Synthesis and Anticholinesterase Activity of (-)-N^1-Norphysostigmine, (-)-Eseramine, and Other N(1)-Substituted Analogues of (-)-Physostigmine

Qian-Sheng Yu,,† John R. Atack, Stanley I. Rapoport, and Arnold Brossi*,†

Medicinal Chemistry Section, Laboratory of Analytical Chemistry, NIDDK, Laboratory of Neurosciences, NIA, National Institutes of Health, Bethesda, Maryland 20892. *Received March 28, 1988*

(-)-N^1-Benzylnorphysostigmine (4), prepared from synthetic (-)-*O*-methyl-N^1-noreseroline (1) by N-benzylation, ether cleavage, and reaction of (-)-N^1-benzylnoreseroline (3) with methyl isocyanate, was the intermediate used to prepare the title compounds. Catalytic debenzylation of 4 afforded (-)-N^1-norphysostigmine (5), and (-)-eseramine (6) was obtained by reaction of 5 with methyl isocyanate. Reductive N-methylation of 5 gave (-)-physostigmine (9) while reaction of 5 with allyl bromide and phenethyl bromide afforded carbamates 7 and 8, respectively. Data on the in vitro potencies (IC_{50}) and activities of certain of these compounds (4–8) as inhibitors of electric eel acetyl cholinesterase are reported. (-)-N^1-Norphysostigmine (5) was found to be similarly potent against AChE as (-)-physostigmine (9).

(-)-Physostigmine ((-)-Phy, 9), the major alkaloid from Calabar beans,[1,2] inhibits acetylcholinesteras (AChE)[3] and is used clinically in the treatment of glaucoma[4] and myestenia gravis[5] and protects against organophosphate poisoning.[6] There is relatively little information available on structural modifications at the N(1) nitrogen. This substitution seems important for the anti-AChE effect as demonstrated with the highly potent (-)-physovenine, which as an oxygen atom instead of the N(1) nitrogen atom, and with the low activity reported for (-)-eseramine, a natural alkaloid that has the N(1) nitrogen substituted with a methylcarbamoyl group.[2] N(1)-Substituted analogues of Phy are not easily available by classical routes, since the Julian total synthesis is directed to N^1-methyl-substituted (-)-eserethole as the crucial intermediate.[7] In addition, N-demethylation of ethers like eserethole with chloroformates leads to ring-open products.[8] With the availability of (-)-*O*-methyl-N^1-noreseroline (1) by a modification of the Julian synthesis,[9] we were able to prepare the compounds shown in Figure 1, including (-)-N^1-norphysostigmine (5), a putative metabolite of (-)-physostigmine,[10] and the naturally occurring alkaloid (-)-eseramine (6)[11] prepared synthetically in racemic form.[12] We also made the *N*-allyl derivative 7 and the *N*-phenethyl analogue 8 with N-substitution known to often potentiate pharmacological effects.[13] Reductive N-methylation of (-)-N^1-norphysostigimine (5) to (-)-Phy (9) represents a vairation of the route to the natural alkaloid chosen earlier.

Chemistry

(±)-*O*-Methylnoreseroline obtained by total synthesis affords with (*S*)-(-)-1-phenylethyl isocyanate two ureas which are separated by chromatography. The slower moving urea 10 (silica gel; CH_2Cl_2/MeOH, 100:1) is hydrolyzed with sodium pentoxide in refluxing pentanol to amine 1 isolated as a fumarate salt and used to prepare the compounds listed in Figure 1. Benzylation of 1 with benzyl bromide in DMF in the presence of potassium carbonate afforded oily 2 purified by chromatography. Demethylation of 2 with boron tribromide in dichloromethane followed procedures used earlier[14,15] to afford phenol 3, which reacted with methyl isocyanate in ether to give the oily carbamate 4. Conversion of 4 into (-)-N^1-norphysostigmine (5) was achieved by reduction over $Pd(OH)_2$[16] catalyst in methanol, and 5 was isolated as the highly crystalline fumarate salt. Reaction of 5 with methyl isocyanate gave (-)-eseramine (6), which gave physical data identical with those reported in the literature.[11] This synthesis of 6 is much superior to that used to prepare (-)-6[17] by a direct N-methylcarbamoylation of (-)-N^1-noreseroline.[15] Allylation and phenethylation of 5 was carried out with the fumarate salt in acetonitrile by addition of potassium carbonate to afford, after usual workup and chromatography, the oily bases 7 and 8 converted into salicylates. Reductive N-methylation of the fumarate salt

Table I. Comparison of IC_{50} of (-)-Physostigmine and N(1)-Substituted Analogues against Electric Eel Acetylcholinesterase[a]

compound	IC_{50}, NM	relative potency, %
physostigmine (9)	61 ± 18	100
norphysostigmine (5)	56 ± 2	109
N^1-allylnorphysostigmine (7)	69 ± 25	81
N^1-benzylnorphysostigmine (4)	990 ± 450	5
N^1-phenethylnorphysostigmine (8)	1030 ± 410	5
eseramine (6)	9300 ± 1500	0.7
neostigmine	87 ± 8	70
isofluorophate/DFP	480 ± 400	13

[a] Values shown are mean ± standard deviation of three to five assays.

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(9) Schönenberger, B.; Brossi, A. *Helv. Chim. Acta* **1986**, *69*, 1486.
(10) Although (-)-N^1-norphysostigmine has not been reported to be a putative metabolite, the ease of N-demethylation of tertiary amines in metabolic conversion in particularly the series of many centrally acting drugs, such as opiates, is well demonstrated.
(11) Robinson, B.; Spiteller, G. *Chem. Ind.* **1964**, 459.
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(13) For example, see: Hellerbach, J.; Schnider, O.; Bejendorf, H.; Pellmont, B. In *Synthetic Analgetics*; Pergamon: Oxford, 1966; p 75.
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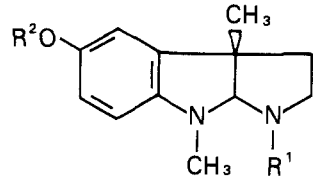
(15) See ref 8.
(16) Aldrich Chem. Co., catalogue 1986–1987, No. 21, 291-1.
(17) Reaction of (-)-*O*-methyl-N^1-noreseroline with methyl isocyanate afforded in our hands a mixture of products from which (-)-eseramine could only be isolated in 15% yield after tedious chromatography.

† NIDDK.
‡ NIA.



1: $R^1 = H, R^2 = CH_3$
2: $R^1 = Bn, R^2 = CH_3$
3: $R^1 = Bn, R^2 = H$
4: $R^1 = Bn, R^2 = CONHCH_3$
5: $R^1 = H, R^2 = CONHCH_3$
6: $R^1 = CONHCH_3, R^2 = CONHCH_3$
7: $R^1 = CH_2CH{=}CH_2, R^2 = CONHCH_3$
8: $R^1 = CH_2CH_2Ph, R^2 = CONHCH_3$
9: $R^1 = CH_3, R^2 = CONHCH_3$
10: $R^1 = PhCHNHCO, R^2 = Me$ (CH_3)

Figure 1.

of **5** afforded **9**, which was isolated as a salicylate and found to be identical with a commercial sample in every respect.[18]

Biological Evaluation

Compounds were evaluated in vitro for inhibition of acetylcholinesterase from electric eel. Since the carbamoyl group in Phy is required for anticholinesterase action[19] and since (-)-eseroline inhibited AChE from electric eel about 400 times less than (-)-Phy,[20] we considered a reevaluation of **1–3** unnecessary.

Results. A comparison of the IC_{50} values of (-)-Phy (**9**), N^1-norphysostigmine (**5**), N^1-allylnorphysostigmine (**7**), N^1-benzylnorphysostigmine (**4**), N^1-phenethylnorphysostigmine (**8**), and eseramine (**6**) is presented in Table I and representative plots of percent activity/log concentration and logit/log concentration are shown in Figure 2. N-(1)-Demethylation of Phy, or replacing the methyl group at N(1) with an allyl group, does not seem to greatly alter the potency of the compound since the IC_{50} values of Phy and its nor and allyl derivatives were very similar (61 ± 18, 56 ± 2, and 69 ± 25 nM, respectively). However, substitution with the more bulky benzyl and phenethyl groups reduces the potency by approximately 20-fold (IC_{50} = 990 ± 450 and 1030 ± 410 nM, respectively). Eseramine was a relatively poor antiacetylcholinesterase compound with an IC_{50} value of 9300 ± 1500 nM and had only 0.7% of the potency of (-)-Phy (**9**).[1]

Discussion. (-)-N^1-Norphysostigmine (**5**), prepared here by debenzylation of **4**, served as a useful intermediate to prepare natural (-)-eseramine (**6**) and the N(1)-alkylated analogues **7** and **8**. Successful N-methylation of **5** to (-)-physostigmine (**9**) completes yet another variation of the Julian total synthesis of this alkaloid. Substitution with bulky groups at this position such as present in the benzyl- and phenethylnorphysostigmine analogues (**4** and **8**, respectively) greatly reduced the potency of the compound. In this respect, it is interesting to note that the putative metabolite (-)-N^1-norphysostigmine (**5**) is equally potent in this assay as (-)-Phy (**9**).

The active site of AChE consists of two sites: the esteratic site (which contains the activated serine residue and is where the inactive acylated enzyme intermediate is formed when the carbonyl group bond of the R^2 side chain of Phy is cleaved) and an adjacent anionic site that is

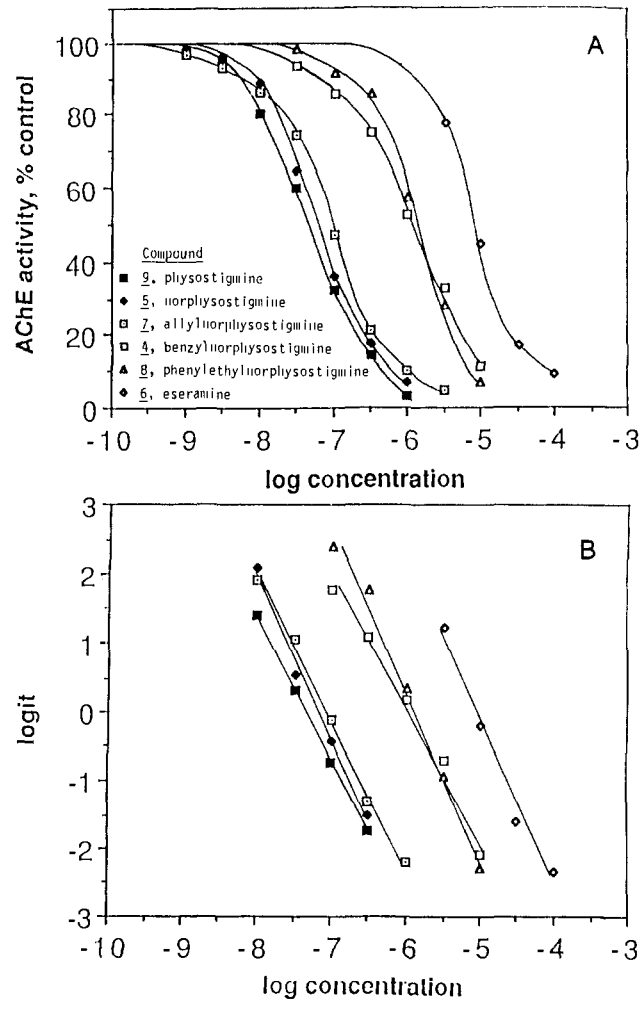


Figure 2. Representative plots of (A) acetylcholinesterase (AChE) activity (expressed as a percentage of activity in the absence of compound versus -log concentration ($M - 1$) and (B) logit [ln [% activity/(100 - % activity)]] versus -log concentration.

important for the orientation of molecules with respect to the esteratic site. Bulky groups at the N(1) position presumably alter the positioning of the compound so that it can be no longer conveniently occupy both the anionic and esteratic sites, thereby reducing the ability of the physostigmine carbonyl group to interact with the esteratic site.

Conclusions. The findings that (-)-N^1-norphysostigmine (**5**) inhibits AChE in vitro similarly as (-)-Phy (**9**) marks the secondary amine **5** as an interesting compound. Further biochemical and pharamacological studies with **5** and carbamate analogues of **9** including their inhibition of other esterases have been initiated.[21]

Experimental Section

Chemistry. Melting points were determined on Fisher-Johns melting point apparatus, and optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. ^1H NMR spectra were measured on a Varian XL-300 (300 MHz) spectrometer, and chemical shifts are reported in δ with tetramethylsilane as internal reference. Mass spectra were taken on a Finigan 1015 D instrument (CI). Silica gel GHLF plates from Analtech, Inc. were used for TLC. Flash column chromatography was done with Kieselguhr 60 (Merck; 40–63 μm).

(-)-*O*-Methyl-N^1-noreseroline (1). Sodium (8.05 g) was dissolved in pentanol (350 mL), and after its disappearance urea **10** (7.99 g, 21.86 mmol) was added, and the reaction mixture was

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refluxed for 2 h in a nitrogen atmosphere. After evaporation of solvent under vacuum, the residue was dissolved in H_2O (150 mL) and extracted with Et_2O (2 × 200 + 2 × 100). The extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, concentrated, and then added to a saturated ethanol solution of fumaric acid (3.04 g). Crystallization gave fumarate of 1 (6.95 g, 95%): mp 197–198 °C; $[\alpha]_D$ −68.2° (c 0.5, MeOH). Anal. ($C_{13}H_{18}N_{20}\cdot C_4H_4O_4$) C, H, N.

The physical properties of base obtained from the above salt was identical with published data.

(-)-**N^1-Benzyl-*O*-methylnoreseroline (2)**. The fumarate of 1 (2 g, 5.98 mmol) was dispersed between a mixture of $NaHCO_3$ solution (2 M, 50 mL) and ether (400 mL) by shaking. The ether layer was separated and dried over Na_2SO_4 to give, after evaporation of solvent, an oily base. The base was dissolved in CH_3CN (30 mL) and K_2CO_3 (30 mg) and benzyl bromide (2.03 g, 11.92 mmol) added, and the reaction mixture was stirred for 1 h at room temperature in a nitrogen atmosphere. After evaporation of solvent, the residue was flash chromatographed on silica gel column (CH_2Cl_2/MeOH, 100:1) to give **2** as an oil (1.3 g, 70.5%): $[\alpha]_D$ −51.4° (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.46 (s, 3 H, C10-CH_3), 1.92 (m, 2 H, C3-H_2), 2.62–2.74 (m, 2 H, C2-H_2), 2.77 (s, 3 H, N8-CH_3), 3.75 (s, 3 H, OCH_3), 3.86 (d, 1 H, J_{gem} = 13, PhCH′-H), 3.98 (d, 1 H, J_{gem} = 13, PhCH-H′), 4.28 (s, 1 H, C9-H), 6.35 (d, $J_{6,7}$ = 9, C7-H), 6.64–6.67 (m, 2 H, C4-H and C6-H), 7.24–7.42 (m, 5 H, aromatic H); MS(CI), m/z 309 (M^+ + 1). Anal. ($C_{20}H_{24}N_2O$) C, H, N.

(-)-**N^1-Benzyleseroline (3)**. Compound **2** (1.3 g, 4.22 mmol) was dissolved in CH_2Cl_2 (20 mL), and a CH_2Cl_2 solution of BBr_3 (1.0 M, 20 mL) was added dropwise with stirring. The reaction mixture was stirred for 1 h at room temperature in a nitrogen atmosphere. After evaporation of solvent, the residue was dissolved in MeOH (20 mL) and stirred for 5 min. The solvent was evaporated again, and the residue dissolved in H_2O (20 mL), basified with $NaHCO_3$, extracted with Et_2O (2 × 100 + 2 × 50 mL), washed with brine (50 mL), and dried (Na_2SO_4). Evaporation of solvent gave **3** as a foam (1.2 g, 96.7%): $[\alpha]_D$ −60.2° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.57 (s, 3 H, C10-CH_3), 1.91 (m, 2 H, C3-H_2), 2.59–2.67 (m, 2 H, C2-H_2), 2.76 (s, 3 H, N8-CH_3), 3.86 (d, 1 H, J_{gem} = 13, PhCH′-H), 3.98 (d, 1 H, J_{gem} = 13, PhCH-H′), 4.27 (s, 1 H, C9-H), 6.30 (m, 1 H, C7-H), 6.56 (m, 2 H, C4-H and C6-H), 7.22–7.42 (m, 5 H, aromatic H); MS(CI), m/z 295 (M^+ + 1). Anal. ($C_{19}H_{22}N_2O\cdot{}^1/_4H_2O$) C, H, N.

(-)-**N^1-Benzylnorphysostigmine (4)**. Compound **3** (2.47 g, 8.39 mmol) was dissolved in anhydrous Et_2O (200 mL), and then five pieces of Na (each about 5 mg) were added. After the mixture was stirred for 1.5 min at room temperature, methyl isocyanate (0.57 g, 10.07 mmol) was added dropwise during 5 min. The mixture was stirred for 30 min at room temperature in nitrogen atmosphere. After evaporation of solvent, the residue was flash chromatographed on silica gel column (CH_2Cl_2/MeOH, 100:1) to give **4** as a gum (2.1 g, 71.43%): $[\alpha]_D$ −35.6° (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H, C10-CH_3), 1.91 (m, 2 H, C3-H_2), 2.60–2.76 (m, 2 H, C2-H), 2.79 (s, 3 H, N8-CH_3), 2.87 (d, 3 H, J = 5, $CONHCH_3$), 3.86 (d, 1 H, J_{gem} = 13, PhCH′-H), 3.98 (d, 1 H, J_{gem} = 13, PhCH-H′), 4.34 (s, 1 H, C9-H), 6.32 (m, 1 H, C7-H), 6.77 (m, 2 H, C4-H and C6-H), 7.22–7.41 (m, 5 H, aromatic H); MS(CI), m/z 352 (M^+ + 1). Anal. ($C_{21}H_{25}N_3O_2$) C, H, N.

(-)-**N^1-Norphysostigmine (5)**. Compound **4** (2.1 g, 5.97 mmol) was dissolved in MeOH (200 mL), and palladium hydroxide on carbon (40 mg) was added. After hydrogenation under atmospheric pressure for 1 h, the palladium catalyst was filtered through Celite and the solvent was evaporated by vacuo. The residue was dissolved in Et_2O (20 mL) and EtOH (0.5 mL) was added to make a clear solution to which was added a saturated alcohol solution of fumaric acid (830 mg). After the mixture was kept at 4 °C overnight, a crude fumarate of **5** was obtained, which was recrystallized from EtOH to give the fumarate of **5** as white cyrstals (1.68 g, 74.20%): mp 178–180 °C; $[\alpha]_D$ −65.8° (c 1, MeOH); ^1H NMR (D_2O) δ 1.47 (s, 3 H, C10-H), 2.20–2.50 (m, 2 H, C3-H_2), 2.78 (s, 3 H, N8-CH_3), 2.80–3.45 (m, 2 H, C2-H_2), 3.02 (s, 3 H, $CONHCH_3$), 5.17 (s, 1 H, C9-H), 6.62 (m, 1 H, C7-H), 7.02 (m, 2 H, C4-H and C6-H); MS(CI), m/z 262 (M^+ + 1). Anal. Calcd ($C_{14}H_{19}O_2\cdot C_4H_4O_4$) C, H, N.

(-)-**Eseramine (6)**. The fumarate of **5** (29 mg, 0.076 mmol) was shaken with a mixture of $NaHCO_3$ (2 M, 2 mL) and ether (10 mL). The ether layer was separated, washed with brine (1 mL), and dried with Na_2SO_4 to give, after evaporation of solvent, the base of **5**. The base was dissolved in Et_2O (5 mL), then methyl isocyanate (0.1 mL) was added, and shaking was continued during which a precipitate appeared. After evaporation of solvent in vacuo, the residue was crystallized from EtOH to give **6** as white crystals (24 mg, 98%): mp 227–229 °C (lit.[22] mp 216–218 or 240–242 °C); $[\alpha]_D$ −274.1° (c 0.25, EtOH) (lit.[22] $[\alpha]_D$ −289° in EtOH); MS(CI), m/z 319 (M^+ + 1). Anal. ($C_{16}H_{22}N_4O_3$) C, H, N.

(-)-**N^1-Allylnorphysostigmine (7)**. The fumarate of **5** (200 mg, 0.53 mmol) and K_2CO_3 (100 mg) were added to CH_3CN (10 mL). Then allyl bromide (1 mL) was added to the mixture, which was then stirred at room temperature in a nitrogen atmosphere for 4 h. After evaporation of solvent, the residue was flash chromatographed on a silica gel column (CH_2Cl_2/MeOH, 100:1) to give **7** as a gum (99 mg, 62.0%): $[\alpha]_D$ −95.3° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H, C10-CH_3), 1.92 (m, 2 H, C3-H_2), 2.61–2.82 (m, 2 H, C2-H_2), 2.87 (s, 3 H, N8-CH_3), 2.88 (d, 3 H, $CONHCH_3$), 3.31–3.49 (m, 2 H, N1-CH_2), 4.24 (s 1 H, C9-H), 4.86 (br s, 1 H, N-H), 5.11–5.26 (m, 2 H, =CH_2), 5.91–6.00 (m, 1 H, =CH), 6.30 (m, 1 H, C7-H), 6.77 (m, 2 H, C4-H and C6-H); MS(CI), m/z 302 (M^+ + 1). Anal. ($C_{17}H_{23}N_3O_2$) C, H, N.

7 (20 mg) was dissolved in Et_2O (1 mL), and an ether solution (1 mL) of salicylic acid (11 mg) was added to the above solution. Staying overnight at 4 °C gave the salicylate of **7** as white crystals (23 mg, 78.86%): mp 72–74 °C; $[\alpha]_D$ −100.9° (c 1, EtOH). Anal. ($C_{17}H_{23}N_3O_2\cdot C_7H_6O_3\cdot{}^1/_2H_2O$) C, H, N.

(-)-**N^1-Phenethylnorphysostigmine (8)**. The fumarate of **5** (200 mg, 0.53 mmol) and K_2CO_3 (100 mg) were added to CH_3CN (10 mL), and then (2-bromoethyl)benzene and KI (2 mg) were added. The mixture was stirred for 60 h at room temperature in a nitrogen atmosphere. Evaporation of the solvent gave a brown residue which was flash chromatographed on a silica gel column (CH_2Cl_2/MeOH, 100:1) to give **8** as a foam (50 mg, 26%): $[\alpha]_D$ −152.5° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H, C10-CH_3), 1.91–1.98 (m, 2 H, C3-H_2), 2.81–3.03 (m, 12 H, N8-CH_3, $NHCH_3$, N1-CH_2, $PhCH_2$, and C2-H_2), 4.52 (s, 1 H, C9-H), 4.86 (br s, 1 H, NH), 6.30 (m, 1 H, C7-H), 6.77 (m, 2 H, C4-H and C6-H), 7.18–7.32 (m, 5 H, aromatic H); MS(CI), m/z 366 (M^+ + 1).

8 (20 mg) was dissolved in Et_2O (1 mL), and an ether solution (1 mL) of salicylic acid (10 mg) was added to the above solution. When the mixture was left overnight at 4 °C, the salicylate of **8** was recovered as a powder (21 mg, 80%): $[\alpha]_D$ −127.1° (c 0.3, EtOH). Anal. ($C_{22}H_{27}N_3O_2\cdot C_7H_6O_3\cdot{}^1/_2H_2O$) C, H, N.

(-)-**Physostigmine (9)**. The fumarate of **5** (50 mg, 0.13 mmol) was dissolved in MeOH (1 mL), and then Et_3N (0.05 mL) and CH_2O (0.08 mL) were added. The reaction mixture was stirred for 2 h at room temperature in a nitrogen atmosphere. After the mixture was cooled to 0 °C, $NaBH_4$ (23 mg) was added slowly, and the mixture was stirred for 0.5 h at room temperature. The residue obtained after evaporation of solvent was dissolved in 2 N HCl (4 mL). The solution was washed with Et_2O (5 mL), basified with saturated $NaHCO_3$, and extracted with Et_2O (4 × 10 mL). The Et_2O solution was washed with brine (5 mL) and dried with Na_2SO_4. Evaporation of solvent gave a crude product of **9** as a gum (40 mg, 97.19%). The base of **9** was dissolved in Et_2O (1 mL), and to make a clear solution the mixture was added to an Et_2O solution (1 mL) of salicylic acid (30 mg). After the mixture was allowed to stand overnight at 4 °C, the crystalline salicylate of **9** was recrystallized from EtOH to give the pure salicylate of **9** (35 mg, 62.70%): mp 180–184 °C (Fluka: 180–184 °C); mp of mixture with standard sample was not decreased; $[\alpha]_D$ −78° (c 1, EtOH) (Fluka: −77 ± 2°).

Biology. AChE activity was determined by the spectrophotometric method of Ellman[23] using 0.5 mM acetyl-β-methylthiocholine as a specific substrate for AChE in an incubation volume of 1.0 mL. Aliquots of 1:40 000 diluted AChE (electric eel, type III, 1000 units/mg of protein, Sigma Chemical Co., St. Louis, MO) were incubated at 37 °C in varying concentrations (10^{-4} to 10^{-10} M) of compound, and the concentrations of 4–8

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required to inhibit acetycholinesterase activity in vitro by 50% (IC_{50}) were compared to that of (-)-Phy (9). A preincubation of 30 min was used for each assay prior to initiation of the reaction (addition of the substrate). The production of a yellow 5-mercapto-2-nitrobenzoate anion was followed spectrophotometrically at a wavelength of 412 nm.

Registry No. 1, 104069-11-6; 1·fumarate, 116181-31-8; 2, 116103-15-2; 3, 116103-16-3; 4, 116103-17-4; 5, 116103-18-5; 5·fumarate, 116181-32-9; 6, 6091-57-2; 7, 116103-19-6; 7·salicylate, 116181-33-0; 8, 114546-08-6; 8·salicylate, 116181-34-1; 9, 57-47-6; 9·salicylate, 57-64-7; 10, 107485-89-2; $Br(CH_2)_2Ph$, 103-63-9; $BrCH_2CH{=}CH_2$, 106-95-6.

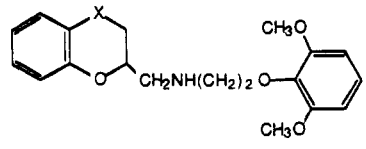
Structure-Activity Relationships in 1,4-Benzodioxan-Related Compounds. Investigation on the Role of the Dehydrodioxane Ring on α_1-Adrenoreceptor Blocking Activity

Maria Pigini, Livio Brasili, Mario Giannella, Dario Giardinà, Ugo Gulini, Wilma Quaglia, and Carlo Melchiorre*

Department of Chemical Sciences, University of Camerino, 62032 Camerino (MC), Italy. *Received April 27, 1988*

Several analogues of 2-[[[2-(2,6-dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxan (WB 4101, 1) were prepared and evaluated for their blocking activity on α_1- and α_2-adrenoreceptors in the isolated rat vas deferens. The results were compared with those obtained for 1 and benoxathian (2). It was shown that the two oxygens at positions 1 and 4 may have a different role in receptor binding. It seems that the oxygen at position 4 as such does not contribute to the binding while it is important in stabilizing an optimal conformation for drug-receptor interaction mechanism. On the other hand, the oxygen at position 1 might interact with a receptor polar pocket of reduced size by way of a donor-acceptor dipolar interaction. Furthermore, it was shown that replacement of the dehydrodioxane ring of 1 by a phenyl or a pyrrole nucleus causes a significant decrease in activity.

Benzodioxans represent one of the oldest and best known classes of α-adrenoreceptor antagonists whose chemical structure incorporates a 1,4-benzodioxan-2-yl moiety as a basic feature.[1] Structure-activity relationship studies have revealed that the preferential selectivity toward α_1- or α_2-adrenoreceptors depends on the 2-substituent of the benzodioxan moiety. In fact, 2-[[[2-(2,6-dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxan (WB 4101, 1)[2] and 2-(1,4-benzodioxan-2-yl)-2-imidazoline (idazoxan, RX 781094)[3] both carrying a benzodioxan nucleus but having a different 2-substituent proved to be potent and highly selective α_1- and α_2-adrenoreceptor antagonists, respectively. Several investigations were devoted to improving both activity and selectivity of 1.[1] Both benzodioxan and (2,6-dimethoxyphenoxy)ethyl moieties were reported to be essential for activity.[4] In contrast with this view, however, we showed that opening of the dehydrodioxane ring of 1 did not result in a loss of α_1-adrenoreceptor blocking activity.[5,6] Furthermore, the replacement of the ring oxygen at position 4 of the dehydrodioxane ring of 1 with a sulfur atom, giving benoxathian (2), did not modify the biological profile but rather gave a potent and highly selective α_1-adrenoreceptor antagonist.[7,8]



1 (WB4101): X=O
2 (benoxathian): X=S

The objectives of this study were to clarify the role of the dehydrodioxane ring and in particular of the oxygens at positions 1 and 4 of 1 in drug-receptor interaction. To this end, we describe here the synthesis and the pharmacological profile in the isolated rat vas deferens of several compounds (3-12) related to 1 and 2. Furthermore, to evaluate a possible role of π electrons, the dehydrodioxane moiety of 1 was replaced by a phenyl ring as in 13 and 14. Since the indole system is present in the structure of some α_1-adrenoreceptor antagonists such as corynanthine[9] and indoramin,[10] we included in this study compound 15, which bears that moiety instead of a benzodioxan nucleus.

Chemistry. All the compounds were synthesized by standard procedures and were characterized by IR, ^1H NMR, and elemental analysis. Their structure is shown in Scheme I and Table I.

Oxidation of 2[7] with hydrogen peroxide, in different conditions, gave sulfone 5 or a mixture of the corresponding sulfoxides 3 and 4, which were separated by column chromatography. The structure of the isomeric sulfoxides was attributed on the basis of their ^1H NMR spectra with measurement of the deshielding effect caused by the heteronuclear substituent on the proton at position 2 of the dehydrodioxane ring. Thus, a trans relation between the sulfoxide function and the side chain was as-

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