Short Communication

The Absolute Configuration of Oxyphencyclimine, a Parasympatholytic Drug. Syntheses of Both Enantiomers

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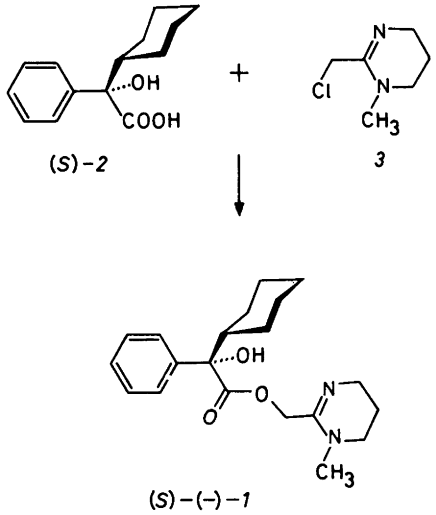
Oxyphencyclimine hydrochloride ((±)-1-methyl-1,4,5,6-tetrahydro-2-pyrimidylmethyl 2-cyclohexyl-2-hydroxy-2-phenylethanoate hydrochloride, (±)-*1*), is an anticholinergic agent with effects similar to those of atropine.[1] The drug is used in the racemic form and, to the best of our knowledge, the absolute configurations of its enantiomers have not previously been reported. Optical resolution of the racemic amine *1* employing L-(+)-mandelic acid, L-(+)-tartaric acid, (+)-camphor-10-sulfonic acid, or (+)-3-bromocamphor-8-sulfonic acid as resolving agents have failed; none of the salts crystallized. However, optical resolution of (±)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid ((±)-*2*) utilizing quinine and cinchonine was accomplished by Kuznetsov *et al.*[2] in 1962. The absolute configuration of the acid *2* was established in 1968 by Inch *et al.*[3] who synthesized both the (*S*)-(+)- and the (*R*)-(−)- enantiomers using D-arabinose as chiral starting material. The synthesis of (±)-oxyphencyclimine (*1*) by esterification of (±)-*2* with 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine (*3*) was reported in 1958–59.[4,5] The present communication describes the syntheses of (*S*)-(−)- and (*R*)-(+)-oxyphencyclimine hydrochloride using the acids (*S*)-(+)-*2* and (*R*)-(−)-*2* as building blocks.

Essentially optically pure acid (*S*)-(+)-*2* was obtained on resolution of racemic acid *2* employing quinine as resolving agent.[2] (*R*)-(−)-*2* of lower optical purity was isolated from the mother liquors. The optical activities of the two preparations indicated enantiomeric ratios of (*S*):(*R*) = 94:6, and 22:78, respectively. The cinchonine salt of the (*R*) isomer failed to crystallize preventing further purification of this enantiomer. The partially purified acids (*S*)-*2* and (*R*)-*2* were reacted[4,5] with the chloride *3* furnishing optically active oxyphencyclimine hydrochlorides thus estab-



Scheme 1. Synthesis of (*S*)-(−)-oxyphencyclimine (*1*).

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lishing the absolute configurations of the (−) and the (+) enantiomer as (*S*) and (*R*), respectively (Scheme 1). On examination of the optical purities of the products employing (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol)[6,7] as chiral solvating agent, the (*S*) isomer was found to be optically pure (cf. Fig. 1c), whereas the enantiomeric ratio of the other product was found to be (*R*):(*S*) = 94:6. Disappearance of enantiomeric impurities, and the fact that the IR spectra (KBr) of the optically pure products and that of racemic *1* were perfectly superimposable, indicate that oxyphencyclimine hydrochloride (*1*) crystallizes as a conglomerate from ethanol. Recrystallization of the latter product yielded optically pure (*R*)-oxyphencyclimine hydrochloride (cf. Fig. 1d). Conglomerates are relatively rare; Jacques *et al.*[8,9] have estimated their frequency to be less than 10 % of the crystalline racemates.

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Optical rotations, IR spectra, and mass spectra were recorded on Carl Zeiss, Perkin Elmer 241, Perkin Elmer 597, and Jeol JMS-DX303 instruments, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol JNM GX 270 instrument. TMS, or the central solvent peak of CD_3OD at δ 49.04 (^{13}C) was used as internal references.

(±)-*Oxyphencyclimine hydrochloride* (1). Authentic material was obtained from Pfizer A/S, Oslo, Norway. ^{1}H NMR ($CDCl_3$): δ 1–1.8 (10H, m), 2.0 (2H, m), 2.15 (1H, m), 3.09 (3H, s), 3.51 (4H, m), 5.08 (1H, d, J 15.4 Hz), 5.13 (1H, d, J 15.4 Hz), 6.3 (1H, m), 7.2–7.35 (3H, m; coinciding with solvent peak), 7.60 (2H, d, J 6.6 Hz); ^{13}C NMR (CD_3OD): δ 174.39 (s), 159.50 (s), 141.91 (s), 129.35 (d), 128.92 (d), 126.88 (d), 83.18 (s), 61.51 (t), 49.58 (t), 47.36 (d), 39.47 (t), 39.24 (q), 28.90, 27.58, 27.41, 26.74, 19.60 (t). The multiplicities of some of the signals were not obvious from the off-resonance proton-decoupled spectrum. IR (KBr): 3260 (s), 2940 (s), 1739 (s), 1660 (s), 1450 (m), 1321 (s), 1228 (s), 1202 (s), 705 (m) cm^{-1}.

Enantiomeric composition. Addition of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol)[6,7] to the ^{1}H NMR solution ($CDCl_3$; nonequivalence was not obtained in CD_3OD) of (±)-oxyphencyclimine hydrochloride (*1*) induced spectral nonequivalence of the diastereomeric solvates. A 2:1 molar ratio of chiral solvating agent to substrate effected completely resolved singlets for the N-CH_3 groups (cf. Fig. 1a and 1b). Integration permitted reliable quantification of the enantiomeric composition. (*R*)-solvate: δ 2.65 (N-CH_3), 4.31 and 4.73 (-O-CH_2-, AB-system); (*S*)-solvate: δ 2.76 (N-CH_3), 4.74 (-O-CH_2-, s). The (*R*/*S*) assignments follow from the addition of racemic oxyphencyclimine hydrochloride (*1*) to the ^{1}H NMR solution of (*S*)-(−)-oxyphencyclimine hydrochloride and Pirkle's alcohol.

Optical resolution of 2-cyclohexyl-2-hydroxy-2-phenylethanoic acid (2). Racemic *2* was prepared either by alkaline hydrolysis of (±)-oxyphencyclimine (*1*), or by reacting cyclohexylmagnesium bromide with ethyl benzoylmethanoate as described by Smith *et al.*[10] and Funcke *et al.*[11] Fractional crystallization of the quinine salts of racemic *2*, as has been reported by Kuznetsov and Bobysheva,[2] furnished (*S*)-(+)-*2* on decomposition of the quinine salt. $[\alpha]_D^{23}$ +20.67° (*c* 1.7; EtOH); lit.[2] $[\alpha]_D^{20}$ +23.4° (*c* 5.43; EtOH); lit.[3] $[\alpha]_D$ +22.6° (*c* 1.4; EtOH).

Kuznetsov and Bobysheva[2] obtained (*R*)-(−)-*2* by fractional crystallization of the cinchonine salts of (±)-*2*. However, in our hands, these salts failed to crystallize. Partially purified (*R*)-(−)-*2* was prepared by further removal of (*S*)-(+)-*2* as its quinine salt from the combined mother liquors. After two crystallizations, acid *2* isolated from the final filtrate exhibited $[\alpha]_D^{19}$ −12.9° (*c* 2.5; EtOH); lit.[2] $[\alpha]_D^{20}$ −23.3° (*c* 5.45; EtOH); lit.[3] $[\alpha]_D$ −21.6° (*c* 1.7; EtOH).

(*S*)-(−)-*oxyphencyclimine hydrochloride* ((*S*)-(−)-*1*). A mixture of (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid (239 mg; 1.02 mmol) 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride (*3*; 195 mg; 1.08 mmol), triethylamine (103 mg; 1.02 mmol), and potassium iodide (12 mg; 0.07 mmol) in 2-propanol (6 ml) was refluxed for 6 h 15 min. The reaction mixture was diluted with water (50 ml), basified with 2 M NaOH to pH 10 and extracted twice with EtOAc. The solvent was removed and the residue acidified with HCl/EtOH. The solu-

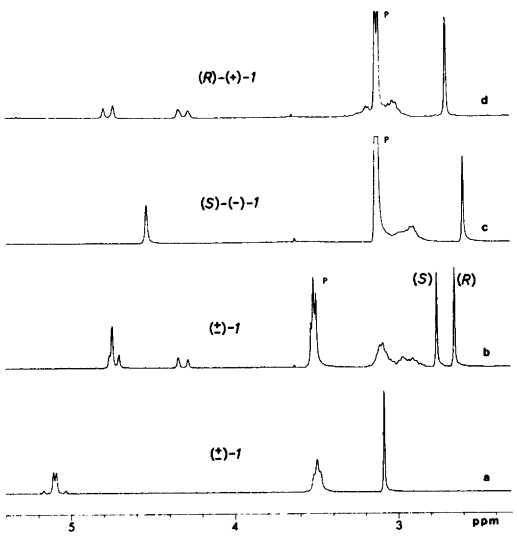

Fig. 1. Partial ^{1}H NMR spectra of oxyphencyclimine hydrochloride. a: (±)-*1*; b,c, and d: (±)-*1*, (*S*)-(−)-*1*, and (*R*)-(+)-*1*, respectively, in the presence of Pirkle's alcohol (P = OH group).

tion was evaporated to dryness and the remaining solid recrystallized from EtOH (5 ml). Yield: 271 mg (70 %); m.p. 229–230 °C (dec.); lit.[5] m.p. 231–232 °C (dec.) for the racemate; $[\alpha]_D^{20}$ −9.51 (*c* 2.2; MeOH). The ^{1}H NMR, ^{13}C NMR, and IR (KBr) spectra of (*S*)-(−)-*1* were indistinguishable from those of racemic *1*. The product appeared to be optically pure as judged from its ^{1}H NMR spectrum in the presence of Pirkle's alcohol (cf. Fig. 1c).

(R)-(+)-Oxyphencyclimine hydrochloride ((*R*)-(+)-*1*). (*R*)-(+)-*1* (231 mg; 77 %) was prepared from (*R*)-(−)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid (184 mg; 0.79 mmol; optical purity, see above), 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride (*3*; 143 mg; 0.79 mmol), and potassium iodide (13 mg; 0.08 mmol) in 2-propanol (4.5 ml) similarly to the procedure described above for the (*S*) isomer. Recrystallization thrice from EtOH and subsequent examination of the product by ^{1}H NMR in the presence of Pirkle's alcohol revealed the enantiomeric ratio (*R*):(*S*) = 94:6. An additional recrystallization furnished optically pure (*R*)-(+)-oxyphencyclimine ((*R*)-(+)-*1*); cf. Fig. 1d. M.p. 234–236 °C (dec.); $[\alpha]_D^{20}$ + 9.69° (*c* 2.1; MeOH). The ^{1}H NMR, ^{13}C NMR, and IR (KBr) spectra were virtually identical with those of racemic oxyphencyclimine hydrochloride (*1*).

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