Absolute Configuration of Glycerol Derivatives. 7.[1] Enantiomers of 2-[[[2-(2,6-Dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxane (WB-4101), a Potent Competitive α-Adrenergic Antagonist

Wendel L. Nelson,* Mark L. Powell,

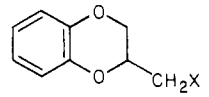
Department of Pharmaceutical Sciences, University of Washington, Seattle, Washington 98195

and Donald C. Dyer

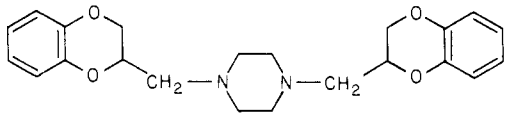
Department of Veterinary Pharmacology and Physiology, Iowa State University, Ames, Iowa 50011. *Received March 22, 1979*

The enantiomers of 2-[[[2-(2,6-dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxane (4) were prepared from the chiral 2-[(tosyloxy)methyl]-1,4-benzodioxanes [(2*S*)- and (2*R*)-**5**]. The corresponding (2*R*)- and (2*S*)-2-(aminomethyl)-1,4-benzodioxanes [(2*R*)- and (2*S*)-**7**] were prepared by a modified Gabriel synthesis and converted to the enantiomers of 4 by condensation with 2,6-dimethoxyphenoxyacetaldehyde (**8**) and reduction of the intermediate imine with $NaBH_4$. The enantiomer (2*S*)-4 was 40–50 times as potent as the enantiomer (2*R*)-**4** in antagonizing the α-adrenergic response of methoxamine-induced contraction of rabbit aortic strips, showing a $pA_2 = 9.0$. This result is consistent with the previous observation that *S* enantiomers of 2-[(alkylamino)methyl]benzodioxanes are more potent antagonists at α-adrenergic receptors than the *R* enantiomers.

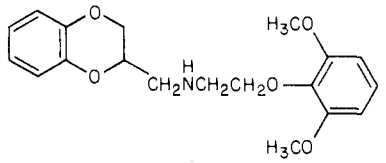
Several 2-[(alkylamino)methyl]benzodioxanes have been of considerable interest because of their antihypertensive potential based on α-adrenergic receptor blocking activity and because of other pharmacological properties.[2-4] Among early members of interest were 2-[(diethylamino)-methyl]benzodioxane (prosympal; **1**),[3-5] 2-(piperidino-



1, X = NEt_2
2, X = piperidinyl



3

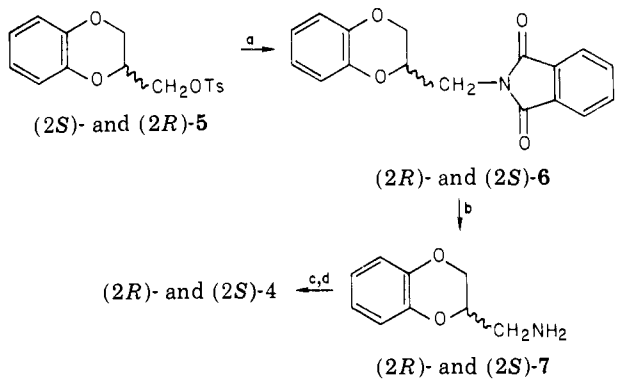


4

methyl)benzodioxane (piperoxan; **2**),[5-11] and dibozane (**3**).[7-11] Other related derivatives, e.g., guanoxan,[12] acetoxatrine,[13] and spiroxamide,[14] have also been extensively studied.

In 1969, Green[15] reported the synthesis of several 2-[[*N*-[(aryloxy)alkyl]amino]methyl]-1,4-benzodioxanes which had incorporated into the aryloxylalkyl group structural features found to be important in imparting antihypertensive properties into members of a series of α-adrenergic receptor antagonist *N*-[(aryloxy)alkyl]-phenethylamines.[16,17] The most potent agent in this series was **4** (WB-4101), which in mice protected against epinephrine toxicity at a dose of 0.2–0.3 mg/kg[15,18] when given orally. Prosympal and piperoxan (**1** and **2**) are ineffective at 50 mg/kg in this assay.[15,19] Additionally, **4** was a potent antagonist of the epinephrine- and norepinephrine-induced increase in blood pressure. More recently, **4** has been shown to be a very potent postsynaptic α-adrenergic receptor antagonist in rat vas deferens tissue ($pA_2 = 9.8$),[20-22] less potent as a presynaptic antagonist ($pA_2 = 6.24$),[22] and is tightly bound in α-adrenergic receptor preparations from central nervous system tissue, $-\log K_D = 9.2$.[23]

Scheme I



(2*S*)- and (2*R*)-**5**

(2*R*)- and (2*S*)-**6**

(2*R*)- and (2*S*)-4

(2*R*)- and (2*S*)-**7**

a, potassium phthalimide; b, hydrazine hydrate; c, 2,6-dimethoxyphenoxyacetaldehyde; d, sodium borohydride

Our investigation of the 2-[(alkylamino)methyl]-benzodioxanes has focused on preparation of individual enantiomers of known absolute configuration from simple chiral starting materials. In an earlier study, we prepared the 2*R* and 2*S* enantiomers of **1**–**3** (*R*,*R* and *S*,*S*) and noted differences in their activity in α-adrenergic receptor preparations.[24] Because of the reported high order of activity of **4**, we have extended this study to include it. In this paper, the synthesis of (2*R*)- and (2*S*)-**4** and their activity in an α-adrenergic receptor preparation are reported.

Synthesis. The individual enantiomers (2*R*)- and (2*S*)-2-(aminomethyl)-1,4-benzodioxanes [(2*R*)- and (2*S*)-**7**] were prepared from the (2*S*)- and (2*R*)-2-[(tosyloxy)-methyl]-1,4-benzodioxane enantiomers [(2*S*)- and (2*R*)-**5**], respectively,[24,25] by a modified Gabriel synthesis, similar to that reported by Green[15] (phthalimide displacement of a primary halide). The amines obtained after hydrazinolysis of intermediate phthalimides (2*R*)- and (2*S*)-**6** were obtained as oils: bp 75 °C (0.08 mm); (2*R*)-**7**, $[\alpha]_D$ +58.5°; (2*S*)-**7**, $[\alpha]_D$ −57.8°. Whereas Green chose to prepare and utilize 2,6-dimethoxyphenoxyethyl chloride[15] to complete the synthesis, we allowed (2*R*)- and (2*S*)-**7** to condense with 2,6-dimethoxyphenoxyacetaldehyde (**8**) and reduced the intermediate imines with $NaBH_4$ (Scheme I). Aldehyde **8** was prepared from 2,6-dimethoxyphenol and α-bromoacetaldehyde diethyl acetal. Carefully controlled conditions were required for the hydrolysis of intermediate acetal **9** to aldehyde **8** in order to prevent decomposition.

0022-2623/79/1822-1125$01.00/0

Table I. Competitive Antagonist Effects of Chiral Benzodioxanes on Methoxamine-Induced Contraction of Rabbit Aortic Strips

compd	pA_2[a,b]	S/R ratio
(2S)-4	9.02 ± 0.33 (6)	
(2R)-4	7.35 ± 0.29 (5)	47
racemic 4	8.83 ± 0.33 (6)	

[a] Plus or minus SEM (n). [b] The slopes of the Schild plots were 0.96 ± 0.17 for (2S)-4, 0.86 ± 0.16 for (2R)-4, and 0.94 ± 0.08 for racemic 4, respectively, consistent with competitive inhibition.

The final products were obtained as HCl salts: (2R)-4 [from (2S)-5], $[\alpha]_D$ +46.1°; (2S)-4 [from (2R)-5], $[\alpha]_D$ −45.0°. The circular dichroism spectra of (2R)- and (2S)-4 were similar to those of the corresponding enantiomers of 1–3 previously reported,[24] showing a short-wavelength maximum at ca. 230 nm, $[\theta] \simeq 12000$, and showing two nearly overlapping long-wavelength maxima at ca. 275 and 280 nm, $[\theta] \simeq 1300$, of opposite sign from the short-wavelength transition. The 2R enantiomer of 4 showed positive Cotton effects in the 275–280-nm region and a negative transition in the 230-nm region. The 2S enantiomer of 4 showed an inverted CD spectrum.

Pharmacological Testing. The compounds were tested for α-adrenergic antagonist effects in rabbit aortic strips using methoxamine as the agonist. Results appear in Table I. The 2S enantiomer is more potent than the 2R enantiomer, by a factor of ca. 40- to 50-fold, 1.6–1.7 log units. In separate experiments in rabbit stomach and aortic tissues, using phenylephrine as the agonist, a 35- to 40-fold difference between the 2S and 2R enantiomers (2S > 2R) was noted.[26]

Discussion

In our previous paper, we rationalized the up to ca. 20-fold greater α-adrenergic antagonist activity of the 2S enantiomer of the 2-[(alkylamino)methyl]benzodioxanes (1–3) over the 2R enantiomer in terms of the preferred conformation of the more active benzodioxane enantiomer having a closer relationship to the conformation of (R)-epinephrine.[22] However tenuous this argument may be, it does explain the data. The results in this study are similar to those of the previous study, with about a twofold increase in stereoselectivity of the enantiomers of 4 over the enantiomers of 1–3 (40–50 vs. up to 20). These results suggest that the greater affinity for the α-adrenergic receptor of the optical isomers of 4 over 1–3 must result primarily from the interactions which occur because of the additional achiral aryloxyethyl residue, which has been suggested to bind to one of the two aromatic subsites of the α-adrenergic receptor.[21,22,27] The greater affinity of the enantiomers of 4 which results in the presence of this substituent must occur in a portion(s) of the receptor which has no major chiral restrictions. Likewise, it seems that the additional affinity evoked by this substituent group does not influence significantly the stereochemical requirements in other areas of receptor interaction.

Experimental Section

Melting points were determined on a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si as internal standard. Notations used in the NMR descriptions are the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR and NMR data are provided for only one enantiomer from each set of two. Circular dichroism spectra were recorded on a Jobin Yvon Dichrographe R. J. Mark III instrument. Optical rotations were determined on a Jasco DIP-4 digital polarimeter. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England, and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

(2R)-2-(Phthalimidomethyl)-1,4-benzodioxane [(2R)-6]. Potassium phthalimide was prepared according to the method of Salzberg and Supniewski.[28] Phthalimide, 40.0 g (0.270 mol), was dissolved in 800 mL of absolute ethanol and the solution was refluxed for 30 min. The hot solution was decanted into a previously prepared solution containing 30.5 g (0.544 mol) of KOH in 30 mL of H_2O with 90 mL of absolute ethanol added. The mixture was cooled to room temperature and the precipitate was separated by filtration, washed with acetone (4 × 50 mL), and dried at 100 °C for 16 h, to yield 34.5 g (70%) of potassium phthalimide, which was used without further purification.

Potassium phthalimide, 4.15 g (0.022 mol), was added to 4.51 g (0.014 mol) of (2S)-2-[(tosyloxy)methyl]-1,4-benzodioxane [(2S)-5][24] in 250 mL of DMF and the mixture refluxed for 2.5 h. After cooling, the mixture was poured into 600 mL of H_2O, and the resulting precipitate was filtered; washed sequentially with H_2O (4 × 100 mL), 2% NaOH (3 × 100 mL), and H_2O (5 × 100 mL); and oven dried to yield a cream-colored solid. Recrystallization from 2-ethoxyethanol afforded 3.46 g (84%) of (2R)-6 as white plates: mp 241–242 °C (lit.[15] racemic mp 206–207 °C); IR (KBr) 2.84, 3.24, 3.40, 5.63, 5.82, 6.27, 6.71, 6.83, 7.12, 7.44, 7.67, 7.92, 8.34, 8.71, 9.22, 9.56, 10.79, 11.30, 11.73, 12.14, 12.53, 13.22, and 13.83 μm. Anal. ($C_{17}H_{13}O_4N$) C, H, N.

(2S)-2-(Phthalimidomethyl)-1,4-benzodioxane [(2S)-6]. (2S)-6 was prepared by a method analogous to the preparation of (2R)-6, starting from (2R)-2-[(tosyloxy)methyl]-1,4-benzodioxane [(2R)-5][24] and potassium phthalimide. The product was obtained in 68% yield, mp 240–242 °C (2-ethoxyethanol). Anal. ($C_{17}H_{13}O_4N$) H, N; C: calcd, 69.14; found, 68.69.

(2R)-2-(Aminomethyl)-1,4-benzodioxane [(2R)-7]. To a stirred, refluxing solution of 3.70 g (0.013 mol) of (2R)-2-(phthalimidomethyl)-1,4-benzodioxane [(2R)-6] in 100 mL of 2-ethoxyethanol was added dropwise a solution of 0.75 g (0.015 mol) of hydrazine hydrate (100%) in 20 mL of 2-ethoxyethanol over 10 min. After refluxing the solution for 1 h, concentrated HCl was added dropwise until pH 2 was reached. The resulting mixture was cooled, and the solid was removed by filtration followed by washing with ethanol (3 × 100 mL). Solvents were removed in vacuo to yield a white solid, which was redissolved in H_2O and the solution made alkaline (pH 11) with aqueous 10% NaOH. The alkaline solution was extracted with ether (4 × 75 mL), and the combined ether layers were dried (Na_2SO_4). The solvent was evaporated to yield a pale-yellow oil, which upon vacuum distillation afforded 1.83 g (85%) of (2R)-7 as a clear oil: bp 75 °C (0.08 mm), lit.[15] racemic bp 121–122 °C (2 mm); $[\alpha]_D$ +58.5° (c 1.2, $CHCl_3$); IR (neat) 2.96, 3.25, 3.46, 6.27, 6.70, 6.86, 7.68, 7.89, 8.33, 9.10, 9.38, 9.63, 9.86, 10.96, 12.04, 13.36 μm; NMR ($CDCl_3$) δ 6.80 (s, 4, Ar H), 4.00 (m, 3, H_2 and H_3), 2.81 (m, 2, CH_2), 1.22 (s, 2, NH_2); CD (c 1.0, absolute MeOH) $[\theta]_{325}$ 0, $[\theta]_{300}$ 0, $[\theta]_{285}$ +1200, $[\theta]_{280}$ +1360, $[\theta]_{270}$ +930, $[\theta]_{260}$ +165, $[\theta]_{250}$ 0, $[\theta]_{240}$ −1500, $[\theta]_{235}$ −10 905, $[\theta]_{230}$ −18 130, $[\theta]_{220}$ −955.

(2S)-2-(Aminomethyl)-1,4-benzodioxane [(2S)-7]. (2S)-7 was prepared by a method analogous to the preparation of (2R)-7, starting from (2S)-2-(phalimidomethyl)-1,4-benzodioxane [(2S)-6] and hydrazine hydrate. The product was obtained in 53% yield: bp 75 °C (0.08 mm); $[\alpha]_D$ −57.8° (c 1.2 $CHCl_3$); CD (c 1.0, absolute MeOH) $[\theta]_{325}$ 0, $[\theta]_{300}$ 0, $[\theta]_{285}$ −1415, $[\theta]_{280}$ −1530, $[\theta]_{270}$ −1310, $[\theta]_{260}$ −270, $[\theta]_{250}$ 0, θ_{240} +1090, $[\theta]_{235}$ +9270, $[\theta]_{230}$ +19 355, $[\theta]_{225}$ +8450.

2-(2,6-Dimethoxyphenoxy)acetaldehyde (8). A mixture of 25.0 g (0.127 mol) of bromoacetaldehyde diethyl acetal, 19.5 g (0.127 mol) of 2,6-dimethoxyphenol, and 17.5 g (0.127 mol) of K_2CO_3 in 250 mL of DMF was heated for 24 h at 125–130 °C with vigorous stirring. After cooling the mixture, 300 mL of 5% NaOH was added and the solution was extracted with ether (7 × 100 mL). The combined ether layers were washed with 5% NaOH (4 × 100 mL) and H_2O (8 × 100 mL) and dried (Na_2SO_4), and the solvent was evaporated to yield an orange oil. Vacuum distillation afforded 19.2 g (56%) of diethyl acetal (9) as a pale yellow oil: bp 116 °C (0.2 mm); IR (neat) 3.40, 3.46, 6.30, 6.80, 6.98, 7.73, 8.02, 8.23, 8.48, 9.02, 9.36, 9.84, 12.96, 13.70 μm; NMR ($CDCl_3$) δ 7.10–6.40 (m, Ar H), 4.82 (t, 1, CH, J = 5 Hz), 4.00 (d, 2, CH_2, J = 6 Hz), 3.79 (s, 6, OCH_3), 3.80–3.40 (2 q, 4, OCH_2CH_3),

1.20 (t, 6, OCH_2CH_3, J = 7 Hz).

Acetal **9**, 5.00 g (0.018 mol), was added to 30 mL of aqueous 2 N HCl in 50 mL of acetone, and the solution was heated to 60 °C for 15 min with stirring. After cooling, 200 mL of ether and 80 mL of H_2O were added. The ether layer was separated and washed with 5% Na_2CO_3 (1 × 100 mL) and H_2O (2 × 100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to yield a viscous oil. Vacuum distillation afforded 1.41 g (40%) of **8** as a clear oil: bp 90 °C (0.2 mm); IR (neat) 3.38, 3.52, 3.68, 5.78, 6.25, 6.72, 6.97, 7.28, 7.70, 7.95, 8.28, 8.44, 9.00, 9.67, 11.36, 12.90, 13.60 and 14.45 μm; NMR ($CDCl_3$) δ 9.95 (t, 1, aldehyde H, J = 2 Hz), 7.20–6.40 (m, 3, Ar H), 4.45 (d, 2, OCH_2, J = 2 Hz), 3.80 (s, 6, OCH_3).

(2*R*)-2-[[[2-(2,6-Dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxane Hydrochloride [(2*R*)-4·HCl]. To a solution of 1.50 g (0.009 mol) of (2*R*)-2-(aminomethyl)-1,4-benzodioxane [(2*R*)-**7**] in 50 mL of absolute ethanol was added a solution of 3.61 g (0.018 mol) of 2-(2,6-dimethoxyphenoxy)-acetaldehyde (**8**) in absolute ethanol with stirring at room temperature. After stirring the solution for 20 min, the temperature was lowered to 0 °C and 0.76 g (0.020 mol) of $NaBH_4$ was added. After stirring the mixture for 20 min at 0 °C, the temperature was raised to room temperature and stirring was continued for 1.5 h. Following dropwise acidification to pH 2 with aqueous 2 N HCl, the solution was partitioned between 100 mL of H_2O and 100 mL of ether. The aqueous layer was basified with 5% NaOH to pH 11 and extracted with ether (3 × 100 mL). The combined ether layers were washed with H_2O (1 × 100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to yield a viscous yellow oil. The oil was dissolved in ether, and the HCl salt was precipitated by addition of ether-saturated gaseous HCl. The precipitated oil was crystallized from ethyl acetate–methanol to yield 1.69 g (50%) of (2*R*)-4·HCl as white needles: mp 140–141 °C, lit.[15] racemic mp 155–157 °C; $[\alpha]_D$ +46.1° (*c* 1.0, absolute MeOH); IR (KBr) 2.93, 3.40, 3.70–4.40 (broad), 6.25, 6.77, 7.71, 7.95, 8.30, 9.00, 9.57, 9.70, 10.05, 10.45, 10.90, 12.00, 13.05, 13.50, 13.75, 14.40 μm; NMR (Me_2SO-d_6) δ 10.00–9.40 (br s, 2, NH_2), 7.30–6.50 (m, 7, Ar H), 5.00–4.60 (m, 1, H_2), 4.60–4.10 (m, 2, H_3), 3.80 (s, 6, OCH_3), 3.70–3.20 (m, 6, CH_2N and $-NCH_2CH_2O-$); CD (*c* 1.0, absolute MeOH) $[\theta]_{320}$ 0, $[\theta]_{290}$ 0, $[\theta]_{285}$ +755, $[\theta]_{282}$ +1450, $[\theta]_{280}$ +1260, $[\theta]_{276}$ +1640, $[\theta]_{270}$ +1010, $[\theta]_{260}$ +410, $[\theta]_{250}$ 0, $[\theta]_{240}$ −190, $[\theta]_{235}$ −3215, $[\theta]_{230}$ −12 475, $[\theta]_{225}$ −3780. Anal. ($C_{19}H_{24}NO_5Cl·0.5H_2O$) C, H, N.

(2*S*)-2-[[[2-(2,6-Dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxane Hydrochloride [(2*S*)-4·HCl]. (2*S*)-4 was prepared by a method analogous to the preparation of (2*R*)-4 starting from (2*S*)-2-(aminomethyl)-1,4-benzodioxane [(2*S*)-**7**] and aldehyde **8**. The product was obtained in 56% yield (HCl salt) as white needles: mp 138–140 °C; $[\alpha]_D$ −45.0° (*c* 1.0, absolute MeOH); CD (*c* 1.0, absolute MeOH) $[\theta]_{320}$ 0, $[\theta]_{290}$ 0, $[\theta]_{285}$ −665, $[\theta]_{282}$ −1270, $[\theta]_{280}$ −1150, $[\theta]_{276}$ −1515, $[\theta]_{270}$ −1090, $[\theta]_{260}$ −430, $[\theta]_{250}$ 0, $[\theta]_{240}$ +20, $[\theta]_{235}$ +2665, $[\theta]_{230}$ +12 100, $[\theta]_{225}$ +3880. Anal. ($C_{19}H_{24}NO_5Cl·0.5H_2O$) C, H, N.

Pharmacological Testing. Aortas from male New Zealand rabbits (204 kg) were placed in a modified Krebs–Henseleit (Krebs) solution[29] and cut into helical strips approximately 1.5-mm wide and 2-cm long. The isolated strips were suspended in 10-mL organ baths under 2 g of tension. The tissues were bathed in Krebs solution maintained at 37 °C and aerated by bubbling with 95% O_2–5% CO_2. The strips were allowed to equilibrate for 2 h prior to adding drugs. Muscle activity was magnified tenfold on a lymograph drum. All strips were maximally contracted by adding methoxamine in a cumulative manner. Following the maximal response, the tissues were repeatedly washed until the original base line was reached. Each strip was then incubated for 45 min with a specific concentration of the antagonist under study. Following the incubation period, a second cumulative concentration–effect relationship to methoxamine was obtained. The ED_{50} for methoxamine in the control period and antagonist-treated period was obtained for each strip using the appropriate concentration–effect curve. Three to four concentrations of antagonist were used per experiment, with one concentration of antagonist per strip. All ED_{50} values were appropriately corrected for changes in sensitivity during the course of the experiment by running a "time control" tissue, which received only methoxamine. The pA_2 of each antagonist was obtained according to the method of Arunlakshana and Schild.[30]

Acknowledgment. The authors acknowledge partial support of M. L. Powell by a fellowship from the American Foundation for Pharmaceutical Education and support from the Iowa Heart Association for the pharmacological experiments.

References and Notes

(1) For part 6 of this series, see: W. L. Nelson, M. L. Powell, and J. E. Wennerstrom, *J. Org. Chem.*, **43**, 4907 (1978).
(2) For a review of antihypertensive α-adrenergic antagonists, see: L. H. Werner and W. E. Barnett in "Antihypertensive Agents", E. Schlittler Ed., Academic Press, New York, 1967, Chapter X, pp 331–392.
(3) E. Fourneau, D. Bovet, and P. Maderni, *J. Pharm. Clin.*, 18, 185 (1933).
(4) E. Fourneau and D. Bovet, *C. R. Seances Soc. Biol., Ses. Fil.*, **113**, 388 (1933).
(5) E. Fourneau and D. Bovet, *Arch. Int. Pharmacodyn. Ther.*, **46**, 178 (1933).
(6) D. Bovet and A. Simon, *Arch. Int. Pharmacodyn. Ther.*, **55**, 15 (1937).
(7) A. P. Swain, U.S. Patent 2695294 (1954); *Chem. Abstr.*, **49**, 14039 (1955).
(8) C. E. Rapela and H. D. Green, *J. Pharmacol. Exp. Ther.*, **132**, 29 (1961).
(9) M. Nickerson, *Pharmacol. Rev.*, **9**, 246 (1957).
(10) A. B. Demson, Jr., S. B. Bardhanabaedyba, and H. D. Green, *Circ. Res.*, **2**, 537 (1954).
(11) W. Rosenblatt, T. M. Haymond, S. Bellet, and G. Koelle, *Am. J. Med. Sci.*, **227**, 179 (1954).
(12) J. Augstein and S. M. Green, *Nature (London)*, **201**, 628 (1964).
(13) C. J. E. Niemegan, J. C. Vergauggen, F. J. Van Neuten, and P. A. Janssen, *Int. J. Neuropharmacol.*, **2**, 349 (1963).
(14) W. K. A. Schapers, A. H. M. Jageneau, and P. A. J. Janssen, *Arzneim.*-Forsch., **13**, 579 (1963).
(15) P. N. Green, M. Shapero, and C. Wilson, *J. Med. Chem.*, **12**, 326 (1969).
(16) J. Augstein, W. C. Austin, R. J. Boscott, S. M. Green, and C. R. Worthing, *J. Med. Chem.*, **8**, 356 (1965).
(17) J. Augstein, W. C. Austin, C. A. Bartram, and R. J. Boscott, *J. Med. Chem.*, **9**, 812 (1966).
(18) H. Fenton, P. N. Green, M. Shapero, and C. Wilson, *Nature (London)*, **206**, 725 (1965).
(19) E. R. Loew and C. Micetich, *J. Pharmacol. Exp. Ther.*, **93**, 434 (1948).
(20) D. R. Mottram and H. Kapur, *J. Pharm. Pharmacol.*, **27**, 295 (1975).
(21) H. Kapur, D. R. Mottram, and P. N. Green, *J. Pharm. Pharmacol.*, **30**, 259 (1978).
(22) H. Kapur and D. R. Mottram, *Biochem. Pharmacol.*, **27**, 1879 (1978).
(23) D. A. Greenberg, D. C. U'Prichard, and S. H. Snyder, *Life Sci.* **19**, 69 (1976).
(24) W. L. Nelson, J. E. Wennerstrom, D. C. Dyer, and M. Engel, *J. Med. Chem.*, **20**, 880 (1977).
(25) The absolute stereochemistry as designated by the Cahn–Ingold–Prelog system changes with different substituents from **5** to **6**, although no stereochemical change at the asymmetric carbon has occurred; R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).
(26) H. Fuder, F. Hsu, D. D. Miller, W. L. Nelson, and P. N. Patil, *Pharmacologist*, in press (1979).
(27) H. Kapur, P. N. Green, and D. R. Mottram, *J. Pharm. Pharmacol.*, **31**, 188 (1979).
(28) P. L. Salzberg and J. V. Supniewski, in "Organic Syntheses", Collect Vol. I, Wiley, New York, 1932, p 119.
(29) X. Nair and D. C. Dyer, *Can. J. Physiol. Pharmacol.*, **50**, 1 (1972).
(30) O. Arunlakshana and H. O. Schild, *Br. J. Pharmacol.*, 14, 48 (1959).