromatic signals (base-line widths are centred around 20—30 c./sec.), it seems that the rotation of the phenyl rings is somewhat restricted in this series of compounds.[22,23]

In the spectrum of α-2,6-diphenylpiperidin-4-ol (III), the C-2 protons give rise to the X-part of an ABX system, and the C-4 proton shows the typical splitting of the X-part of two ABX systems. First-order analysis of the spectrum [14] (this should be valid [15] in the present case as δ_{AB} is greater than 20 c./sec.), yielding the data given in Table 2, indicates that the configuration of compound (III) must be either (D) or (E) with $R^1 = R^2 = H$, because any other configuration having the bulky phenyl groups diaxial could be eliminated.[24] Consideration of non-bonded interactions certainly favours configuration (D). The same argument should also apply to α-1-methyl-2,6-diphenylpiperidin-4-ol (V). However, in the cases of 3,5-dimethyl-2,6-diphenylpiperidin-4-ol (VII) and its *N*-methyl derivative (IX), direct physical evidence is available to prove that these compounds have the configuration (D), with $R^1 = H$, $R^2 = CH_3$, and $R^1 = R^2 = CH_3$, respectively. As the C-4 proton of (IX) gives rise to the A-part of an AX_2 system with $J_{AX} = 9{\cdot}7$ c./sec., and the C-2 protons exhibit an AB doublet with $J_{AB} = 10{\cdot}1$ c./sec., the configuration of compound (IX) must be, again, either (D) or (E) with $R^1 = R^2 = Me$. It has been shown [25] that (IX) is capable of forming an intramolecular hydrogen bond, and, since the hydroxyl group in (E) can never be brought close enough to the lone-pair of the nitrogen atom to form such a bond, the infrared evidence in ref. 25 thus indicates

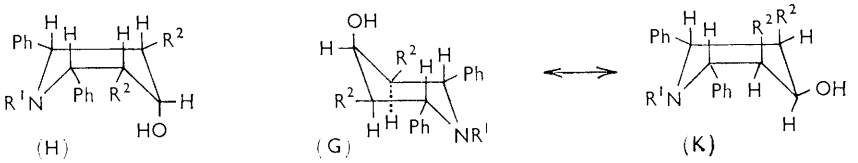
[22] D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Amer. Chem. Soc.*, 1961, **83**, 4838.
[23] C.-Y. Chen and R. J. W. Le Fèvre, *J.*, 1965, 558.
[24] E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, 1960, **82**, 1367.
[25] M. Balasubramanian and N. Padma, *Tetrahedron Letters*, 1963, 49.

that α-1,3,5-trimethyl-2,6-diphenylpiperidin-4-ol (IX) must have the configuration (D) with $R^1 = R^2 = CH_3$; this should also be the configuration for (VII) with $R^1 = H$ and $R^2 = CH_3$. Further, the intramolecular hydrogen bonding in compound (IX) requires the occurrence of an equilibrium such as (D) ⟷ (F). Since, in the conformer (F), the C-4 proton is in an equatorial position and it is generally accepted [15] that J_{ea} or J_{ee} cannot be much larger than 2·5—3·2 c./sec., the observed coupling constants listed in Table 2



require that the contribution of the conformer (F) in the equilibrium (D) ⟷ (F) must be small for the α-isomers of the substituted 2,6-diphenylpiperidin-4-ols, the molecular conformations of which can be adequately represented by (D), although there are some signs that the contributions from the boat conformers (F) are more important in compounds (VII) and (IX) than in compounds (III) and (V): J_{aa} for the C-4 proton decreases from about 11 c./sec. in (III) and (V) to 9·7 c./sec. in (VII) and (IX), and this seems consistent with the fact that intramolecular hydrogen bonding occurs in (IX) but not (V). Detailed discussion, however, will be deferred to a later section in this Paper.

As for the β-epimers of the 2,6-diphenylpiperidin-4-ols, significant information regarding their configurations may be deduced from β-1-methyl-2,6-diphenylpiperidin-4-ol (VI). Although the accidental equivalence [26] of the hydrogens at C-3 and C-5 (as illustrated by



the 1 : 2 : 1 triplet exhibited by the C-2 protons) in (VI) prevents the extraction of the exact coupling constants involved, the spacing between the terminal lines of the X-part of the ABX system, which in any case is equal to $(J_{AX} + J_{BX})$,[27] together with the signal from the C-4 proton, still demand that the configuration of (VI) be either (G) or (H) with $R^1 = CH_3$ and $R^2 = H$. If the configuration of the compound (VI) were (H), there is no reason why an intramolecular hydrogen bond should not occur and be detected. The absence of such bonding [25] suggests that the configuration (G) is to be preferred for compound (VI), and, in turn, for compound (IV) as well. Furthermore, from our experience, the six-membered ring in configuration (G) is unlikely to be rigid. Inversion of the ring may occur as indicated, (G) ⟷ (K).

Nevertheless, from Table 2, it is obvious that in compounds (IV) and (VI) none of the coupling constants involving the C-4 protons can be greater than 4 c./sec. (the base-line widths of the C-4 signals in these compounds are 16·0 and 16·4 c./sec., respectively). The boat conformer (K) should call for a "*trans*"-coupling of the magnitude of *ca.* 11 c./sec. for the C-4 protons; observed spectra thus require that the molecular conformations of compounds (IV) and (VI) are predominantly as (G). Similar reasoning should be applicable to the configuration of β-3,5-dimethyl-2,6-diphenylpiperidin-4-ol (VIII) and its *N*-methyl derivative (X). The coupling constants observed, once more, are reconcilable with molecules existing mainly as conformers (G) with $R^1 = H$, $R^2 = CH_3$ for (VIII), and $R^1 = R^2 = CH_3$ for (X).

[26] R. J. Abraham and H. J. Bernstein, *Canad. J. Chem.*, 1961, **39**, 216.
[27] E. W. Garbisch, jun., *J. Amer. Chem. Soc.*, 1964, **86**, 1780.

The chemical shifts of the C-2 and C-6 protons of the β-epimers as tabulated in Table 2 illustrate clearly that these protons are deshielded by an axial 4-hydroxyl group [the C-2 and C-6 protons of compound (VIII), in deuteriochloroform, show an AB doublet centred at τ 6·12 p.p.m. and J_{AB} = 10·4 c./sec.] as the result of 1,3-diaxial spatial proximity;[28] this serves to confirm our configurational and conformational assignments given above.

Intramolecular Hydrogen Bonding in α-1,3,5-Trimethyl-2,6-diphenylpiperidin-4-ol (IX) *and the Occurrence of Boat Conformers Among the Epimeric 2,6-Diphenylpiperidin-4-ols.*— As our foregoing configurational and conformational assignments for the epimeric 2,6-diphenylpiperidin-4-ols depend crucially on the presence of intramolecular hydrogen bonding in (IX) and its absence in (VI), a more detailed investigation of the infrared spectrum of (IX) seems desirable. Our spectrum, showing two peaks for compound (IX) in the hydroxyl stretching region (one at 3626 and the other at 3588 cm.$^{-1}$) is in perfect agreement with those given in ref. 25. The spectrum was taken on a Perkin-Elmer model 221 spectrophotometer equipped with a grating prism. The concentration of the solution was 0·01M in carbon disulphide. After exchange with deuterium oxide,[29] we found two new peaks in the O–D stretching region (2680 and 2649 cm.$^{-1}$) in addition to those just mentioned in the O–H stretching region. The spacing and the shapes of the new peaks prove, beyond any reasonable doubt, that the absorptions at 3626 and 3588 cm.$^{-1}$ must be due to the free and the bonded hydroxyl groups in the compound (IX) and not to overtones or Fermi resonance. Since intramolecular hydrogen bonding necessitates a boat form (a classical boat form) of the six-membered ring, it is not surprising that the contribution from boat conformations is greater in (IX) than in (V) which does not show intramolecular hydrogen bonding.[25] As the coupling constants are virtually the same for compounds (IX) and (VII), we suspect that (VII) should also be intramolecularly hydrogen bonded, although the presence of both OH and NH groups makes difficult, if not impossible, any confirmation from infrared studies. To estimate the percentage contribution of the conformer (F) (or its flexible form) in the equilibria (D) ⟷ (F) for compounds (IX) and (VII) is also difficult because of our lack of knowledge of the precise coupling constants and geometric distortions involved. However, if we assume that compounds (III) and (V) exist almost exclusively in the conformation (D) [which should be reasonable as there is nothing present to counterbalance the free-energy difference between a normal chair form and a boat form (flexible forms are included) of the ring [19]] then, by taking J_{aa} = 11·0 c./sec. [the average in compounds (III) and (V)] and $J_{ee} = J_{ea}$ = 2·5 c./sec. [from J_{ea} of compounds (VIII) and (X)], we calculate the maximum contribution from the conformation (F) for compounds (VII) and (IX) to be 16%. The equation used in our calculation is:

$$J_{obs.} = N_{(F)}J_{ee} + (1 - N_{(F)})J_{aa},$$

where $N_{(F)}$ is the percentage contribution of the conformer (F) in the equilibria (D) ⟷ (F), and $J_{obs.}$ is taken as 9·7 c./sec. [the same value is observed in carbon disulphide solutions for compound (IX)]. As for the β-epimers, the observed coupling constants of *ca.* 2·6 c./sec. for the C-4 protons of compounds (VIII) and (X) counterindicate any significant participation of the boat conformation (K) in the possible equilibria (G) ⟷ (K). Contribution from the conformation (K) may be greater in compounds (IV) and (VI), in which the more bulky groups at the C-3 and C-5 positions are replaced by hydrogens. Such a tendency is reflected in the increase of the coupling constants to *ca.* 3 c./sec. in (IV) and (VI). Nevertheless, if this increase can be regarded as real, and if a J_{aa} of 11·0 c./sec. is assumed, the contribution from a boat conformer should not exceed 6% .

Thus, we conclude that, except in those compounds where intramolecular hydrogen bonding and overcrowding of three equatorial sustituents [30] plays an important role, *viz.* (IX) and (VII), all the piperidin-4-ols studied can adequately be represented by chair

[28] J. B. Carr and A. C. Huitric, *J. Org. Chem.*, 1964, **29**, 2506, and references therein.
[29] H. M. Fales and A. V. Robertson, *Tetrahedron Letters*, 1962, 111.
[30] Ref. 1, p. 79.

forms of rings having equatorial hydroxyl groups in the α-isomers and axial ones in the β-epimers. Such a conclusion indirectly confirms all the arguments and implications, based purely on chemical grounds, which were presented in ref. 8.

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