Pharmaceutical Research, Vol. 5, No. 4, 1988

Report

Antimuscarinic Effects of (*R*)- and (*S*)-Oxyphencyclimine Hydrochloride

Lise Schjelderup,[1] Michael R. Kozlowski,[2] Albert Weissman,[3] and Arne J. Aasen[1,4]

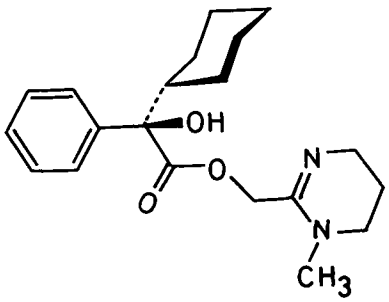
Received July 7, 1987; accepted November 4, 1987

The (*R*)-(+)- and (*S*)-(−)-enantiomers of the anticholinergic compound, oxyphencyclimine, were synthesized from (*R*)-(−)- and (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid, respectively. The potencies of the enantiomers were compared using a cholinergic receptor binding assay. The (*R*)-(+)-enantiomer inhibited binding 29 times more potently than the (*S*)-(−)-enantiomer.

KEY WORDS: Oxyphencyclimine; enantiomers; anticholinergic; antimuscarinic activity.

INTRODUCTION

Oxyphencyclimine hydrochloride [(±)-1-methyl-1,4,5,6 - tetrahydro - 2 - pyrimidylmethyl 2 - cyclohexyl - 2 - hydroxy-2-phenylethanoate hydrochloride] is an antimuscarinic agent used in racemic form in the treatment of gastrointestinal and genitourinary disorders (1). In the related anticholinergic drugs, procyclidine and trihexyphenidyl hydrochloride, as well as in a series of other substituted 1-cyclohexylbenzyl alcohols that possess anticholinergic activity, the (*R*)-enantiomers are more potent than the (*S*)-enantiomers (2–8). We have synthesized both the (*R*)- and the (*S*)-enantiomer of oxyphencyclimine (9), and their relative potencies are described here.



(R)-(+)-1

Scheme I

MATERIALS AND METHODS

Melting points were determined on a Reichert melting-point apparatus and are uncorrected. Optical rotations, mass spectra, and IR spectra were recorded on Perkin Elmer 241, Jeol JMS-DX303, and Perkin Elmer 597 instruments, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol GX 270 instrument using tetramethylsilane or the central solvent peak of CD_3OD at δ 49.04 (^{13}C) as internal references. ^{3}H-Quinuclidinyl benzilate (^{3}H-QNB; 30 Ci/mmol) was purchased from New England Nuclear and atropine sulfate was a gift from Merck and Co.

(S)-(−)-Oxyphencyclimine Hydrochloride [(S)-(−)-1]. A mixture of (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid [418 mg, 1.79 mmol, $[\alpha]_D^{23}$ 24.8° (*c* 4.1, ethanol)] which had been obtained by optical resolution of racemic acid employing quinine (10) as the resolving agent, triethylamine (180 mg, 1.78 mmol), 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride (323 mg, 1.79 mmol), and potassium iodide (7 mg, 0.004 mmol) in 10 ml of 2-propanol was refluxed for 5 hr, 20 min and subsequently stored at 5°C overnight. The crystalline residue (671 mg) was washed with cold 2-propanol and recrystallized twice from ethanol, furnishing (*S*)-(−)-oxyphencyclimine hydrochloride (405 mg, 60%). $[\alpha]_D^{22}$ −8.79° (*c* 1.87, methanol); for additional data, see Ref. 9. Detectable amounts of (*R*)-(+)-oxyphencyclimine were not revealed when (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol was added to the ^{1}H NMR solution according to the method of Pirkle *et al.* (11,12)

(R)-(+)-Oxyphencyclimine Hydrochloride [(R)-(+)-*1*]. (*R*)-(−)-2-Cyclohexyl-2-hydroxy-2-phenylethanoic acid [700 mg, 2.99 mmol, $[\alpha]_D^{23}$ −21.8° (*c* 4.3, ethanol)] which had been prepared by optical resolution of racemic acid using (−)-ephedrine as the resolving agent (2), triethylamine (302 mg, 2.99 mmol), 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride (541 mg, 2.99 mmol), and potassium iodide (25 mg, 0.15 mmol) were refluxed in 17 ml of 2-propanol for 5.5 hr. (*R*)-(+)-Oxyphencyclimine hydrochloride (668 mg, 59%) was isolated as described above for the (*S*)-enantiomer. $[\alpha]_D^{22}$ 8.95° (*c* 1.90, methanol); for further data, see Ref. 9.

Cholinergic Receptor Binding. Muscarinic receptor binding was measured using an adaption of previously de-

[1] Department of Chemistry, The Agricultural University of Norway, Box 30, N 1432 Ås-NLH, Norway.
[2] Bristol-Myers Company, Wallingford, Connecticut 06492.
[3] Pfizer Central Research, Groton, Connecticut 06340.
[4] To whom correspondence should be addressed.

0724-8741/88/0400-0236$06.00/0

Table I. Inhibition of ^{3}H-Quinuclidinyl Benzilate (^{3}H-QNB) Binding to Bovine Cortex

Compound	IC_{50} (n*M*)[a]
Atropine	0.67 ± 0.30
Scopolamine	1.03 ± 0.41
(*R*)-(+)-Oxyphencyclimine hydrochloride	25.8 ± 4.1
(*S*)-(−)-Oxyphencyclimine hydrochloride	737 ± 90

[a] Values are the mean ± SE of three determinations.

scribed techniques (13,14). Bovine cerebral cortex was homogenized in 50 m*M* Tris–acetate buffer (pH 7.4) using a polytron (setting 6, 30 sec). The homogenate was centrifuged (30.000*g*, 30 min), the pellet resuspended in fresh buffer, and the process repeated. Aliquots of 800 μl of the final homogenate were mixed with 100 μl of buffer containing ^{3}H-QNB, and 100 μl of buffer, or buffer containing a drug. The final ligand concentration was 0.1 n*M*, and the final tissue concentration was 10 mg wet wt/ml. The mixture was incubated at room temperature for 1 hr and then filtered. The radioactivity trapped on the filters was measured by scintillation counting. Nonspecific binding was defined as that occurring in the presence of a 1 μ*M* concentration of atropine.

RESULTS

Synthesis

The (*R*)-(+)- and (*S*)-(−)-enantiomers of oxyphencyclimine were synthesized using (*R*)-(−)- and (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid as the chiral synthon essentially as previously described (9) except for using (−)-ephedrine as the resolving agent for the (*R*)-enantiomer of the chiral synthon. The stereochemical purity of (*S*)-(−)-oxyphencyclimine hydrochloride was examined by the addition of a chiral solvating agent to the ^{1}H NMR solution according to the method of Pirkle *et al.* (11,12); the applicability of the method for oxyphencyclimine hydrochloride has been described in Ref. 9. Detectable amounts of (*R*)-(+)-oxyphencyclimine hydrochloride were not revealed. This fact, together with the nearly coinciding numerical values of rotations, suggests that the samples employed in the present study are of a high optical purity. Previously reported values are slightly higher (ca. 9.6° vs ca. 8.9° for the present samples), presumably because of differences in temperatures, concentrations, and instrumental conditions (different polarimeter). Oxyphencyclimine hydrochloride appears (9) to crystallize as a conglomerate from ethanol, eliminating the requirement of having a strictly pure chiral synthon, 2-cyclohexyl-2-hydroxy-2-phenylethanoic acid.

Biological Evaluation

The relative anticholinergic potencies of the enantiomers of oxyphencyclimine were inferred from their abilities to inhibit binding of the muscarinic ligand ^{3}H-QNB to bovine cortex (13,14). IC_{50} values of the muscarinic antagonists, atropine and scopolamine, determined by our assay (Table I) agreed with those reported in the literature (14) using a similar concentration of ^{3}H-QNB. Both enantiomers of oxyphencyclimine also inhibited muscarinic binding, although less potently than atropine or scopolamine. The (*R*)-(+)-enantiomer was 29 times more potent than the (*S*)-(−)-enantiomer.

DISCUSSION

The present results are consistent with earlier observations that in substituted 1-cyclohexylbenzyl alcohols with anticholinergic properties, the greater activity lies in the enantiomer with the (*R*)-configuration. Thus, the potencies of the (*R*)-enantiomers of procyclidine and trihexyphenidyl hydrochloride are 380 and 5.5 times, respectively, greater than those of the (*S*)-enantiomers (6,7). Furthermore, potency differences within this range have been reported for other substituted 1-cyclohexylbenzyl alcohols that exhibit anticholinergic activity (2–5). In the case of oxyphencyclimine, the (*R*)-(+)-enantiomer is 29 times more potent in inhibiting muscarinic receptor binding than the (*S*)-(−)-enantiomer.

REFERENCES

1. A. Osol, G. D. Chase, A. R. Genmaro, M. R. Gibson, C. B. Granberg, S. C. Harvey, R. E. King, A. N. Martin, E. A. Swinyard, and G. L. Zink. *Remington's Pharmaceutical Sciences,* 16th. ed., Mack, Easton, Pa., 1980.
2. R. B. Barlow, F. M. Franks, and J. D. M. Pearson. *J. Med. Chem.* 16:439–446 (1973).
3. R. W. Brimblecombe, D. M. Green, T. D. Inch, and P. B. J. Thompson. *J. Pharm. Pharmacol.* 23:745–757 (1971).
4. R. W. Brimblecombe, T. D. Inch, J. Wetherell, and N. Williams. *J. Pharm. Pharmacol.* 23:649–661 (1971).
5. B. W. J. Ellenbroek, R. J. F. Nivard, J. M. van Rossum, and E. J. Ariëns. *J. Pharm. Pharmacol.* 17:393–404 (1965).
6. R. Tacke, H. Linoh, D. Schomburg, L. Ernst, U. Moser, E. Mutschler, and G. Lambrecht. *Justus Liebigs Ann. Chem.* 242–250 (1986).
7. R. B. Barlow. *J. Pharm. Pharmacol.* 23:90–97 (1971).
8. L. Schjelderup, O. Harbitz, P. Groth, and A. J. Aasen. *Acta Chem. Scand.* B 41:356–361 (1987).
9. L. Schjelderup and A. J. Aasen. *Acta Chem. Scand.* B40:601–603 (1986).
10. S. G. Kuznetsov and Z. I. Bobysheva. *Zh. Obshch. Khim.* 32:3779–3783 (1962) (Engl., p. 3707).
11. W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin. *J. Org. Chem.* 43:384–387 (1977).
12. W. H. Pirkle and C. W. Boeder. *J. Org. Chem.* 42:3697–3700 (1977).
13. G. R. Luthin and B. B. Wolfe. *Mol. Pharmacol.* 26:164–169 (1984).
14. H. I. Yamamura and S. H. Snyder. *Proc. Natl. Acad. Sci. USA* 71:1725–1729 (1974).