and left in spontaneous breathing. The hexapolar-electrode catheter inserted via a femoral artery into the noncoronary cusp of the aorta was connected to an Elema Mingograf 61 recorder, equipped with EMT 12 preamplifiers. With a bipolar electrode facing the sinus node area, the heart was paced at progressively increased rates. Before injection of the drug and 5 and 15 min after each dose administered intravenously, His bundle potentials were recorded at different pacing. The following intervals were measured: SH, the interval between the stimulation and the intrinsic His bundle deflection (this interval represents atrial His bundle conduction time); HV, the interval between the His bundle intrinsic deflection and the onset of ventricular activation (this interval represents conduction time in specific intraventricular tissue). For the determination of conduction times (His bundle electrogram), the dogs were anesthetized with sodium phenobarbital (30 mg/kg iv). The drugs were administered by the iv route at 5 mg/kg.

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Registry No. **4c**, 29950-40-1; (*E*)-**4d**, 29946-73-4; (*Z*)-**4d**, 29946-74-5; (*E*)-**4e**, 35365-37-8; (*Z*)-**4e**, 83918-31-4; **4f**, 29950-41-2; (*E*)-**4g**, 83917-89-9; (*Z*)-**4g**, 83918-32-5; (*E*)-**4h**, 83917-90-2; (*Z*)-**4h**, 83918-33-6; (*E*)-**4i**, 83917-91-3; (*Z*)-**4i**, 83918-34-7; (*E*)-**4j**, 83917-92-4; (*Z*)-**4j**, 83918-35-8; (*E*)-**4k**, 83917-93-5; (*Z*)-**4k**, 83918-36-9; (*E*)-**4l**, 83917-94-6; (*Z*)-**4l**, 83918-37-0; (*E*)-**4m**, 83917-95-7; (*Z*)-**4m**, 83918-38-1; (*E*)-**4n**, 83917-96-8; (*Z*)-**4n**, 83918-39-2; **5a**, 83917-97-9; **5b**, 4226-82-8; **5c**, 32081-58-6; **5d**, 83917-98-0; **5e**, 13427-10-6; **5f**, 83917-99-1; **5g**, 78833-04-2; **5h**, 83918-00-7; **5i**, 83918-01-8; **5j**, 74607-41-3; **5k**, 83918-02-9; **5l**, 83918-03-0; **5m**, 83918-04-1; **5n**, 72434-26-5; **6** [2-pyridyl; R = H; R_2, R_3 = $N[CH(CH_3)_2]_2$], 68284-77-5; **6** [2-pyridyl; R = $C_6H_5CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-05-2; **6** [2-pyridyl; R = C_6H_{11}; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-06-3; **6** [2-pyridyl; R = $(CH_3)_2CH$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-07-4; **6** [2-pyridyl; R = $C_2H_5(CH_3)CH$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-08-5; **6** [2-pyridyl; R = C_2H_5; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-09-6; **6** [2-pyridyl; R = $(C_2H_5)_2CH$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-10-9; **6** [2-pyridyl; R = $CH_3CH_2CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-11-0; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 78833-05-3; **6** [2-pyridyl; R = $CH_3(CH_2)_3$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-12-1; **6** [2-pyridyl; R = $C_6H_{11}CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-13-2; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-14-3; **6** [2-pyridyl; R = $(CH_3)_2CCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-15-4; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = 1-(2,6-dimethylpiperidino)], 83918-16-5; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N(C_2H_5)_2$], 83918-17-6; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = 1-morpholino], 83918-18-7; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = *N*-cyclohexyl-*N*-isopropylamino], 83918-19-8; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = di-*sec*-butylamino], 83918-20-1; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-21-2; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = dicyclohexylamino], 83918-22-3; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-24-5; **6** [4-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-25-6; **7**, 56265-38-4; **8**, 83918-26-7; **9**, 78833-08-6; **10**, 78833-09-7; **11**, 78833-10-0; **12**, 78833-11-1; **13**, 78833-12-2; **14**, 78833-13-3; **15**, 78833-03-1; **16**, 78833-14-4; **17**, 78833-15-5; **18**, 78833-18-8; **19**, 78833-20-2; **20**, 78833-16-6; **21**, 78833-17-7; **22**, 78833-19-9; **23**, 78833-21-3; **24**, 83918-27-8; **25**, 78833-23-5; **26**, 78833-25-7; **27**, 78833-24-6; **28**, 78833-27-9; **29**, 78833-26-8; $[C_2H_5(CH_3)CH]_2NH$, 626-23-3; $[C_2H_5(CH_3)CH]NHC_6H_{11}$, 42966-62-1; $(C_6H_{11})_2NH$, 101-83-7; $[C_2H_5(CH_3)CH]_2NCH_2CH_2OH$, 4535-71-1; $[C_2H_5(CH_3)CH]C_6H_{11}NCH_2CH_2OH$, 83918-28-9; $(C_6H_{11})_2NCH_2CH_2OH$, 4500-31-6; $[C_2H_5(CH_3)CH]_2NCH_2CH_2Cl$, 83918-29-0; $[C_2H_5(CH_3)CH]C_6H_{11}NCH_2CH_2Cl$, 83918-30-3; $(C_6H_{11})_2NCH_2CH_2Cl$, 75308-28-0; 2-(2,6-dimethylpiperidinyl)ethanol, 23502-32-1; 2-(2,6-dimethylpiperidinyl)ethyl chloride, 34846-30-5; 2-[2-(diisopropylamino)propyl]-4-methyl-2-(2-pyridyl)pentanenitrile, 83918-23-4; 2,6-dimethylpiperidine, 504-03-0; 2-pyridineacetonitrile, 2739-97-1; 3-pyridineacetonitrile, 6443-85-2; 4-pyridineacetonitrile, 13121-99-8.

Derivatives of β-Adrenergic Antagonists. *N*-Nitrosopropranolol and *N*-Hydroxypropranolol and Its Aldonitrone

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Potential precursors to chemically reactive species derived from the β-adrenergic antagonist propranolol were synthesized and tested for mutagenicity in the Ames *Salmonella* assay. *N*-Hydroxypropranolol (1), the corresponding aldonitrone, 3-(1-naphthoxy)-2-hydroxypropionaldehyde *N*-isopropylnitrone (2), and *N*-nitrosopropranolol (3) were prepared and tested. *N*-Hydroxypropranolol (1) was obtained by direct alkylation of 3-(1-naphthoxy)-1-bromo-2-propanol with *N*-isopropylhydroxylamine and isolated as its neutral oxalate or HBr salt. The aldonitrone (2) was obtained by mercuric oxide oxidation of the hydroxylamine. *N*-Nitrosopropranolol (3) was prepared by treating propranolol with nitrous acid. None of the compounds was mutagenic in the Ames assay with *Salmonella typhimurium* TA-98 and TA-100 strains, either in the absence or in the presence of the S-9 liver fraction from Arochlor 1254 treated rats. None of the compounds was significantly toxic to the bacteria, except for slight toxicity of the oxalate salt of 1.

Propranolol is a β-adrenergic antagonist widely used in the treatment of a variety of cardiovascular disorders. It is extensively metabolized in man and other species via several pathways, including oxidative N-dealkylation, aromatic hydroxylation, and glucuronidation.[1-7] Radiolabel from [^{3}H]propranolol has been shown to be covalently bound to the rat liver microsomal fraction when propranolol is administered systemically, suggesting the formation of a chemically reactive metabolite(s).[8,9] A marked inhibition of propranolol metabolism occurred when rats

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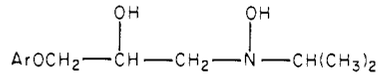
were pretreated with propranolol.[9] Similarly, pharmacokinetic studies in man have shown greater propranolol accumulation upon chronic dosing than in single dose studies.[10,11] Propranolol has not been shown to be hazardous; however, the structurally related agents practolol and proethalol have been reported to be toxic[12-14] and tumorigenic,[15-17] respectively. In each case, metabolic activation to chemically reactive metabolites has been suggested.

Since propranolol and other β-adrenergic antagonists are secondary amines, potentially reactive species could arise following oxidation of the basic nitrogen atom to form the corresponding hydroxylamines and possibly other intermediates.[18-21] Recently, various alkylhydroxylamines have been reported to be mutagenic in several bacterial systems.[22] In addition, *N*-nitrosoamines, which are readily formed via the reaction of amines with nitrites, have been shown to be mutagenic in various in vitro test systems.[23-25]

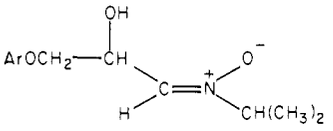
Because propranolol is widely used therapeutically and is extensively metabolized, both in vivo and in vitro, we chose to prepare analogues that could possibly serve as precursors for the formation of chemically reactive metabolites of propranolol. In this paper, we describe the synthesis of *N*-hydroxypropranolol (**1**), the corresponding aldonitrone (**2**), and *N*-nitrosopropranolol (**3**) and report their mutagenic activity in the Ames *Salmonella* test system.

Results and Discussion

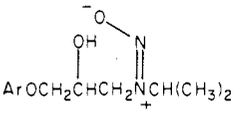
The synthesis and characterization of *N*-hydroxypropranolol (**1**), the corresponding aldonitrone (**2**), and *N*-nitrosopropranolol (**3**) were readily accomplished. Although a synthesis of *N*-hydroxypropranolol (**1**) by direct oxidation of propranolol[26] was not successful, N-alkylation of *N*-isopropylhydroxylamine with 3-(1-naphthoxy)-1-bromo-2-propranol provided a mixture of products, from which the desired hydroxylamine was readily separated. The methane CI mass spectrum (probe) of its salts (neutral oxalate and HBr) showed the expected QM at m/z 276, as well as the expected QM of the reduction product propranolol (QM = 260), since hydroxylamines readily undergo reduction on the probe of the mass spectrometer.[19] Chemical reduction (Zn–EtOH) afforded propranolol (determined by TLC), further confirming the structure of **1**.



1, Ar = 1-naphthyl



2 (*Z* isomer), Ar = 1-naphthyl



3 (*E* isomer), Ar = 1-naphthyl

The corresponding nitrone (**2**) was prepared by yellow mercuric oxide oxidation of **1**. The proton NMR spectrum of **2** was consistent with the aldonitrone structure and the C-methyl groups were observed as a doublet at δ 1.41 (J = 7 Hz), requiring an intact isopropyl group. A signal at δ 7.15 (J = 5 Hz) assigned to the methine proton at C′-1, is also consistent with the aldnitrone structure, tentatively assigned the *Z* configuration, similar to other aldonitrones.[27]

Direct nitrosation of propranolol afforded desired *N*-nitrosamine **3** in good yield. The methane CI mass spectrum (probe) showed the expected QM at m/z 289. The proton NMR spectrum showed two sets of isopropylmethyl groups, δ 1.05 and 1.15, in the ratio of 9:1. Similar results have been reported with other aliphatic *N*-nitrosoamines,[28] consistent with considerable N–N double-bond character. The major conformer in solution is assigned the *E* configuration (syn) based on the greater integration of the upfield signal, consistent with earlier work.[28,29]

The compounds were assayed for mutagenic activity in the Ames *Salmonella* test system both in the presence and absence of a metabolic activity system consisting of the S-9 liver fraction from Arochlor 1254 treated male rats and NADPH. None of the compounds, however, was mutagenic, either in the presence or absence of rat liver S-9 fractions in the TA-98 and TA-100 strains. A summary of the results in the presence of the S-9 fraction appears in Table I. In addition, none of the compounds was significantly toxic to the bacteria, except for the oxalate salt of **1**, which was slightly toxic. This toxicity may be related to additive or superadditive effects of oxalic acid and the *N*-hydroxylamine, since neither was as toxic by itself.

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Table I. Summary of Mutagenicity and Toxicity Testing Data

compd		mutagenicity[a] TA-98	mutagenicity[a] TA-100	toxicity (TA-100)[b] 4×10^7 dilution	toxicity (TA-100)[b] 4×10^6 dilution
1·HBr	+S9[c]	12	117	28	265
	(1000 μg) +S9	8	134		183
1 oxalate	+S9	18	143	18	165
	(1000 μg) +S9	20	61		60
2 (nitrone)	+S9	18	162	ND[d]	232
3 (*N*-nitroso)	+S9	14	137	25	255
	(1000 μg) +S9	13	131		
propranolol hydrochloride	+S9	12	131	ND	232
	(1000 μg) +S9	10	111		
isopropylhydroxylamine	+S9	18	150	ND	230
controls					
Me_2SO only	+S9	13	152	28	240
2-AAF	(5 μg) +S9	102	218	30	235
	(10 μg) +S9	242	248		
oxalic acid dihydrate	(100 μg) +S9			ND	178
	(200 μg) +S9				188

[a] Average of two plates. Results from testing in the absence of the S-9 fraction are not shown. None were significantly greater than the Me_2SO control. [b] Average of at least three plates. [c] Data reported for testing in the presence of NADPH with 500 μg of compound per plate, except as noted. At lower concentrations (10–250 μg/plate), no significant differences were noted. Testing in the absence of the S-9 fractions is not shown. None were significantly greater than the Me_2SO control. [d] ND = not done.

Oxalic acid (dihydrate) at 100 μg is approximately the same amount present in 500 μg of **1** oxalate.

The lack of mutagenicity and toxicity of hydroxylamine **1** and nitrone **2** suggests that even if formed from propranolol, these compounds may not be hazardous in vivo. Other nitrones have also proved to be only very weakly mutagenic, at best.[30] The potential for the hydroxylamine to form metabolic inhibitor complexes similar to those formed with other *N*-hydroxylamines[31] warrants investigation, in view of reported covalent binding of radiolabeled propranolol metabolites to the rat liver microsomal fraction when administered systemically.[9] In addition, **1** and **2** will be useful in the investigation of possible microsomal mixed-function amine oxidase[32] metabolism of propranolol. The lack of mutagenic activity and toxicity of nitrosamine **3** suggests that this compound may also not be hazardous, although more extensive testing is needed to evaluate this possibility. *N*-Nitrosamines of other related β-adrenergic antagonists also warrant preparation and investigation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded on Varian T-60 and EM-360 spectrometers with Me_4Si at internal standard. Mass spectra were recorded on the VG-7070H mass spectrometer operated in the CI mode. Notations used in the description are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

***N*-Hydroxy-1-(isopropylamino)-3-(1-naphthoxy)-2-propanol (1, *N*-Hydroxypropranolol).** A mixture of *N*-hydroxyisopropylamine (0.45 g, 6.0 mmol), 1-naphthoxy-3-bromo-2-propanol (2.25 g, 8.0 mmol), and (0.83 g, 6.0 mmol), K_2CO_3 in 25 mL of MeOH was refluxed with vigorous stirring for 10 h. The mixture was made acidic (pH 3) with 1 N HCl and then water (~20 mL) was added until the solid dissolved. Most of the MeOH was removed by rotary evaporation, and the aqueous residue was washed with benzene (2 × 20 mL) and then saturated with solid NaCl and extracted with ether (5 × 20 mL). The combined ethereal extracts were dried ($MgSO_4$); after evaporation, a viscous oil (1.2 g) was obtained, which was chromatographed on 50 g of silica gel, eluting with ether–*n*-BuOH (95:5). The fraction eluting in 80–130 mL, R_f 0.69 (silica gel; ether–*n*-BuOH, 95:5), afforded a pale yellow oil upon evaporation of the solvent. The oil proved to be unstable, turning yellow-brown after standing for a short time. The neutral oxalate and hydrobromide salts were prepared.

A 1.0-g sample of the oil was dissolved in 5 mL of absolute EtOH, and a solution of 0.50 g of oxalic acid dihydrate in 5 mL absolute EtOH was added. A white precipitate was obtained, which was recrystallized from absolute EtOH, affording the neutral oxalate salt: yield 700 mg (36%): mp 153 °C dec; IR (KBr) 3275, 3005, 2940, 2885, 2810, 1575, 1450, 1400, 1320, 1270, 1235, 1105, 1090, 1020, 965, 780, 770 cm^{-1}; NMR (60 MHz) (CD_3SOCD_3) δ 8.26 (dd, 1 H_8 of Ar ring, $J_{8,7}$ = 7 Hz and $J_{8,6}$ = 3 Hz), 7.83 (m, 1, H_5 of Ar ring), 7.65–7.30 (m, 4, H_3, H_4, H_4, H_6, and H_7 or Ar ring), 6.90 (distorted dd, 1, H_2 of Ar ring, $J_{2,3}$ = 6 *Hz*, $J_{2,4}$ = 3 Hz), 6.95 (br s, OH, NH, exchanged with D_2O), 4.20 (br s, 3, OCH_2, OCH_2), 3.00 (m, 3, NCH_2, NCH), 1.06 (s, 6, CH_3); CIMS (methane), *m/z* 276 (QM, 100), 260 (QM – O, 30), 258 (QM – H_2O, 33), 145 (naphthol, 30), 132 (QM – naphthol, 48). Anal. [$(C_{16}H_{21}NO_3)_2 \cdot C_2H_2O_4$] C, H, N. In order to prepare the HBr salt of **1**, the oil was dissolved in absolute ether, and dry HBr gas was bubbled into the solution. A white precipitate separated. Absolute EtOH was added until the precipitate dissolved, and a small amount of activated charcoal was added. The mixture was filtered and then cooled to afford a white solid, mp 118–120 °C. Anal. ($C_{16}H_{21}NO_3 \cdot HBr$) C, H, N.

3-(1-Naphthoxy)-2-hydroxypropionaldehyde *N*-Isopropylnitrone (2). To a solution of 200 mg (0.56 mmol) of **1**·HBr in 5 mL of water was added 1 mL of aqueous 20% K_2CO_3 and sufficient acetone (ca. 4 mL) to dissolve the free base. Excess yellow mercuric oxide (150 mg, 0.69 mmol) was added, and the mixture was stirred at room temperature for 30 min. Activated charcoal, ~50 mg, was added, and after stirring for an additional 5 min, the mixture was filtered. To the filtrate was added 10 mL of water, and the mixture was extracted with ether (5 × 15 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated to 3 mL, and the nitrone was obtained by filtration, 112 mg (73% yield), as a white solid: mp 120–122 °C dec; IR (KBr) 3180 (broad), 3060, 3015, 2980, 2920, 2860, 1580, 1560, 1400, 1265, 1240, 1105, 1060, 1050, 785, 740 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 8.20 (dd, 1, H_8 of Ar ring, $J_{8,7}$ = 8 Hz), 7.80 (dd, 1, H_5 of Ar ring, $J_{5,6}$ = 8 Hz and $J_{5,7}$ = 3 Hz), 7.70–7.30 (m, 4, H_3, H_4, H_6, and H_7 of Ar ring), 7.15 (d, 1, HC=N, $J_{1,2}$ = 5 Hz), 6.83 (dd,

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1, H_2 of Ar ring, $J_{2,3}$ = 7 Hz and $J_{2,4}$ = 3 Hz), 5.10 (q, 1, HCOH, J = 6 Hz), 4.37 (d, 2, OCH_2, J = 6 Hz), 4.03 [m (septet), 1, $NCH(CH_3)_2$, J = 7 Hz], 1.41 [d, 6, $(CH_3)_2$, J = 7 Hz]; CIMS (methane), m/z 274 (QM, 62), 256 (QM - H_2O, 91), 238 (QM - $2H_2O$, 45) 199 (36), 145 (naphthol QM, 100), 130 (67). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

***N*-Nitroso-1-(isopropylamino)-3-(1-naphthoxy)-2-propanol (3, *N*-Nitrosopropanolol).** To a stirred solution of 4.00 g (14.0 mmol) of propranolol hydrochloride (Sigma Chemical Co.) in 150 mL of 10 M acetate buffer (pH 4.0) was added dropwise a solution of 18.7 g (0.270 mol) of $NaNO_2$ in H_2O over 1.5 h, while the temperature was maintained at 95 °C. After stirring for 3 h, the mixture was cooled and extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ extracts were washed with a saturated NaCl solution (2 × 100 mL) and aqueous 10% Na_2CO_3 (3 × 100 mL) and dried (Na_2SO_4), and the solvent was evaporated to yield an orange oil, which solidified on standing. Recrystallization from EtOAc–cyclohexane afforded 3.00 g (77%) of *N*-nitrosopropanolol (3) as a pale orange crystals: mp 83–89 °C; NMR (60 MHz) ($CDCl_3$) δ 8.25 (dd, 1, H_8 of Ar ring, $J_{8,7}$ = 8 Hz and $J_{8,6}$ = 2 Hz), 7.80–7.60 (m, 1, H_5 of Ar ring), 7.60–7.30 (m, 4, H_4, H_6, and H_7 of Ar ring), 6.75 (dd, 1, H_2 of Ar ring, $J_{2,3}$ = 8 Hz and $J_{2,4}$ = 2 Hz), 4.90–3.70 [m, 6, H_1, H_2, H_3, $NCH(CH_3)_2$], 3.60 (d, 1, OH, J = 4 Hz), 1.45 (d, 5.4, CH_3, J = 6 Hz), 1.15 (d, 0.6, CH_3, J = 6 Hz); IR (KBr) 3300, 3105, 3030, 2965, 1635, 1585, 1575, 1460, 1445, 1400, 1355, 1280, 1235, 1180, 1110, 1075, 1025, 1000, 965, 930, 795, 770, 740 cm^{-1}; CIMS (methane), m/z 289 (QM, 30), 288 (M, 18) 259 (QM - NO, 22), 215 (15), 145 (naphthol, 100), 72 (64). Anal. C, H, N.

Mutagenesis Testing. Male Sprague–Dawley rats (150–200 g) were obtained from the National Institutes of Health animal supply and maintained as previously described.[33] Animals were treated with Arochlor 1254 (500 mg/kg) dissolved in corn oil and sacrificed 48 h later. Preparation of liver fractions was performed as previously described.[34]

Mutagenesis assay was performed according to the method of Ames et al.[35] with minor modifications. To 2.2 mL of molten top agar containing 17 μmol of $MgCl_2$, 0.125 μmol of biotin, 0.215 μmol of histidine, 33 μmol of KCl, and 100 μmol of sodium phosphate buffer at 45 °C were added 0.1 mL of the bacterial tester strains (TA-98 or TA-100) grown in nutrient broth overnight (2–3 × 10^9 bacteria/mL), 0.1 mL of solution containing the compounds to be tested dissolved in Me_2SO, and 0.1 mL of the 9000*g* supernatant fraction containing 1.0 mg of protein. Prior to addition, liver fractions were diluted with phosphate-buffered saline to the desired protein concentrations and filtered through a 0.45-μm Swinnex filter unit (Millipore). The concentrations of protein in the filtrates were then determined after filtration to estimate losses during this process. NADPH (1 mg/plate) was added to 0.1 mL of phosphate-buffered saline. In all experiments, test compounds were added last. The colonies on each plate (histidine-independent revertants) were scored on a Count-all (Model 600) colony counter (Fisher Scientific Co., Pittsburgh, PA) after a 40-h incubation in the dark at 37 °C. The toxicity of the test compounds to the bacteria was tested by determining the number of colonies formed in histidine-enriched (4.5 mM) agar after the bacteria had been exposed to varying concentrations of the test compounds for 30 min at 37 °C and diluted to approximately 10^3 bacteria/mL before plating.

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Registry No. 1, 84418-31-5; 1·0.5-oxalate, 84418-32-6; 1·HBr, 84418-33-7; 2, 84418-34-8; 3, 84418-35-9; *N*-hydroxyisopropylamine, 5080-22-8; 1-naphthoxy-3-bromo-2-propanol, 2007-16-1; propranolol hydrochloride, 318-98-9.

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Book Reviews

Introductory Medicinal Chemistry. By John B. Taylor and Peter D. Kennewell. Halsted Press (A Division of Wiley), New York. 1981. 202 pp. 15.5 × 23.5 cm. ISBN 0-470-2752-X. $59.95.

The declared intention of the authors is to provide an introduction to medicinal chemistry research for scientists with an organic chemistry background but minimal knowledge of the biological and pharmaceutical sciences.

The book is divided into six chapters. Chapter 1 deals with definitions of subject areas, such as pharmacy, pharmacology, microbiology, etc. A historical drug development section is included, followed by a classification of pharmacological agents and a brief mention of the major processes involved in drug action. Chapter 2 deals with drug formulations, routes of administration, and dosage forms. The treatment is very concise and readable and is an adequate introduction to this branch of the pharmaceutical sciences.

Chapter 3 is entitled "The Pharmacokinetic Phase" and includes a section on cell biology (20 pages) and a useful section on QSAR. The pharmacokinetics of drug distribution are not discussed. Chapter 4 is concerned with the interaction of a drug with its site of action. The concept of receptors, receptor structures, agonists, and antagonists are discussed, and a section on radiolabeled ligands is included. The types of binding involved in drug–receptor interactions is also discussed, but the examples quoted deal mainly with enzyme models only. A section on receptor topography is given that is restricted to a summary of the structure–activity relationships of morphine and its synthetic derivatives. Finally, there is a topic on molecular design, which suffers from some rather poor illustrative examples chosen by the authors.

Chapter 5 is entitled "Neurotransmitters and Receptors". Half the chapter (16 pages) is concerned with the histology and anatomy off the nervous system and the rest is devoted to a rather classical pharmacological description of agonists and antagonists acting at peripheral receptors. A mention of receptors in the CNS is restricted to a list of central neurotransmitters. Surprisingly, there is no mention of the important role of enkephalins, endorphins, or γ-aminobutyric acid as neurotransmitters.

Chapter 6 deals with drug metabolism and is a concise, well-written, and useful introduction to this topic.

A useful reference section, a glossary of terms, and a subject index are provided. The book is adequately bound.

This book represents a rather basic introduction to medicinal chemistry, considering the intended readership suggested by the authors. Because of the broad, multidisciplinary approach chosen by the authors, the treatment is not comprehensive, some notable omissions being chemotherapeutic agents, prostaglandins, and antiinflammatory drugs. In addition, the authors have not emphasized the underlying chemical basis of drug action as forcefully as they might have done, and few examples of chemical mechanisms in drug action are given. Although this book may be of some interest to organic chemists wishing to persue a career in industrial medicinal chemistry, I doubt if it will become a useful text for undergraduate pharmacy or pharmacology students. At