(26 × 2.8 cm). Elution with $CHCl_3$–MeOH, 99:1, removal of the solvent under vacuum, and drying under vacuum over P_2O_5 at 65 °C gave 2.55 g (67%) of 11: mp 107.5–113.5 °C; TLC R_f 0.17 (Whatman KC18F reverse phase, MeOH–H_2O, 8:2); NMR ($CDCl_3$) δ 1.18 [s, 9, $C(CH_3)_3$], 3.87 (s, 3, CH_3), 5.22 (s, 2, CH_2O), 5.94 (s, 2, $COOCH_2$), 6.98 (d, 2, 3′, 5′, J_o = 8.88 Hz), 7.77 (d, 1, H_8, $J_{8,7}$ = 8.37 Hz), 7.85 (dd, 1, H_7, $J_{7,8}$ = 8.37 Hz, $J_{7,5}$ = 1.95 Hz), 7.98 (d, 2, 2′, 6′, J_o = 8.85 Hz), 8.33 (s, 1, H_2), 8.37 (d, 1, H_5, $J_{5,7}$ = 1.71 Hz). Anal. ($C_{23}H_{24}N_2O_6$) C, H, N.

6-[(4-Carboxyphenoxy)methyl]-3,4-dihydro-4-oxoquinazoline (12). A mixture of 11 (2.4 g, 5.65 mmol), EtOH (65 mL), H_2O (65 mL), and 1 N NaOH (20 mL) was stirred at ambient temperature for 48 h. The solution was filtered and the filtrate acidified to pH 5.0 with 1 N HCl. The mixture was stirred and then cooled in the refrigerator for 1 h. The precipitated solid was separated by filtration, washed with water (75 mL), and dried under vacuum over P_2O_5 at 100 °C for 5 h. There was obtained 1.36 g (81%) of a white solid: mp >300 °C; TLC R_f 0.08; NMR (Me_2SO-d_6) δ 5.35 (s, 2, CH_2), 7.13 (d, 2, 3′, 5′, J_o = 8.28 Hz), 7.71 (d, 1, H_8, $J_{8,7}$ = 8.37 Hz), 7.90 (d, 2, 2′, 6′, J_o = 8.19 Hz, superimposed upon dd, 1, H_7), 8.11 (s, 1, H_5), 8.20 (s, 1, H_2), 12.31 (s, 1, lactam NH), 12.48 (br s, 1, COOH). Anal. ($C_{16}H_{12}N_2O_4 \cdot 0.15H_2O$) C, H, N.

Di-*tert*-butyl 2-Desamino-5,8-dideaza-10-oxafolate (13). A solution of Et_3N (0.10 g, 0.99 mmol) in 2 mL of dry DMF was added to a stirred solution of **12** (0.15 g, 0.5 mmol) in 20 mL of DMF under a N_2 atmosphere. This was followed by the addition of a solution of diethyl phosphorocyanidate (0.16 g, 0.98 mmol) in 2 mL of DMF. The clear colorless solution was stirred at ambient temperature for 3 h when it attained a yellow color. To this solution was added a solution of di-*tert*-butyl L-glutamate hydrochloride (Sigma Chemical Co.) (0.16 g, 0.54 mmol) in 2 mL of DMF. The resulting mixture was then stirred at ambient temperature for 3 h. The solvent was removed under reduced pressure and the residue dissolved in $CHCl_3$ (30 mL). The solution was washed with 15 mL of 10% $NaHCO_3$, saturated NaCl, and dried over $MgSO_4$. Removal of the solvent at reduced pressure gave a yellow oil which was dissolved in $CHCl_3$ (0.6 mL) and applied to a silica gel column (24.5 × 0.9 cm). The column was eluted first with $CHCl_3$–MeOH, 99:1, followed by elution of the product with $CHCl_3$–MeOH, 98:2. Removal of the solvent gave a solid which was dried under vacuum over P_2O_5 at 65 °C for 20 h. There was obtained 0.21 g (79%) of a white solid: mp 172–173.5 °C dec (with preliminary softening); TLC R_f 0.38 ($CHCl_3$–MeOH, 95:5); NMR (Me_2SO-d_6) δ 1.38 [s, 9, $C(CH_3)_3$], 1.40 [s, 9, $C(CH_3)_3$], 1.84–2.12 (m, 2, glu β-CH_2), 2.33 (t, 2, glu γ-CH_2, J = 9.0 Hz), 4.20–4.36 (m, 1, glu α-CH), 5.35 (s, 2, CH_2O), 7.13 (d, 2, 3′, 5′, J_o = 8.70 Hz), 7.70 (d, 1, H_8, $J_{7,8}$ = 8.34 Hz), 7.86 (d, 2, 2′, 6′, J_o = 8.67 Hz, superimposed upon d, 1, H_7), 8.11 (s, 1, H_5), 8.21 (s, 1, H_2), 8.45 (d, 1, CONH, J = 7.44 Hz), 12.32 (s, 1, lactam NH). Anal. ($C_{29}H_{35}N_3O_7 \cdot 0.5H_2O$) C, H, N.

2-Desamino-5,8-dideaza-10-oxafolic Acid (2d). A 0.10 g (0.18 mmol) sample of **13** was dissolved in 2 mL of CF_3COOH and stirred at ambient temperature for 2 h. The CF_3COOH was removed under vacuum and the residue triturated three times with Et_2O. The dried solid was suspended in 3 mL of H_2O and basified to pH 11.0 with 15% NH_4OH. Insoluble material was removed by filtration and the filtrate acidified to pH 3.0 with 5 N HCl. After refrigeration, the precipitate was separated by filtration, washed with H_2O, and dried under vacuum over P_2O_5 at 50 °C for 17 h to yield 49 mg (59%) of a white powder: mp 222–228 °C dec (with preliminary softening); TLC R_f 0.32; UV λ_{max} 230 nm (ε 30.3 × 10^3), 256 (ε 22.5 × 10^3); NMR (Me_2SO-d_6) δ 1.80–2.20 (m, 2, glu β-CH_2), 2.35 (t, 2, glu γ-CH_2, J = 7.32 Hz), 4.38 (m, 1, glu α-CH), 5.35 (s, 2, CH_2O), 7.13 (d, 2, 3′, 5′, J_o = 8.55 Hz), 7.70 (d, 1, H_8, $J_{8,7}$ = 8.25 Hz), 7.87 (d, 2, 2′, 6′, superimposed upon dd, 1, H_7), 8.11 (app d, 1, H_5), 8.21 (s, 1, H_2), 8.47 (d, 1, CONH, J = 7.41 Hz), 12.34 (two partially overlapping broad singlets, 3, 2 COOH and lactam NH); FAB/MS 426 (M + 1). Anal. ($C_{21}H_{19}N_3O_7 \cdot 1.95H_2O$) C, H; N: calcd, 9.12; found, 8.71.

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Registry No. **2a**, 106585-65-3; **2b**, 118895-95-7; **2c**, 118895-96-8; **2d**, 118895-97-9; **3**, 4693-02-1; **4**, 6943-17-5; **5**, 17329-31-6; **6**, 87597-84-0; **7**, 118895-90-2; **8**, 106585-53-9; **10**, 118895-91-3; **11**, 118895-92-4; **12**, 118895-93-5; **13**, 118895-94-6; TS, 9031-61-2; DHFR, 9002-03-3; H-Glu(OBu-*t*)-OBu-*t*·HCl, 32677-01-3; HO-*p*-C_6H_4COOMe, 99-76-3; (S-*p*-C_6H_4CO-Glu(OEt)-OEt)$_2$, 56527-28-7.

Synthesis and Evaluation of the Pharmacological Activity of Rigid Analogues of Sympathomimetic Catecholamines Derived from Bicyclo[2.2.1]heptane[1]

A. Balsamo,[†] M. C. Breschi,[‡] A. Lapucci,[†] B. Macchia,*[,†] F. Macchia,[§] E. Martinotti,[‡] S. Nencetti,[†] P. Nieri,[‡] and E. Orlandini[†]

Istituto di Chimica Farmaceutica, Istituto Policattedra di Discipline Biologiche, and Istituto di Chimica Organica, Facoltà di Farmacia, Università di Pisa, 56100 Pisa, Italy. *Received March 21, 1988*

endo-3-Amino-*exo*-2-(3,4-dihydroxyphenyl)-2-hydroxybicyclo[2.2.1]heptane (**4a**) and its *N*-isopropyl derivative (**4b**) were synthesized and assayed for their adrenergic activity on various isolated preparations. Compounds **4a** and **4b**, tested up to a dose of 10^{-4} M, did not reveal any activity, either stimulant or blocking, on the α- and β-adrenoceptors. Possible rationalizations of the results obtained, however, are suggested.

Natural catecholamines are flexible molecules that can exist in several conformations. The free energy differences between the various conformers are not high enough to make it possible to define a priori the precise molecular shape (i.e., conformation) required for effective direct interaction with α- and β-adrenoceptors. The problem of the identification of the conformation(s) of these compounds that is(are) active at the receptor site has been faced in various ways;[3] one of these consists of the comparative study of the adrenergic properties of a variety of cyclic compounds in which certain portions of the cathe-

[†] Istituto di Chimica Farmaceutica.
[‡] Istituto Policattedra di Discipline Biologiche.
[§] Istituto di Chimica Organica.

(1) Twelfth paper in the series: Conformational effects on the activity of drugs. For the preceding paper, see ref 2.
(2) Macchia, B.; Balsamo, A.; Epifani, E.; Lapucci, A.; Nencetti, S.; Macchia, F.; Breschi, M. C.; Martinotti, E.; Ceserani, R. *J. Med. Chem.* **1986**, *290*, 740, and references cited therein.
(3) Burger, A. *A Guide to the Chemical Basis of the Drug Design*; Wiley-Interscience: New York, 1983; p 90.

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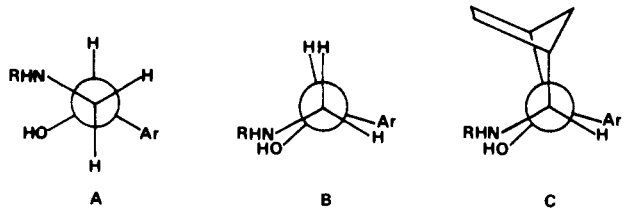
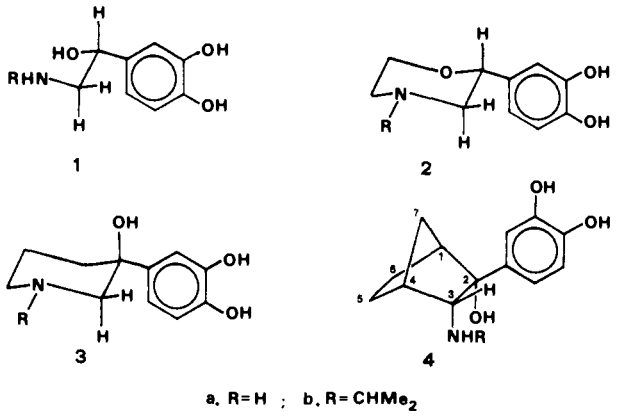


Figure 1. Newman projections of (A) the preferred staggered rotamer of the 1-aryl-2-aminoethanol derivatives **1**, (B) a possible eclipsed conformer of **1**, and (C) the bicyclo[2.2.1]heptane derivatives **4**.

cholamines are inserted into rigid or semirigid structures.

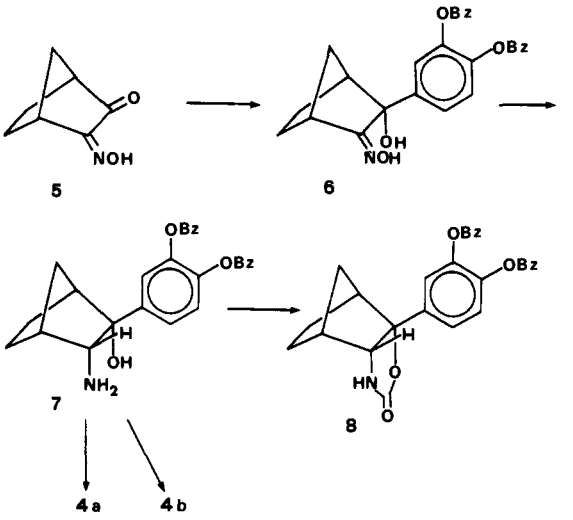
In the course of studies carried out in the field of adrenergic drugs, our attention had been devoted to an examination of the influence that the conformation around the C(1)–C(2), bond in type 1 catecholamines may exert on biological activity.[2] These studies had shown that morpholine (**2a,b**) and piperidine (**3a,b**) cyclic analogues



of norepinephrine (NE, **1a**) and of isoproterenol (ISO, **1b**) possess an α- and β-adrenergic stimulating activity comparable to that of NE and ISO. In the cyclic compounds **2** and **3**, the C(1)–C(2) side chain of amino alcohols **1** is incorporated in the morpholine and piperidine rings of **2** and **3**, respectively. The comparison of the stereo structures of these compounds and of their pharmacological properties suggested that semirigid analogues **2** and **3** interact at the receptor sites in their preferred conformations. In this conformation, the groups presumed to be pharmacologically active[2,4] (aryl moiety, amine nitrogen, and alcoholic or ethereal benzylic oxygen) present a spatial arrangement that corresponds to the one found for the same groups in NE and ISO in their preferred conformation shown in A (Figure 1).[2,4b,5] In this conformer (A) the torsion angle RHN–C–C–OH is approximately 60°. The results obtained in this study lead to the identification of a spatial arrangement of the presumed pharmacophoric groups corresponding to conformer A which allows a positive drug–receptor interaction.[2] However these results can not exclude that other spatial arrangements different from this one could be pharmacophoric as well.

In an attempt to gain further knowledge about the conformational requirements for the direct activation of

Scheme I



α- and β-adrenoceptors, we synthesized the *endo*-3-amino-*exo*-2-(3,4-dihydroxyphenyl)-2-hydroxybicyclo-[2.2.1]heptane (**4a,b**) derivatives in which the C(1)–C(2) side chain of catecholamines **1a,b** is fixed in the rigid norbornyl system. In the derivatives **4**, the torsion angle RHN–C–C–OH is close to 0° [see the projection of **4** shown in C (Figure 1)][6] and the relative positions of the pharmacologically active groups approximate to the ones shown by NE (**1a**) and ISO (**1b**) in the eclipsed conformation shown in B (Figure 1).

Chemistry

Compounds **4a** and **4b** were synthesized as indicated in Scheme I.[8] Treatment of the hydroxyimino derivative **5**[9] with [3,4-bis(benzyloxy)phenyl]magnesium bromide[10] yielded the hydroxyimino alcohol **6**. Reduction of **6** with LAH afforded the amino alcohol **7**, which was catalytically hydrogenolyzed to **4a**. Treatment of **7** with acetone and hydrogen in the presence of palladium on charcoal gave the *N*-isopropylamino derivative **4b**; the removal of the benzyloxy protecting groups also occurred during the catalytic reductive alkylation of **7**. Compounds **4a** and **4b** were isolated as hydrochlorides because of their instability as free bases.

The stereochemistry at C(2) of **6**, and consequently of **7**, **4a**, and **4b**, was assigned on the basis of the known stereoselectivity of the addition of the Grignard reagents to bicyclo[2.2.1]heptan-2-one derivatives unsubstituted on C(7). The attack of the Grignard on the carbonyl group in these compounds occurs from the sterically less hindered exo side, leading to *endo*-2-hydroxy derivatives.[11] The

(4) See for example: (a) Ariens, E. J. *Ann. N.Y. Acad. Sci.* **1967**, *139*, 606. (b) Petrongolo, C.; Tomasi, J.; Macchia, B.; Macchia, F. *J. Med. Chem.* **1974**, *17*, 501. (c) Triggle, D. J. *Burger's Medicinal Chemistry*; Wolff, M. E., Ed.; Wiley-Interscience: New York, 1981; Chapter 41. (d) Albert, A. *Selective Toxicity*; Chapman and Hall: London, 1985; p 510.

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(6) In compounds of type **4** the value of the torsion angle RHN–C–C–OH may differ slightly from 0° as a result of deformations of the asymmetrically substituted bicyclic ring.[7]

(7) Altona, C. *Conformational Analysis. Scope and Present Limitations*; Chiurdoglu, C., Ed.; Academic Press: New York, 1971; p 1.

(8) For clarity, a single enantiomer is shown. The compounds were prepared and tested as racemates.

(9) Collins, C. J.; Benjamin, B. M.; Raaen, V. F.; Glover, I. T.; Eckart, M. D. *Justus Liebigs Ann. Chem.* **1970**, *739*, 7.

(10) Pines, S. H.; Karady, S.; Sletzinger, M. *J. Org. Chem.* **1968**, *33*, 1758.

(11) See for example: Beckmann, S.; Schaber, R.; Bamberger, R. *Ber.* **1954**, *87*, 977. Toivonen, N. J.; Siltanen, E.; Ojala, K. *Ann. Acad. Sci. Fenn.* AII, n. 64. Toivonen, N. J. *XIV Int. Congr. Pure Appl.* Chem. Zurich, July 1955, Abstr, p 45.

configuration at C(3) of **7**, and therefore of **4a** and **4b**, was determined on the basis of its ^1H NMR spectral data. In particular, for the proton linked to C(3), the values of its chemical shift (3.39 ppm) and of the vicinal coupling constant with the hydrogen atom on C(4) (J = 4.5 Hz), are in agreement with the corresponding ones reported for exo protons linked to C(3) of the norbornyl system.[12-15] The stereochemistry at C(3) of **7** is in agreement with expectations for the LAH reduction of **6**, bearing in mind that the LAH reduction of 3-(hydroxyimino)bicyclo[2.2.1]heptane derivatives substituted on C(2) with a polar group preferentially leads to products in which the 3-amino group presents a cis relationship with the polar substituent linked to C(2).[15] Confirmation of this steric relationship between the amino group and the hydroxyl group in compound **7** was obtained by an examination of its IR spectrum in the 3-μm range in a dilute solution, showing a strong absorption at 3330 cm^{-1} that can be attributed to an intramolecular OH···N interaction,[15] and by the reaction of **7** with phosgene, leading to **8**. Both the existence of the intramolecular hydrogen bond in **7**[15,16] and the formation from the same compound of the cyclic carbamate **8** are for steric reasons only possible if the OH and NH_2 groups are in a cis relationship.

Results and Discussion

The rigid derivatives **4a** and **4b** were tested in vitro for their adrenergic activity by functional tests on isolated preparations, using rat vas deferens for the α-receptors and male guinea pig atria and trachea for the β_1- and β_2-adrenoceptors, respectively. Compounds **4a** and **4b**, tested up to a dose of 10^{-4} M, did not reveal any receptor activity that either stimulated or blocked the receptors under examination. The tested compounds, in general, did not induce any variation in the basal tone of the various organs, with the exception of **4a**, which exhibited a slight spontaneous, but not dose-dependent, activity on α-receptors.

In the preferred conformation A (which has been shown to be biologically active),[2] catecholamines **1** present a spatial arrangement of the groups presumed to be pharmacologically active, which is different from the one exhibited by the eclipsed conformation B. By superimposing the alcoholic hydroxyl and the aryl moiety of the stereo structures (Dreiding stereomodels) of the two rotamers A and B, it can be noted that the spatial position occupied by the amine nitrogen in conformer B is about 1.5 Å away from the one that the same group occupies in conformer A. The complete inactivity both on the α- and β-adrenergic receptors of compounds **4** which represent catecholamines **1** fixed in the B conformation might be due to an improper pharmacophoric conformation of the arylethanolamine moiety, i.e. to a spatial position of the amino group, with respect to other active groups (hydroxyl and aryl moiety), which is not suitable for any active drug–receptor interaction. Alternatively, the lack of activity of compounds **4** might be caused by steric interferences from the norbornyl ring, that is to say, the rigidity of the norbornyl system and/or the steric hindrances due to the additional atoms that are necessary to achieve structural rigidity. The latter factors might have a negative influence on the rotameric preference of the dihydroxyphenyl moiety, which recent works[17] indicate as playing an important role in the structure–activity relationships of catecholamines and their derivatives.

Experimental Section

All compounds were routinely checked for their structure by IR and ^1H NMR spectroscopy. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra for comparison between compounds were taken as Nujol mulls or as liquid film on a Perkin-Elmer Model 1310 spectrophotometer, and those for determination of OH stretching band frequency of **7** were measured with a Perkin-Elmer Model 257 double-beam grating instrument in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2 cm optical length was employed, and the concentration of the solutions was lower than 5×10^{-3} M to prevent intermolecular associations. ^1H NMR spectra were obtained in ca. 5% $CDCl_3$ solution for the free bases (Me_4Si) and in D_2O solution for HCl salts ($Me_3Si/CD_2CD_2/COONa$) with a Varian EM 360 A spectrometer operating at 80 MHz. Analytical TLC were carried out on 0.25-mm layer silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under UV light (254 nm). Magnesium sulfate was always used as the drying agent. Evaporations were made in vacuo (rotating evaporator). Elemental analyses were performed by our analytical laboratory and agreed with the theoretical values to within ±0.4%.

***exo*-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxy-3-(hydroxyimino)bicyclo[2.2.1]heptane (6).** A solution of 3-(hydroxyimino)-2-oxobicyclo[2.2.1]heptane (**5**)[9] (1.6 g, 0.011 mol) in anhydrous Et_2O (30 mL) was added dropwise to a stirred solution of [3,4-bis(benzyloxy)phenyl]magnesium bromide,[10] prepared from Mg (2.86 g, 0.117 g-atom) and 3,4-bis(benzyloxy)phenyl bromide (16.0 g, 0.043 mol) in anhydrous THF (15 mL). The reaction mixture was stirred under reflux for 7 h, hydrolyzed with cold 25% aqueous NH_4Cl (200 ml), and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried, and evaporated to yield impure **6** as an oily residue (14.5 g), which was directly used in the subsequent reaction. An analytical sample of **6** (oil) was obtained with low yield by chromatography through a 70–230-mesh silica gel column, eluting with 35:65 ethyl acetate/petroleum ether (bp 40–70 °C). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

***endo*-3-Amino-*exo*-2-[3,4-bis(benzyloxy)phenyl]-2-hydroxybicyclo[2.2.1]heptane Hydrochloride (7·HCl).** A solution of the crude hydroxyimino derivative **6** (4.0 g) in anhydrous Et_2O (32 mL) was added dropwise to a stirred suspension of LAH (1.5 g, 40 mmol) in anhydrous Et_2O (32 mL). After the addition was complete, the reaction mixture was refluxed for 6 h, cooled at room temperature, and hydrolyzed with H_2O (3 mL), 10% aqueous NaOH (6 mL), and H_2O (6 mL). The organic layers were separated, washed with H_2O, and treated with 10% aqueous HCl. The solid precipitate was collected by filtration and crystallized from $EtOH/Et_2O$ to gave pure **7**·HCl (1.8 g): mp 178–180 °C; ^1H NMR δ 1.07–2.18 (br, 6 H), 2.36–2.84 (br, 2 H), 3.38 (d, 1 H, J = 4.6 Hz, $CHNH_2$), 5.14 (s, 4 H, OCH_2Ph), 7.02 (s, 2 H), and 7.40 (s, 11 H). Anal. ($C_{27}H_{30}ClNO_3$) C, H, N.

Compound **7**·HCl was converted to the free base by treating an aqueous solution of the salt with 50% aqueous KOH and extracting the free base with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, filtered, and evaporated to give a solid residue, which was crystallized from toluene/petroleum ether (bp 30–60 °C) to yield pure **7** (1.2 g): mp 116–118 °C; IR (CCl_4) ν 3330 cm^{-1} (OH···N); ^1H NMR δ 1.18–1.72 (br, 5 H), 1.99–2.69 (br, 6 H), 3.14 (d, 1 H, J = 4.6 Hz, $CHNH_2$), 5.14 (s, 4 H , OCH_2Ph), 6.87–7.05 (m, 3 H), and 7.26–7.52 (m, 10 H). Anal. ($C_{27}H_{29}NO_3$) C, H, N.

Reaction of 7 with Phosgene. A solution of **7** (0.20 g, 0.48 mmol) in benzene (2 mL) was stratified with a solution of 10% aqueous NaOH (3.8 mL) and the resulting mixture was cooled at 0 °C and then treated dropwise with stirring with a solution of phosgene (12%) in anhydrous benzene (2 mL). After 2 h at

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(15) Daniel, A.; Pavia, A. A. *Bull. Soc. Chim. Fr.* **1971**, 1060.
(16) Tichy, M. *Advances in Organic Chemistry. Methods and Results*; Raphael, R. A., Taylor, E. C., Wynberg, H., Eds.; Interscience: New York, 1965; p 146.
(17) See for example: (a) Motohashy, M.; Nishikawa, M. *Mol. Pharmacol.* **1981**, *20*, 22. (b) DeBernardis, F.; Arendsen, D. L.; Kyncl, J. J.; Kerkman, D. J. *J. Med. Chem.* **1987**, *30*, 178, and references therein cited.

the same temperature, the organic phase was separated, washed with H_2O, filtered, and evaporated at reduced pressure to afford a solid residue (0.18 g), which was crystallized from benzene/petroleum ether (bp 30–60 °C) to yield pure cyclic carbamate **8** (0.09 g, 42%): mp 173–174 °C; IR (Nujol) ν 1735 cm^{-1} (C=O). Anal. ($C_{28}H_{27}NO_4$) C, H, N.

***endo*-3-Amino-*exo*-2-(3,4-dihydroxyphenyl)-2-hydroxybicyclo[2.2.1]heptane Hydrochloride (4a·HCl).** A solution of **7** (0.50 g, 1.2 mmol) in 1:1 CH_2Cl_2/anhydrous EtOH (20 mL) was stirred under hydrogen at 50 °C and atmospheric pressure in the presence of 10% palladium on charcoal (0.20 g). When the absorption stopped, the catalyst was filtered off and the solution was acidified to pH 5 with Et_2O·HCl. Evaporation of the solution gave a solid residue, which was crystallized from MeOH/Et_2O to yield pure **4a**·HCl (0.18 g, 55%): mp 199–201 °C dec; ^1H NMR δ 1.13–2.18 (br, 6 H), 2.38–2.76 (br, 2 H), 3.39 (d, 1 H, J = 4.5 Hz, C*H*N), and 6.63–7.18 (m, 3 H). Anal. ($C_{13}H_{18}ClNO_3$) C, H, N.

***exo*-2-(3,4-Dihydroxyphenyl)-2-hydroxy-*endo*-3-(isopropylamino)bicyclo[2.2.1]heptane Hydrochloride (4b·HCl).** A solution of **7** (0.40 g, 0.96 mmol) was dissolved in anhydrous MeOH (2 mL) and treated for 14 h with Me_2CO (2 mL). The solution was then shaken under hydrogen at 50 °C and atmospheric pressure in the presence of 10% palladium on charcoal (0.20 g). After 7 h at the same temperature, the catalyst was removed by filtration and the resulting solution was made slightly acid (ca. pH 5.5) with Et_2O·HCl. Evaporation of the solution yielded a semisolid residue, which was crystallized from MeOH/Et_2O to give pure **4b**·HCl (0.040 g, 32%): mp 158–160 °C dec; ^1H NMR δ 1.26 (2 d, 6 H, J = 6.6 Hz, CH*Me*$_2$), 1.40–2.12 (br, 6 H), 2.43–2.73 (br, 2 H), 2.54 (m, 1 H, J = 6.6 Hz, C*H*Me$_2$), 3.60 (d, 1 H, J = 4.4 Hz, C*H*NHCHMe$_2$), and 6.74–7.15 (m, 3 H). Anal. ($C_{16}H_{24}ClNO_3$) C, H, N.

Pharmacological Methods. Isolated Rat Vas Deferens. α-Adrenoceptor activity was evaluated on isolated vasa deferentia obtained from reserpinized adult albino Sprague–Dawley rats as previously described.[18]

Isolated Guinea Pig Atria and Tracheal Strips. The tests for β_1- and β_2-adrenoceptor activity were performed, in accordance to ref 2, on isolated preparations obtained from male adult guinea pigs (weight range 300–350 g).

The following drugs were used as salts: **1a** (*l*-norepinephrine) as bitartrate, **1b** (*l*-isoproterenol), carbachol, phentolamine, and the cyclic compounds **4a** and **4b**, as hydrochlorides. Reserpine was used as a free base solution (Serpasil).

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Registry No. **4a**, 118891-94-4; **4a**·HCl, 118891-92-2; **4b**, 118891-95-5; **4b**·HCl, 118891-93-3; **5**, 28043-14-3; **6**, 118891-89-7; **7**, 118920-11-9; **7**·HCl, 118891-90-0; **8**, 118891-91-1; [3,4-bis(benzyloxy)phenyl]magnesium bromide, 16047-57-7.

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Design and Synthesis of Propranolol Analogues as Serotonergic Agents

M. Edward Pierson,† Robert A. Lyon,‡ Milt Titeler,‡ Paul Kowalski,‡ and Richard A. Glennon*,†

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0581, and Department of Pharmacology and Toxicology, Neil Hellman Medical Research Building, Albany Medical College, Albany, New York 12208. *Received August 22, 1988*

Serotonin (5-HT) binds with nearly identical affinity at the various central 5-HT binding sites. Few agents bind with selectivity for 5-HT_{1A} sites. The β-adrenergic antagonist propranolol binds stereoselectively both at 5-HT_{1A} and 5-HT_{1B} sites (with a several-fold selectivity for the latter) and, whereas it is a 5-HT_{1A} antagonist, it appears to be a 5-HT_{1B} agonist. As such, it could serve as a lead compound for the development of new 5-HT_{1A} and 5-HT_{1B} agents. The purpose of the present study was to modify the structure of propranolol in such a manner so as to reduce its affinity for 5-HT_{1B} and β-adrenergic sites while, at the same time, retaining its affinity for 5-HT_{1A} sites. Removal of the side-chain hydroxyl group of propranolol, and conversion of its secondary amine to a tertiary amine, reduced affinity for 5-HT_{1B} and β-adrenergic sites. In addition, shortening the side chain by one carbon atom resulted in compounds with affinity for hippocampal 5-HT_{1A} sites comparable to that of racemic propranolol, but with a 30- to 500-fold lower affinity for 5-HT_{1B} sites and a greater than 1000-fold lower affinity for β-adrenergic sites. The results of these preliminary studies attest to the utility of this approach for the development of novel serotonergic agents.

The last several years have seen a growing interest in the neurotransmitter serotonin (5-HT); this is primarily due to the identification of several central 5-HT binding sites (i.e., 5-HT_1, 5-HT_2, 5-HT_3 sites) and the realization that these sites may be responsible for controlling various physiological functions of 5-HT. Of the various populations of central 5-HT binding sites, the 5-HT_{1A} sites have perhaps been the best studied and have generated the most interest.[1,2] It has been proposed that 5-HT_{1A} receptors may be involved in, for example, temperature regulation, sexual activity, appetite control, and, most recently, the mechanism of action of a new class of anxiolytic agents (i.e., second-generation arylpiperazine anxiolytics).[1-3]

The most useful and selective 5-HT_{1A} agonist is 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; **1**), and [^3H]8-OH-DPAT is now employed as a radioligand to label 5-HT_{1A} sites.[2] At one time, it was suspected that 5-HT_1 sites might represent "agonist" sites and that 5-HT_2 sites were "antagonist" sites [for discussion, see ref 1 and 3]. Currently, there is little support for this notion; nevertheless, there is still a lack of 5-HT_{1A}-selective antagonists. To date, the only agents consistently shown to behave as 5-HT_{1A} antagonists (other than a few nonselective

† Virginia Commonwealth University.
‡ Albany Medical College.

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