Stereochemistry of the Four Diastereoisomeric 1,2,5-Trimethyl-4-phenylpiperidines

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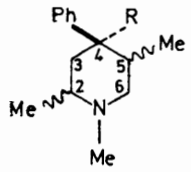
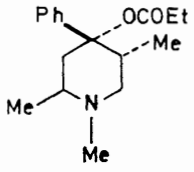
Four isomeric 1,2,5-trimethyl-4-phenylpiperidines have been obtained from appropriate alcohols by dehydration–catalytic hydrogenation or hydrogenolysis. Their ^{13}C and ^{1}H n.m.r. spectra are interpreted in terms of preferred chair conformations with configurations *c*-2-Me, *c*-5-Me, *r*-4-Ph (δ); *t*-2-Me, *c*-5-Me, *r*-4-Ph (β); *c*-2-Me, *t*-5-Me, *r*-4-Ph (γ); and *t*-2-Me, *t*-5-Me, *r*-4-Ph (α) for these isomers. Evidence for isomerization during catalytic hydrogenation of the binary mixture of alkenes obtained on dehydration of γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol is presented

THIS paper is an extension of our interest in ^{13}C and ^{1}H n.m.r. spectroscopy as aids in establishing the configuration and preferred conformation of 4-phenylpiperidines with two or more methyl substituents in the heterocyclic ring[1-8] and is concerned with 1,2,5-trimethyl-4-phenylpiperidines (1a), the oxygen-free analogues of the

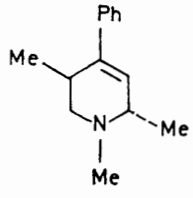


(1) a, R = H
b, R = OH



(2)

narcotic analgesic trimeperidine [(2) γ-promedol] and its isomers. Two of the four possible diastereoisomeric piperidines (1a) were obtained by hydrogenolysis of the corresponding α- and β-4-piperidinols (1b) with Raney nickel and these are designated α- and β- (1a), respectively.‡ The β-isomer also formed the minor component of the binary mixture obtained when the mixture of alkenes (3) and (4) [derived from γ- (1b) by acid-catalysed dehydration] was catalytically hydrogenated; the major product was a third isomer δ- (1a). The final isomer [γ- (1a)] was obtained by reduction of 2,5-dimethyl-4-phenylpyridine with Na–EtOH followed by *N*-methylation, and a sample was kindly provided by Professor N. S. Prostakov. N.m.r. data for these isomers are shown in the Table along with information on the reference compounds 1-methyl-, 1,*c*-2-dimethyl- (α-), 1,*c*-3-dimethyl- (β-), and 1,*t*-3-dimethyl- (α-)-4-phenylpiperidine.[8,12] Using empirical additivity relationships established in related 4-piperidones,[1] and 4-piperidinols,[2-4] it is possible to derive the configuration



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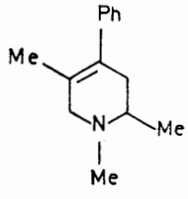

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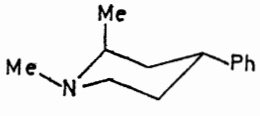
and preferred conformation of all the 4-phenylpiperidine bases described. The most valuable of these relationships is the upfield shift of ^{13}C signals due to the carbon atoms involved in 1,3-*syn*-axial interactions (the γ-effect).[13] In the ^{1}H n.m.r. the downfield shift of the ^{1}H signal due to the axial 3-methyl group in piperidine derivatives upon protonation of nitrogen also characterized the configuration at C-3 (≡5).[14] Thus, comparing the ^{13}C shifts of the α-1,2- and β-1,3-dimethylpiperidines with those of the 1-methyl derivative (Table, items 1—3) § the structures (5) and (6) are established, in



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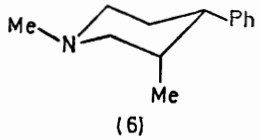

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agreement with those deduced from ^{1}H n.m.r. studies.[8,12] Most significant are the high field shifts arising from

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‡ The α- and β-isomers (1b) are difficult to distinguish using m.p. data and it is now known that our α- and β-samples correspond with β- and α-forms, respectively, of the Russian literature.[9-11]

§ Numerals preceded by 'item' refer to the first column of the Table.

[1] A. J. Jones and M. M. A. Hassan, *J. Org. Chem.*, 1972, **37**, 2332.
[2] A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Tetrahedron Letters*, 1972, 1727.
[3] A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Canad. J. Chem.*, 1973, **51**, 1782.
[4] A. J. Jones, C. P. Beeman, A. F. Casy, and K. M. J. McErlane, *Canad. J. Chem.*, 1973, **51**, 1790.
[5] A. F. Casy, *Tetrahedron*, 1966, **22**, 2711.
[6] A. F. Casy and K. M. J. McErlane, *J.C.S. Perkin I*, 1972, 334.
[7] K. M. J. McErlane and A. F. Casy, *J.C.S. Perkin I*, 1972, 339.
[8] A. F. Casy and K. M. J. McErlane, *J.C.S. Perkin I*, 1972, 726.
[9] N. S. Prostakov, B. E. Zaitsev, N. M. Mikhailova, and N. N. Mikheeva, *J. Gen. Chem. (U.S.S.R.)*, 1964, **34**, 465.
[10] T. F. Vlasova and Yu. N. Sheiner, *Zhur. strukt. Khim.*, 1970, **11**, 640.
[11] N. S. Prostakov, N. M. Mikhailova, and S. Simo, *Khim. geterotsikl. Soedinenii*, 1970, 1356.
[12] K. M. J. McErlane and A. F. Casy, *Canad. J. Chem.*, 1972, **50**, 2149.
[13] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1972, **94**, 5318.
[14] A. F. Casy, 'Proton Magnetic Resonance Spectroscopy in Medicinal and Biological Chemistry,' Academic Press, London, 1971, p. 203.

steric contributions at C-2′, C-6, C-4, and C-1′ in (5), and at C-5 in (6) compared with 1-methyl-4-phenylpiperidine, which indicate the axial conformation of the 2- and 3-methyl substituents in the 1,2- and 1,3-dimethyl derivatives, respectively. These results also show that hydrogenolyses of the 4-piperidinol precursors of (5) and (6) occur with retention of configuration.

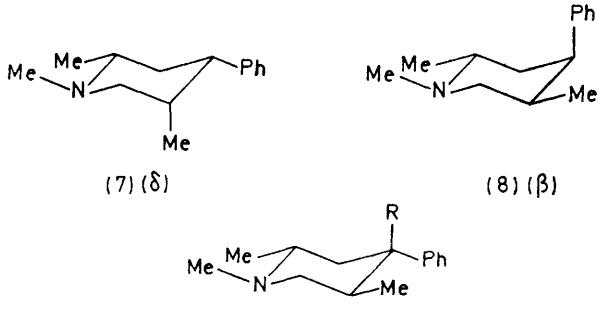
(item 6) is evidence for an axial phenyl orientation. A similar effect was observed in the corresponding 4-piperidinols.[2,4] The shift (12·8 p.p.m.) assigned to the 5-methyl carbon in the δ-isomer (item 5) is identical with that in (6) (item 3, 3-Me ≡ 5-Me) indicating its axial orientation, while the ^{13}C resonance at 20·9 p.p.m. is typical of an equatorial 2-methyl carbon.[3,4] The

N.m.r. characteristics of some substituted 4-phenyl piperidines [a]

Item	Substituents	Form	^{13}C Resonances [b] C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-5′(3′)	C-*q* [c]	^{1}H Resonances [d] 2-Me	5-Me
1	1-Me	Base	$56{\cdot}3_9$	$32{\cdot}9_3$	$42{\cdot}0_0$	$32{\cdot}9_3$	$56{\cdot}3_9$	$46{\cdot}3_9$			$146{\cdot}5_4$		
		HCl	$54{\cdot}9_3$	$30{\cdot}4_8$	$39{\cdot}5_5$	$30{\cdot}4_8$	$54{\cdot}9_3$	$43{\cdot}8_1$			$143{\cdot}2_5$		
2	1,*c*-2-Me_2 (α)	Base	$53{\cdot}8_9$	$35{\cdot}8_7$	$39{\cdot}2_7$	$33{\cdot}0_1$	$48{\cdot}4_4$	$42{\cdot}8_3$	$10{\cdot}3_6$ [e]		$146{\cdot}3_0$		
		HCl	$56{\cdot}2_7$	$33{\cdot}5_5$	$36{\cdot}3_1$	$30{\cdot}3_2$	$48{\cdot}3_3$	$40{\cdot}7_8$	$10{\cdot}8_9$		$143{\cdot}1_2$	$1{\cdot}47_8$	
3	1,*c*-3-Me_2 (β)	Base	$63{\cdot}2_3$	$35{\cdot}1_7$	$44{\cdot}1_8$	$24{\cdot}7_6$	$56{\cdot}7_5$	$46{\cdot}7_2$		$12{\cdot}8_9$	$144{\cdot}5_8$		0·73 (3-Me)[12]
		HCl	$60{\cdot}5_2$	$33{\cdot}8_8$	$41{\cdot}7_5$	$22{\cdot}3_3$	$55{\cdot}2_9$	$44{\cdot}6_7$		$12{\cdot}5_2$	$141{\cdot}5_6$		1·14 (3-Me)[12]
4	1,*t*-3-Me_2 (α)	HCl	$60{\cdot}6_4$	$34{\cdot}2_0$	$43{\cdot}8_0$	$31{\cdot}0_7$	$54{\cdot}9_2$	$47{\cdot}5_8$		$16{\cdot}7_0$	$141{\cdot}9_3$		0·73 (3-Me)
5	δ-1,2,5-Me_3 (7)	Base	$60{\cdot}3_3$	$33{\cdot}4_2$	$44{\cdot}9_6$	$35{\cdot}4_2$	$64{\cdot}6_4$	$43{\cdot}4_5$	$20{\cdot}8_6$	$12{\cdot}7_8$	$144{\cdot}5_9$	1·18	0·8
		HCl	$62{\cdot}1_6$	$30{\cdot}9_4$	$43{\cdot}1_8$	$34{\cdot}1_3$	$62{\cdot}8_1$	$42{\cdot}0_5$	$17{\cdot}5_7$	$12{\cdot}8_3$	$141{\cdot}3_0$	1·69	1·11
6	β-1,2,5-Me_3 (8)	Base	$56{\cdot}2_7$	$(32{\cdot}3_7)$	$39{\cdot}0_6$	$(33{\cdot}4_5)$	$56{\cdot}6_5$	$41{\cdot}2_2$	$18{\cdot}5_7$	$14{\cdot}6_8$	$141{\cdot}2_0$	1·05	0·75
		HCl [f,g]	$57{\cdot}7_9$	$(31{\cdot}4_6)$	$41{\cdot}3_3$	$(33{\cdot}1_8)$	$57{\cdot}1_9$	$(41{\cdot}8_2)$	$17{\cdot}7_5$	$11{\cdot}1_1$	$141{\cdot}3_1$	1·50 [h]	1·13, 0·8
			$56{\cdot}0_1$	$(35{\cdot}9_9)$	$41{\cdot}0_6$	$(37{\cdot}7_7)$	$54{\cdot}5_5$	$(28{\cdot}6_5)$	$12{\cdot}9_5$	$16{\cdot}4_0$	$140{\cdot}8_2$		
7	γ-1,2,5-Me_3 (9)	Base [i]	$60{\cdot}0_0$	$42{\cdot}6_2$	$50{\cdot}9_3$	$36{\cdot}4_2$	$65{\cdot}1_8$	$43{\cdot}2_2$	$20{\cdot}1_3$	$17{\cdot}1_6$	$144{\cdot}7_6$	1·12	0·67
		HBr	$62{\cdot}2_5$	$39{\cdot}7_0$	$49{\cdot}2_5$	$34{\cdot}2_6$	$62{\cdot}5_8$	$40{\cdot}9_4$	$17{\cdot}4_8$	$16{\cdot}5_1$	$141{\cdot}8_3$	1·58	0·74

[a] Chemical shifts in p.p.m. from internal tetramethylsilane with deuteriochloroform as solvent. [b] The conventional labelling system for the piperidine ring is employed [see (1)]. Carbon atoms in substituents are identified by a prime symbol on the number appropriate to the position of substitution on the ring. Phenyl ring carbons are labelled C-*q*, C-*o*, C-*m*, and C-*p* to indicate the positions C-1, C-2, C-3,5, and C-4 on the aryl ring respectively. Assignment of individual resonances to appropriate carbon positions, involving use of data on related compounds, signal intensities, and off-resonance decoupled spectra, has been described in detail elsewhere.[1,3,13] [c] C-*o*, *m*, and *p*-resonances occur in the range 129·3—125·1 p.p.m. except C-*m* for item 5 as base (117·3$_4$). [d] Doublets, ^3J 6—7 Hz. [e] *eq*-C_2' resonances in 1,2-dimethylpiperidines occur near 20 p.p.m.[1,3] [f] Epimeric conjugate acids studied as a *ca.* 1 : 1 mixture in $CDCl_3$ at 26°; assignments are tentative and based on similarities in shift differences for β- (1b) and its hydrochlorides.[3] [g] ^1H N.m.r. data on total product from reduction of (3) and (4): δ 2-Me 1·15, 1·05 (base), 1·69, 1·53, 1·45 (HCl); 5-Me 0·8, 0·75 (base), 1·11, 1·08, 0·74 (HCl). [h] Centre of overlapping pair of doublets. [i] ^1H N.m.r. data on α- (1a) in $(CD_3)_2SO$: δ 2-Me 1·04 (base), 1·37 (HCl); 5-Me 0·6 (base), 0·63 (HCl).

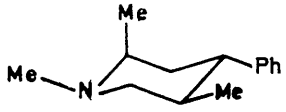
In the 1,2,5-trimethylpiperidines (1a) the preferred conformations (7) (δ; *c*-2-Me, *c*-5-Me, *r*-4-Ph), (8) (β; *t*-2-Me, *c*-5-Me, *r*-4-Ph), and (9a) (γ; *c*-2-Me, *t*-5-Me,



r-4-Ph) may be deduced. In δ- and γ- (1a), correspondence in the shifts of the phenyl ring quaternary carbon (144·7 p.p.m.) with those of the two 1,3-dimethyl derivatives (items 3—5, 7) suggests the equatorial conformation for the 4-phenyl substituent. In contrast the upfield shift (3·5 p.p.m.) at this site in the β-isomer contrast provided by the shift of the quaternary phenyl carbon in the β-isomer is complemented by the upfield shifts of the C-2, C-6, and C-5′ resonances compared with those of other isomers. Structure (8) thus represents the preferred conformation of β- (1a). It is noteworthy that both conjugate acids are similarly populated in β- (1a) hydrochloride, a characteristic of piperidine bases with axial phenyl groups;[3,4,6-8] ^{13}C data for the salt indicate conformational equilibria similar to those deduced for β- (1b) hydrochlorides.[4] In γ- (1a), the equatorial conformations of the 1- and 2-methyl, and 4-phenyl groups are defined by their typical shifts. The 5-methyl resonance is close to that of the 3-methyl in α-1,3-dimethyl-4-phenylpiperidine (items 7 and 4) and thus is also assigned an equatorial conformation, all data being compatible with (9a) as the preferred conformation of the γ-isomer. The 5 (≡ 3)-methyl chemical shifts (items 4 and 7) are at lower field than those of the corresponding axial 5 (≡ 3)-methyl isomers while the reverse is true in related 4-piperidinols such as α- and β-prodinol.[3] Removal of the axial 4-hydroxy-group of the γ-4-piperidinol (9b), however, removes the steric interactions of this group at C-2, C-6, and C-5′. Thus the ^{13}C signal of these atoms in (9b) should all be at

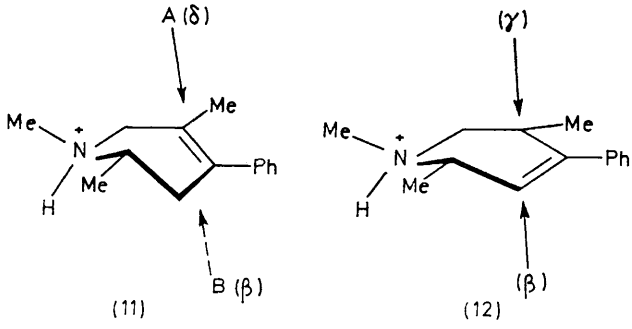
higher field than the corresponding signals of (9a), as is observed [(9a), (9b) chemical shifts: 60·0, 54·8 (C-2), 65·2, 60·1 (C-6), 17·2, 12·0 (C-5)].[2,4]

^{1}H N.m.r. evidence corroborates the 5-methyl stereochemistry of the isomers (1a). A significant protonation shift for this group was found only in δ- (1a) and one of the conjugate acids of β- (1a), in confirmation of their axial 5-methyl orientations (item 5, 6). No such shifts occurred in the cases of γ- and α- (1a). No ^{13}C n.m.r. data were recorded for α- (1a), an isomer in short supply, but its configuration may be deduced as *t*-2-Me, *t*-5-Me, *r*-4-Ph, by difference. This stereochemistry is consistent with the fact that α- (1a) was derived by Raney nickel hydrogenolysis of the α-4-piperidinol (1b) of known configuration (several examples in these studies have shown that this reaction in 4-piperidinols proceeds with retention of configuration), while ^{1}H n.m.r. evidence supports (10) as the preferred conformation.



(10) (α)

Assuming that catalytic hydrogenation of the alkene mixture (3) and (4) proceeds by *cis*-attack,[15] formation of δ- and β- (1a) is accounted for by addition of hydrogen to (11) from directions A and B, respectively. Similar attack upon the tri-substituted alkene (12) would yield β- and γ- (1a) and as the latter is not formed, the reaction may proceed *via* (11) exclusively and involve isomerization of (3) to (4). The alternative explanation of *cis*-addition from side A being favoured for (11) [giving δ- (1a)] but not for (12) [giving γ- (1a)] seems unlikely.



The *trans* configuration of (3), previously incorrectly assigned,[7] is established by its formation by the dehydration of both β- and γ- (1b). The γ- (1a) derivative is the most thermodynamically stable member of the isomeric quartet and its formation from the corresponding substituted pyridine[11] probably occurs under equilibrium conditions.

In contrast with the 4-acyloxy-derivatives of 1,2,5-trimethyl-4-piperidines, δ- (1a) was inactive at sub-toxic doses (100 mg Kg^{-1}) in the hot plate test for analgesia performed on mice.

EXPERIMENTAL

The ^{13}C n.m.r. spectra were determined at 22·63 MHz in the Fourier mode using a Bruker HFX-90 spectrometer in conjunction with a Nicolet-1085, 20K memory computer. The spectrometer features a deuterium lock system, a BSV-2 random noise (800 Hz bandwidth) proton decoupler and a BSV-2 pulse-generator-amplifier. All compounds were examined as solutions in deuteriochloroform (which also provided the lock signal) with 2—5% tetramethylsilane as internal standard, and the solutions were contained in precision ground 10 mm o.d. tubes (Wilmad Glass Co.). The spectrometer was used in the cross-coil configuration. On average a 30 μs pulse, corresponding to an approximate tilt angle of 45°, was employed. For the average spectral width of 5000 Hz the delay between pulses was 70 μs. Acquisition times averaged 0·5 h over 8 K data points for concentrations of the order of 0·1—0·5M. For off resonance or coupled spectra this time was approximately doubled. ^{1}H N.m.r. spectra were recorded at 60 MHz using a Varian A-60D instrument.

α- *and* β-1,2,5-*Trimethyl*-4-*phenylpiperidine* (1a).—A mixture of Raney nickel (2 g) (Grace, Chattanooga; active grade), α- (1b) (0·2 g), and ethanol (50 ml) was stirred and heated under reflux for 12 h. The product was cooled, filtered, and the filtrate evaporated to give α- (1a) isolated as a *hydrochloride*, m.p. 149—151° (from ethanol–ether) (Found: C, 69·9; H, 9·35; N, 5·9. $C_{14}H_{22}ClN$ requires C, 70·1; H, 9·25; N, 5·85%). The same treatment of the β-4-piperidinol (1b) gave β- (1a) *hydrochloride*, m.p. 206—209° (from ethanol–ether) (Found: C, 70·3; H, 9·3; N, 5·9%).

Dehydration of γ- (1b) *and Hydrogenation of the Product.*—A mixture of γ- (1b) (5 g), concentrated hydrochloric acid (66 ml), and glacial acetic acid (124 ml) was heated under reflux for 8 h. The product was concentrated, made alkaline with aqueous ammonia and extracted with chloroform. The dried extracts were evaporated to give an oily mixture (4·5 g) of the tetrahydropyridines (3) and (4) in a ratio of *ca.* 1 : 1 from ^{1}H n.m.r. integrations of signals at δ 1·55br [s, vinylic Me of (4)] and 0·85 [d, *J* 6·5 Hz, 5-Me of (3)]. Fractional crystallization of the mixed hydrochlorides gave (3a) hydrochloride, m.p. 175—179°, identical with the tetrahydropyridine derived from β- (1b).[7] A mixture of (3) and (4) hydrochlorides derived from γ- (1b) (5 g) in ethanol was stirred with 10% palladium–charcoal (0·5 g) and hydrogen at room temperature and pressure. When gas absorption ceased the mixture was filtered and the filtrate evaporated. The ^{1}H n.m.r. spectrum of the residue displayed signals characteristic of β- (1a) hydrochloride together with those of a novel isomer (the major component from integration data). Fractional crystallization of the mixture from ethanol gave δ- (1a) *hydrochloride* (1·5 g), m.p. 265—267° (Found: C, 70·0; H, 9·05; N, 6·15%).

We thank the National and Medical Research Councils of Canada for financial support and Dr. E. L. May, National Institute of Health (U.S.A.), for the analgesic assay.

[15] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965.

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