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CONFIGURATIONAL ASSIGNMENTS TO *CIS*- AND *TRANS*-1-ALKYL (AND ARALKYL)-4-ARYL-3-METHYLPIPERIDIN-4-OLS BY PMR SPECTROSCOPY

A. F. CASY
School of Pharmacy, Chelsea College of Science and Technology, London

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Abstract—The PMR spectra of some diastereoisomeric 1-alkyl (and aralkyl)-4-aryl-3-methylpiperidin-4-ols and derived esters are reported and it is shown how spectral differences between isomers may be used to assign configurations and probable conformations. The influence of solvent upon conformational equilibria in α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol hydrochloride is discussed.

KNOWLEDGE of the steric relationships obtaining in the two diastereoisomeric propionyloxy esters of 1,3-dimethyl-1-phenylpiperidin-4-ol (the hydrochlorides are α- and β-prodine) is of importance in view of their marked difference in analgesic potency and of the stereospecificity of the analgesic receptor site.[1] Their configuration has been the subject of several papers[2] and is now firmly established as *trans* (3-Me/4-Ph) for α- and *cis* for β-prodine and X-ray crystallography.[3] Other examples of related diastereoisomers that also differ in their analgesic activity have now been reported[4,5] and it would be of value if a physical method, more convenient than that of X-ray crystallography, were available for establishing their configurations. To this end, a PMR study of the alcohols derived from α- and β-prodine has been made and it is shown that differences in their spectra allow configurational and conformational assignments to be made. Further, the method described should have general applicability to isomers of this type.

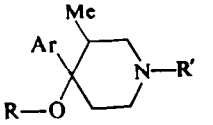
The PMR characteristics of α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol (derived from α- and β- prodine respectively) are shown in Table 1. Differences in the spectra are shown to be consistent with the α-isomer having the *trans* (3-Me/4-Ph) configuration, and the β-isomer, the *cis* configuration, and support structures I and II as the most probable conformations, respectively, of the two isomers (these conformers differ in the configuration of the 3-methyl group and the relative orientation of the 4-phenyl group and the piperidine ring).

1. *The 4-phenyl signal*

In I the preferred orientation of the 4-phenyl group will be a plane approximately at right angles to that of the piperidine ring, the equatorial 3-methyl/*ortho* aromatic hydrogen interaction being minimum in this conformation (cf. Allinger *et al.*).[6] In II, however, the same orientation is not favoured since it would bring an *ortho* aromatic hydrogen in close proximity to an axial methyl group. Hence, at any given

[1] A. H. Beckett and A. F. Casy, *Progress in Medicinal Chemistry* (Edited by G. P. Ellis and G. B. West) Vol. 4. Butterworths, London (1965).
[2] A. H. Beckett, A. F. Casy and N. J. Harper, *Chem. & Ind.* **19**, (1959), and Refs there cited.
[3] G. Kartha, F. R. Ahmed and W. H. Barnes, *Acta Cryst.* **13**, 525 (1960); F. R. Ahmed, W. H. Barnes and L. Di Marco Masironi, *Ibid.* **16**, 237 (1663).
[4] A. H. Beckett, A. F. Casy and G. Kirk, *J. Med. Pharm. Chem.* **1**, 37 (1959).
[5] A. Ziering, A. Motchane and J. Lee, *J. Org. Chem.* **22**, 1521 (1957).
[6] N. L. Allinger, J. Allinger, M. A. Da Rooge and S. Greenburg, *J. Org. Chem.* **27**, 4603 (1962).

TABLE 1. PMR CHARACTERISTICS OF SOME 1-ALKYL (AND ARALKYL)-4-ARYL-3-METHYLPIPERIDIN-4-OLS AND PROPIONYLOXY ESTERS



No	Ar	R	R′	Isomer and form	Solvent	PMR signals[a] 4-Aryl	3-Me	4-OH	4-OCOCH$_2$Me	Others
1	Ph	H	Me	α-base	$CDCl_3$	447[b] (W_H12)	37·5[c] (peak separation 6)	135[d]	—	139[d] (N–Me)
2	Ph	H	Me	β-base	$CDCl_3$	445[b] (W_H8·5–9)	44[e] (J 7·5)	125[d]	—	135[d] (N–Me)
3	Ph	H	Me	α-base	CCl_4	442·5, 438[b] (W_H14)	35[f] (outer peaks separation 5·5)	166[d]	—	132[d] (N–Me)
4	Ph	H	Me	β-base	CCl_4	439, 437[b] (W_H5)	39·5[e] (J 7)	139[d]	—	126[d] (N–Me)
5	Ph	H	Me	α-HCl	$CDCl_3$	441[b] (W_H19)	39·5[e] (J 7)	—	—	167[d] (N–Me)
6	Ph	H	Me	β-HCl	$CDCl_3$	443[b] (W_H8)	58[e] (J 7)	—	—	163[d] (N–Me)
7	Ph	H	Me	α-HCl	D_2O	477[d]	66·8[e] (J 6·5)	—	—	205[d] (N–Me)
8	Ph	H	Me	β-HCl	D_2O	477[d]	74·5[e] (J 7)	—	—	204[d] (N–Me)
9	*p*-C_6H_4Me	H	Et	α-base	$CDCl_3$	450, 442, 435, 426[g]	38[e] (peak separation 6)	108·5[d]	—	141[d] (Ar–Me) 67·5[h] (J 7) (N-CH_2Me)
10	*p*-C_6H_4Me	H	Et	β-base	$CDCl_3$	447, 438·5, 433·5, 425[g]	44·5[e] (J 7)	110·5[d]	—	140[d] (Ar–Me) 64[h] (J 7) (N-CH_2Me)

11	*p*-C_6H_4Me	H	Et	α-HCl	$CDCl_3$	451·5, 443, 430·5, 422·5[g]	40[e] (J 5·5)	—	—	138[d] (Ar–Me) 87[h] (J 7) ($N–CH_2Me$)
12	*p*-C_6H_4Me	H	Et	β-HCl	$CDCl_3$	445, 440, 437, 431·5[g]	56·5[e] (J 7)	—	—	139[d] (Ar–Me) 82[h] (J 7) ($N–CH_2Me$)
13	*p*-C_6H_4Me	H	$PhCH_2$	α-base	$CDCl_3$	439[b,k]	36[e] (peak separation 6)	96[d]	—	139[d] (Ar–Me) 215[d] ($N–CH_2Ph$)
14	*p*-C_6H_4Me	H	$PhCH_2$	α-HCl	$CDCl_3$	444[b,k]	37[e] (J 6)	—	—	135[d] (Ar–Me) 250[d] ($N–CH_2Ph$)
15	Ph	EtCO	Me	α-base	$CDCl_3$	436·5[b] (W_H5)	41[c] (peak separation 6·5)	—	73·5[h] (J 7–7·5)	139[d] (N–Me)
16	Ph	EtCO	Me	β-base	$CDCl_3$	440[b] (W_H1–2)	44[e] (J 7)	—	65[h] (J 7–7·5)	136[d] (N–Me)
17	Ph	EtCO	Me	α-HCl	$CDCl_3$	439[b] (W_H6)	44[e] (J 6)	—	74[h] (J 7) (non-symmetrical)	173[d] (N–Me) (broad) 157[j] (J 7)(OCH_2Me)
18	Ph	EtCO	Me	β-HCl	$CDCl_3$	441[b] (W_H3)	62[i] (J 7)	—	65[h] (J 7)	175[e] (N–Me) (J 4) 143[j] (J 7)(OCH_2Me)
19 (cf. 11 and 12)	*p*-C_6H_4Me	H	Et	α-, β-HCl mixture	$CDCl_3$	444, 432[b]	38[g] (J 6) (integral 14) 58[g] (J 7) (integral 13·5)	—	—	137[d] (Ar–Me) 84[f] (J 7) (broad) ($N–CH_2Me$)

[a] chemical shifts in c/s from TMS(CCl_4 and $CDCl_3$ as solvents) or DSS (D_2O as solvent), spectra being measured at a frequency of 60 Mc; coupling constants and widths at half height (W_H) in c/s; concentrations approx. 10 per cent.

[b] main peak(s) of multiplet

[c] non-symmetrical doublet

[d] singlet

[e] near-symmetrical doublet

[f] triplet, inner peak smaller than outer peaks

[g] peaks of A_2B_2 quartet

[h] near 1:2:1 triplet

[i] doublet, signal overlaps with that of OCH_2Me

[j] quartet

[k] includes $N–CH_2Ph$ signal

instant, the population of conformers with phenyl approximately at right angles to the plane of the piperidine ring (as in I) should be greater in the *trans*-isomer.

The environments of the *ortho* hydrogens differ least from each other and from the two *meta* protons when the two rings are approximately coplanar (cf. the aromatic signal of 1-ethyl-3-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (phenyl approximately coplanar with the piperidine ring) which is essentially a singlet).[7] Averaged environments will be experienced if rotation about the bond linking the two rings is rapid; in both I and II, however, such rotation is probably impeded by the 3-methyl substituent

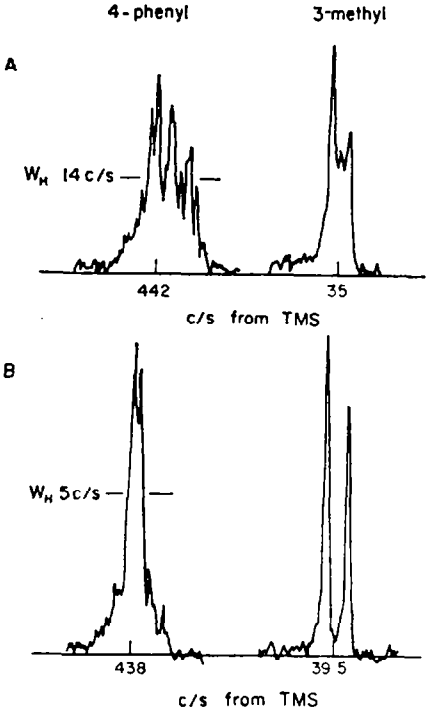


FIG. 1. Part of the PMR spectra of α-1,3-dimethyl-4-phenyl-4-piperidinol (*A*) and of the corresponding β-isomer (*B*). Recorded on a Varian A-60 instrument in CCl_4.

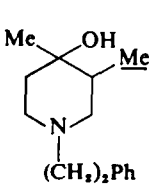
(evidence of Catalan models) leading to the time-averaged positions depicted in the two formulae. Hence chemical shift differences among the aromatic protons are expected to be more pronounced in the *trans*- isomer with the result that the *trans*-aromatic signal should be more complex than that due to the *cis*-isomer. This conclusion is confirmed experimentally, the aromatic signal (α-isomer) being markedly broader than the corresponding β-signal (Table 1, Nos. 1–6 and Fig. 1).

2. *The 3-methyl signal*

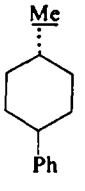
(a) *Chemical shift.* When the 4-phenyl group adopts a near-perpendicular orientation with respect to the plane of the piperidine ring (as in I), the equatorial 3-methyl group falls within the diamagnetic screening zone of the benzene nucleus; the axial 3-methyl group falls within the same zone when phenyl is orientated as in II (these conclusions were reached by study of Dreiding models and application of the Johnson-Bovey screening data for benzene).[8] Hence 3-methyl substituents should be screened

[7] A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef, *Tetrahedron* **21**, 3387 (1965).
[8] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.* **29**, 1012 (1958).

from the applied field in both isomers and in similar degree as far as may be assessed from models. In fact, the 3-methyl signals of both isomers are upfield relative to those of 3-methyl in cyclic analogues in which a phenyl group is not adjacent to methyl (e.g. III and IV)[9,10] the α-methyl signal being slightly higher (5–6·5 cycles) than the corresponding β-signal. Deshielding due to the lone-pair on nitrogen may contribute



III
54·5 c/s

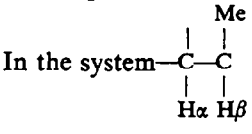


IV
60·5 c/s (in $CDCl_3$)

to the small chemical shift difference between the α- and β-3-methyl groups; this influence should be greater in the β-isomer because, in this case, the 3-methyl group and the lone-pair orbital have a 1,3-diaxial relationship.

(b) *Effect of protonation of the basic centre.* When the α- and β-isomers are converted to hydrochlorides the α-3-methyl signal suffers a relatively small downfield shift (2 c/s) whereas the corresponding β-signal is moved downfield by 14 c/s (Table 1, Nos. 1–5 and 2–6). These results also indicate α- to be the *trans* isomer (I) and β, the *cis* (II). In II (protonated), the axial methyl group is close to the positively charged nitrogen atom and its signal should be downfield relative to that of 3-methyl in the free base; equatorial methyl in I (protonated) is, however, further removed from charged nitrogen and should be less deshielded by this group [cf. the chemical shifts of 3-methyl in *cis* (1-Et/3-Me) 1-ethyl-3-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (*equatorial* methyl 56 c/s) and the corresponding *trans* isomer (*axial* methyl, 77 c/s)[7]].*

(c) *Multiplicity.* While the 3-methyl signal of the β-isomer (base in $CDCl_3$ and CCl_4) is a near-symmetrical doublet (J 7–7·5 c/s), that of the α-isomer is a narrower (peak separation 5–5·6 c/s), non-symmetrical doublet and shows evidence of a third peak midway between the main peaks, most clearly apparent in CCl_4 (Table 1, Nos. 1–4 and Fig. 1). Distortion of a methyl doublet is a typical result of virtual long-range coupling[11] (cf. the methyl signals of *cis* and *trans* 1-methyl-4-phenylcyclohexane)[10] and its occurrence in the α-rather than the β-isomer, is interpreted in terms of I and II (as the predominant conformations of the α- and β-isomers respectively), as follows:



* The deshielding influence of protonated nitrogen upon the axial 3-methyl group appears to be a novel effect and its mechanism has not been established-results with the α-isomer show that the inductive withdrawal of electrons by positively charged nitrogen makes only a small contribution to deshielding, hence magnetic anisotropic effects (induced by the positively charged centre) must be involved.

[9] H. Z. Youssef, Ph.D. Thesis, University of London (1964).
[10] E. W. Garbisch Jr., *J. Amer. Chem. Soc.* **85**, 3228 (1963).
[11] J. I. Musher and E. J. Corey, *Tetrahedron* **18**, 791 (1962).

virtual coupling between methyl and Hα occurs when the coupling constant between Hα and Hβ is large and of the same order as the chemical shift difference between the two protons. These conditions are more likely to prevail in I than in II. I contains an *axial* proton at C-3 which will be strongly coupled to the C-2 *axial* proton; II contains an equatorial proton at C-3 which is only weakly coupled to the methylene protons at C-2 (Jaa > Jae ≃ Jee).* It is significant that virtual coupling effects are not seen in the α-base hydrochloride, a result probably due to the fact that conditions for virtual coupling no longer obtain in I when a strong deshielding influence (the protonated nitrogen atom), which affects C-2 protons more than that at C-3, is introduced into the molecule.

The PMR spectroscopic analysis described here is advanced as a convenient method of configurational assignment which should be generally applicable to isomeric 1-substituted-4-aryl-3-methylpiperidin-4-ols. Assignments to the two isomeric 1-ethyl-3-methyl-4-*p*-tolylpiperidin-4-ols (obtained by reaction between 1-ethyl-3-methyl-4-piperidone and lithium *p*-tolyl) are given as an example (Table 1, Nos 9–12). The isomer of higher m.p. (α-) is considered to have the *trans* (Me/*p*-tolyl) configuration on the following grounds:

(1) its aromatic signal (an A_2B_2 quartet) is broader than that of the lower m.p. isomer (β-);

(2) the chemical shift of its 3-methyl signal is little affected when the base is protonated (38 c/s base, 40 c/s hydrochloride)—the corresponding values for the β-isomer are 44·5 c/s (base) and 56·5 c/s (hydrochloride)· i.e., the 3-β-methyl signal suffers a downfield shift of 12 cycles upon base protonation;†

(3) the α-3-methyl signal shows evidence of virtual coupling (it is narrower than the β-signal and displays a small peak midway between the main peaks, this third peak being absent in the hydrochloride).

It is considered that good evidence of configuration may be obtained even when only one pure (3-methyl/4-aryl)-isomer is available, by comparing the chemical shift values of 3-methyl in the base and base hydrochloride [in the *trans* isomer, the two values should be similar, whereas in the *cis*, the salt value should be at a field strength significantly lower (10 cycles or greater) than that of the free base]· Thus evidence for the *trans* configuration of 1-benzyl-3-methyl-4-*p*-tolylpiperidin-4-ol (Table 1, No 13–14) is provided by the near-coincidence of the 3-methyl chemical shift values for the base (36 c/s) and the hydrochloride (37 c/s) in $CDCl_3$ [these values also show close correspondence with those of 3-methyl in the α-1,3-dimethyl and 1-ethyl-3-methyl-analogues (Table 1, Nos 1–5 and 9–11 respectively)].

The PMR characteristics of 4-arylpiperidin-4-ol derivatives also provides evidence of conformation in $CDCl_3$ solution. The data given here are consistent with the most probable conformations of both α- and β-pairs considered being those in which the

* The actual coupling constant (Jαβ) for the β-isomer is probably somewhat greater than that deduced on the basis of II alone on account of contributions from other conformations (e.g., the inverted chair of II); however, its value should still be significantly less than Jαβ for the α-isomer.

† The chemical shifts of 3-methyl in the isomeric 4-*p*-tolylpiperidinols (Table 1, Nos 9 and 10) differ by only a cycle from those of the same signal in the corresponding α- and β-4-phenylpiperidinols (Table 1, Nos 1 and 2). It appears to be generally true, therefore, that a β-3-methyl (of lower chemical shift) is more deshielded than an α-3-methyl group (possibly as a result of the 1,3-diaxial relationship of the β-group to the nitrogen lone-pair orbital). This observation provides a further means of assigning configurations to isomers of this type.

4-aryl group is equatorial* and there is evidence that similar conformations are favoured for the derived propionyloxy-esters of α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol (Table 1, Nos 15–18) in the same solvent. The α- and β-3-methyl signals of the esters differ in the same way as those in the two piperidinols; the α-3-methyl signal (a deformed doublet, 41 c/s) of the base appears at 44 c/s in the hydrochloride, corresponding values for the β-signal being 44 c/s (base) and 62 c/s (hydrochloride). The esters also differ in the positions of their $CO{\cdot}CH_2Me$ and $CO{\cdot}\underline{CH_2}Me$ signals, the former being triplets near 73·5 c/s (α) and 65 c/s (β) in both bases and hydrochlorides, and the latter quartets near 157 c/s (α) and 143 c/s (β) in the hydrochlorides. The higher field values of the β-signals are consistent with the *cis*-ester having a preferred conformation analogous to structure (II), because the ester $CO{\cdot}CH_2Me$ group will spend some of its time above the plane of the phenyl group (i.e. well within the aromatic shielding zone) if the plane of the C—O bond and aromatic ring are approximately perpendicular.

The PMR spectra of α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol hydrochlorides undergo downfield shifts when $CDCl_3$ is replaced by D_2O as solvent. While the downfield shifts of the aromatic and N-methyl signals (resulting from this solvent change) are similar in the two isomers, that of the β-3-methyl group is almost 11 cycles less than that observed for the α-signal (Table 2). In addition, the chemical shift difference between the α- and β-3-methyl groups is much less in D_2O than in $CDCl_3$ (7·7 cycles in the former and 18·5 cycles in the latter solvent). These results may be taken to indicate an increase in the population of equatorial 3-methyl (chair) and/or skew-boat conformers at the expense of axial-methyl conformers in the β-isomer when $CDCl_3$ is replaced by D_2O. Such an increase would reduce the deshielding influence of protonated nitrogen upon 3-methyl, the chemical shift of this group moving nearer to that of 3-methyl in the α-isomer.

A decrease in the conformational preference of axial-3-methyl conformers may be accounted for in terms of solvation effects. A considerable increase in the degree of solvation of both the protonated basic centre and the hydroxyl group of α- and β-1,3-dimethyl-4-phenylpiperidin-4-ol hydrochloride is probable when $CDCl_3$ is replaced by D_2O as solvent, and, in consequence, the effective bulks of these structural features should become greater. While such increases should not significantly alter conformational preferences in the α-derivative, preference for the β-conformer (II) would be expected to decrease since the destabilizing Me/H and OH/H 1,3-diaxial interactions obtaining in the latter will be larger in the more solvated molecule.† A study of the

* Assuming the additivity of $-\Delta F_x^0$ values, the conformational free energy difference ($-\Delta F$) between the 1,3-dimethyl conformer II (β) and the corresponding inverted chair form is 3·1 (Ph) − [1·7 (Me) + 0·7 (OH)] = 0·7 kcal/mole [this calculation is only approximate since reported $-\Delta F_x^0$ values for OH, Me and Ph show rather wide variations–the values chosen were obtained by PMR methods, solvents being CCl_4 (for OH and Me) and dimethylsulphoxide (for Ph)].[12] The value of 0·7 for $-\Delta F$ corresponds to a 70–75 per cent population of the more stable (*e*-Ph) isomer. $-\Delta F$ For conformer I (α) and its inverted form is 4·1 kcal/mole, i.e. the population of more stable conformer is almost 100 per cent in this case.

† Anet[13] has measured the $-\Delta F_x^0$ value of the hydroxyl group in CCl_4 and D_2O; he found the value to be higher in the more polar solvent (1·0 for CCl_4, 1·25 for D_2O at 28°).

[12] E. L. Eliel. N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, J. Wiley, New York (1965).

[13] F. A. L. Anet, *J. Amer. Chem. Soc.* **84**, 1053 (1962).

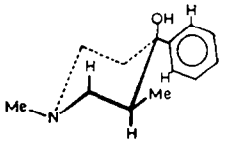
TABLE 2. SOLVENT EFFECTS UPON CHEMICAL SHIFTS IN α- AND β-1,3-DIMETHYL-4-PHENYLPIPERIDIN-4-OL HYDROCHLORIDES

Proton group	Chemical Shift (c/s) in (a) D_2O[a]	(b) $CDCl_3$[b]	Difference (c/s)
α-Ph	477	441	36
β-Ph	477	443	34
α-N-Me	205	167	38
β-N-Me	204	163	41
α-3-Me	66·8	39·5	27·3
β-3-Me	74·5	58	16·5

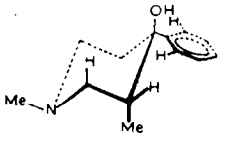
[a] from DSS (60 Mc)
[b] from TMS (60 Mc)

influence of solvent upon conformational equilibria in corresponding 4-alkyloxypiperidine derivatives will be reported elsewhere.

The 4-hydroxyl proton of α-1,3-dimethyl-4-phenylpiperidin-4-ol comes to resonance at lower fields than that of the β-isomer [α-OH, 145·5 c/s in CCl_4, 133 c/s in $CDCl_3$; β-OH, 122 c/s in CCl_4, 115 c/s in $CDCl_3$ (concentrations 70 mg/ml in all cases)]. This difference is considered to be a result of both differential hydrogen bonding and differential deshielding by the 4-phenyl group in the two isomers. On the basis of conformations (I and II), the latter effect should be greater in the α-isomer



I
trans 3-Me/4-Ph



II
cis 3-Me/4-Ph

[when the 4-phenyl group is approximately at right angles to the plane of the piperidine ring (as in I), the 4-hydroxyl proton falls well within the deshielding zone of the aromatic nucleus; when the 4-phenyl group has the orientation shown in II (β), the hydroxyl proton is estimated to be just inside the same zone]. It is difficult, however, to predict the relative extents of hydrogen bonding in the two isomers because of the sensitivity of such bonding (both intermolecular and that involving solvent) to concentration, temperature and structure. Both the α- and β-4-hydroxyl chemical shifts were far more sensitive to concentration changes in CCl_4 than in $CDCl_3$ [α- 145 c/s (70 mg/ml) to 111 c/s (70 mg/3 ml) in CCl_4; 154 c/s (70 mg/ml) to 154·5 c/s (70 mg/2 ml) in $CDCl_3$. β- 122 c/s (70 mg/ml) to 95·5 c/s (70 mg/3 ml) in CCl_4; 133 c/s (70 mg/0·5 ml) to 122 c/s (70 mg/3 ml) in $CDCl_3$], results which indicate hydrogen bonding to be largely intermolecular in the former and to involve solvent in the latter case. The 4-hydroxyl chemical shifts of α- and β-1-ethyl-3-methyl-4-*p*-tolylpiperidin-4-ol showed similar degrees of sensitivity to concentration changes in $CDCl_3$ [α- 122·5 c/s (56 mg/0·5 ml) to 111 c/s (56 mg/3 ml); β- 127 c/s (56 mg/0·5 ml/ to 113 c/s (56 mg/3 ml)] but in this case the β signal had the lower field position.

The interpretation of the 4-hydroxyl chemical shift differences of isomers of this type in terms of configuration is considered impracticable at this stage on account of the number of unknown variables involved.

EXPERIMENTAL

Most of the PMR spectra were recorded on a Varian A-60 spectrometer operating at the normal running temp with TMS as internal standard (a Perkin–Elmer R-10 instrument was used for measurement of the hydroxyl proton resonances). α-1,3-Dimethyl-4-phenyl-4-propionyloxypiperidine hydrochloride (α-prodine), m.p. 220° (lit.[14] 220–221)° was obtained by fractional crystallization of the α,β-mixture of ester hydrochlorides; the corresponding β-isomer (β-prodine), m.p. 204° (lit.[14] 195–196°) was obtained by treating the β-piperidin-4-ol with propionic anhydride and pyridine. α-1,3-Dimethyl-4-phenyl-piperidin-4-ol, m.p. 101° (lit.[14] 101–102°) was obtained by hydrolysis of α-prodine with alcoholic KOH; the corresponding β-piperidin-4-ol, m.p. 113–116° (lit.[14] 118–119°) was kindly supplied by Dr. J. Lee. 1-Ethyl-3-methyl.-4-piperidone (30 g) with lithium *p*-tolyl prepared from Li (3·5 g) and *p*-bromotoluene (36 g) gave a crude mixture of alcohols which partially solidified on storage. The solid fraction (31 g), m.p. 79–85°, was recrystallized from pet. ether b.p. 40° to give α-1-ethyl-3-methyl-4-*p*-tolylpiperidin-4-ol, m.p. 89–90° (lit.[7] 89°); it gave a hydrochloride m.p. 220–221° from EtOH–ether. The liquid fraction was distilled at 124–126°/0·5 mm and treated with excess of ethanolic HCl to give *β-1-ethyl-3-methyl-4-p-tolylpiperidin-4-ol hydrochloride*, m.p. 214–215° from EtOH–ether. (Found: C, 66·6; H, 9·15; N, 5·3. $C_{15}H_{24}CINO$ requires: C, 66·8; H, 9·0; N, 5·2%.) The base, in contrast with the α-base and in common with other β-isomers of this type,[9,16] had no absorption band in the region 990–1020 cm^{-1}. A fraction, m.p. 178° was shown to be a mixture of approximately equal parts of the α- and β-hydrochlorides by PMR spectroscopy* (Table 1, No. 19). The previously reported[7] α-1-benzyl-3-methyl-4-*p*-tolylpiperidin-4-ol hydrochloride, m.p. 212–213°; gave a base m.p. 78° from pet. ether b.p. 40°.

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* A further application of the chemical shift difference between the α- and β-3-methyl protons in 4-aryl-3-methylpiperidin-4-ol hydrochlorides, is the ready estimation of sample purity, integrals for the two signals being well separated.

[14] A. H. Beckett, A. F. Casy, G. Kirk and J. Walker, *J. Pharm. Pharmacol.* **9**, 939 (1957).