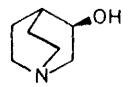
Optical Rotatory Dispersion and Absolute Configuration. Part 32.[1] Circular Dichroism and Conformation of 3-Hydroxypiperidines

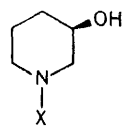
By **Bjorn Ringdahl, Ulrich F. W. Ohnsorge,** and **J. Cymerman Craig,*** Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143, U.S.A.

C.d. measurements show that a simple piperidine helicity rule gives the correct sign of the Cotton effect for the conformationally rigid (*R*)-quinuclidin-3-ol. Application of the same helicity rule also supports logical conformations and configurational assignments for (*R*)-1-methylpiperidin-3-ol and (*R*)-piperidin-3-ol.

ESTERS of the cyclic aminoalcohols quinuclidin-3-ol (1) and 1-methylpiperidin-3-ol (2) possess marked cholinergic or anticholinergic properties,[2] and the enantiomers of such esters usually differ widely in pharmacological potency.[2-5] The relationship between configuration, conformation and biological activity in this series is therefore of considerable interest. Earlier observations on the c.d. of 2-substituted piperidines [6] revealed a sign



(*R*)-(−)-(1)



(*R*)-(+)-(2) X = CH_3

(*R*)-(+)-(3) X = H

reversal of the c.d. maximum on *N*-methylation, explained by the different orientation of the nitrogen lone pair with regard to the 2-substituent in the secondary and tertiary amines. Moreover, a simple helicity rule could be deduced [6] linking the sign of the observed Cotton effect (C.e.) to the screw sense of the helicity between the nitrogen lone pair and the 2-substituent, positive helicity (right-handed screw) giving a negative C.e. and *vice versa*.†[,7,8] The possibility of using c.d. as a probe for the conformational preference of the 3-hydroxypiperidine system in a hydroxylic solvent is therefore of interest, and we now report c.d. measurements on (−)-(1), (+)-(2), and (+)-piperidin-3-ol (3) in 95% ethanol.

The absolute configuration of (−)-(1), resolved with tartaric acid,[9] is known to be *R* from *X*-ray diffraction studies of both the acetate methiodide [10] and the benzilate hydrobromide.[5] The secondary amine (3) has been resolved using 4-chlorotartranilic acid.[4,11] We resolved (3) by crystallization of its (+)-camphor-10-sulphonate (m.p. 134—135 °C) from which (+)-(3) was liberated by continuous ether extraction. The tertiary amine (+)-(2) was obtained from (+)-(3) by methylation with formaldehyde–formic acid.[4] The absolute configuration of (+)-(3) and thus of (+)-(2) is known to be *R* from the stereospecific synthesis [12] of (*S*)-(−)-(3) from mannitol.

Saturated aliphatic and cyclic amines generally have a rather broad absorption band in the 200 nm region, which disappears in acid solution and therefore involves the non-bonding electrons of nitrogen.[13,14] It is generally assigned either to an $n \longrightarrow \sigma^*$ transition [14] or to a Rydberg transition.[15] In nonpolar solvents the band undergoes a red shift; thus *N*-methylpiperidine and quinolizidine showed $\lambda_{max.}$ at 213 and 215 nm, respectively, in ether solution.[16]

The c.d. maxima of compounds (1)—(3) in 95% ethanol were found in the 190—210 nm region (Table) and disappeared completely in acid solution, as expected for a transition involving the lone pair electrons of nitrogen. For the OH group, the expected region of absorption is well below 190 nm, and it has been demonstrated earlier [17-20] that the OH function does not interfere in the assignment of the absolute configuration of the chiral centres in amino alcohols.

Physical and chiroptical data for compounds (1)—(3)

Compound	M.p. or b.p. (°C) [*p*/mmHg]	$[\alpha]_D^{20}$ (°) (*c*, 95% EtOH)	C.d. [θ] [a] (λ/nm)
(*R*)-(1) [c]	223.5—224.5 [b]	−1.7 (0.9)	+1 360 (208)
(*R*)-(2) [d]	78—80 [15]	+5.4 (2.1)	+1 615 (195)
(*R*)-(3) [e]	91—92 [b]	+8.9 (2.2)	−820 (203)

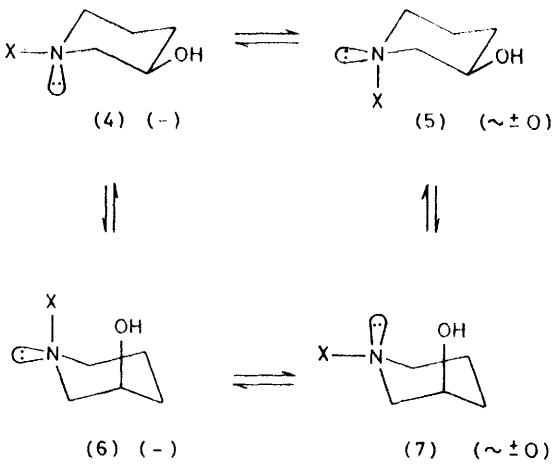
[a] Molecular ellipticity in 95% ethanol at 20 °C. [b] Recrystallized from acetone–ether. [c] Lit.,[9] m.p. 223.5—224.5 °C, $[\alpha]_D^{22}$ −45.7° (*c* 2.9, 1M-HCl). [d] Lit.,[4] b.p. 84—86 °C at 18 mmHg, $[\alpha]_D^{25}$ + 5.9° (*c* 1.2, MeOH). [e] Lit.,[4] m.p. 92—93 °C, $[\alpha]_D^{25}$ + 10.5° (*c* 2.3, MeOH).

For quinuclidine, the lone pair electrons are known from ^{13}C n.m.r. evidence to occupy the equatorial position.[21] In the similarly conformationally fixed aminoalcohol (*R*)-(1), the screw sense of the helicity may be deduced using Brewster's method [7] of 'end-to-end projection.' Tracing along the symmetry axis of the equatorial nitrogen lone pair lobe, the nitrogen–chiral carbon connecting line, and the C–O bond, the sign of the helicity between the nitrogen lone pair and the C–O bond is negative. Since the observed C.e. is positive, the piperidine helicity rule described earlier [6] appears to apply also to the 3-substituted compounds, *i.e.* a clockwise screw sense of the helicity indicates a negative C.e. and *vice versa*.[7,8]

As in the case of 2-substituted piperidines, *N*-methylation of piperidin-3-ol (*R*)-(3) reversed the sign of the

† In a previous publication [6] positive helicity was associated with a positive C.e. and *vice versa*. However, using Brewster's method [7] of end-to-end projection for deducing the helicity between a chain of bonds, the relationship between helicity and sign of the C.e. should appropriately be as stated in the text. We thank Professor Brewster for bringing this to our attention.[8]

C.e. (Table). In the 2-substituted compounds, this sign reversal was explained [6] by the change in orientation of the nitrogen lone pair. The piperidine system is known to exist [22] in a cyclohexane chair conformation in which both ring-inversion and nitrogen inversion may occur. Thus conformers (4)—(7) may be depicted for (*R*)-(2) and (*R*)-(3) (Scheme); with each of these is shown the sign of the helicity between the nitrogen lone pair and the C–O bond.



SCHEME

Since it is well documented [22,23] that the methyl group in *N*-methylpiperidines has a decided preference for the equatorial position with an axial lone pair of electrons, only conformers (4) and (7) (X = CH_3) need be considered in the conformational equilibrium of (*R*)-(2). In (4) the sign of the helicity is negative while in (7) the lone pair orbital and the C–O bond are essentially coplanar. Thus the observed positive C.e. for (*R*)-(2), of similar magnitude to that of (*R*)-(1), suggests a predominance of conformer (4) with equatorially oriented methyl and OH groups and indicates that stabilization of conformer (7) by intramolecular OH · · · N hydrogen bonding is less important in alcohol solution than in CCl_4 where (2) exists partially (57%) as (7) as shown by i.r. studies.[24]

The finding [4] that esters of (1) on *N*-methylation had greatly decreased biological activity, approximately equal to that shown by esters of (2) or their *N*-methylated derivatives, supports the conclusion [4] that an equatorially oriented *N*-methyl group is responsible for the distherapeutic effect and also lends support for the presence of such a methyl group in the predominant conformer of (2).

The comparatively weak negative C.e. observed for (*R*)-(3) (Table) excludes a predominance of conformers (4) and (6) (X = H) with a negative helicity between the nitrogen lone pair and the C–O bond. It was previously found [6] that the c.d. maximum of 2-alkylpiperidines with an equatorial electron pair is at higher wavelength (205 nm) than that of 1,2-dialkylpiperidines with an axial electron pair (<200 nm). Therefore the position of the C.e. of (*R*)-(3) at 203 nm (Table) supports the conclusion that, as in the 2-substituted piperidines, conformer (5) is the most abundant in the equilibrium mixture of (*R*)-(3). Stabilization of conformer (7) by intramolecular OH · · · N bonding would again be much less likely in the polar solvent used than in CCl_4 solution, where i.r. studies showed (3) to exist to 45% as (7) and 14% in the conformation (5).[24]

EXPERIMENTAL

C.d. spectra were measured using a Jouan Mark II dichrograph and a JASCO J-500 A spectropolarimeter at 20 °C.

Resolution of Piperidin-3-ol (3).—A solution of piperidin-3-ol (10.1 g, 0.1 mol) and (+)-camphor-10-sulphonic acid (11.6 g, 0.05 mol) in ethanol (25 ml) was treated with dry ether to turbidity and allowed to stand at room temperature. Crystals (12 g) were separated by filtration and recrystallized from ethanol (3×) to constant m.p. and rotation, m.p. 134—135 °C; $[\alpha]_D^{20}$ +23.0° (*c* 1.5, 50% ethanol) (Found: C, 54.15; H, 7.75; N, 4.25. Calc. for $C_{15}H_{27}NO_5S$: C, 54.05; H, 8.1; N, 4.2%). The free base was obtained by continuous ether extraction and after recrystallization from acetone–ether had m.p. 91—92 °C, $[\alpha]_D^{20}$ +8.9° (*c* 2.2, 95% ethanol).

[0/1656 *Received*, 30*th October*, 1980]

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