run with 1 mM procaine hydrochloride and 5 mM procainamide hydrochloride.

**Testing of Fluorescent Probes.** The nerve bundles were immersed in artificial sea water (423 mM NaCl, 9 mM KCl, 10 mM $CaCl_2$, 23 mM $MgCl_2$, 25.5 mM $MgSO_4$ buffered to pH 8 with Tris) containing the fluorescent probe in concentrations ranging from 25 to 50 $\mu$M for a period of 30 min. The poor solubility of some of the dyes in water could be overcome by dissolving the compounds in 0.1 mL of 95% EtOH and then diluting to 100 mL with artificial sea water. This concentration of EtOH had no measurable effect on conduction. Fluorescence emission was studied using the apparatus described by Tasaki et al.[20] The stained nerves were exposed to quasimonochromatic light (365 ± 10 nm) from a 200-W xenon–mercury lamp through a Kodak interference filter. The fluorescence emission from the nerve was detected at right angles to the incident light with a photomultipilier tube (RCA C70109E) through an absorption filter (Wratten 2A). A polarizer (Polaroid MBP'B) could be inserted between the interference filter and the nerve and an analyzer (HN38 or KN36) between the nerve and the absorption filter. Averaging (64 to 256 scans) was carried out with a Nicolet 1070 signal averaging computer to visualize fluorescence signals. All experiments were carried out at 8 °C.

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# Antihypertensive Indole Derivatives of Phenoxypropanolamines with β-Adrenergic Receptor Antagonist and Vasodilating Activity

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A series of 25 aryloxypropanolamines containing the 3-indolyl-*tert*-butyl [i.e., 1,1-dimethyl-2-(1*H*-indol-3-yl)ethyl] or substituted 3-indolyl-*tert*-butyl moiety as the N substituent is reported. These compounds have been tested for antihypertensive activity in spontaneously hypertensive rats (SHR), β-adrenergic receptor antagonist action in conscious normotensive rats, vasodilating activity in ganglion-blocked rats with blood pressure maintained by angiotensin II infusion, and for intrinsic sympathomimetic action (ISA) in reserpinized rats. Some of the compounds exhibit antihypertensive activity in combination with β-adrenergic receptor antagonist and vasodilating action. The structure–activity relationships in these tests are discussed.

The past few years have seen greatly expanded use of β-adrenergic receptor antagonists (β blockers) for the treatment of essential hypertension. Limitations to this form of therapy, for patients in whom they are not contraindicated, lie mainly in the fact that (a) β blockers are effective in only about 50% of hypertensive patients, (b) onset of action is often slow, and (c) therapy may be, at least initially, accompanied by an increase in peripheral vascular resistance. Clinically it has been shown that addition of a vasodilator to β-blocker therapy tends to overcome these shortcomings of β-blocker therapy alone and increases the controlled population to about 70%.[1]

Several recent reports describe compounds that combine β-blocking and vasodilating activity in single molecules.[2-4] We now report the synthesis and biological properties of a new series of agents, VI, which exhibit this dual action. These compounds have a 1,1-dimethyl-2-(1*H*-indol-3-yl)-ethyl group, referred to as 3-indolyl-*tert*-butyl, for the nitrogen substituent.

**Chemistry.** The indole derivatives in Table I (compounds **1–25**) were prepared by the general reaction sequence shown in Scheme I. The aniline derivative **13** was obtained by catalytic reduction of the corresponding nitro compound **12**.

The phenolic precursors I were either available commercially or, in the case of 2-methyl-4-(methylsulfonyl)-phenol,[5] prepared by the literature procedure. Alkylation of the appropriate I with epichlorohydrin was followed by treatment with alkali to afford the epoxide II, which was then aminated with an indolyl-*tert*-butylamine, V, to produce the product VI.

Indolyl-*tert*-butylamines Va–d were obtained by conversion of the appropriate commercially available indole derivative to the corresponding gramine[6] IIIa–d which was, in turn, transformed by a two-step sequence[7] to the desired material. The $N^1$-methyl derivative Ve of indolyl-*tert*-butylamine was obtained from Va by a general procedure for the N-alkylation of indoles.[8]

**Biology.** The compounds in Table I were tested for β-blocking, intrinsic sympathomimetic (ISA), antihypertensive, and vasodilator activities as shown in Table II.

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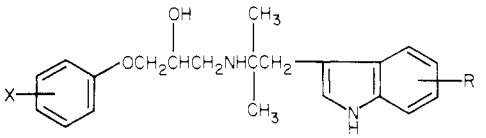
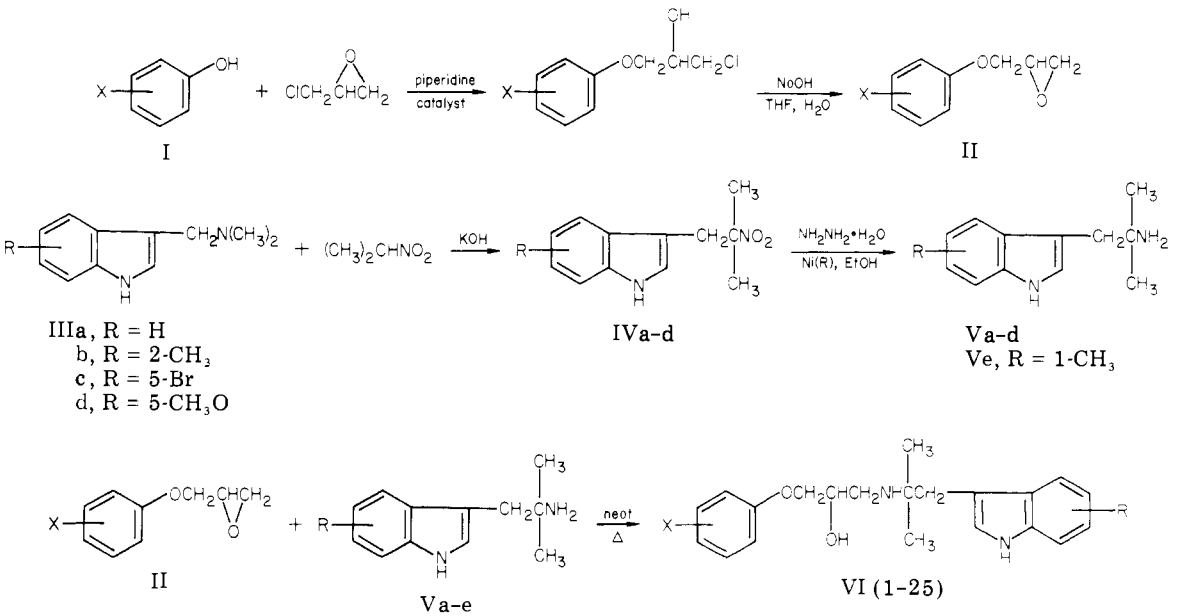
Table I. Aryloxypropanolamines



| no. | X | R | recrystn solvent | yield, % | mp, °C[a] | formula[b] |
|---|---|---|---|---|---|---|
| 1 | H | H | MeCN | 66 | 176.0-177.0 | $C_{21}H_{26}N_2O_2 \cdot HCl$ |
| 2 | 2-$CH_3$ | H | MeOH-EtOAc | 48 | 173.0-174.5 | $C_{22}H_{28}N_2O_2 \cdot HCl$ |
| 3 | 2-$C_2H_5$ | H | 95% EtOH | 68 | 170.0-171.5 | $C_{23}H_{30}N_2O_2 \cdot HCl$ |
| 4 | 2-$CH_2CH{=}CH_2$ | H | MeOH-$(i\text{-Pr})_2O$ | 65 | 163.0-168.5 | $C_{24}H_{30}N_2O_2 \cdot HCl$ |
| 5 | 2-$CH(CH_3)C_2H_5$ | H | MeOH-$CH_3CN$ | 21 | 163.0-166.0 | $C_{25}H_{34}N_2O_2 \cdot HCl$ |
| 6 | 2-$CH(CH_2)_4CH_2$ | H | $CH_3CN$ | 30 | 189.5-191.5 | $C_{27}H_{36}N_2O_2 \cdot HCl$ |
| 7 | 2-$C_6H_5$ | H | *i*-PrOAc | 52 | 79-82.5[c] | $C_{27}H_{30}N_2O_2 \cdot 0.5C_5H_{10}O_2$[d] |
| 8 | 2-$CF_3$ | H | DMF-abs EtOH | 44 | 202.5 dec | $C_{22}H_{25}F_3N_2O_2 \cdot 0.5C_2H_2O_4 \cdot 0.5H_2O$ |
| 9 | 2-CN | H | abs EtOH | 55 | 185-187[c] | $C_{22}H_{25}N_3O_2 \cdot HCl$ |
| 10 | 2-$CONH_2$ | H | EtOAc-$(i\text{-Pr})_2O$ | 45 | 66.0-75.0 | $C_{22}H_{27}N_3O_3 \cdot 0.75C_4H_8O_2$[e] |
| 11 | 2-F | H | DMF-$H_2O$ | 39 | 203.0-205.0 | $C_{23}H_{25}FN_2O_2 \cdot 0.5C_2H_2O_4$ |
| 12 | 2-$NO_2$ | H | MeCN | 25 | 127.0-128.0 | $C_{21}H_{25}N_3O_4$ |
| 13 | 2-$NH_2$ | H | MeOH-$H_2O$-EtOAc | 55 | 253.5-255.5 dec | $C_{21}H_{27}N_3O_2 \cdot 2HCl$ |
| 14 | 2-$SCH_3$ | H | MeOH-EtOH | 10 | 195.0-197.0 | $C_{22}H_{28}N_2O_2S \cdot 0.5C_2H_2O_4 \cdot 0.5H_2O$ |
| 15 | 2,3-$(CH_3)_2$ | H | *i*-PrOH | 50 | 173.5-175.5 | $C_{23}H_{30}N_2O_2 \cdot HCl$ |
| 16 | 2,4-$(CH_3)_2$ | H | MeOH-EtOAc | 62 | 161.5-164.5 | $C_{23}H_{30}N_2O_2 \cdot HCl$ |
| 17 | 2,6-$(CH_3)_2$ | H | MeOH-*i*-PrOH | 77 | 221.5-224.5 | $C_{23}H_{30}N_2O_2 \cdot HCl \cdot 0.33C_3H_8O$[f] |
| 18 | 2-$CH_3$-4-Cl | H | DMF-$H_2O$ | 35 | 168-172 dec[c] | $C_{22}H_{27}ClN_2O_2 \cdot 0.5C_2H_2O_4 \cdot 0.5H_2O$ |
| 19 | 2-$CH_3$-4-$CH_3SO_2$ | H | DMF-abs EtOH | 19 | 209.5-211.5 dec | $C_{23}H_{30}N_2O_4S \cdot 0.5C_2H_2O_4 \cdot 0.66H_2O$ |
| 20 | 2-$CH_3$ | 2-$CH_3$ | DMF-abs EtOH | 48 | 212.0-214.0 dec | $C_{23}H_{30}N_2O_2 \cdot 0.5C_2H_2O_4 \cdot 0.25H_2O$ |
| 21 | 2-$CH_3$ | 1-$CH_3$ | abs EtOH | 55 | 189.5-192.5 | $C_{23}H_{30}N_2O_2 \cdot HCl$ |
| 22 | 2-$CH_3$ | 5-Br | MeOH-*i*-PrOH | 68 | 198.0-200.0 dec | $C_{22}H_{27}BrN_2O_2 \cdot HCl$ |
| 23 | 2-$CH_3$ | 5-$CH_3O$ | MeOH-*i*-PrOH | 71 | 201.0-203.0 | $C_{25}H_{30}N_2O_3 \cdot HCl$ |
| 24 | 2-CN | 2-$CH_3$ | *i*-PrOH | 24 | 218-221[c] | $C_{23}H_{27}N_3O_2 \cdot 0.5C_2H_2O_4$ |
| 25 | 2-CN | 5-$CH_3O$ | EtOH-AcMe | 56 | 164-166[c] | $C_{23}H_{27}N_3O_3 \cdot HCl$ |

[a] Corrected melting point. [b] All compounds gave satisfactory analyses for C, H, and N. [c] Uncorrected melting point. [d] Isopropyl acetate solvate. [e] Ethyl acetate solvate. [f] 2-Propanol solvate.

Scheme I




β-Blocking potency was estimated in a conscious rat model and is reported as a percent inhibition of the isoproterenol-induced increase in heart rate 2 h after oral dosing with the test compound. Data for the reference β blockers propranolol and pindolol in this model are shown for comparison.

The presence of ISA in some of these compounds was demonstrated in anesthetized, reserpinized rats.[9] The increase in heart rate due to injected test agent is shown and compared with the effect of pindolol, a clinically used agent with substantial agonist action.

Antihypertensive activity was measured[10] in the spontaneous hypertensive rat (SHR). Ratings listed in Table II represent the maximum decrease in blood pressure of

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(10) For a detailed description of the general procedure for this screen, see S. S. Klioze and W. J. Novick, Jr., *J. Med. Chem.*, 21, 400 (1978).

Table II. Biological Data

| compd | β-blocking act.[a] dose, mg/kg | β-blocking act.[a] % inhibn | ISA:[b] ΔHR, bpm | antihypertensive act.[c] | vasodilator act.:[d] % Δ MAP |
|---|---|---|---|---|---|
| 1 | 1.25[e] | 61 ± 10 | 141 ± 3 | ± | −26 ± 3 |
| 2 | 1.25 | 73 ± 10 | 100 ± 5 | + | −18 ± 2 |
| 2a[f] | 1.25 | 40 ± 10 | | *g* | −13 ± 3 |
| 3 | 1.25 | 73 ± 5 | | ± | −27[e,h] |
| 4 | 1.25 | 71 ± 10 | | ± | +19 ± 7 |
| 5 | 1.25 | 53 ± 17 | −8 ± 12 | ± | +22 ± 7 |
| 6 | 1.25 | 45 ± 16 | | ± | +18[e] |
| 7 | | | | ± | +12[e] |
| 8 | 1.25 | 91 ± 7 | 88 ± 14 | ++ | −34 ± 4 |
| 9 | 2.0 | 71 ± 11 | 77 ± 6 | +++ | −26 ± 3 |
| 10 | 1.25 | 45 ± 16 | 74 ± 6 | ++ | −25 ± 7 |
| 11 | 0.5 | 58 ± 22 | | ± | −33 ± 4 |
| 12 | 1.25 | 53 ± 13 | 106 ± 8 | ± | −38 ± 3 |
| 13 | 1.25 | 40 ± 12 | 105 ± 8 | ++ | −11 ± 3 |
| 14 | 1.25 | 57 ± 18 | | ± | −29 ± 2 |
| 15 | 0.5 | 79 ± 8 | | ++ | +8[e] |
| 16 | 1.25 | 63 ± 11 | | + | +13 ± 4 |
| 17 | 5.0 | 47 ± 6 | | ± | −4 ± 3 |
| 18 | 5.0 | 60 ± 16 | | ± | +11[e] |
| 19 | 1.25[e] | 30 ± 10 | | ± | −8 ± 1 |
| 20 | 0.5 | 37 ± 11 | | + | −22 ± 7 |
| 21 | 0.5 | 49 ± 18 | 73 ± 9 | ± | −10 ± 3 |
| 22 | 0.5 | 36 ± 14 | | + | −13 ± 5 |
| 23 | 0.5 | 19 ± 10 | | ± | −41 ± 5 |
| 24 | 0.5 | 37 ± 15 | | ± | −36 ± 3 |
| 25 | 0.5 | 64 ± 6 | 71 ± 10 | + | −49 ± 3 |
| propranolol | 1.25 | 26 ± 10 | | ± | −9 ± 1[h] |
| | 5.0 | 56 ± 16 | | | |
| pindolol | 1.25 | 84 ± 3 | 120 ± 5 | ±[i] | −32 ± 2 |
| hydralazine | | | | ++[j] | −52 ± 2[k] |
| vehicle control | | 14 ± 8[l] | | *m* | +3 ± 1[n] |

[a] Values are means ± SEM of percent inhibition of isoproterenol-induced tachycardia in rats ($n$ = 3-5) 2 h after the indicated oral dose. [b] Intrinsic sympathomimetic activity; values represent mean ± SEM increase in heart rate (bpm) of reserpinized rats ($n$ = 3-6) given 0.3 mg/kg iv. The maximum response elicited by isoproterenol in this model was 180 ± 4 bpm. [c] Rating represents a range of maximum mean decreases in systolic blood pressure of five rats given 100 mg/kg, po: less than 25 mmHg (±), 25-34 mmHg (+), 35-44 mmHg (++), 45 mmHg and over (+++). [d] Values denote percent change in mean arterial blood pressure (mean ± SEM) 30 min after dosing rats ($n$ = 3-7) at 3 mg/kg iv. [e] Data obtained in two rats. [f] Literature compound, ref 16. 1-[[2-(3-Indolyl)ethyl]amino]-3-(2-methylphenoxy)-2-propanol. [g] Lethal at 100 mg/kg po. [h] Dosed at 10 mg/kg iv. [i] Dosed at 30 mg/kg po. [j] Dosed at 4 mg/kg po. [k] Dosed at 1 mg/kg iv. [l] Data obtained in eight rats. [m] 3.6 ± 3.7 mmHg ($n$ = 5). [n] Data obtained in 21 rats.

animals dosed orally at 0 and 22 h. Maximum blood-pressure decreases were observed at 2 or 4 h after the second dose of test compound. The reference β blockers are inactive in this model, whereas the vasodilator hydralazine exhibits a potent hypotensive response.

The vasodilator component of these compounds was evaluated in anesthetized, ganglion-blocked rats in which blood pressure was supported by infusion of angiotensin II. Many drugs which relax smooth muscle (such as atrial strips and hind limb vasculature) and are known as classical vasodilators are virtually ineffective as antihypertensive agents (e.g., papaverine). The method[11] used in the present study effectively identifies the antihypertensive vasodilators and is similar to a previously reported model.[12] Values listed in Table II represent mean percent changes in blood pressure 30 min after iv dosing with test substance. Hydralazine gives a potent response in this model. The reference β blocker propranolol is inactive at the dose used, whereas pindolol is active, possibly due to its ISA.

## Discussion

Examination of the biological data indicates that there are no common structure–activity relationships in this series for β-blocking, vasodilating, and antihypertensive activity. The individual tests are therefore discussed separately.

**β-Adrenergic Receptor Blockade.** Early work on β-blocking agents concentrated almost exclusively on isopropyl and *tert*-butyl as N substituents, since those groups generally conferred the best activity. More recently, numerous agents have appeared which bear arylalkyl (e.g., 3,4-dimethoxyphenethyl[13] and 4-phenyl-2-butyl[14]) and aryloxyalkyl (e.g., 4-carboxamidophenoxyethyl[15]) groups on nitrogen. In the present work, we have found that the indolyl-*tert*-butyl group allows potent β-blocking activity. Furthermore, compounds substituted on the carbocyclic ring or the pyrrole ring of the indole moiety generally retain β-blocking activity; however, **2a**, the indolylethylamino analogue[16] of **2**, which lacks the quaternary carbon, is also a β blocker. When the substituent on nitrogen is kept constant at indolyl-*tert*-butyl, β-blocking activity is not greatly dependent upon the aromatic substituent.

**Antihypertensive Activity.** The SHR is a useful model for demonstrating the activity of several classes of

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(15) J. Augstein, D. A. Cox, A. L. Ham, P. R. Leeming, and M. Snarey, *J. Med. Chem.*, 16, 1245 (1973).
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antihypertensive drugs such as vasodilators, sympathetic inhibitors, and ganglionic blockers. Intrinsically, however, β-blocking agents do not lower blood pressure acutely in this model, as shown by the lack of activity of propranolol and pindolol. In the present series, therefore, this test was used primarily as a measure of the non-β-blocking component of activity. The most active compounds (**8**–**10**) have an unsubstituted idolyl-*tert*-butyl group and an electron-withdrawing aromatic substituent ortho to the side chain, although **13** and the 2,3-dimethyl analogue **15** are also quite active. The 2,4-dimethyl compound **16** is comparable in potency to the 2-methyl derivative **2**, but the 2,6-dimethyl analogue **17** is weaker. Compounds **20**–**25** with substituents on the indole ring are relatively weak antihypertensives. The indolylethylamine **2a**, which lacks the *gem*-dimethyl substituents, shows β-blocking activity but is lethal at the dose employed in this model. In contrast to vasodilators such as hydralazine which increase heart rate, these indole derivatives decrease heart rate (0–25%) in the SHR, in addition to lowering blood pressure.

**Vasodilating Activity.** The structure–activity relationships which emerge from this test are similar to, but do not parallel exactly, those for activity in the spontaneous hypertensive rat model. Most ortho substituents leading to good activity are relatively small (H, F) or strongly electronegative ($CF_3$, $NO_2$, CN, $CONH_2$). More bulky hydrocarbon substituents in the ortho position lead to increased blood pressure in this test (**4**–**7**), while disubstitution is also detrimental (**15**–**19**). The 2-Me substituted indoles (**20** and **24**) and especially the 5-methoxy substituted indoles (**23** and **25**) lead to good vasodilator activity, while removing the bulk around the amino nitrogen (**2a** vs. **2**) causes little change. Substitution of the indole nitrogen by methyl (**21**) reduces activity.

## Conclusion

Compounds **2**, **8**, **9**, **10**, **20**, and **25** from this series show β-blocking, antihypertensive, and vasodilating activities of sufficient magnitude to warrant further study. Of these compounds, **9** has been chosen for more extensive pharmacology and toxicology preliminary to evaluation in man as an antihypertensive agent.

The extent to which ISA, α-adrenergic receptor blockade, and direct-acting vasodilation contribute to the antihypertensive and vasodilator components of compound **9** will be reported elsewhere.[17]

## Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected where indicated. All compounds have NMR and IR spectra consistent with the assigned structures. Where analyses are indicated for C, H, and N, analytical values are within ±0.4% of calculated values. Where hydrates are indicated by molecular formula, $H_2O$ analyses were obtained with a micro Karl Fischer apparatus and are within ±0.6% of calculated values. TLC was done in the appropriate solvent using 0.2-mm silica gel plates with F254 indicator and visualized under UVS-Mineralite.

**General Synthesis. a. Substituted 1,2-Epoxy-3-(aryloxy)propanes (II).** A solution of 0.2 mol of the appropriate phenol in 110 g (1.2 mol) of epichlorohydrin was treated with 5 drops of piperidine and heated at reflux for 2–8 h.[18] Unreacted epichlorohydrin was removed in vacuo [90 °C (70 mm)]. Toluene (150 mL) was added twice to the residue and removed in vacuo. The residual oil was stirred with 200 mL of THF and 250 mL of 1 N NaOH for 10 min at 45–60 °C and for 30 min at ambient temperature. The bulk of the THF was distilled and the resulting suspension was extracted with methylene chloride. The organic layer was dried ($Na_2SO_4$) and evaporated. The residual oil was used without further purification. TLC usually indicated a single material, and crude yields were generally 85–90%. 2-(2,3-Epoxypropoxy)benzonitrile afforded the following spectral data as an example of this class of compounds: IR (KBr) 2220 (C≡N), 1600 and 1495 (aromatic C=C), 1290 ($OCH_2$), 1260 (aromatic $OCH_2$), 750 $cm^{-1}$ (ortho disubstituted aromatic); NMR ($CDCl_3$) δ 2.8 ($\overline{CHCH_2O}$, 2, m), 3.4 ($\overline{CHCH_2O}$, 1, m), 4.1 and 4.4 ($OCH_2$, 2, dd), 7.0 and 7.5 (aromatics, 2 each, m).

**b. Substituted 1-[[2-(3-Indolyl)-1,1-dimethylethyl]amino]-3-(aryloxy)-2-propanols (VI; Table I).** A mixture of 0.2 mol of epoxide II and 0.18 mol of amine V was fused in an oil bath at 120–140 °C. The reaction was generally complete in 0.5 h, as determined by TLC [methylene chloride–methanol–ammonium hydroxide (90:9:1)]. Products were isolated (1) as the free base (only in the case of compound **12**) by crystallization of the crude melt from the appropriate solvent, (2) as the oxalate salts by adding a stoichiometric amount of oxalic acid dihydrate in a small amount of methanol to an ether solution of the crude free base, and (3) as the hydrochloride salts by addition of 5 N HCl in ethanol to an ether solution of the free base. Crude materials were recrystallized to afford the pure aryloxypropanolamines (VI, compounds **1**–**12**, **14**–**25**). The following spectral data was obtained on compound **23** as an example of this class of compounds: IR (KBr) 3310 (NH), 2940 (aliphatic CH), 2780 (HCl), 1250 (aromatic $OCH_2$), 1125 (*sec*-aliphatic alcohol), 750 $cm^{-1}$ (ortho disubstituted aromatic); NMR ($Me_2SO$-$d_6$) δ 1.3 (*gem*-dimethyls, 6, s), 2.2 (aromatic $CH_3$, 3, s), 3.2 (aromatic $CH_2$ and $CH_2NH$, 4, m), 3.8 ($OCH_3$, 3, s), 4.1 ($OCH_2$, 2, d), 4.4 (OCH, 1, m), 6.0 (OH, 1, br s), 7.0 (aromatics, 8, m), 8.9 ($NH_2^+$, 2, br s), 11.0 (indole NH, 1 br s).

**1-(2-Aminophenoxy)-3-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-2-propanol Dihydrochloride (13).** A 500-mL hydrogenation bottle containing 100 mL of THF was charged with 3.83 g (0.01 mol) of **12**. One-half gram of 10% Pd/carbon catalyst was added and the mixture was shaken with hydrogen until uptake was complete (about 30 min). Suction filtration, followed by concentration of the filtrates, afforded a pale amber syrup which was converted to the dihydrochloride salt with ethanolic hydrogen chloride. Recrystallization of the crude solid from MeOH–$H_2O$ by addition of EtOAc gave 2.35 g of crystals (Table I).

**α,α,2-Trimethyl-1*H*-indole-3-ethanamine (Vb).** The general literature procedure[7] was modified as follows. A mixture of 13.0 g (0.069 mol) of 2-methylgramine,[19] 44 g (0.49 mol) of 2-nitropropane, and 2.9 g (0.072 mol) of NaOH pellets was stirred and heated at reflux for 18 h. After the mixture had cooled to 25 °C, 60 mL of 10% HOAc was added and stirring was continued for 1 h. The mixture was partitioned between 150 mL each of $Et_2O$ and water to afford an organic layer, which was separated, washed three times with water, and dried over $MgSO_4$. Evaporation afforded 16.5 g of dark oil which slowly crystallized on standing at 25 °C. Recrystallization of the crude product from EtOH–$H_2O$ gave 12.6 g (78%) of **2-methyl-3-(2,2-dimethyl-2-nitroethyl)-1*H*-indole (IVb)** as tan crystals, mp 101–103 °C. To a solution of IVb in 150 mL of 95% EtOH was added with stirring 8 g of activated Raney nickel. The mixture was heated to reflux, heating was then stopped, and a solution of 13.1 g of 85% hydrazine hydrate in 13 mL of EtOH was added at a rate sufficient to maintain reflux throughout the addition. Heat was reapplied to continue the reflux for 2 h, after which the mixture was filtered and the filtrates were concentrated in vacuo. The brown residue was reprecipitated from dilute HCl with 4 N NaOH, extracted with $CH_2Cl_2$, and recrystallized from $(i\text{-}Pr)_2O$ to give 5.7 g (52%) of material: mp 97–99 °C. Anal. ($C_{13}H_{18}N_2$) C, H, N.

The following compounds were prepared by the same procedure, and were used without extensive purification.

**3-(2,2-Dimethyl-2-nitroethyl)-1*H*-indole (IVa)**: yield 70%; mp 72–74 °C (lit.[7] mp 66.5–68.0 °C).

**α,α-Dimethyl-1*H*-indole-3-ethanamine (Va)**: yield 99%; mp 122–126 °C (lit.[7] mp 130–131 °C).

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**5-Bromo-3-(2,2-dimethyl-2-nitroethyl)-1*H*-indole (IVc)**: yield 68%; mp 106–109 °C (lit.[20] mp 109.0–109.5 °C).

**5-Bromo-α,α-dimethyl-1*H*-indole-3-ethanamine (Vc)**: yield 99%; mp 151–154 °C (lit.[20] mp 161.5–162.0 °C).

**5-Methoxy-3-(2,2-dimethyl-2-nitroethyl)-1*H*-indole (IVd)**: yield 79%; mp 83–85 °C (lit.[21] mp 84–85 °C).

**5-Methoxy-α,α-dimethyl-1*H*-indole-3-ethanamine (Vd)**: yield 94%; mp 114–116 °C (lit.[21] mp 117–118 °C).

**α,α,1-Trimethyl-1*H*-indole-3-ethanamine (Ve).** Seven grams (0.106 mol) of 85% KOH was ground in a mortar and quickly transferred to a $N_2$-flushed, 25-mL Erlenmeyer flask. $Me_2SO$ (55 mL) was added and the mixture was stirred for 5 min. Additions of Va (5 g, 0.027 mol) and iodomethane (3.78 g, 0.027 mol) were each followed by 45 min of stirring, after which the suspension was quenched in 300 mL of water. Extraction of the mixture with EtOAc, followed by washing of the extracts with water and brine, afforded a clear solution which was dried ($MgSO_4$) and evaporated at 20 mm to give 5 g of yellow oil.

For characterization, a sample of the crude base in EtOAc solution was converted to the hydrochloride salt by addition of 5 N ethanolic hydrogen chloride. Recrystallization from *i*-PrOH–EtOAc gave material melting at 246–249 °C. Anal. ($C_{13}H_{18}N_2$·HCl) C, H, N.

**Adrenergic β-Receptor Antagonist Test in Conscious Rats.** Male Sprague–Dawley rats, weighing between 275 and 400 g, were anesthetized with metafane and the right femoral artery and vein cannulated. Catheters were passed subcutaneously along the dorsal midline and exteriorized between the scapulae. The cannulas were filled with heparinized saline and occluded with metal plugs.

Two to three days after surgery, and subsequent to an 18-h fast, the conscious rat was restrained in a rectangular wire-mesh cage. Heart rate was counted directly from the pulse tracing. The venous cannula was prepared for the administration of isoproterenol hydrochloride, 0.32 μg/kg (the dose causing 80% of the maximal response), contained in a volume equivalent to 0.5 mL/kg.

After a stabilization interval of 30 min and prior to administration of test drug, the heart-rate response to isoproterenol was obtained. Eight to ten minutes later, test drug (aqueous solution or methocel suspension) was administered orally in a volume of 5 mL/kg. Responses to isoproterenol were obtained 2 h following drug administration. The antagonism by a test drug (β blockade) was determined as a mean percentage inhibition (± SEM) by comparing the pre- and posttest drug chronotropic response to isoproterenol.

**Spontaneous Hypertensive Rat (SHR) Test.**[10] Male SHR (Okamoto Aoki, Charles River), approximately 5 months of age and weighing 300 to 350 g, were used. On the day of the study, indirect systolic blood pressure was determined by means of the tailcuff technique utilizing a Narco Bio-Systems pneumatic pulse transducer. All rats were prewarmed to 37 °C in a heating chamber for approximately 20 min prior to blood-pressure determinations.

In a 3-day test, systolic blood pressure readings were made at 0 (control), 22, 24, 26, and 46 h. Oral dosing (0 and 22 h) was at 100 mg/kg or as indicated by footnote in Table II. Activity was determined on groups of five animals per compound by comparing the posttreatment blood pressure with the control reading.

**Vasodilator Test in Ganglion-Blocked Rats (with Blood Pressure Supported by Angiotensin II).**[11] Male albino rats (Wistar) weighing between 275 and 450 g were anesthetized with a combination of urethane (800 mg/kg) and chloralose (60 mg/kg) administered intraperitoneally in a volume of 10 mL/kg. Following induction of anesthesia, chlorisondamine (2.5 mg/kg) was injected into the peritoneal cavity to abolish sympathetic and parasympathetic nerve activity. The right femoral artery was cannulated to monitor blood pressure (Statham pressure transducer, P23Db). Both femoral veins were cannulated to administer drugs and infuse angiotensin. The trachea was intubated, and the animals were allowed to breathe spontaneously. Following a stabilization interval of 10 to 15 min, angiotensin II was infused at a rate of 0.25 or 0.35 μg/min in a volume equivalent to 0.05 mL/min. Blood pressure increased and a new elevated steady-state pressure was established within 15 to 20 min. Drugs were subsequently injected intravenously over an interval of 3 min in a volume equivalent to 2 mL/kg. Mean arterial blood pressure was recorded (Beckman Offner dynograph) 30 min after initiation of drug administration, and the data were presented as the percent change (± SEM).

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