filtrate and washings were concentrated under reduced pressure. The oily residue was crystallized from hexane to give 340 mg (71%), mp 71–73 °C. Anal. ($C_{16}H_{24}N_2O_2$) C, H, N. ^{1}H NMR δ 1.05 (s, 3 H), 1.07 (s, 3 H), 2.35 (s, 3 H), 2.73 (m, 2 H), 2.91 (m, 3 H), 4.86 (s, 3 H), 4.92 (s, 3 H), 6.76 (s, 1 H), 6.80 (s, 1 H), 6.93 (s, 1 H), 7.90 (br s, 1 H, ex with D_2O).

The following protocol was approved by the Research Committee. Five subjects took part in the screening of these materials. They ranged in age from 26–62 and all had physical examinations within the 6-month period prior to this study. All were found to be in excellent health. The subjects had prior study experience with a variety of psychopharmaceuticals.

The studies were carried out in a controlled, comfortable environment. Doses of the test compounds were chosen on the basis of the known effects of closely related materials, e.g., 5-methoxy-α-methyltryptamine, 0.03 mg/kg (effective dose in man) and psilocin, 0.13 mg/kg (effective dose in man).[40,41] All experiments were conducted in the "double conscious" technique of Alles;[42] i.e., the subjects were aware of which drug they were taking and at what dosage level. Discussion followed each session and comments of the partipicants were recorded. All substances were administered po. Test sessions were conducted at 7–10-day intervals that assured the absence of tolerance or cross-tolerance. A rough dose–response curve for each compound was established by increasing incremental doses until a threshold level was reached. Dose regimen began at 0.003 mg/kg and increased by increments of 0.005 mg/kg. Thereafter dosage was increased by 0.03 mg/kg (2.25 mg/75 kg subject) per session at the subject's discretion. The effective dose was established when all subjects agreed that higher doses did not add significantly to the character of the experience. Table I represents trials conducted at the effective dose for each substance. (An effective response for **5–8** could not be obtained with the doses employed.)

Acknowledgment. We thank Linda Repke and Joan Caroon for their valuable discussions concerning this work.

Registry No. 1, 96096-52-5; **2**, 77872-43-6; **3**, 96096-53-6; **4**, 96096-54-7; **4** free base, 96096-55-8; **5**, 96096-56-9; **6**, 96096-57-0; **7**, 96096-58-1; **8**, 96096-59-2; **9d**, 3189-22-8; **10a**, 96096-60-5; **10b**, 68935-49-9; **10c**, 96096-61-6; **10d**, 96096-62-7; **11d**, 2436-04-6; **13a**, 96096-64-9; **13b**, 96096-65-0; **13c**, 96096-66-1; **13d**, 96096-67-2; **14**, 38750-13-9; **17**, 96096-63-8; β-pyrrolidino-2-nitro-3-methoxystyrene, 96096-68-3; 2-nitro-3-methoxytoluene, 5345-42-6; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; hydrazine, 302-01-2; 2-nitroethyl acetate, 18942-89-7; benzyl chloroformate, 501-53-1; 5,6-dimethoxyindole, 14430-23-0; oxalyl chloride, 79-37-8; *N*-isopropylmethylamine, 4747-21-1.

(40) Kantor, R. E.; Dudlettes, S. D; Shulgin, A. T. *Biol. Psychiatry* **1980**, *15*, 349.
(41) Hofmann, A. *Bull. Nar.* **1971**, *23*, 3.
(42) Alles, G. A. In "Neuropharmacology"; Abramson, H. A., Ed.; Josiah Macy, Jr. Foundation: New York, 1957; pp 181–268.

New Chiral and Isomeric Cyclopropyl Ketoxime Propanolamine Derivatives with Potent β-Adrenergic Blocking Properties

Mohamed Bouzoubaa,[†] Gérard Leclerc,*[†] Suman Rakhit,[†,§] and Guy Andermann[‡]

Institut de Pharmacologie, Département de Pharmacochimie (ERA 142 CNRS, U.206 INSERM), 67000 Strasbourg, and Laboratoires P.O.S., 68240 Kaysersberg, France. *Received May 15, 1984*

The synthesis of *R*-(+) and *S*-(−) isomers of *O*-[3-(*tert*-butylamino)-2-hydroxypropyl] cyclopropyl methyl ketone oxime (falintolol) is described. The syn and anti isomers of falintolol were obtained in two different ways from cyclopropyl methyl ketoxime or from falintolol. For comparison purposes, the enantiomers of the dicyclopropyl ketone oxime derivatives were also prepared. Structure–activity relationships are described.

O-[3-(*tert*-Butylamino)-2-hydroxypropyl] cyclopropyl methyl ketone oxime (falintolol) is a new β-adrenergic blocking agent synthesized by our group.[1] It has been found useful in the treatment of glaucoma and is at present under clinical trial.[2,3] This molecule is characterized by the presence of an oxime function and exists as a mixture of syn and anti isomers. In view of the potent activity of falintolol and our continued interest in synthesizing the enantiomers in this series of agents,[4] the syn and anti isomers of falintolol, their corresponding enantiomers, and some related substances were prepared in order to gain further insight into the structural requirements of the β-adrenergic receptor. In this paper we present the results of that study.

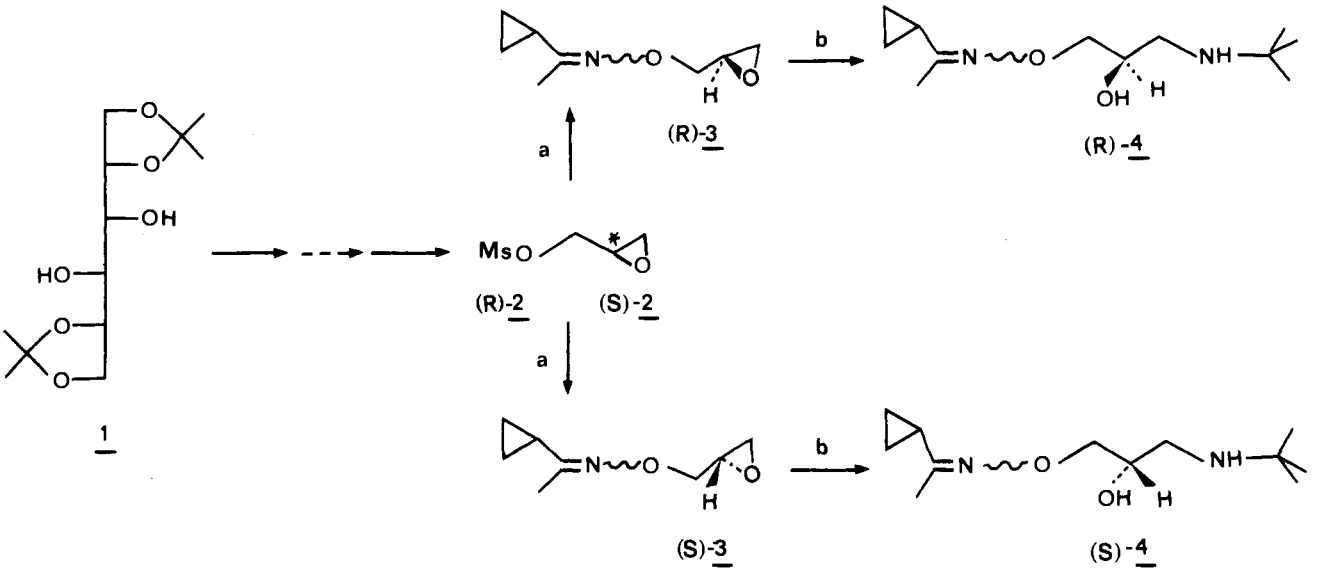
Chemistry. The stereospecific synthesis of 3-(mesyloxy)-1,2-epoxypropane [(*S*)-**2** and (*R*)-**2**] was carried out as described by Baldwin et al.[5] and more recently by Leclerc et al.[4] (Scheme I). The mesylate (*S*)-**2** or (*R*)-**2** was reacted with the sodium salt of the cyclopropyl methyl ketone oxime **5** in THF, giving the enantiomeric epoxides (*S*)-**3** and (*R*)-**3**, respectively. Treating (*S*)-**3** and (*R*)-**3** with excess *t*-BuNH$_2$ gave (*S*)-**4** and (*R*)-**4**, respectively. The action of hydroxylamine on cyclopropyl methyl ketone under basic conditions[6] (AcONa or aqueous NaOH) gave a mixture of anti and syn oxime derivatives in a ratio of ca. 7:3 as analyzed by ^{1}H NMR. The major anti isomer **5** was separated in pure form by recrystallizations from petroleum ether. The anti configuration of **5** was proved by the 0.15–0.20-ppm deshielding of the methyl protons by the hydroxyl group in the NMR spectra.[7,8] The Beckmann rearrangement of *anti*-**5** carried out with the method of Graig and Naik[9] gave the cyclopropylacetamide,[10] which confirmed this anti conformation. Furthermore, melting point and ^{1}H NMR and MS spectra

[†] Département de Pharmacochimie.
[‡] Laboratoires P.O.S.
[§] Present address: Biomega Inc., 1 Complexe Desjardins, Montreal H5B 1B3, Canada.

(1) Bouzoubaa, M.; Leclerc, G.; Decker, N.; Andermann, G.; Schwartz, J. *J. Med. Chem.* **1984**, *27*, 1291.
(2) Leclerc, G.; Bouzoubaa, M.; Andermann, G. Fr. Patent 8 202 740, 1982.
(3) Himber, J.; Andermann, G.; Bouzoubaa, M.; Leclerc, G., unpublished results.
(4) Leclerc, G.; Amlaiky, N.; Rouot, B. *Eur. J. Med. Chem.* **1982**, *17*, 69.
(5) Baldwin, J. J.; Raab, A. W.; Meuster, K.; Arisson, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.
(6) Vogel, A. I., Ed. "Practical Organic Chemistry"; Longmans: London, 1967; p 343.
(7) Huitric, A. C.; Roll, D. B.; Deber, J. R. *J. Am. Chem. Soc.* **1967**, *32*, 1661.
(8) Karabastos, G. J.; Hsi *Tetrahedron* **1967**, *23*, 1079.
(9) Graig, J. C.; Naik, A. R. *J. Am. Chem. Soc.* **1962**, *84*, 3410.
(10) Paquette, L. A.; Malpass, J. R.; Krow, G. R. *J. Am. Chem. Soc.* **1970**, *92*, 1980.

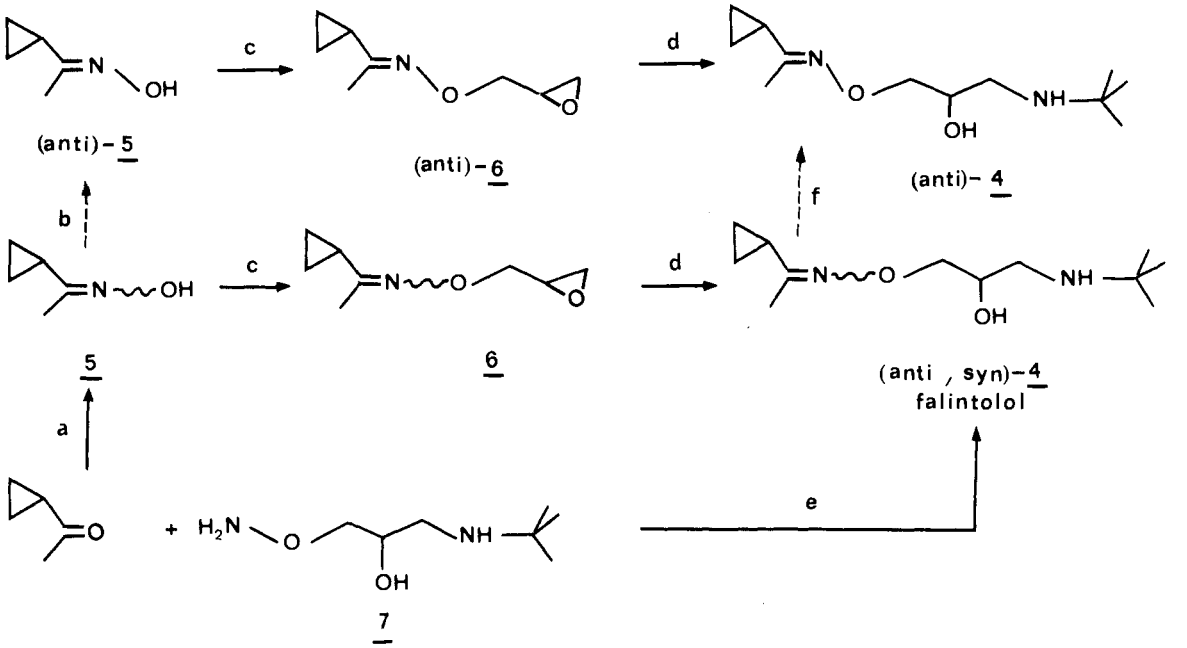
0022-2623/85/1828-0896$01.50/0

Scheme I[a]



[a] a, cyclopropyl methyl ketone oxime/THF, NaH; b, *t*-BuNH$_2$/EtOH.

Scheme II[a]



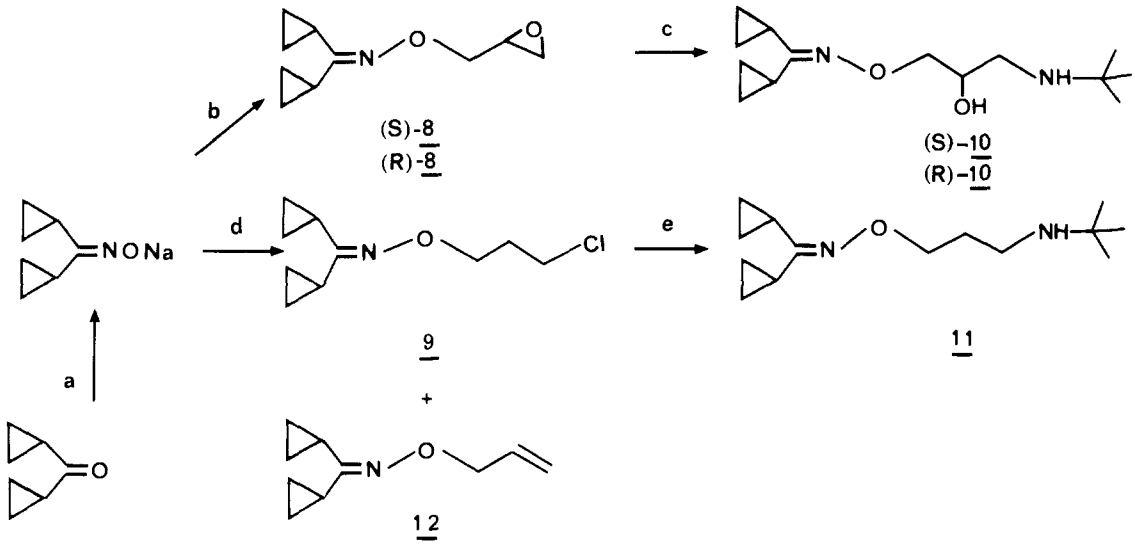
[a] a, NH_2OH, HCl, CH_3COONa/H_2O; b, recrystallization, petroleum ether; c, NaH/THF, epibromohydrin; d, *t*-BuNH$_2$/EtOH; e, EtOH, reflux; f, chromatographic separation.

were identical with those of an authentic sample obtained from cyclopropylamine and acetic anhydride. Compound *anti*-**4** was synthesized from **5** (Scheme II) without any isomerization being observed. Alternatively, the condensation[11] of cyclopropyl methyl ketone with the oxyamine **7**[12,13] gave a mixture of anti and syn isomers of compound **4**, in a ratio of ca. 7:3 as indicated by ^{1}H NMR, GC, and HPLC. The two isomers were isolated and characterized (see Experimental Section). It was noted that a D_2O solution of the oxalate salt of *anti*-**4** (pH ca. 3) isomerized into a 7:3 mixture of *anti*- and *syn*-**4** in ca. 30 min at room temperature. However, no isomerization of **4** was detected under neutral or basic conditions (pH ca. 7–9). The deshielded methyl group of the anti isomer appeared at δ 1.85 and the methyl group in the syn isomer at δ 1.72 in D_2O in ^{1}H NMR.[14] The mechanism of this isomerization is well documented.[15-17]

Similarly, the enantiomers of the dicyclopropyl derivatives (*R*)-**10** and (*S*)-**10** were prepared by reacting the sodium salt of dicyclopropyl ketone oxime with the mesylate epoxide (*R*)-**2** and (*S*)-**2** (Scheme III). The desoxy analogue **11** (Scheme III) was synthesized as described by Leclerc,[4] starting with the chloro compound **9**. The displacement of the halogen in **9** by *t*-BuNH$_2$, which gave **11**,

(11) Kusumi, T.; Yoneda, K.; Kakisawa, H. *Synthesis* **1979**, 221.
(12) Amlaiky, N.; Leclerc, G.; Carpy, A. *J. Org. Chem.* **1981**, *47*, 517.
(13) Bouzoubaa, M.; Leclerc, G. *Tetrahedron Lett.* **1984**, *29*, 3067.
(14) Spassov, S. L.; Jovtscheff, A.; Grekova, E. A. *Dokl. Bolg. Akad. Nauk* **1967**, *20*, 197.
(15) Jennings, W. B.; Showiman, S. A.; Tollay, M. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, *14*, 1535.
(16) Rosenberg, S.; Silver, S. M.; Sayer, J. M.; Jeanks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7986.
(17) Cocivera, M.; Fyfe, C. A.; Effio, A.; Vaish, S. P.; Chen, H. E. *J. Am. Chem. Soc.* **1976**, *98*, 1573.

Scheme III[a]



[a] a, NH_2OH, HCl, CH_3COONa/H_2O; b, (2*R*)- or (2*S*)-3-(mesyloxy)-1,2-epoxypropane/THF; c, *t*-$BuNH_2$/EtOH; d, $Br(CH_2)_3Cl$ or $TsO(CH_2)_3Br$/DMF; e, *t*-$BuNH_2$.

Table I. β-Blocking Activity of Alicyclic Oxime Ether Isomers

compd[a]	pA_2[b] ± SE (*n*) atria	pA_2[b] ± SE (*n*) trachea
syn,anti-**4**	7.98 ± 0.15 (6)	7.90 ± 0.54[c] (10)
anti-(*S,R*)-**4**	7.63 ± 0.33 (9)	8.16 ± 0.22 (11)
syn-(*S,R*)-**4**	7.02 ± 0.9 (9)	7.32 ± 0.11 (8)
syn,anti-(*S*)-(−)-**4**	7.56 ± 0.12 (6)	8.01 ± 0.22 (8)
syn,anti-(*R*)-(+)-**4**	8.07 ± 0.46 (11)	7.72 ± 0.25 (7)
(*R,S*)-**10**	8.17 ± 0.11 (13)	8.67 ± 0.24[d] (7)
(*S*)-(−)-**10**	7.92 ± 0.18 (14)	7.90 ± 0.30 (7)
(*R*)-(+)-**10**	7.48 ± 0.14 (7)	8.05 ± 0.22 (7)
11	4[e] (6)	5.19[d] (7)
propranolol	8.62 ± 0.17 (13)	8.47 ± 0.22 (9)

[a] Compounds **4** and **11** were tested as oxalates whereas **10** and its enantiomers were tested as 0.5 fumarates. [b] pA_2 ± standard error, with the number of experimental values in parentheses. [c] Graphical estimation. [d] Schild plot slopes differ significantly from 1. [e] Noncompetitive antagonist: pAH.

also gave the allylic compound **12** (ca. 30%) produced by eliminating hydrogen chloride.

Pharmacology and Discussion

The β-adrenergic receptor antagonist activities of the compounds were assessed in vitro from pA_2 values for guinea pig atria (β_1) and trachea (β_2). The pA_2 values in Table I provide several indications as to the β-adrenergic receptor requirements.

The syn and anti isomers of **4** display comparable biological effects; the anti isomer is 7 times more potent than the syn isomer on the trachea and twice as active as **4** itself. On atria, the anti isomer of **4** is 4 times more potent than the syn isomer. None of the compounds showed any significant selectivity in vitro, although experiments in the dog[18] seem to indicate some β_2 selectivity for falintolol. Thus, it appears that the steric requirements of the β-adrenergic receptor in the oxime area are not too strict. The dicyclopropyl derivative **10** is ca. 2 times more potent on atria than the cyclopropyl methyl derivative **4**. However, further increases in the size of the substituents on the oxime function gave compounds of lower potency. Thus, the 1-[[3-(*tert*-butylamino)-2-hydroxypropyl]oximino]-3,3,5-trimethylcyclohexyl derivative is ca. 100 times less potent on atria than **4**.[1]

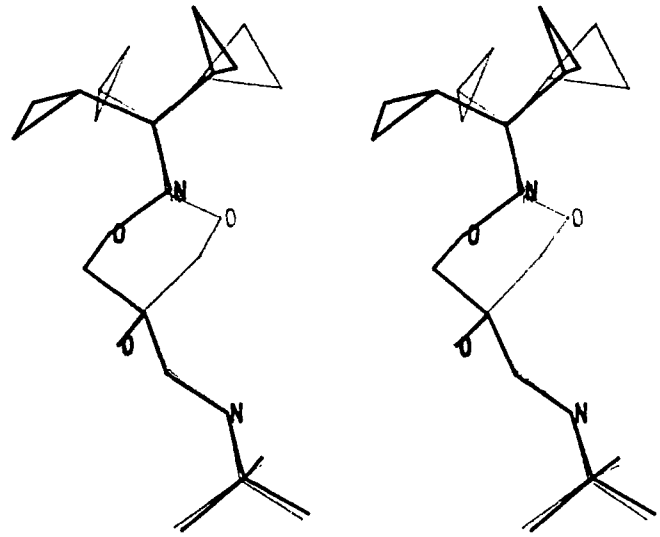


Figure 1. Stereoscopic view of (*R*)-**10** (light) and (*S*)-**10** (heavy) illustrating superposition.

Table I also allows certain conclusions to be drawn regarding the chiral requirements of the β-adrenergic receptor. The *R* and *S* isomers of **10** have similar potencies. On atria (*S*)-(−)-**10** is ca. 3 times as active as (*R*)-(+)-**10**, but on trachea, the latter is ca. 2 times more active. An analogous observation was already made with the enantiomers of 9-[[3-(*tert*-butylamino)-2-hydroxypropyl]oximino]fluorene (IPS 339).[4] Baldwin et al.[19] subsequently confirmed this observation and, to account for it, proposed that the enantiomers might be superimposed because of the pseudosymmetry in the IPS 339 molecule. A similar explanation may be put forward for the *R* and *S* enantiomers of the dicyclopropyl derivatives **10** (Figure 1). However, this model shows that the two enantiomers are only partially superimposed, which might account for the slight differences in potency.

Since the receptor can accommodate either a methyl or a cyclopropyl group (as shown by the comparable biological effects of **4** and **10**), the enantiomers of the

(18) A report of the animal pharmacology of **4** will be published elsewhere.

(19) Baldwin, J. J.; McClure, D. E.; Gross, D. M.; Williams, M. *J. Med. Chem.* 1982, *25*, 931.

"pseudosymmetric" molecule 4 also appear comparable. On the atria, (R)-(+)-4 was 3 times more potent than (S)-(−)-4 while on the trachea it is roughly half as potent. Interestingly, the desoxy derivative 11 has less than $^1/_{1000}$th of the potency of the parent compound 10, which confirms that the OH group plays an important role in the β-receptor interaction.

In conclusion, our observations led us to retain Belleau's scheme for the interaction of β-adrenergic drugs with the receptor.[20] However, it should be pointed out that the receptor can accommodate the large but flat fluorenone ring (IPS 339) as well as the dicyclopropyl ketone but less so the bulky 3,3,5-trimethylcyclohexyl group. The electron-deficient area of the receptor can therefore be considered as a pocket of limited size. The unusual absence of a marked stereochemical selectivity among the enantiomeric pairs of 10, 4, and IPS 339 might be due to a quasi-superpositioning of these enantiomers. Thus, the Easson–Stedman hypothesis[21] of a three-point attachment for active chiral molecules remains valid.

Experimental Section

Melting points were obtained on a calibrated Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ with a Beckman IR 33 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R 12 A spectrometer or at 200 MHz on a WP 200 SY spectrometer using Me_4Si in a capillary as an external reference (chemical shifts in ppm). Mass spectra were recorded on LKB 2009. Fumarate salts were made by dissolving the base in MeOH and adding 0.5 equiv of fumaric acid in MeOH. After evaporation of the solvent, the salts were induced to crystallize by scratching and were recrystallized as indicated.

Oxalate salts were made by dissolving the base in $(Et)_2O$ and adding 1 equiv of oxalic acid dihydrate in $(Et)_2O$. The salts were filtered and recrystallized as indicated. The spectral data were analyzed for C, H, and N and gave results within 0.4% of the theoretical values.

Pharmacological Tests of β-Adrenergic Blocking Activity. β_1- and β_2-adrenolytic activities were determined on the atria and trachea of guinea pigs. The antagonism of isoproterenol-induced positive chronotropism and isoproterenol-induced relaxation were measured on isolated spontaneously beating right atria according to Horii et al.[22] and trachea according to Levy and Wilkenfeld.[23] The preparations were suspended in Krebs–Henseleit solution, aerated with 95% O_2 and 5% CO_2, at temperatures and resting tensions of 32 °C and 0.5 g for atria and 37 °C and 1 g for trachea. The physiological solution was composed as follows (in mM): NaCl 120, KCl 4.80, $MgSO_4 \cdot 7H_2O$ 1.20, $CaCl_2 \cdot 2H_2O$ 2.53, KH_2PO_4 1.20, $NaHCO_3$ 25, glucose 10. Tracheal chain preparations were allowed to gain tone spontaneously. Ascorbic acid (1.13×10^{-5} M) was present during the elaboration of each isoproterenol dose–response curve (3×10^{-10} to 3×10^{-8} M). Preincubation time with the antagonists was 30 min. The β-antagonistic activities were expressed in terms of pA_2 values for competitive antagonists according to Arunlakshana et al.[24] When the antagonism was not competitive, it was expressed as pAH (−log of the molar concentration of antagonist that inhibits 50% of the maximal effect of the agonist) according to Ariens and Van Rossum.[25]

***O*-[3-(*tert*-Butylamino)-2-hydroxypropyl] Dicyclopropyl Ketone Oxime [(*R*)- and (*S*)-10].** Dicyclopropyl ketone oxime was synthesized according to ref 6. NaH (18 mmol) was added slowly to 18 mmol of dicyclopropyl ketone oxime in 100 mL of dry THF. The solution was stirred magnetically until no hydrogen was evolved. This solution was then added dropwise to a solution of 1.48 mL (18 mmol) of epibromohydrin in 10 mL of dry THF and the mixture was stirred for 48 h during which a precipitation of NaBr occurred. The NaBr was filtered off and the THF was evaporated. The crude epoxide was dissolved in 20 mL of dry ethanol containing 5 mL of t-$BuNH_2$ and the mixture was stirred magnetically at room temperature for 24 h. The solvent were removed at a reduced pressure and the oily residue was dissolved in dilute HCl (10%). Neutral and acidic materials were extracted twice with Et_2O.

The aqueous layer was made alkaline with K_2CO_3 and extracted twice with EtOAc. The organic phase was dried over $MgSO_4$ and the solvent evaporated. A 0.5-g sample of fumaric acid was dissolved in a minimum of EtOAc and was added to the crude base. The salt formed was induced to crystallize by scratching; two recrystallizations from EtOAc–MeOH (90:10) gave 0.84 g of 10 (0.5 fumarate), yield 15%; mp 159 ± 1 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 3.95 (m, 2 H), 3.80 (m, 1 H), 2.70 (m, 2 H), 2.45 (m, 2 H), 1.45 (m, 2 H), 0.8 (m, 8 H). Anal. ($C_{16}H_{28}N_2O_4$) C, H, N.

(2*R*)- or (2*S*)-*O*-(1,2-Epoxypropyl) Cyclopropyl Methyl Ketone Oxime [(*R*)-3 or (*S*)-3]. The action of hydroxylamine hydrochloride on cyclopropyl methyl ketone in aqueous CH_3C-OONa solution or in aqueous NaOH according to procedures in ref 6 and 26 gave a 7:3 anti/syn mixture of methyl cyclopropyl ketone oxime isomers. To this mixture (1.5 g, 17.8 mmol) in 50 mL of THF was added NaH (0.5 g, 50% in mineral oil, 17.8 mmol). To the sodium salt of the oxime thus produced was added a solution of (2*R*)- or (2*S*)-3-(mesyloxy)-1,2-epoxypropane[5] (2.7 g, 17.8 mmol) [(*R*)-**2**, α^{21}_D −14.5° (*c* 6.62, MeOH); (*S*)-**2**, α^{21}_D +16.9° (*c* 6.56, MeOH)] in 20 mL THF and the mixture was stirred for 48 h at room temperature. After this, water was added and the mixture was extracted with EtOAc, the extracts were dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The crude epoxide was chromatographed on silica gel with hexane–EtOAc (95:5) as eluent. The yield was 1.5 g (57%) of (*R*)-**3**: ^{1}H NMR (CCl_4) δ 3.80 (d, J = 5 Hz, 2 H), 2.95 (m, 1 H), 2.45 (m, 2 H), 1.60 (s, 2 H), 1.40 (s, 1 H), 1.40 (m, 1 H), 0.60 (m, 4 H); (*R*)-**3**, α^{21}_D −10.3° (*c* 4.56, MeOH); (*S*)-**3**, α^{21}_D +12.3° (*c* 4.16, MeOH).

(2*R*)- or (2*S*)-*O*-[3-(*tert*-Butylamino)-2-hydroxypropyl] Cyclopropyl Methyl Ketone Oxime [(*R*)-4 or (*S*)-4]. To a solution of the epoxide (*R*)-**3** or (*S*)-**3** (1.2 g, 5.3 mmol) in 20 mL of absolute EtOH was added 2 equiv (1.1 mL) of *tert*-butylamine and the mixture was stirred for 24 h at room temperature. The solvents were evaporated under reduced pressure, and the crude oil was chromatographed on silica gel (EtOAc–$(Et)_3N$, 95:5) to give 0.6 g of the product: ^{1}H NMR (C_6D_6) δ 4.55 (m, 2 H), 4.35 (m, 1 H), 2.85 (m, 2 H), ~2.50 (1, 2 H), 1.65 (s, 2 H), 1.40 (s, 1 H), 1.50 (m, 1 H), 1.05 (s, 9 H), 0.55 (m, 4 H); (*R*)-**4**, α^{21}_D ~+1° (*c* 3.14, MeOH); (*S*)-**4**, α^{21}_D ~−1° (*c* 2.60, MeOH). (*R*)-**4** oxalate salt: mp 130 °C (EtOAc); α^{21}_D +2.7° (*c* 2.95, MeOH). Anal. ($C_{14}H_{26}N_2O_6$) C, H, N. Similarly, (*S*)-**4** oxalate salt: mp 129 °C (EtOAc); α^{21}_D −3.3° (*c* 6.36, MeOH). Anal. ($C_{14}H_{26}N_2O_6$) C, H, N.

(2*R*)- or (2*S*)-*O*-[3-(*tert*-Butylamino)-2-hydroxypropyl] Dicyclopropyl Ketone Oxime [(*R*)-10 or (*S*)-10]. Compounds (2*R*)- and (2*S*)-**10** were prepared as described above. (*R*)-**10**·0.5fumarate salt: mp 158 °C (2-PrOH); α^{21}_D +3.4° (*c* 5.6, MeOH). (*S*)-**10**·0.5 fumarate salt: mp 159 °C (2-PrOH); α^{21}_D −4.2° (*c* 5.3, MeOH). Anal. for the two enantiomers ($C_{16}H_{28}N_2O_4$) C, H, N. ^{1}H NMR (C_6D_6) of the free base δ 4.40 (m, 2 H), 4.20 (m, 1 H), 2.7 (m, 2 H), 2.50 (1, 2 H), 1.40 (m, 2 H), 1.10 (s, 9 H), 0.70 (m, 8 H).

Characterization and Beckmann Rearrangment of *anti*-Cyclopropyl Methyl Oxime (5). Cyclopropyl methyl ketone oxime (**5**)[6,26] was obtained in a quantitative yield as a mixture of anti and syn isomers in a ratio of ca. 7:3. Five recrystallizations from petroleum ether gave pure anti ketone oxime **5**: mp 52 °C; ^{1}H NMR (CCl_4) δ 9.30 (s, 1 H), 1.45 (s, 3 H), 1.40 (m, 1 H), 0.52 (m, 4 H), no methyl proton signal was observed at δ 1.30.

The Beckmann rearrangement was carried out with use of the method of Craig and Naik[9] on the *p*-toluenesulfonate ester of the anti ketone oxime **5**. The intermediate ester was isolated and

(20) Belleau, B. *Ann. N.Y. Acad. Sci.* **1967**, *139*, 580.
(21) Easson, L. H.; Stedman, E. *J. Biochem.* **1933**, *27*, 1257.
(22) Horii, D.; Kawada, T.; Takeda, K.; Imai, S. *Arzneim.-Forsch.* **1974**, *24*, 1275.
(23) Levy, B.; Wilkenfeld, B. E. *Eur. J. Pharmacol.* **1970**, *11*, 67.
(24) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.
(25) Ariens, E. J.; Van Rossum, J. M. *Arch. Int. Pharmacodyn.* **1957**, *110*, 275.
(26) Roberts, J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951**, *73*, 3176.

recrystallized from CH_2Cl_2: mp 93 °C; ^1H NMR ($CDCl_3$) δ 7.90 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H), 2.45 (s, 3 H), 1.78 (s, 3 H), 1.60 (m, 1 H), 0.80 (m, 4 H). The ester (2.5 g, 9.8 mmol) was heated under reflux for 4 h in 10% sodium hydroxide in aqueous acetone. The acetone was evaporated under reduced pressure at room temperature and the amide was taken up in $CHCl_3$ by continuous extraction; the $CHCl_3$ solution was evaporated under reduced pressure, and the oily residue was chromatographed on neutral alumina and eluted with graded mixtures of C_6H_6–$CHCl_3$. The appropriate fractions were combined to give 0.6 g of *N*-cyclopropylacetamide after recrystallization from hexane; mp 54 °C; ^1H NMR, IR, and MS spectra were in agreement with those of an authentic sample of *N*-cyclopropylacetamide synthesized from cyclopropylamine and acetic anhydride in C_6H_6; ^1H NMR (CCl_4) δ 7.75 (1 H), 2.60 (m, 1 H), 1.85 (s, 3 H), 0.60 (m, 4 H); IR ($CHCl_3$) 1690 (C=O), 3440–3625 cm^{-1} (NH); MS, *m/e* 43, 56, 84, 99.

***O*-[3-(*tert*-Butylamino)-2-hydroxypropyl] Cyclopropyl Methyl Ketone Oxime (*anti*-4).** The *anti*-4 isomer was separated in two ways.

Method A. To the sodium salt of *anti*-cyclopropyl methyl ketone oxime (1.5 g, 12 mmol) in 20 mL of THF was added epibromohydrin (1.7 g, 12 mmol) and the mixture was stirred for 48 h at room temperature. The NaBr formed was filtered off and the solvents evaporated. The 200-MHz NMR (C_6D_6) spectrum of the residual oil **6** showed the presence of methyl protons at δ 1.65 (s, 3 H), indicating its anti configuration. No methyl proton signal appeared at δ 1.45, which corresponds to the syn isomer. To *anti*-**6** (1.5 g, 10 mmol) in 10 mL of absolute EtOH was added 2 equiv of *tert*-butylamine (2.2 mL) and the mixture was stirred for 24 h at room temperature to give *anti*-**4**: 200-MHz ^1H NMR (C_6D_6) δ 1.65 (s, 3 H). The free base was converted to the oxalate salt, which was recrystallized from EtOAc, giving 1.5 g of *anti*-**4**, mp 133 °C. Anal. ($C_{14}H_{26}N_2O_6$) C, H, N.

Method B. A sample (1 g) of crude **4** was chromatographed on silica gel (ca. 100 g) with EtOAc–$N(Et)_3$ (98:2) as eluent; 300 mg of practically pure *anti*-**4** was obtained and then converted to the oxalate salt. It was recrystallized five times from EtOAc, giving 400 mg, mp 133 °C. Anal. ($C_{14}H_{26}N_2O_6$) C, H, N. The two isomers of **4** were separated with high-performance liquid chromatography. The liquid chromatographic system consisted of a Waters U6K syringe loading sample injector, a nucleosil 7C18 column (20 cm × 4 mm), and a Waters 6000 A pump with a differential refractometer set at 38 °C. The eluent was H_2O–MeOH–heptanesulfonic acid (70:30:3, v/v); flow rate was 1.8 mL/min. The two geometric isomers *anti*- and *syn*-**4** were identified and quantified respectively by their retention times and the integrals of their signal areas. These data were very close to those observed in 200-MHz ^1H NMR and GC.

***O*-[3-(*tert*-Butylamino)-2-hydroxypropyl] Cyclopropyl Methyl Ketone Oxime (*syn*-4).** The *syn*-**4** isomer could not be separated in a pure form with column chromatography. ^1H NMR and GC indicated a purity of ca. 95% for the syn isomer [200-MHz ^1H NMR (C_6D_6) δ 1.65 (s, CH_3)] and ca. 5% for the anti isomer [200-MHz ^1H NMR (C_6D_6) δ 1.45 (s, CH_3)]. Oxalate salt: mp 149 °C. Anal. ($C_{14}H_{26}N_2O_6 \cdot {}^1/_2H_2O$) C, H, N.

***O*-[3-(*tert*-Butylamino)-2-hydroxypropyl] Cyclopropyl Methyl Ketone Oxime (4).** A solution of cyclopropyl methyl ketone (0.5 g, 5.9 mmol) in 10 mL of EtOH and oxyamine **7** (0.96 g, 5.9 mmol)[11,12] was heated under reflux for 12 h (Scheme II). The solvents were evaporated, and the oily residue was converted to the oxalate salt and recrystallized from EtOAc, giving 1.08 g, mp 129 °C. ^1H NMR (CCl_4) of the free base showed the ratio of anti and syn isomers to be ca. 7:3. Anal. ($C_{14}H_{26}N_2O_6$) C, H, N.

***O*-[3-(*tert*-Butylamino)propyl] Dicyclopropyl Ketone Oxime (11).** This compound was synthesized according to the method of Leclerc[4] by the reaction of 3-chloro-1-bromopropane or 3-(tosyloxy)-1-chloropropane and the sodium salt of dicyclopropyl ketone oxime in DMF (Scheme III). The desired product **9** (70%) was accompanied by the allyl oxime **12** (30%). **9**: ^1H NMR (CCl_4) δ 4.00 (t, J = 6 Hz, 2 H), 3.50 (t, J = 6 Hz, 2 H), 2.00 (t, J = 6 Hz, 2 H), 2.10 (m, 2 H), 0.70 (m, 8 H). **12**: ^1H NMR (CCl_4) δ 5.70 (m, 1 H), 4.90 (t, J = 12 Hz, 2 H), 4.20 (d, J = 6 Hz, 2 H), 2.10 (m, 2 H), 0.70 (m, 8 H); bp 57 °C (0.5 mmHg).

The mixture of **9** and **12** was heated at 70 °C with 10 equiv of *tert*-butylamine in a sealed tube for 12 h. The solvents were evaporated, and the oily residue was purified by crystallization of the oxalate salt: mp 134 °C (EtOAc); ^1H NMR (CCl_4) of the free base, δ 4.35 (1 H), 3.92 (t, J = 5 Hz, 2 H), 2.75 (t, J = 5 Hz, 2 H), 2.00 (m, 2 H), 1.85 (t, J = 5 Hz, 2 H), 1.10 (s, 9 H), 0.60 (m, 8 H).

Registry No. (*R*)-**2**, 96427-97-3; (*S*)-**2**, 67800-62-8; *anti*-(*R*)-**3**, 96427-98-4; *syn*-(*R*)-**3**, 96427-99-5; *anti*-(*S*)-**3**, 96428-00-1; *syn*-(*S*)-**3**, 96428-01-2; *anti*-(*R*)-**4**, 96479-87-7; *anti*-(*R*)-**4** oxalate, 96479-88-8; *syn*-(*R*)-**4**, 96479-89-9; *syn*-(*R*)-**4** oxalate, 96479-90-2; *anti*-(*S*)-**4**, 96479-91-3; *anti*-(*S*)-**4** oxalate, 96479-92-4; *syn*-(*S*)-**4**, 96479-93-5; *syn*-(*S*)-**4** oxalate, 96479-94-6; *anti*-**5**, 80606-74-2; *anti*-**5** *p*-toluenesulfate, 96428-02-3; *anti*-**6**, 96479-95-7; **7**, 67435-25-0; (*R*)-**8**, 96428-03-4; (*S*)-**8**, 96428-04-5; **9**, 96428-05-6; (*R*)-**10**, 96428-06-7; (*R*)-**10**·0.5fumarate, 96428-07-8; (*S*)-**10**, 96428-08-9; (*S*)-**10**·0.5fumarate, 96444-44-9; **11**, 96428-09-0; **11** oxalate, 96428-10-3; **12**, 96428-11-4; $Br(CH_2)_3Cl$, 109-70-6; $TsO(CH_2)_3Cl$, 632-02-0; dicyclopropyl ketone oxime, 1453-52-7; dicylcopropyl ketone oxime sodium salt, 96428-12-5; cyclopropyl methyl ketone, 765-43-5; *anti*-methyl cyclopropyl ketone oxime, 80606-74-2; *syn*-methyl cyclopropyl ketone oxime, 96428-13-6; *anti*-methyl cyclopropyl ketone oxime sodium salt, 96428-14-7; *syn*-methyl cyclopropyl ketone oxime sodium salt, 96428-15-8; (*R*)-epibromohydrin, 51594-57-1; (*S*)-epibromohydrin, 96479-96-8; *N*-cyclopropylacetamide, 29512-07-0.