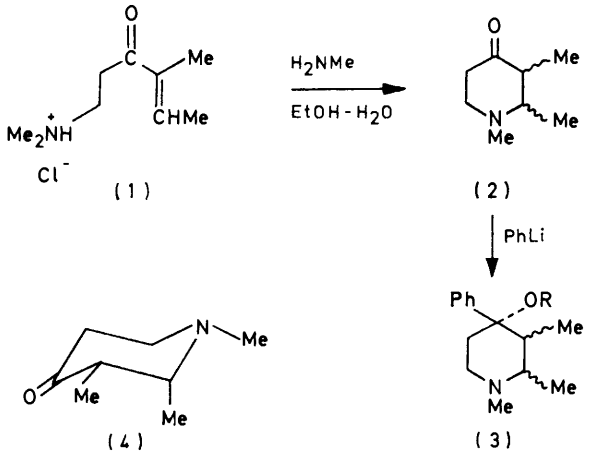
Stereochemistry of 2,3-Dimethyl Analogues of the Reversed Ester of Pethidine and Related Compounds: Examples of Vicinal Diaxial Methyl Groups in 2,3-Dimethylpiperidine Derivatives

By **Alan F. Casy*** and **Francis O. Ogungbamila**, School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY
Christopher Rostron, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF

The configurations and preferred solute conformations of three diastereoisomeric forms of 1,2,3-trimethyl-4-phenylpiperidin-4-ol, isolated from the product of reaction between 1,2,3-trimethyl-4-piperidone and phenyl-lithium, are established from n.m.r. and other data as α, *c*-2-Me, *c*-3-Me, *r*-4-OH; β, *t*-2-Me, *c*-3-Me, *r*-4-OH (both *eq*-4-Ph chairs), and γ, *c*-2-Me, *t*-3-Me, *r*-4-OH (boat in $CDCl_3$). Hydrochlorides of all three isomeric forms of corresponding acetates and propionates have preferred *eq*-4-Ph chair conformations in $CDCl_3$. In cases of the γ-ester and γ-piperidin-4-ol hydrochlorides and the γ-piperidin-4-ol base in $(CD_3)_2SO$, avoidance of the 2,3-dimethyl γ-gauche interaction appears to be a determinant conformational factor. Isomeric potency rankings of the propionate esters in animal antinociceptive tests are γ > α > β.

DURING the past ten years efforts have been made to characterise the stereochemistry of mono- and di-*C*-methyl analogues of the reversed ester of pethidine (1-methyl-4-phenyl-4-propionyloxypiperidine) in attempts to rationalise analgesic potency variations amongst such compounds.[1] The present report on 2,3-dimethyl congeners (3c), compounds described in 1961 [2] without evidence of stereochemistry, completes work on relative configuration for the entire group.

1,2,3-Trimethyl-4-piperidone (2), the key intermediate for making the reversed esters, was produced by treating *N*,*N*,4-trimethyl-3-oxohex-4-enylammonium chloride (1) with an excess of methylamine in ethanol–water; the amino-ketone hydrochloride (1) was obtained from a



(1) (2) (3) (4)

a ; R = H
b ; R = COMe
c ; R = COEt

Mannich reaction involving 3-methylpent-3-en-2-one rather than the original two-step process from 3-methylpent-3-en-1-yne.[3] The distilled 4-piperidone (2) was a *cis–trans* mixture of isomers: its ^{13}C n.m.r. spectrum displayed sixteen major resonances (eight per isomer). Intensities of related carbonyl, 2-methyl and 3-methyl resonances from a spectrum run with proton decoupling and suppressed nuclear Overhauser enhancement indicated 37—43% of the minor component, close to the value (36%) established by g.l.c.[4] Chemical shift assignments (Table 4) establish the minor component to be the *cis*-isomer with a preferred axial 2-methyl chair conformation (4); crystalline salts derived from the mixture have the *trans* configuration. *N*-Benzyl and *N*-phenethyl analogues of the ketone (2) were made by exchange reactions between the methiodide of (2) and the appropriate primary amine.[5] Fractionation of the mixture of diastereoisomeric piperidin-4-ols (3a) obtained by treating the 4-piperidones (2) with phenyl-lithium gave the α- and β-bases (from toluene) and the γ-hydrochloride (from the residues acidified with ethanolic HCl) with m.p.s close to reported values. Hydrochloride salts of the esters (3b and c) were made by treating individual alcohols with acetyl or propionyl chloride in toluene at reflux temperature.

Evidence of the stereochemistry of the piperidin-4-ols (3a) was first sought from n.m.r. data, following previous studies of related 2- and 3-monomethyl, and 2,5-, 3,5-, and 2,6-dimethyl-4-phenylpiperidin-4-ols.[6-10] ^{13}C chemical shifts of the three isomeric 2,3-dimethylpiperidin-4-ols (3a) are given in Table 1, together with those of the unsubstituted parent alcohol. The 2- and 3-CH_3 shifts of the β-isomer (typical of equatorial methyls in 4-phenylpiperidin-4-ols) [6,7] and the similar shifts of C-5 and C-6 in spectra of β-(3a) and 1-methyl-4-phenylpiperidin-4-ol are evidence for the β-conformation and configuration (5). The α-stereochemistry (6) is likewise supported by the 2- and 3-CH_3 chemical shifts (a significant shielding contribution is made to methyl carbon when it has an antiperiplanar relationship with a nitrogen lone pair of electrons) and by the shift of C-6, which is 7 p.p.m. upfield of that in the β-system, in accord with the γ-shielding influence anticipated if the C-2 methyl is axial. Extents of coupling between 2-H and 3-H, as established by spin-decoupling experiments at 220 MHz, are typical of axially related protons in β-(3a) (10 Hz), and of an *eq*/*ax* orientation in α-(3a)

TABLE 1

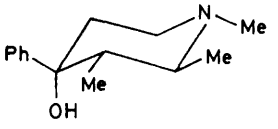
^{13}C Chemical shifts (δ) of some 1-methyl-4-phenylpiperidin-4-ols in $CDCl_3$ [a] and $(CD_3)_2SO$ [b] (Me_4Si standard)

	C-2	C-3	C-4	C-5	C-6	1-CH_3	2-CH_3	3-CH_3	C-q [c]
1-Methyl-4-phenylpiperidin-4-ol	51.6_9	38.3_6	70.0_9	38.3_6	51.6_9	46.2_9			149.0_2
	(51.3_6)	(38.0_0)	(69.3_5)	(38.0_0)	(51.3_6)	(46.0_6)			(150.0_0)
β-(3a)	60.9_5	45.0_7	74.9_8	40.4_7	52.3_9	43.3_3	17.3_3	12.0_2	148.0_0
	(60.1_9)	(44.7_5)	(73.6_8)	(39.5_5)	(51.8_4)	(42.8_0)	(17.1_2)	(12.0_8)	(149.2_5)
α-(3a)	59.0_0	*42.8_0*	75.0_3	39.8_7	45.4_5	*42.4_7*	7.6_4	11.7_6	147.9_0
γ-(3a)	63.3_8	49.1_4	75.4_7	31.0_4	51.9_8	41.9_3	19.0_2	16.7_4	145.6_3
	(61.0_5)	(46.4_3)	(73.1_4)	(34.9_4)	(47.7_8)	(42.5_8)	(*16.0_4*)	(*15.1_7*)	(147.8_4)
1-Methyl-4-phenylpiperidin-4-ol HCl [d]	51.5_3	35.9_3	69.3_0	35.9_3	51.5_3	44.1_6			146.7_7
γ-(3a) HCl [e]	64.0_9	45.5_6 [f]	73.4_6	31.7_5	45.5_6 [f]	41.5_0	*16.2_0*	*15.7_6*	145.6_2
γ-(3a) HCl [d]	63.8_8	45.1_4 [g]	73.5_8	31.8_7 [g]	45.1_4 [g]	41.5_0	15.8 [g]	15.8 [g]	145.2_4

[a] Assignments based on off-resonance spectra and chemical shifts of related compounds (refs. 6—9); shifts in italics may be interchanged. [b] Values in parentheses. [c] Quaternary carbon of 4-phenyl group; other Ph resonances were near δ 128, 126, and 125 in all cases. [d] In D_2O with internal dioxan (δ 67.4). [e] In 50 : 50 methanol–D_2O with Me_4Si. [f] Coincident resonances which form broad signals in proton-noise decoupled and broad multiplets in off-resonance spectra. [g] Broad signal.

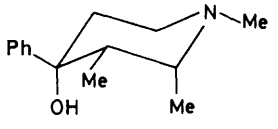
(4—5 Hz), in support of conformations (5) and (6), respectively.

^{13}C N.m.r. data for γ-(3a) were first interpreted in terms of an *eq*-2-Me, *ax*-3-Me chair, as indicated by C-5, 2-CH_3, and 3-CH_3 chemical shifts, but demonstration of



(5)

t-2-Me, *c*-3-Me, *r*-4-OH

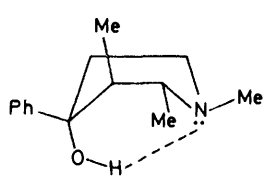


(6)

c-2-Me, *c*-3-Me, *r*-4-OH

The 4*R* configuration only is shown in all conformational drawings

strong intramolecular hydrogen bonding in dilute solutions of γ-(3a) in CCl_4 (ν_{OH}(f) : ν_{OH}(b) **14** : 86) showed that a boat conformation is preferred for this isomer. The n.m.r. data, including a proton $^3J_{2,3}$ value of 6 Hz, are in accord with the stereochemistry (7) in which the



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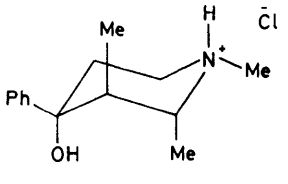


(8)

3-methyl is pseudoaxial and shields C-5 by steric polarisation, with the 2-methyl remote from C-6. Subsequent *X*-ray crystallographic analyses confirmed relative configurations of these isomers and showed that solid and solute state conformations of the α- and β-alcohols are similar, whereas the γ-isomer, examined as a hydrochloride salt, exists in the diaxial methyl chair conformation (8). The C-5 and C-6 shifts of the γ-base in $(CD_3)_2SO$ were both upfield relative to those of 1-methyl-4-phenylpiperidin-4-ol, evidence that the 2,3-diaxial methyl chair makes significant contribution to the conformational equilibrium in a solvent capable of forming strong hydrogen bonds with the piperidin-4-ol [the OH chemical shift of the γ-alcohol was about 2 p.p.m. to lower field of corresponding α- and β-signals in $CDCl_3$, whereas all three resonances were near δ 4.7 in $(CD_3)_2SO$]. That these chemical shift variations are not merely solvent effects is evident from the similar shifts of the β-isomer in the two solvents concerned. Some difficulty was experienced in obtaining the complete ^{13}C n.m.r. spectrum of γ-(3a) hydrochloride, since in polar solvents (necessary for reasons of solubility) several of the resonance lines were broad and ill-defined (a frequent problem in recording the spectra of piperidines with charged nitrogen as in hydrochloride and methiodide salts). The best results were obtained with a methanol–D_2O mixture (the latter provided the lock signal) and overnight runs. Full assignments (with certain reservations as to the C-3 and C-6 shifts) were then possible, and usual shift comparisons with data for the demethyl standard indicates that the diaxial methyl chair (8) is favoured as solute conformation once the strong OH–N interaction is abolished by *N*-protonation (Table 1; hydrochlorides).*

^{13}C N.m.r. data for acetate and propionate ester hydrochlorides of the isomeric piperidin-4-ols (3a), together with those for the reversed ester of pethidine and α-prodine standards, are given in Table 2. The chemical shift results support equatorial-phenyl chairs as preferred conformations for all three isomeric salts as solutes in $CDCl_3$; of special significance are the absence of large upfield shifts of β-C-5 and C-6 signals, and the pronounced

* Spectral data of hydrochlorides are interpreted in terms of the axially *N*-protonated epimer; although epimeric mixtures have been detected by n.m.r. in related compounds by duplication of N-Me and other signals (notably in the case of isomers with preferred axial 4-phenylpiperidine conformations),[6,8] no such evidence was found in spectra of the present series and ^{13}C N–Me chemical shifts were typical of α-methylpiperidines with equatorial *N*-methyl groups.[11]

upfield shift of the α-C-6 signal in comparison with corresponding shifts of the standard compounds, and also the high-field position of the α-2-methyl signal. Upfield shifts of about 5 p.p.m. are apparent at both C-5 and C-6 in the γ-esters, in accord with axial orientations

^{1}H N.m.r. data also support the diaxial methyl chair (13) as the preferred conformer of the γ-ester hydrochloride in D_2O. Successive irradiation of the 2- and 3-Me proton resonances revealed the 2-H (δ *ca.* 3.6) and 3-H (δ *ca.* 2.6) signals as broad singlets ($W_{\frac{1}{2}}$ 5 Hz); only

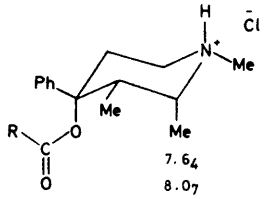
TABLE 2

^{13}C Chemical shifts (δ) of esters of 1,2,3-trimethyl-4-phenylpiperidinols and related standard compounds in $CDCl_3$ (standard Me_4Si) [a, b]

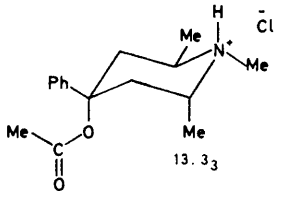
HCl Salt	C-2	C-3	C-4	C-5	C-6	1-CH_3	2-CH_3	3-CH_3	C-q [c]
1-Methyl-4-phenyl-4-propionyloxypiperidine	50.4_9	32.8_3	77.3_1	32.8_3	50.4_9	43.3_4			141.6_1
α-Prodine [d]	56.6_5	40.3_6	81.5_3	30.4_8	50.5_6	43.6_0		11.9_8	139.5_3
β-(3c)	62.8_4	45.9_4	83.1_6	30.3_9	51.7_4	41.5_0	14.7_9	11.9_2	139.8_2
β-(3b)	62.6_3	45.7_8	83.4_3	30.2_8	51.5_7	41.3_4	14.7_4	11.8_1	139.7_8
α-(3c)	60.5_1	40.7_9	82.5_6	29.8_0	45.6_7	42.3_1	7.6_4	11.6_5	139.2_8
α-(3b)	60.5_1	40.6_1	82.7_2	29.6_3	45.3_4	42.2_0	8.0_7	11.6_5	139.1_2
γ-(3c)	61.1_6	44.8_0	81.7_0	25.2_5	46.3_5	41.1_7	*16.0*$_9$	*15.2*$_2$	141.0_2
γ-(3b)	61.2_2	44.9_1	82.1_3	25.2_5	45.9_6	41.2_3	*16.1*$_4$	*15.2*$_2$	140.8_5

[a] Footnote *a* of Table 1 applies. [b] Acyloxy resonances: OCOEt 172.1_1—172.7_6 (CO), 28.4_4—28.8_8 (CH_2), 9.0_5—9.3_7 (Me); OCOMe 168.6_0—169.5_1 (CO), 22.1_0—22.3_7 (Me). [c] Quaternary carbon of 4-phenyl; other Ph resonances were near δ 128(2) and 125 in all cases. [d] 1,*c*-3-dimethyl-4-phenyl-*r*-4-propionyloxypiperidine hydrochloride.

of methyl substituents at C-2 and C-3. The 2- and 3-methyl shifts are to lower field than the corresponding α- and β-resonances (the difference between α- and γ-2-methyl shifts is particularly noteworthy), a result which may be attributed to deshielding factors appropriate only to the γ-esters, namely (i) γ-anti-deshielding of axial 3-methyl by oxygen [7] and (ii) the absence of mutual γ-gauche shielding of methyl groups as occurs in the α-2,3-dimethyl esters [*cf.* chemical shift data of (9)—(11)].



(9)
(R = Me)
(R = Et)



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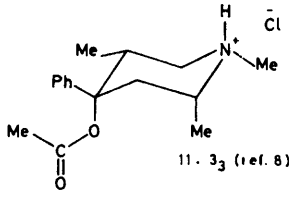
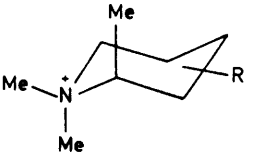


(11)

There is also evidence, from ^{13}C n.m.r. studies of the MeN^+CMe system of the quaternary piperidine salts (12), that antiperiplanar methyl groups deshield one another by 2—3 p.p.m.[12] Axial *N*-methyl protons of *N*,*N*-dimethylpiperidinium salts are likewise deshielded by α-axial methyl substituents,[13] and it may be of significance in this respect that 2- and 3-methyl proton chemical shifts of the γ-ester (3c) are to lower field than the corresponding α- and β-signals; δ values (2,3-Me) are α 1.58, 0.79; β 1.45, 0.83; γ 1.67, 1.02.

small $^4J_{2,3}$ values plus possible ^4J couplings are expected for conformation (13). Because six-membered alicyclic derivatives with preferred antiperiplanar methyls are rare, a 400 MHz Fourier transform spectrum of γ-(3c)



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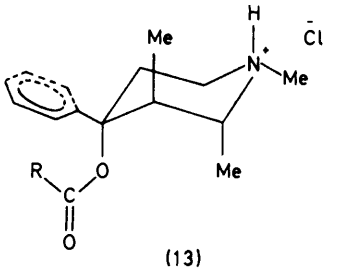
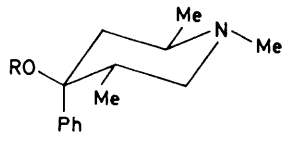


(13)

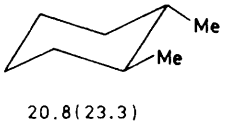
hydrochloride in D_2O was recorded to extract all the ^3J values; a triplet of doublets (δ 3.5_8, J 12—13, 3—4 Hz, axial 5- or 6-H) and a doublet of triplets (δ 3.4_2, J 12—13, 3—4 Hz, equatorial 6-H) of equal intensity were resolved (evident but poorly defined in the 220 MHz spectrum) and hence all vicinal couplings have magnitudes typical of cyclohexane or piperidine chairs. The γ-acyloxy resonances, to higher field than the related α- and β-signals [δ ($OCOCH_2$) α 2.55, β 2.64, γ 2.40; δ ($OCOCH_2Me$) α 1.26, β 1.20, γ 1.08], further corroborate the stereochemical deductions since axial 3-methyl as in (13) will raise the population of conformers in which the aromatic group shields the acyloxy function.[14]

In 2,5-dimethyl analogues of γ-(3) of related relative configuration, axial-phenyl chairs (14) are preferred;[8] hence the determinant conformational factor in the γ-2,3-dimethyl isomer must be the avoidance of the additional dimethyl gauche interaction, absent in the 2,5-dimethyl derivatives (a MeCNMe gauche interaction is present in both types of compound). Although an equatorial 2,3-dimethyl conformation is clearly preferred in β-isomers of the ester hydrochloride series (the inverted chair requires an axial phenyl substituent and entails a 1,3-*syn*-diaxial Ph/Me interaction), there is chemical



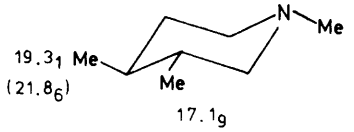
(14)

R = H, COMe, or COEt



20.8(23.3)

(15)



17.1₉
(19.7₂)

(16)

^{13}C chemical shifts of demethyl analogues in parentheses

shift evidence of the relief of Me/Me interactions by ring deformation and/or inversion. Thus an unusual ^{13}C n.m.r. feature of *t*-2,3-dimethyl-*N*-methylpiperidines is the fact that the mutual shielding consequence of the γ-gauche interaction of vicinal equatorial methyls, as evident from data on *t*-2,3-dimethylcyclohexane (15) [15] and *t*-3,4-dimethyl-*N*-methylpiperidine (16),[16] is seen only for 2-methyl resonances in the *t*-2,3-dimethyl-*N*-methylpiperidines (Table 3). This anomaly may reflect the attenuation of Me/Me interactions in the piperidines with a 1,2,3-triequatorial methyl system.

TABLE 3

^{13}C Chemical shifts (δ) of *C*-methyl groups in some *trans*-2,3-dimethyl-*N*-methylpiperidines and monomethyl analogues (in $CDCl_3$ or neat; Me_4Si standard)

Parent structure	Mono-2- or 3-methyl derivative	*t*-2,3-Dimethyl derivative
N-Methylpiperidine [a]	20.4_2 (C-2)	17.1_3 (C-2)
	19.7_2 (C-3)	19.7_6 (C-3)
N-Methyl-4-phenylpiperidin-4-ol [b]	20.3_4 (C-2)	17.3_3 (C-2)
	12.3_0 (C-3)	12.0_2 (C-3)
N-Methyl-4-piperidone [c]	19.7 (C-2)	18.1 (C-2)
	11.9 (C-3)	11.4 (C-3)

[a] Ref. 15. [b] Ref. 6 and this work. [c] Ref. 16 and this work.

Potency rankings of the isomeric esters (3c) were γ > α > β (ED_{50}/mg kg^{-1} in mouse hot-plate s.c. γ 0.28; α 1.6; β 30.7; in rat tail-withdrawal, i.v. γ 0.04; α 1.25; β 10). The significance of these findings will be discussed elsewhere.[20]

EXPERIMENTAL

Proton noise- and off-resonance-decoupled ^{13}C n.m.r. spectra were recorded with a JEOL FX90Q spectrometer operating at 22.5 MHz. Samples were prepared in 5 mm o.d. tubes as *ca.* 10% solutions in $CDCl_3$ or $(CD_3)_2SO$ with Me_4Si as reference. The deuterium of the solvent provided the lock signal. Spectra were recorded with 8 K data points and the probe temperature was 23 °C. For an average spectral width of 5 000 Hz a 4 μs pulse corresponding to a tilt angle of 30° was employed with a 1.819 s interval (acquisition time plus 1 s pulse delay) between pulses. 220 MHz ^{1}H N.m.r. spectra were provided by the P.C.M.U., Harwell. Hydrochloride salts were recrystallised from ethanol–ether.

1,2,3-Trimethyl-4-piperidone (2).—The product of an alkali-catalysed (10% NaOH–H_2O) aldol condensation of acetaldehyde with an excess of butanone under conditions which minimised self-condensation was dehydrated with 47% hydrogen bromide to give 3-methylpent-3-en-2-one in 57% overall yield; the product, b.p. 137—140° (lit.,[17] 138—141°), $\nu_{max.}$ 1 660 cm^{-1} (C=O), was a *cis–trans* mixture as judged from the m.p. of its 2,4-dinitrophenylhydrazone, 181—182° (lit.,[18] *cis* 140—142°, *trans* 200—202°). The HCl-catalysed procedure of Hinkel [19] was less convenient and gave lower yields of product. A mixture of 3-methylpent-3-en-2-one (98 g, 1 mol), paraformaldehyde (33 g, 1.1 mol) dimethylammonium chloride (89 g, 1.1 mol), ethanol (200 ml) and concentrated hydrochloric acid (5 drops) was heated under reflux for 5 h. The mixture was diluted with hot acetone (150 ml) and left overnight to deposit the hydrochloride (1) (102 g, 52% yield including crops formed at refrigerator temperature), m.p. 165—166°, isomerically pure as judged by its ^{13}C n.m.r. spectrum: δ C-1 53.1_5, C-2 32.3_4, C-3 196.7_1, C-4 137.3_9, C-5 139.8_8, C-6 10.8_9, 4-CH_3 14.9_0, N-Me 43.1. A mixture of the Mannich base hydrochloride (1) (100 g, 0.52 mol), methylamine in ethanol (33%; 160 ml, 1.7 mol), water (60 ml), and ethanol (200 ml) was stirred overnight at room temperature (yields were low in the absence of water [5]). Volatile materials were removed and the base, recovered from the residue by extraction with ether, was distilled to give 1,2,3-trimethyl-4-piperidone (45 g, 60%), b.p. 66—68° at 6 mmHg (lit.,[3] 63—64° at 2.5 mmHg), $\nu_{max.}$ 1 685 cm^{-1} (C=O); trans-*hydrochloride*, m.p. 153° (Found: N, 7.8. $C_8H_{16}ClNO$ requires N, 7.9%); trans-*methiodide*, m.p. 154° (Found: C, 38.0; H, 6.55; N, 4.9. $C_9H_{18}INO$ requires C, 38.15; H, 6.4; N, 4.95%). ^{13}C N.m.r. characteristics of the 4-piperidones (2) are given in Table 4. *N*-Benzyl and *N*-phenethyl analogues of (2) were made by stirring a mixture of (2) methiodide (4.25 g), benzylamine or phenethylamine (1.5 g), and water (2 ml) until a clear solution resulted. The mixture was left overnight and then extracted with ether. Bases recovered from the ether were *cis–trans* mixtures of 4-piperidones (^{13}C n.m.r. evidence), characterized as *hydrochlorides*: N-*benzyl*, m.p. 179—180° (Found: C, 65.95; H, 8.1; N, 5.5. $C_{14}H_{20}ClNO$ requires C, 66.25; H, 7.9; N, 5.3%); N-*phenethyl*, m.p. 158—160° (Found: C, 67.4; H, 8.0; N, 5.3. $C_{15}H_{22}ClNO$ requires C, 67.3; H, 8.2; N, 5.25%).

Isomeric 1,2,3-Trimethyl-4-phenylpiperidin-4-ols (3a) *and Derived Acetates* (3b) *and Propionates* (3c).—The 4-piperidone (2) as a *cis–trans* mixture (65 g, 0.46 mol) in ether (70 ml) was added to ice-cooled phenyl-lithium in ether (200 ml) [from lithium (9.2 g, 1.3 g atom) and bromobenzene (104 g, 0.66 mol)] and the mixture was stirred for 0.5 h at room temperature. The product was returned to the ice-bath, decomposed with dilute hydrochloric acid, and extracted with ether. The aqueous phase was made alkaline with NaOH–H_2O and shaken with ether. A solid (13 g) corresponding to the α-piperidin-4-ol (3a) separated at the ether–water interface and was collected; a mixture of bases (3a) (53 g) was recovered from the ethereal filtrates as an oil which solidified. Fractional crystallisation of the mixture from toluene–iso-octane gave α-(3a) (10 g), m.p. 144—145.5° (lit.,[2] 143—145°), β-(3a) (15 g), m.p. 117.5—119° (lit.,[2] 118—119°) and an α/β-(3a) mixture (12 g). The γ-piperidin-4-ol (3a) hydrochloride (6 g), m.p. 239—242° (lit.,[2] 248°) was obtained from the residual base after

TABLE 4

^{13}C Chemical shifts (δ) of some 1-methyl-4-piperidones in $CDCl_3$ (standard Me_4Si) [a, b]

	C-2	C-3	C-4	C-5	C-6	1-CH_3	2-CH_3	3-CH_3
1-Methyl-4-piperidone base (neat) [c]	55.4_0	40.8_9	206.2_2	40.8_9	55.4_0	45.1_5		
HCl	52.0_3	38.3_9	203.0_8	38.3_9	52.0_3	42.2_0		
t-(2) HCl	65.8_8	47.2_9	203.1_0	38.0_3	54.0_7	40.9_0	16.0_4	10.9_4
t-Base	65.4_4	49.8_4	209.5_5	40.7_4	55.3_7	41.5_0	18.0_9	11.3_2
c-Base [d]	61.9_8	48.8_7	210.6_8	39.7_1	49.9_5	42.0_4	9.2_1	11.0_5

[a] Footnote *a* of Table 1 applies. [b] Stereochemical assignments based on the similar C-5 and C-6 shifts of the major (*trans*) piperidone, (2) and 1-methyl-4-piperidone, and the relatively high field shifts of C-6 and 2-CH_3 in the minor (*cis*) base. [c] Ref. 16. [d] From spectrum of *cis–trans* mixture.

acidification with ethanolic HCl. Ester hydrochlorides of the piperidin-4-ols (3a) were obtained by heating a mixture of the alcohol (1 g), freshly distilled acetyl or propionyl chloride (1 g) and toluene (8 ml) at reflux temperature for 12 h. Solids which separated from the mixtures on storage at 4 °C were recrystallised to give *hydrochlorides* of α-(3b), m.p. 182° (Found: C, 63.05; H, 8.15; N, 4.6. $C_{16}H_{24}ClNO_2,0.5H_2O$ requires C, 62.65; H, 8.15; N, 4.57%); β-(3b), m.p. 244° (Found: C, 64.75; H, 8.35; N, 4.95. $C_{16}H_{24}ClNO_2$ requires C, 64.55; H, 8.15; N, 4.7%); γ-(3b), m.p. 195—196° (Found: C, 64.9; H, 8.35; N, 4.75%); α-(3c), m.p. 154—155° (Found: C, 63.45; H, 8.5; N, 4.2. $C_{17}H_{26}ClNO_2,0.5H_2O$ requires C, 63.55; H, 8.4; N, 4.35%); β-(3c), m.p. 236° (Found: C, 65.25; H, 8.45; N, 4.35. $C_{17}H_{26}ClNO_2$ requires C, 65.45; H, 8.4; N, 4.5%); and γ-(3c), m.p. 189—190° (Found: C, 65.6; H, 8.45; N, 4.5%). Decomposition of the complex of the 4-piperidone (2) and phenyl-lithium with an excess of acetic or propionic anhydride gave a basic mixture from which the β-ester (3b) or (3c) separated as hydrochlorides after acidification with ethanolic HCl.

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