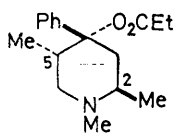
Diastereoisomeric Esters of 1,2-Dimethyl-4-phenylpiperidin-4-ol and Related Compounds

By **A. F. Casy** * and **K. M. J. McErlane**, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

The synthesis of 1,*c*-2- and 1,*t*-2-dimethyl-4-phenylpiperidin-*r*-4-ols and derived esters is reported. Configurations and preferred conformations are assigned on the basis of reactivity of the alcohols towards thionyl chloride and Raney nickel, ^{1}H n.m.r. characteristics, and the observation of epimeric conjugate acids in *cis*-derivatives. The stereochemistry of the hydrogenolysis products is confirmed by comparing *N*-methyl chemical shifts of methiodide derivatives with those calculated from the shielding influence of 2*eq*- and 2*ax*-methyl substituents. The hot-plate ED_{50} values (for mice) of acetate and propionate esters of the piperidinols are reported and compared with those of analogues lacking 2-methyl substituents.

THE narcotic analgesic trimeperidine (1) and its isomers have methyl substituents adjacent to the C-4 ester function and the piperidine nitrogen atom. To study structure–activity relationships in these derivatives the analgesic potencies of analogues which lack (i) 2-methyl



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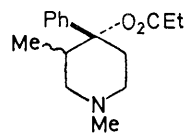

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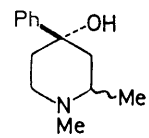
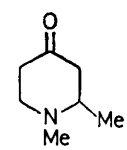


(3)

and (ii) 5-methyl substituents were required. Since data were available only for the former [the prodines (2) [1]], the synthesis and pharmacological evaluation of isomeric esters of 1,2-dimethyl-4-phenylpiperidin-4-ol (3) were undertaken.

The reaction of phenyl-lithium with the intermediate 4-piperidone (4), prepared by Dieckmann cyclization of the diester (5), gave a mixture composed of almost equal amounts of the two isomers (3) as judged by the 1- and



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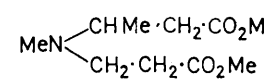
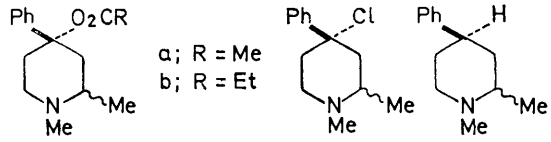


(5)

2-methyl ^{1}H n.m.r. signals. The separated isomers corresponded in m.p. with those previously designated α- and β- and of unassigned stereochemistry.[2] The alcohols were converted into the esters (6).

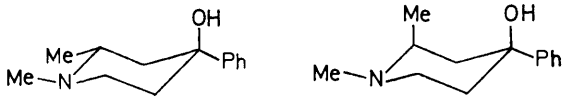
[1] A. F. Casy and K. M. J. McErlane, *J. Pharm. Pharmacol.*, 1971, **23**, 68.

The β-piperidinol (3) was converted into a 4-chloro-derivative (7) with thionyl chloride at room temperature, whereas the α-isomer was unchanged after the same



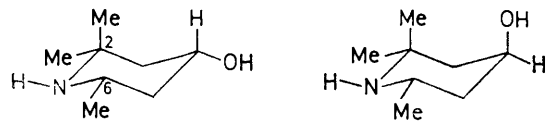
(6) (7) (8)

treatment; both isomers were dehydrated at higher temperatures. Hydrogenolysis of the β-isomer by Raney nickel in boiling ethanol gave a single 1,2-dimethyl-4-phenylpiperidine (8) after 4 h; the analogous conversion of the α-piperidinol required an 8 h treatment and led to an isomeric mixture of compounds (8). These experiments provide evidence that the 4-hydroxy-substituent is more hindered in the α-isomer and support the configurations *c*-2-Me,*r*-4-OH and *t*-2-Me,*r*-4-OH for the α- and β-isomers, respectively. If the isomeric piperidinols preferred piperidine chair conformations with equatorial phenyl substituents, as in (9) and (10),



t-2-Me,*r*-4-OH (9) *c*-2-Me,*r*-4-OH (10)

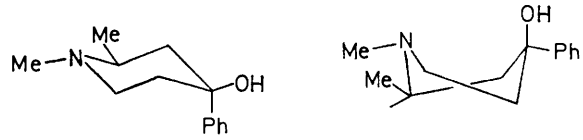
the n.m.r. signal of the *cis*-2-methyl group should be significantly to lower field of that of the *trans*-2-methyl group, because an axial hydroxy-group has a greater deshielding effect upon axial than upon equatorial protons β to the carbinol carbon atom in cyclohexane derivatives.[3-6] Evidence of the differential shielding influence of a 1-hydroxy-group upon axial and equatorial 3-methyl groups in piperidines is provided by the ^1H n.m.r. spectra of solutions in deuteriochloroform of isomeric 2,2,6-trimethylpiperidin-4-ols of preferred conformations (11) and (12).[7] In the spectrum of isomer



(11) (12)

(11) (*eq*-OH), the 2- and 6-methyl signals (2 singlets, 1 doublet) all fall near δ 1·1 p.p.m.; in that of (12) (*ax*-OH) one singlet is about 0·27 p.p.m. to lower field than the other two signals, the assignments being: δ 1·07 (d, 6*eq*-Me), 1·09 (s, 2*eq*-Me), and 1·35 p.p.m. (s, 2*ax*-Me).

In the isomers (3), however, no appreciable difference was found between the chemical shifts of the *cis*- and *trans*-2-methyl groups in three solvents (see Experimental section). This result is evidence that the *cis*-isomer has a preferred axial phenyl group (13) and/or a skew-boat conformation (14) in which the 2-methyl group is well removed from the hydroxy-substituent. In support is the fact that replacement of deuteriochloroform by pyridine as solvent has little influence upon either the α- or the β-2-methyl resonance.



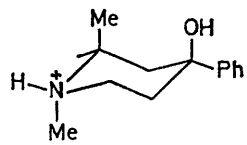
(13) (14)

Single protons or methyl groups that bear a 1,3-diaxial relationship to a hydroxy-group experience deshielding effects of the order of 0·2—0·4 p.p.m. in pyridine relative to deuteriochloroform;[8] in spectra of compound (12), for example, the axial 2-methyl resonance moves downfield by 0·2 p.p.m. while the equatorial signals are almost unaltered after this solvent change.

The ^1H n.m.r. spectrum of α-(3) hydrochloride in [$^2H_6$]dimethyl sulphoxide (plus trace of trifluoroacetic acid), unlike that of the β-salt, displayed a pair of 2-methyl doublets which merged to a single doublet of intermediate position when the temperature was raised to 100°. These observations are evidence of the presence of epimeric conjugate acids, which arise as the result of the two modes (axial and equatorial) of proton uptake at the basic centre.[9-11] Epimeric conjugate acids are not anticipated for the β-isomer (9) because the product of equatorial protonation (*N*-methyl axial) merely introduces additional non-bonded interactions which may not be relieved by a conformation change since any departure from (9) places the 2-methyl and 4-phenyl groups in less favourable orientations. In the α-isomer (10), however, a conformation change of the equatorial epimer (15) to an inverted chair and/or skew-boat as in (13) and (14), would reduce non-bonded interactions of 2-methyl and 4-hydroxy-groups as occur in the axially protonated epimer (16); the latter is stabilized in the form shown by the equatorial *N*-methyl substituent. The α-epimers differ little in energy as judged by the similar intensities of their 2-methyl ^1H n.m.r. signals.

The O_2CR resonances of the α-esters (6) were observed at higher field than those of the β-isomers (Table 1); these results show the α-acyl substituents to be shielded by the aromatic group and are evidence that the axial

[2] E. A. Mistryukov and N. I. Aronova, *Bull. Acad. Sci. U.S.S.R.*, 1967, 128.
[3] J. N. Shoolery and M. R. Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.
[4] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 338.
[5] K. Tori and T. Komeno, *Tetrahedron*, 1965, **21**, 309.
[6] J. B. Carr and A. C. Huitric, *J. Org. Chem.*, 1964, **29**, 2506.
[7] F. Perks and P. J. Russell, *J. Pharm. Pharmacol.*, 1967, **19**, 318.
[8] P. V. Demarko, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, 1968, **90**, 5480.
[9] A. F. Casy, L. G. Chatten, and K. K. Khullar, *Canad. J. Chem.*, 1970, **48**, 2372.
[10] A. F. Casy and K. M. J. McErlane, *J.C.S. Perkin I*, 1971, 334.
[11] A. F. Casy, 'Proton Magnetic Resonance Spectroscopy in Medicinal and Biological Chemistry,' Academic Press, London, 1971, p. 145.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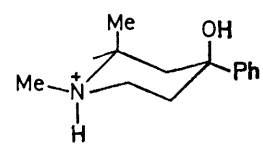
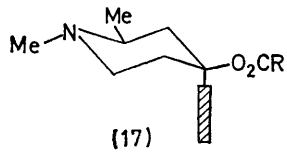

(16)

4-phenyl conformer (17) is a favoured conformation for α-esters. In this conformation the preferred plane of


(17)

the phenyl ring is probably approximately at right angles to the vertical plane drawn through N-1 and C-4,[12] and in this orientation the O_2CR groups will be shielded as they pass above the plane of the aromatic ring during rotation about the C(4)–O bond. In β-esters, clearly of preferred conformation (18), the shielding influence of the equatorial phenyl group upon the acyl protons is small, as seen by data for the analogue (19), which lacks a 4-phenyl substituent [δ_{MeCO} ($CHCl_3$) 2·09 (base) or 2·14 (HCl) p.p.m.].

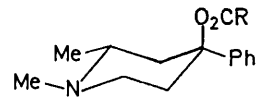
TABLE 1

^{1}H N.m.r. characteristics of isomeric acetates and propionates of 1,2-dimethyl-4-phenylpiperidin-4-ol [a]

Compound	Group	δ (p.p.m.) Base	HCl
α-(6a)	O_2CMe [b]	1·87	2·07, 1·90 [c]
β-(6a)	O_2CMe [b]	2·07	2·12
α-(6b)	$O_2C{\cdot}CH_2Me$ [c]	2·05	2·20, 2·17 [c]
β-(6b)	$O_2C{\cdot}CH_2Me$ [c]	2·42	2·42
α-(6b)	$O_2C{\cdot}CH_2Me$ [d]	1·00	1·08, 0·97 [c]
β-(6b)	$O_2C{\cdot}CH_2Me$ [d]	1·12	1·10

[a] In $CDCl_3$ with internal tetramethylsilane. [b] Singlet. [c] Quartet, J 6—7 Hz. [d] Triplet, J 6—7 Hz. [e] Signal of major epimer.

$CDCl_3$ displayed duplicate NMe, O_2CMe, and 2-Me signals which, as in the case of the α-alcohol salt, indicate that both conjugate acids are significantly populated.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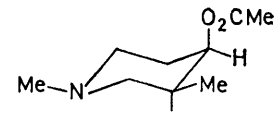
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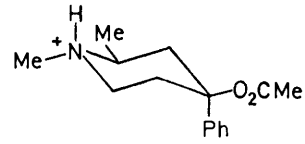
The resolved acetyl peaks had an intensity ratio of 1 (low field) to 2 (high field). Comparison of these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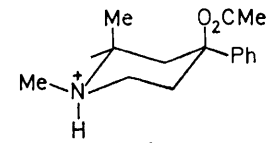
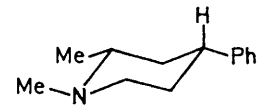

(21)

chemical shifts with those of the corresponding bases indicated stereochemistry (20) and (21) for the major and minor isomer, respectively. Similar evidence was derived from the n.m.r. spectrum of α-(6b) hydrochloride.

The α-piperidinol (3a) suffers some inversion at C-4 during hydrogenolysis;[13,14] the ^{1}H n.m.r. spectrum of the product displayed major and minor 1- and 2-methyl signals [the minor corresponded with those of (8)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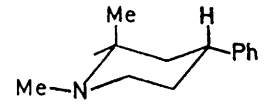
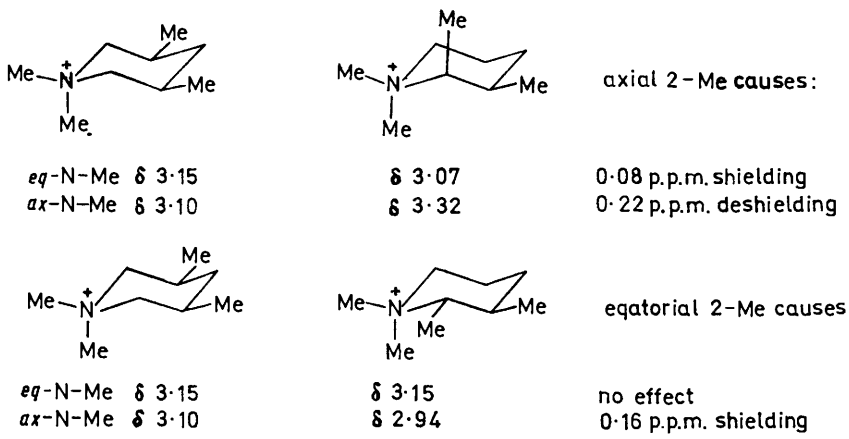

(23)

derived from β-(3a)]. To confirm the stereochemistry (22) for the β-product and (23) for the major α-product of hydrogenolysis, observed *N*-methyl chemical shifts in the corresponding methiodide salts were compared with those calculated from the shielding influences of equatorial and axial 2-methyl groups upon *N*-methyl protons in *NN*-dimethylpiperidinium salts. Shielding



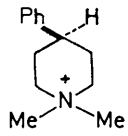
[12] N. L. Allinger and M. T. Tribble, *Tetrahedron Letters*, 1971, 3259.

[13] E. L. Eliel and S. Schroeter, *J. Amer. Chem. Soc.*, 1965, **87**, 5031.

[14] E. L. Eliel and E. Gilbert, *J. Amer. Chem. Soc.*, 1969, **91**, 5487.

data for solutions in $CDCl_3$ and D_2O are available,[15] and shifts anticipated in $(CD_3)_2SO$, the solvent involved in the present cases, are given in the Scheme; included are the reference compounds of essentially 'frozen' conformation † from which these are derived.

Assig[illegible]ents of axial and equatorial signals are based on ^1H n.m.r. spectral comparisons of normal methiodides



(24)

with quaternary salts formed with [$^2H_3$]methyl iodide and the assumption of a preferred axial approach of alkyl halide in the quaternization of cyclic six-membered bases.[11,16] Use of the shielding values in conjunction with data for the reference compound (24), whose *N*-methyl resonances coincide at δ 3·19 in $(CD_3)_2SO$, leads to the calculated and observed *N*-methyl chemical shifts shown in Table 2. The close agreement between observed and calculated values confirms the stereochemistry illustrated [(22) and (23)], and also substantiates the configurations of the precursor alcohols

TABLE 2

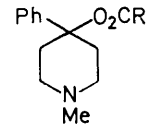
Calculated and observed *N*-methyl chemical shifts in 1,1,2-trimethyl-4-phenylpiperidinium iodides [in $(CD_3)_2SO$]

Value calculated from shielding data	δ_{obs} (p.p.m.)
2*eq*-Me	
3·19 [a] (*eq*-NMe)	3·19 [b]
3·19 − 0·16 = 3·03 (*ax*-NMe)	3·04
2*ax*-Me	
3·19 − 0·08 = 3·11 (*eq*-NMe)	3·10 [c]
3·19 + 0·22 = 3·41 (*ax*-NMe)	3·34

[a] Axial and equatorial NMe chemical shift of (24). [b] Data for β-quaternary salt. [c] Data for α-quaternary salt.

(3) if the former are assumed to be formed without inversion. The relative chemical shifts of the 2-methyl groups in isomeric methiodides of (8) [δ 1·53 (α) and 1·32 (β)] are also consistent with axial (α) and equatorial (β) 2-methyl orientations. Chemical shifts of *N*-methyl and 2-methyl groups in spectra of the β-alcohol (3) and β-acetate (6a) methiodides were close to those of the β-hydrocarbon (8), and all three derivatives must have preferred *eq*-phenyl chair conformations. In spectra of methiodides of α-(3) and α-(6a), however, the 2-methyl signals were at higher field and the *N*-methyl signal separation was less than that seen in the spectrum of α-(8) methiodide; these results indicate that axial 4-phenyl conformers (in which the *trans*-diaxial orientation of the 2-methyl and *N*-methyl groups is lost) are substantially populated in these derivatives. The higher field position of the acetyl resonance in the spectrum of α-(6a) methiodide [δ 1·92 (α) and 2·12 (β)] supports this conclusion. In the α-derivatives, therefore, factors governing preferred conformation appear to be the 1,3-diaxial Me/OR interaction in the alcohol and esters, and the 4-phenyl substituent in the hydrocarbon.

The hot-plate ED_{50} values in mice for pethidine, the esters (6), and their 2-demethyl analogues (25) are given in Table 3. The diastereoisomeric alcohols (3) were



a; R = Me
b; R = Et

(25)

both inactive in this test at a dose level of 100 mg per kg. The relative activities of alcohols, acetates, and propionates in the 2-methylpiperidine series are typical of the 4-phenylpiperidine class of narcotic analgesic.[17,18]

TABLE 3

Hot-plate ED_{50} values (for mice) of some 4-phenylpiperidines after subcutaneous injection *

Compound	ED_{50} (mg per kg)
(25a)	3·62
α-(6a)	2·4
β-(6a)	4·9
(25b)	0·85
α-(6b)	1·3
β(6b)	1·4
Pethidine	4·7

* We thank Dr. E. L. May, National Institutes of Health, Bethseda, for these data.

In the propionates, insertion of a 2-methyl substituent into the piperidine ring has an adverse effect upon potency that is independent of stereochemistry. In the acetates, however, an α-2-methyl group raises, while a β-group lowers, the activity of the parent ester. The marked difference in the preferred conformation of α- and β-(6a) may have significance in this respect; as in 3-methyl and 2,5-dimethyl analogues of (25) [19,20] highest potencies are observed for isomers where the geometry of substitution leads to a departure from 4*eq*-phenyl piperidine chairs as preferred conformation.

EXPERIMENTAL

Dry solvents were used in all reactions. The i.r. spectra (solids as Nujol mulls, liquids as films) were recorded with a Beckman model 10 spectrophotometer, and ^1H n.m.r. spectra with a Varian A-60D instrument.

Dimethyl 3,4-Dimethyl-4-azaheptanedioate (5).—Methyl crotonate (212 g) was added to 33% (w/v) methylamine in

† We thank Dr. Y. Kawazoe for these compounds.

[15] M. Tsuda and Y. Kawazoe, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 2499.
[16] J. McKenna, *Topics Stereochem.*, 1970, **5**, 275.
[17] A. H. Beckett and A. F. Casy, *Progr. Medicin. Chem.*, 1962, **2**, 43.
[18] A. F. Casy, *Progr. Medicin. Chem.*, 1970, **7**, part 2, 229.
[19] A. F. Casy, *J. Medicin. Chem.*, 1968, **11**, 188.
[20] K. M. J. McErlane and A. F. Casy, *J.C.S. Perkin I*, 1971, 339.

ethanol (200 ml); the mixture was heated under reflux for 8 h and then fractionated to give methyl 3-methylaminobutyrate (200 g), b.p. 64—66° at 16 mmHg (lit.,[21] 64—66° at 10 mmHg) (Found: C, 54·9; H, 9·8. Calc. for $C_6H_{13}NO_2$: C, 54·9; H, 10·0%).

A mixture of this base (200 g) and methyl acrylate (172 g) was kept at room temperature for 10 days and then fractionated to give the tertiary amine (5) (223 g), b.p. 97—98° at 0·7 mmHg (lit.,[22] 127—130° at 6 mmHg); *methiodide*, m.p. 131—132° (from acetone) (Found: C, 36·7; H, 6·4; N, 4·0. $C_{11}H_{22}INO_4$ requires C, 36·8; H, 6·2; N, 3·9%).

1,2-*Dimethyl*-4-*piperidone*.—The amine (5) (35 g) was added slowly to a stirred mixture of toluene (300 ml) and potassium ethoxide [from potassium (14·4 g) and ethanol (50 ml) (excess of solvent evaporated off)]. The product was heated under reflux overnight, then cooled and acidified (cautiously) with dilute hydrochloric acid (200 ml). The toluene layer was separated and extracted with dilute acid (5 × 100 ml), and the combined acids were heated under reflux for 15 h; the product then failed to give a red colouration with aqueous iron(III) chloride. The solution was concentrated under reduced pressure, made alkaline with solid sodium hydroxide, and then extracted with chloroform (8 × 100 ml). The extract form was dried (Na_2SO_4) and evaporated, and the residue fractionated to give the piperidone (4) (8·3 g), b.p. 56—69° at 1 mmHg (lit.,[22] 55—57° at 7 mmHg; lit.,[23] 52·5° at 4·5 mmHg); picrate, m.p. 176—177° (from ethanol) (lit.,[24] 175·5—176·5°) (Found: C, 36·9; H, 6·1. Calc. for $C_{13}H_{16}N_4O_8$: C, 36·8; H, 6·2%); *methiodide*, m.p. 185—186° (from acetone) (Found: C, 35·4; H, 6·0. $C_8H_{16}INO$ requires C, 35·7; H, 6·0%). The base with ethanolic hydrogen bromide formed the 4,4-*diethyl acetal hydrobromide*, m.p. 149—151° (Found: C, 47·1; H, 8·75; N, 5·0. $C_{11}H_{24}BrNO_2$ requires C, 46·8; H, 8·6; N, 5·0%), $\nu_{max.}$ 1040 cm^{-1} (C–O–C) ($\nu_{C=O}$ absent), δ ($CDCl_3$) 1·62 (d, 2-Me), 1·22 and 1·27 (t, O·CH_2*Me*), and 3·54 p.p.m. (centre of 2q, O·CH_2Me).

Isomeric 1,2-*Dimethyl*-4-*phenylpiperidin*-4-*ols* (3).—The piperidone (4) (25·4 g) was added to phenyl-lithium in ether (150 ml) [from lithium (3·4 g) and bromobenzene (37·7 g)]. The mixture was stirred overnight and then heated under reflux for 4 h. The cooled product was poured on ice and glacial acetic acid (50 ml). The aqueous phase was combined with dilute acetic acid washings of the ether layer, and the total acid was concentrated under reduced pressure and then made alkaline with strong aqueous ammonia. The liberated free base was extracted with chloroform (10 × 150 ml); the extract was dried (Na_2SO_4) and evaporated to leave the mixture (3) (28 g). This residue was diluted with light petroleum (b.p. 40—60°) and the resultant solid was recrystallized from the same solvent to give the β-isomer of (3) (2·6 g), m.p. 106—108° (as lit.[2]), δ ($CDCl_3$) 2·3 (1-Me) and 1·07 (2-Me), δ [$(CD_3)_2SO$] 2·32 (1-Me) and 1·05 (2-Me), δ (pyridine) 2·3 (1-Me) and 1·08 p.p.m. (2-Me); *methiodide*, m.p. 183—184° (from acetone) (Found: C, 48·7; H, 6·1; N, 4·0. $C_{14}H_{22}INO$ requires C, 48·4; H, 6·4; N, 3·7%); *benzyl chloride*, m.p. 230—231° (from acetone) (Found: C, 72·5; H, 8·05; N, 4·3. $C_{20}H_{26}ClNO$ requires C, 72·4; H, 7·9; N, 4·2%). The residue from the mother liquors was chromatographed on Woelm alumina (neutral, activity 1; 2 × 30 cm column) and eluted with chloroform. Products obtained were unchanged piperidone (4), an αβ-mixture of (3), and finally the α-isomer of (3), m.p. 122—123° (as lit.[2]), δ ($CDCl_3$) 2·14 (1-Me) and 1·08 (2-Me), δ [$(CD_3)_2SO$] 2·17 (1-Me) and 1·08 (2-Me), δ (pyridine) 2·15 (1-Me) and 1·12 p.p.m. (2-Me); *hydrochloride*, m.p. 193—194° (from ethanol–ether) (Found: C, 64·7; H, 8·2; N, 5·7. $C_{13}H_{20}ClNO$ requires C, 64·6; H, 8·3; N, 5·8%); *methiodide*, m.p. 122—123° (from acetone) (Found: C, 48·8; H, 6·4; N, 3·7. $C_{14}H_{22}INO$ requires C, 48·4; H, 6·4; N, 3·7%); *benzyl chloride*, m.p. 221—222° (from acetone) (Found: C, 72·1; H, 7·7; N, 4·3. $C_{20}H_{26}ClNO$ requires C, 72·4; H, 7·9; N, 4·2%).

Esterification of the Piperidinols (3).—Acetyl chloride (1·6 g) was added to β-(3) (0·4 g) in benzene (50 ml) and the mixture was heated under reflux overnight. The cooled product was diluted with ether; the β-*acetate* (6a) *hydrochloride* (0·35 g) separated; m.p. 208—209° (Found: C, 63·1; H, 7·9; N, 4·8. $C_{15}H_{22}ClNO_2$ requires C, 63·5; H, 7·8; N, 4·9%); *methiodide*, m.p. 234—236° (from acetone) (Found: C, 50·2; H, 6·2; N, 4·0. $C_{16}H_{24}INO$ requires C, 49·4; H, 6·2; N, 3·6%). The α-*acetate* (6a) *hydrochloride*, m.p. 184—185° (Found: C, 63·6; H, 7·7; N, 5·2%) was similarly prepared; *methiodide*, m.p. 214—216° (from acetone) (Found: C, 49·4; H, 5·9; N, 3·7%). Use of propionyl chloride in the above procedure yielded β-(6b) *hydrochloride*, m.p. 194—195° (Found: C, 64·8; H, 8·1; N, 4·85. $C_{16}H_{24}ClNO_2$ requires C, 64·5; H, 8·1; N, 4·7%) and α-(6b) *hydrochloride*, m.p. 84—85° (hygroscopic) (Found: C, 64·3; H, 8·1; N, 4·7%).

β-4-*Chloro*-1,2-*dimethyl*-4-*phenylpiperidine* (7).—Freshly distilled thionyl chloride (1 g) was added to a stirred, cooled (0°) solution of β-(3) (0·82 g) in chloroform (100 ml); the product was then stirred at room temperature for 12 h and evaporated. The residue was recrystallized from ethanol–ether to give the β-4-*chloropiperidine* (7) *hydrochloride*, m.p. 159—159·5° (Found: C, 60·1; H, 7·4; Cl, 27·3; N, 5·4. $C_{13}H_{19}Cl_2N$ requires C, 60·1; H, 7·4; Cl, 27·25; N, 5·4%). Treatment of either α- or β-(3) with thionyl chloride as above followed by a 4 h reflux period led to a mixture of 1,2- and 1,6-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine hydrochlorides, m.p. 185—186° (Found: C, 69·7; H, 8·45; N, 6·5. Calc. for $C_{13}H_{18}ClN$: C, 69·8; H, 8·1; N, 6·3%), δ ($CDCl_3$) 1·16 and 1·210 (d, 2-Me), and 5·87 and 6·05 p.p.m. (m, vinyl H). The same product resulted when α-(3) (1 g) was heated under reflux for 4 h with a mixture of concentrated hydrochloric acid (33 ml) and glacial acetic acid (66 ml).

Hydrogenolysis of the Piperidinols (3).—A mixture of β-(3) (0·2 g), Raney nickel (2 g), and ethanol (150 ml) was heated under reflux for 4 h. The product was filtered and the filtrate evaporated to yield oily β-1,2-dimethyl-4-phenylpiperidine (ν_{OH} absent), isolated as a *hydrochloride*, m.p. 174—175° (from ethanol–ether) (Found: C, 69·2; H, 9·0; N, 6·3. $C_{13}H_{20}ClN$ requires C, 69·2; H, 8·9; N, 6·2%), δ ($CDCl_3$) 1·57 (d, 2-Me) and 2·84 p.p.m. (d, HN*Me*); *methiodide*, m.p. 164—165° (from acetone) (Found: C, 50·6; H, 7·0; N, 4·3. $C_{14}H_{22}IN$ requires C, 50·8; H, 6·7; N, 4·2%); for n.m.r. data see Discussion section.

The same treatment of α-(3) gave a product lacking a ν_{OH} band only after an 8 h reflux period. Salts isolated

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(containing minor amounts of the β-isomer) were the hydrochloride (8), m.p. 101—105° (hygroscopic) (Found: C, 69·2; H, 8·9; N, 6·3%), δ ($CDCl_3$) (asterisk denotes minor signals) 1·47 and 1·57* (d, 2-Me), 2·75 and 2·84* (d, HN*Me*); and the *methiodide*, m.p. 172—174° (softens 160°) (from acetone) (Found: C, 51·1; H, 6·6; N, 4·4%); for n.m.r. data see Discussion section.

The acetate and propionate of 1-methyl-4-phenylpiperidin-4-ol were obtained by treating the complex formed between 1-methyl-4-piperidone and phenyl-lithium with the appropriate acid anhydride.[25] Hydrochlorides isolated were those of the acetate (25a), m.p. 228—229° (lit.,[26] 233—234°) (Found: C, 62·2; H, 7·4; N, 4·8. Calc. for $C_{14}H_{20}ClNO_2$: C, 62·3; H, 7·5; N, 5·2%), and the propionate (25b), m.p. 189—190° (lit.,[26] 183—184°) (Found: C, 63·4; H, 7·7; N, 4·9. Calc. for $C_{15}H_{22}ClNO_2$: C, 63·5; H, 7·8; N, 4·9%).

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