SYNTHESIS AND STEREOCHEMISTRY OF (−)-(10s)-6,10-DIMETHYL-6-AZA-$\Delta^{1,9}$-OCTAHYDROQUINOLINE

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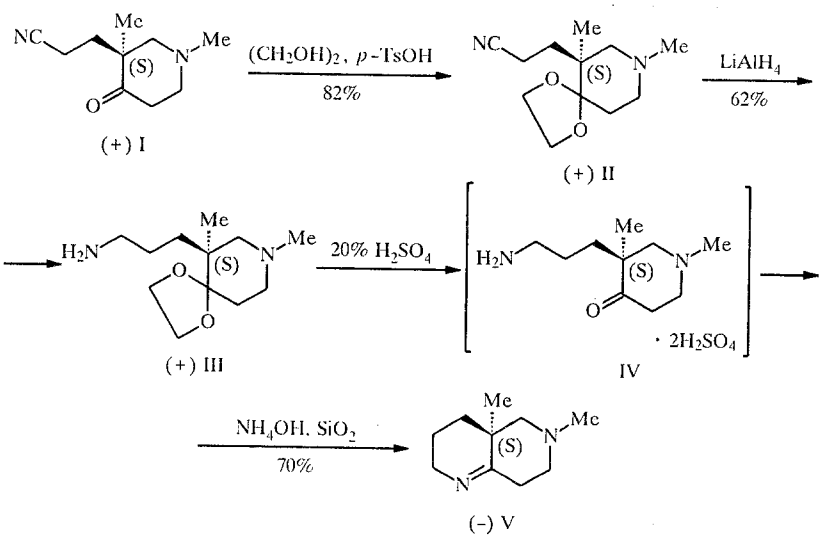
Enantiomerically pure (−)-(10S)-6,10-dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline, which has been obtained from optically pure (3S)-1,3-dimethyl-3-(2-cyanoethyl)piperid-4-one, is a chiral intermediate for the preparation of novel biologically active compounds and an analog of piperidine and decahydroquinoline alkaloids. The chiroptical properties of the synthesized 6-azaoctahydroquinoline are examined.

As part of systematic studies on chiral derivatives of piperidine based on the 3,3-disubstituted piperidin-4-one I with 100% optical purity [1], we carried out the synthesis of enantiomerically pure (−)-(10S)-6,10-dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline (V), which is an aza analog of *Scytantus acutus* Meyen alkaloids and may be regarded as a promising synthon for the preparation of a number of novel biologically active compounds.

Reaction of enatiomerically pure (+)-(3S)-1,3-dimethyl-3-(2-cyanoethyl)piperidin-4-one (I) [1] with ethylene glycol resulted in formation of the (+)-ethyleneketal II. On reduction of the nitrole group of the latter with excess lithium aluminum hydride in absolute ether, the (+)-ethyleneketal III was obtained in 63% yield. Removal of the ketal protective group resulted in the formation of an intermediate ketoamine disulfate (IV), which on reaction with aqueous ammonia immediately underwent cyclization to give the octahydroquinoline V.



The steric structure of the enatiomerically pure (−)-6-azaoctahydroquinoline V was established from the ^1H and ^{13}C NMR spectroscopic data using the INADEQUATE method. The small absolute values of the geminal spin−spin coupling constants of the methylene protons on the $C_{(5)}$ and $C_{(7)}$ atoms (11.04 and 10.80 Hz, Table 2), the high value of the long-range

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TABLE 1. ^1H NMR Chemical Shifts of (−)-(10S)-6,10-dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline (V) (δ, ppm $CDCl_3$, internal stand. TMS, 25°C)

2a	2e	3a	3e	4a	4e	5a	5e	7a	7e	8a	8e	10-CH_3	N-CH_3
3,32	3,54	1,64	1,54	1,34	1,45	1,76	2,53	1,95	2,94	2,62	2,01	1,26	2,20

Table 2. Spin−Spin Coupling Constants of Protons in (−)-(10S)-6,10-Dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline (V) (Hz, 25°C, $CDCl_3$)

Geminal						Long-range			
2a2e	3a3e	4a4e	5a5e	7a7e	8a8e	2e4e	5e7e	5a-10-CH_3	4a-10-CH_3
-17,29	-13,44	-12,81	-11,04	-10,80	-13,70	1,46	2,50	0,68	0,68

Vicinal									
2e3e	2e3a	2a3e	2a3a	3a4e	3a4a	8e7e	8e7a	8a7e	8a7a
2,76	5,00	5,13	10,40	3,54	12,40	1,90	3,28	6,09	13,10

$^4J_{(H(5e),H(73))}$ coupling constants (2.50 Hz, Table 2), conforming to the "W" rule [2], and the large difference between the chemical shifts of the $C_{(5)}$ protons (0.77 ppm) and the $C_{(7)}$ protons (0.99 ppm) (Table 1) provide confirmation that piperidine ring A exists in a chair conformation with an equatorial orientation of the substitutent on the nitrogen atom. In turn, the high trans-diaxial $^3J_{(H(2a),H(3a))}$ and $^3J_{(H(3a),H(4a))}$ coupling constants (10.40 and 12.40 Hz, Table 2), in accordance with the Karplus relationship [3], provide evidence that ring B, containing an endocyclic C−N double bond, has a similar conformation.

The high values of the long-range $^4J_{(H(4),10\text{-}CH_3}$, $= {}^4J_{(H(5),10\text{-}CH_3}$, coupling constants (0.68 Hz, Table 2) provide an indication of the axial orientation of the 10-CH_3 group relative to ring A* in the (−)-octahydroquinoline V. By comparing the direct $^1J_{(C(10),C(10\text{-}CH_3))}$ (34.4 Hz) and $^1J_{(C(10),C(4)}$, (35.4 Hz) coupling constants, taking into account the stereospecificity of these coupling constants in relation to the unshared electron pair of the nitrogen atom in imines ($^1J_{(C,C(ax))}$, $^1J_{(C,C(eq))}$) [4], it may also be definitely concluded that the methyl group on the $C_{(10)}$ atom has an axial orientation. Thus, the enantiomerically pure compound V exists in the conformation shown in Fig. 1.

The asymmetric $C_{(10)}$ center has an (S) configuration, since none of the chemical reactions described above affect the quaternary carbon atom at the 3-position of the piperidine ring in the initial (3S)-1,3-dimethyl-3-(2-cyanoethyl)piperidin-4-one.

The chiroptical properties of (−)-6-azaoctahydroquinoline V are next examined. In the circular dichroism (CD) curve in heptane, a negative Cotton effect occurs at 250 nm with a molecular ellipticity of [θ] −625° and a positive Cotton effect at 282 nm with [θ] +86° (Fig. 2). In methanol the code of the CD curve does not change but there is a hypsochromic shift of the maxima of both bands ($\Delta\lambda_{max} \sim 10$ nm). On protonation of a methanol solution of (−)-6-azaoctahydroquinoline V with trifluoroacetic acid, both Cotton effects disappear completely. Hence, both the longer- and shorter-wavelength Cotton effects depend on electronic transitions of the unshared electron pair of the nitrogen atoms.

According to the literature data, the negative shorter-wavelength Cotton effect at 250 nm may be attributed to the n → π^* transition of the azomethine chromophore [5, 6]. From this rule, which is based on several cases [7, 8], it may be stated that the negative Cotton effect in the case of the cyclic (−)-imine V results from ring B, which contains the azomethine chromophore, existing in the conformation shown in Fig. 3. We have not established the nature of the longer-wavelength Cotton effect at 282 nm.

Thus, the conclusions about the steric structure of (−)-6-azaoctahydroquinoline V based on analysis of the ^1H and ^{13}C NMR spectroscopic data and from examination of the circular dichroism spectra are in agreement.

The bicyclic imine V may have considerable practical significance since it can be used as a starting material for the preparation of novel chiral synthons in good yield and under mild conditions, the latter being used for the synthesis of biologically active compounds with a specific configuration of the asymmetric center.

*Note that the methyl group on $C_{(10)}$ has a pseudoaxial orientation relative to ring B.

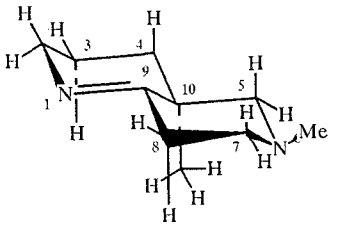

Fig. 1. Conformation of octahydroquinoline V.

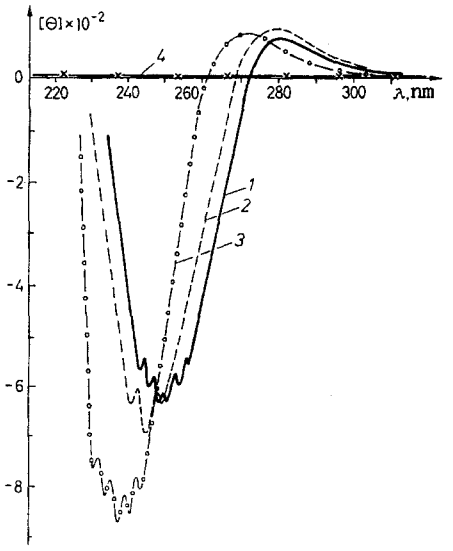

Fig. 2. CD curves of (−)-(10S)-6,10-dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline V: 1) in heptane; 2) in methylene dichloride; 3) in methanol; 4) in methanol + CF_3COOH.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^1H NMR spectra were recorded on Tesla-60 and Bruker WM-400 spectrometers at room temperature in $CDCl_3$ solutions with TMS as internal standard. Mass spectra were recorded on an MKh-1321 spectrometer with direct introduction of sample into the ion source at a vaporization temperature of 150-200°C and an ionization energy of 70 eV. Circular dichroism curves were recorded on a Jobin Yuon Dichrographe 111 Roussel-Joan spectropolarimeter.

The elemental analysis data for C, H, and N corresponded to the calculated values.

(+)-(3S)=1,3-Dimethyl-3-(2-cyanoethyl)piperidin-4-one Ethyleneketal (II, $C_{18}H_{23}N_5O_9$). A mixture of 2.60 g (14.4 mmole) of (+)-(3S)-1,3-dimethyl-3-(2-cyanoethyl)piperidin-4-one (I) ($[\alpha]_D^{24}$ + 31.0°, c 3.44, benzene), 1.80 g (28.8 mmole) of ethylene glycol, and 3.61 g (18.6 mmole) of p-toluenesulfonic acid in 40 ml of absolute benzene was refluxed with a Dean−Stark adapter until the theoretical quantity of water had been extracted. The reaction mixture was cooled to room temperature, neutralized with a saturated solution of sodium carbonate, and extracted with methylene dichloride (4 × 10 ml). The combined organic extracts were dried over $MgSO_4$. The solvent was elvaporated off and the residue (3.22 g, oil) was chromatographed on a column with Silpearl support under HPLC conditions [benzene−acetone (7:1) eluent]. Yield 2.61 g (82%) of (+)-(3S)-1,3-dimethyl-[3-(2-cyanoethyl)piperidin-4-one ethyleneketal (II), R_f 0.45 [Silufol, benzene−acetone (2:1)], $[\alpha]_D^{24}$ +7.4° (c 4.06, benzene). IR spectrum (thin film): 2225 (C≡N), 1060 cm^{-1} (C−O), PMR spectrum ($CDCl_3$): 0.95 (3H, s, 3-CH_3); 2.21 (3H, s, N−CH_3); 1.35-2.71 (10H, m); 3.87 ppm (4H, s, CH_2CH_2). Found: M^+ 224. Picrate: mp 205-206°C (ethanol).

TABLE 3. ^{13}C NMR Chemical Shifts of (−)-(10S)-6,10-dimethyl-aza-6-$\Delta^{1,9}$-octahydroquinoline (V) (δ, ppm $CDCl_3$, 25°C)

C_2	C_3	C_4	C_5	C_7	C_8	C_9	C_{10}	N—CH_3	10-CH3
35,47	19,11	33,25	69,44	57,27	49,67	171,56	37,29	45,64	24,35

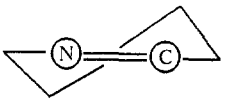

Fig. 3. Conformation giving rise to a negative Cotton effect from to the n-π^* transition of the azomethine chromophore in cyclic imines.

(+)-(3S)-1,3-Dimethyl-3-(3-aminopropyl)piperidin-4-one Ethyleneketal (III). To a suspension of 0.92 g (23.7 mmole) of lithium aluminum hydride in 50 ml of absolute ether with vigorous stirring was added dropwise a solution of 2.61 g (11.8 mmole) of (+)-(3S)-1,3-dimethyl-3-(2-cyanoethyl)piperidin-4-one ethyleneketal (II) in 30 ml of absolute ether. The reaction mixture was refluxed for 15 h in an atmosphere of argon, then cooled to 0°C, and carefully separated with 40 ml of aqueous ether and 10 ml of water until a gel-like precipitate had formed. The ether layer was decanted and the precipitate was washed twice with ether. The combined ether extracts were dried over Na_2SO_4. The ether was distilled off to give 1.74 g (63%) of (+)-(3S)-1,3-dimethyl-3-(3-aminopropyl)piperidin-4-one ethyleneketal (III), R_f 0.35 [Silufol, benzene–acetone–chloroform, saturated with ammonia (2:1:1), $[\alpha]_D^{24}$ +1.2° (c 3.30, benzene). IR spectrum (thin film): 3330 (NH_2), 1060 cm^{-1} (C–O). PMR spectrum ($CDCl_3$): 0.95 (3H, s, 3-CH_3), 2.17 (3H, s, N–CH_3), 1.00-2.78 (14H, m), 3.91 (4H, s, CH_2CH_2). Found: M^+ 228. Calculated: M^+ 228.

(−)-(10S)-6,10-Dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline (V, $C_{22}H_{24}N_8O_{14}$). To a solution of 1.74 g (7.4 mmole) of (+)-(3S)-1,3-dimethyl-3-(3-aminopropyl)piperidin-4-one ethyleneketal (III) in 15 ml of dioxane was added 2.26 g (22.3 mmole) of 20% sulfuric acid. The reaction mixture was heated for 2 h on a water bath (50°C), and it was then concentrated down to half its volume. The acid solution was extracted with chloroform (5 × 7 ml), cooled to 0°C, and neutralized with aqueous ammonia solution. The solution was extracted with chloroform (5 × 15 ml). The solvent was removed and the residue (0.81 g) chromatographed with a support on a Chemapol 40/100μ column, with chloroform saturated with ammonia as eluent. After drying over Na_2SO_4 and removal of solvent, 0.86 g (70%) of (−)-(10S)-6,10-dimethyl-6-aza-$\Delta^{1,9}$-octahydroquinoline (V) was obtained, R_f 0.37 (Silufol, chloroform saturated with ammonia), $[\alpha]_D^{24}$ −122.9° (c 3.37, benzene). IR spectrum (thin film): 1660 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 1.26 (3H, s, 10-CH_3), 2.20 (3H, s, N–CH_3). Found: M^+ 166. Calculated: M^+ 166. Dipicrate: mp 218-219°C (ethanol).

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