4g, 89378-82-5; 5, 89378-68-7; 5d, 89378-93-8; 5d·2HCl, 89378-87-0; 6, 89378-69-8; 6d, 89378-94-9; 6d·2HCl, 89378-88-1; 7, 81814-10-0; 7c, 81821-03-6; 7d, 89378-97-2; 7d·2HCl, 81821-04-7; 8, 70296-73-0; 8b, 70296-74-1; 8c, 70296-69-4; 8f, 76683-79-9; 9, 89397-94-4; 9c, 76661-71-7; 10, 89397-95-5; 10c, 76661-72-8; 11, 89378-70-1; 11c, 76661-70-6; 12, 89378-71-2; 12c, 76506-38-2; 13, 89378-72-3; 13c, 76506-40-6; 14, 73279-30-8; 14c, 76506-41-7; 15, 76823-89-7; 15c, 89378-83-6; 16, 76823-93-3; 16b, 76823-94-4; 16c, 76823-97-7; 16d, 76824-37-8; 16d·2HCl, 76824-02-7; 16f, 76824-10-7; 16h, 76824-16-3; 17, 89378-73-4; 17c, 76824-03-8; 17d, 89378-95-0; 17d·2HCl, 76824-04-9; 18, 89378-74-5; 18c, 89378-84-7; 19, 76824-22-1; 19c, 76824-18-5; 20, 81821-08-1; 20c, 81821-05-8; 20d, 89378-96-1; 20d·2HCl, 81821-06-9; 21, 81814-08-6; 21c, 81821-01-4; 22, 89378-75-6; 23, 89378-76-7; 24, 70296-72-9; 26, 76823-90-0; 27, 76823-91-1; 28, 76823-92-2; 29, 89378-77-8; 30, 89378-78-9; 33, 81152-53-6; 33·HCl, 69014-12-6; 34, 81814-07-5; sodium cyanide, 143-33-9; cyanamide, 420-04-2; 2-(thiomethyl)pyridine, 2044-73-7; acrylonitrile, 107-13-1; chloroacetonitrile, 107-14-2; formic acid hydrazide, 624-84-0; sodium 3-mercaptopropionitrile, 77132-03-7; 5-methyl-4-(chloromethyl)imidazole hydrochloride, 51605-33-5; furfuryl mercaptan, 98-02-2; dimethylamine hydrochloride, 506-59-2; 3-mercaptopropionitrile, 1001-58-7; 5-[(dimethylamino)-methyl]-2-thiophenemethanol, 69340-23-4; 3-[(dimethylamino)-methyl]phenol, 60760-04-5; 4-bromobutyronitrile, 5332-06-9; *S*-[(2-amino-4-thiazoyl)methyl]isothiourea dihydrochloride, 20167-22-0; 3-chloropropionitrile, 542-76-7; benzoyl isothiocyanate, 532-55-8; methyl isothiocyanate, 556-61-6; diazomethane, 334-88-3; 5-chlorovaleryl chloride, 1575-61-7; 1,6-dichloro-2-hexanone, 62343-98-0; amidinothiourea, 2114-02-5; ethyl acetimidate, 1000-84-6; 1,1-dimethylthiosemicarbazide, 2289-53-4; 4-(chloromethyl)imidazole hydrochloride, 38585-61-4; 5-ethyl-4-(chloromethyl)imidazole hydrochloride, 74337-20-5; 5-(trifluoromethyl)-4-(chloromethyl)imidazole hydrochloride, 89378-98-3; 5-[(diaminomethylene)amino]-4-(chloromethyl)-1,2,4-oxadiazole hydrochloride, 89378-99-4; piperidine hydrochloride, 6091-44-7; morpholine hydrochloride, 10024-89-2; dichloroacetone, 534-07-6; thiourea, 62-56-6; 3-(1-pyrrolidinylmethyl)phenol, 69383-70-6; 3-(piperidinomethyl)phenol, 73279-04-6.

The 3,4-Catechol Derivative of Propranolol, a Minor Dihydroxylated Metabolite

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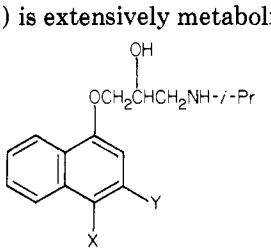
The *O,O*-dibenzyl ether of the 3,4-catechol derivative of propranolol (11) was prepared to determine whether the catechol is a product of metabolic hydroxylation. 4-(Allyloxy)-1,2-naphthoquinone (5) was reduced with sodium dithionite and alkylated with benzyl chloride to produce ether 7. Osmium tetroxide oxidation of 7 afforded glycol 8. Subsequent monotosylation, oxirane formation with KOH, and opening with isopropylamine afforded benzyl ether 11. Although hydrogenolysis was successful, catechol 3 was rapidly oxidized to the corresponding *o*-quinone (12). Reduction of 12 with sodium bisulfite afforded 3, which was derivatized with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) to serve as a standard for the metabolic experiments. Gas chromatography–mass spectrometry of the Me_3Si ethers of the products of metabolism of pseudoracemic propranolol (made up of equal molar (2*R*)-propranolol-d_0/(2*S*)-propranolol-3′,3′-d_2) in the presence of the rat liver 9000*g* supernatant fraction showed four dihydroxylated metabolites, of which catechol 3 was in smallest amount, approximately 9% of the sum of dihydroxylated metabolites. Each of the four dihydroxylated propranolols arises stereoselectively from the 2*R* enantiomer of propranolol (by 1.15- to 2-fold), as determined by parent ion intensities at m/z 507 vs. 509. Quinone 12 was a nonselective competitive β-adrenoceptor antagonist, being about 16-fold less potent than propranolol in both β_1 and β_2 assays.

Propranolol (1) is extensively metabolized in man and



1, X = Y = H (propranolol)
2, X = OH Y = H (4-hydroxypropranolol)
3, X = Y = OH (3,4-dihydroxypropranolol)

other species by several metabolic pathways, including oxidative N-dealkylation, aromatic hydroxylation, and glucuronidation.[1-7] In man, 4-hydroxypropranolol (2) is the major identified product of aromatic hydroxylation, and in rats, regioisomeric products of 2-, 4-, 5-, and 7-hydroxylation have been reported.[3-5,8] These isomeric monohydroxylated propranolols have significant β-adrenergic antagonist activity.[9] Since propranolol is structurally related to the adrenergic transmitters epinephrine and norepinephrine, interest has also focussed on the 3,4-catechol derivative of propranolol (3). In addition, catechol derivatives of other (aryloxy)propanolamines have had significant activity as β-adrenergic agonists and/or antagonists,[10-13] and formation of catechols from phenols

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is a relatively common occurrence in endogenous compounds and in the metabolism of some drugs. About 2–2.5% of propranolol administered chronically to hypertensive patients orally is reported to be converted to methoxyhydroxypropranolols and their corresponding glycol metabolites (products from N-dealkylation).[14]

When propranolol was incubated in the presence of the rat liver 9000*g* supernatant fraction, two dihydroxylated propranolols were identified (in a ratio of 1:12), based on mass spectral evidence, and their possible catechol nature was commented upon.[15] The lack of suitable standard compounds has precluded further work to determine whether the 3,4-catechol is a metabolite. In order to gain further information on this metabolic pathway, we directed efforts toward the synthesis of a derivative of the 3,4-catechol of propranolol and the determination of whether this catechol is a metabolite. In this paper we report the synthesis of the *o*-quinone derivative of this catechol, its use as a standard for determination of the 3,4-catechol, and some results of pharmacological testing.

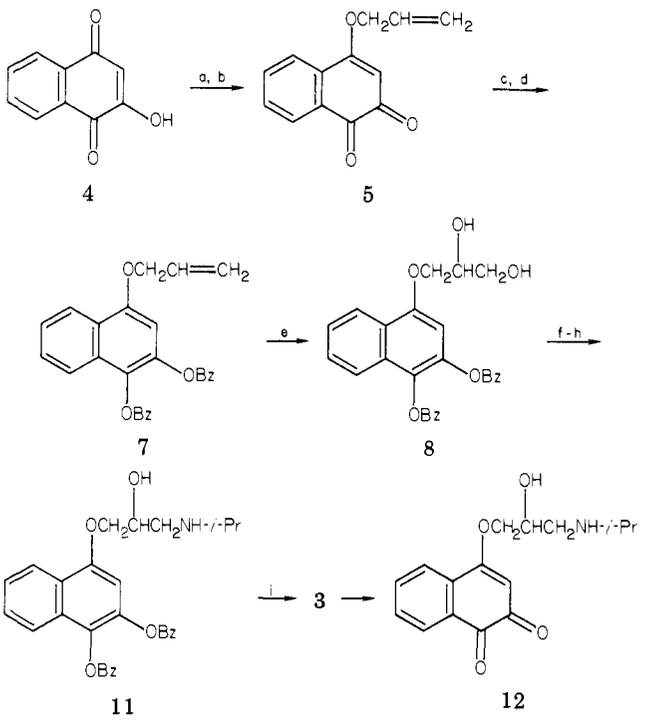
Results and Discussion

Our initial effort in the synthesis of the 3,4-catechol (**3**) was directed toward Fremy salt oxidation of 4-hydroxypropranolol, similar to work on related systems.[13] We were unsuccessful in obtaining identifiable products from this process.

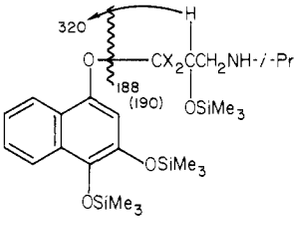
A successful synthesis of the *O,O*-dibenzyl ether of the desired 3,4-catechol (**3**) and the corresponding *o*-quinone (**12**) appears in Scheme I. 4-(Allyloxy)-1,2-naphthoquinone (**5**) was prepared by the method of Fieser[16] by alkylation of the silver salt of 2-hydroxy-1,4-naphthoquinone (**4**) with allyl bromide. Sodium dithionite reduction of **5** afforded the colorless catechol (**6**), which was rapidly oxidized to the green–black quinhydrone. Catechol **6** was converted immediately to the corresponding benzyl ether (**7**) with benzyl chloride. Elaboration of the side chain was accomplished by osmium tetroxide oxidation to form 1,2-glycol **8**. Conversion of **8** to the corresponding propranolamine (**11**) was accomplished by monotosylation, oxirane formation, and ring opening with isopropylamine.[17] Hydrogenolysis of **11** (HCl salt) afforded a colorless solution of the HCl salt of **3**, which was rapidly converted to the corresponding yellow *o*-quinone **12**·HCl. Establishment of the structure of **12** was based on elemental analysis and diagnostic location of the signal for the aromatic proton H_3 in the ^1H NMR spectra of **5** and *o*-quinone **12** at approximately δ 6.0, but downfield at δ 6.5–7.0 in the spectra of the benzyl ether (compounds **7** to **11**).

In order to determine whether the **3** was a metabolite of propranolol in vitro, we repeated the work demonstrating two dihydroxylated metabolites of propranolol (in the ratio of 1:12), with ions at *m/z* 507 in their mass spectra, as Me_3Si derivatives when subjected to GC separation using packed columns. We used an equal molar mixture of (2*R*)-propranolol-d_0 and (2*S*)-propranolol-3′,3′-d_2[18] as substrate to provide metabolites, determined as the Me_3Si derivative, having the twin ions in the mass spectrum at *m/z* 507 and 509, at *m/z* 188 and 190 (side-chain fragments), and the aromatic ring fragment at *m/z* 320 to aid in the determination of whether the 3,4-catechol is a metabolite. In addition, information concerning the enantioselectivity of the metabolic process would be available from relative amounts of *m/z* 507 vs. 509.

Scheme I[a]



[a] Reagents: a = NH_3, $AgNO_3$; b = $BrCH_2CH{=}CH_2$; c = $Na_2S_2O_4$; d = BzCl, DMF, K_2CO_3; e = OsO_4, NMMO; f = TsCl, C_5H_5N; g = KOH; h = $H_2NCH(CH_3)_2$; i = H_2, Pd/C.



X = H (*m/z* 507)
X = D (*m/z* 509)

o-Quinone **12** was converted to **3**, to serve as a standard for metabolic experiments, by aqueous sodium bisulfite reduction and then extracted with EtOAc, similar to the extraction of the metabolic samples. Both were derivatized with BSTFA. In Figure 1 is a portion of the ion current traces of parent ions *m/z* 507 and 509 of peaks emerging from 9 to 11 min when derivatized extracts of the metabolic samples were subjected to GC–mass spectrometry. The Me_3Si derivative of the standard 3,4-catechol (**3**) showed a retention time of 9.50 min, corresponding to the smallest of the four sets of twin ions observed. The appropriate side chain ions of *m/z* 188 and 190 and the common ring fragment of *m/z* 320 were also observed. This metabolite accounted for about 9% of the total ion current for *m/z* 507 and 509 over this time period. The

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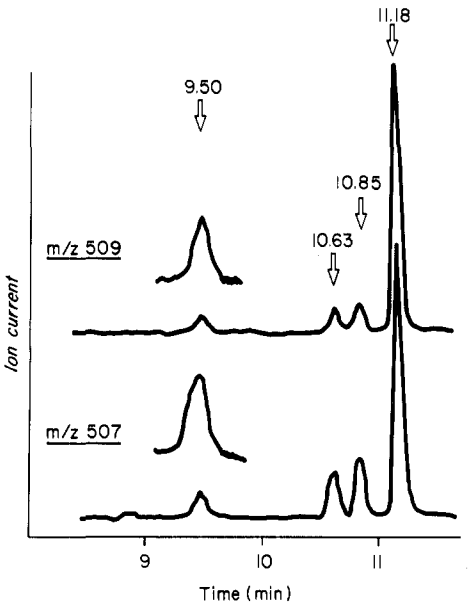

Figure 1. Partial ion current traces of m/z 507 and 509 of Me_3Si derivatives of propranolol metabolites.

other three components that emerged had retention times of 10.63, 10.85, and 11.18 min. All three showed parent ions at m/z 507 and 509 and expected fragment ions at m/z 188 and 190 and at m/z 320. These three compounds account for ca. 90% of dihydroxylated metabolites observed. Thus, we conclude that the 3,4-catechol (**3**) is a metabolite, but it is present only in a very small amount in the incubation of propranolol with the rat liver 9000*g* supernatant fraction.

From selected ion current measurements, we noted that the enantioselectivity for formation of all four dihydroxylated metabolites was greater from (2*R*)-propranolol than from (2*S*)-propranolol, although the ratios were less than 2, the major peak showing a total ion current ratio of m/z 507/509 of ca. 1.15. Significant differences in the enantioselectivity of monohydroxylation occur in vivo, and to a lesser extent in vitro, in rats for formation of 4- and 5-hydroxypropranolol (in vitro both are only slightly stereoselective for the 2*S* enantiomer; R/S ratio 0.9), and 7-hydroxylation is highly stereoselective for the 2*R* enantiomer (R/S ratio > 2.5).[8,19,20] Hydroxylation at the 2-position in a very minor pathway.[8,20] Thus, if more than one hydroxylation occurred, the stereochemical nature of these products would be difficult to predict.

Although only a small amount of 3,4-catechol was observed, it may not be because only a small amount of **3** was formed. One possibility is that the catechol is very unstable under the conditions of the metabolic experiment. Since we were able to obtain it by chemical reduction of **12** and to extract and derivatize it, this seems to be very likely. Another possibility is that the 3,4-catechol, if formed, might be N-dealkylated. Mass spectral data consistent with formation of monomethyl ethers of dihydroxylated metabolites of propranolol glycol (and of propranolol itself) have been reported from experiments performed in vivo in man.[14]

We conclude that the major dihydroxylated metabolites of propranolol are compounds other than the 3,4-catechol. Our observation of four dihydroxylated propranolols rather than two found by Tindell et al.[15] may result from our increased ability to separate these compounds by capillary GC methods. It seems possible that the three unidentified dihydroxylated compounds are metabolites arising from multiple hydroxylaions of the regioselectivities noted previously for hydroxylation of propranolol in the rat, i.e., primarily hydroxylation at C-4, C-5, and C-7 of the naphthalene ring. However, since no evidence is yet available, we cannot evaluate this possibility. Upon monohydroxylation of the aromatic ring, the regioselectivity for the second hydroxylation seems likely to change, since hydroxylation at position 4, 5, or 7 would result in increased electron density of ring positions not activated in propranolol. For example, in the structurally related compound carbaryl (1-naphthyl methylcarbamate), hydroxylations at C-5 and at C-5 and C-6 are reported in phenolic and catechol metabolites respectively.[21] Further work is needed to identify these metabolites and to evaluate their possible importance.

Table I. Competitive Antagonism Effects in β_1- and β_2-Adrenoceptor Assays

	guinea pig atria (β_1)		rat uterus (β_2)	
compd	pA_2[a]	slope[b]	pA_2[a]	slope[b]
propranolol-3,4-quinone (**12**)	7.30 ± 0.21	0.94	7.53 ± 0.12	1.05
propranolol (**1**)	8.51 ± 0.09	0.93	8.75 ± 0.04	1.08
4-hydroxypropranolol (**2**)	8.24 ± 0.10	0.99	8.62 ± 0.06	0.91

[a] $pA_2 = -\log K_B$ (see ref 25). [b] Theoretical value equals unity.

The dissociation constants (K_B) of *o*-quinone **12**, **1**, and **2** for β_1- and β_2-adrenoceptors were determined by the technique of Arunlakshana and Schild.[22] We were unable to test catechol **3** because of the toxicity of sodium bisulfite to the test tissues. Affinity for the β_1-adrenoceptor was assessed in guinea pig atria with norepinephrine as the agonist, while affinity for the β_2-adrenoceptor was assessed in rat uterus with isoproterenol as the agonist. Since myocardium possesses both β_1- and β_2-adrenoceptors,[23] all studies in guinea pig atria were performed in the presence of 10 nM ICI 118551, a potent β_2-adrenoceptor antagonist.[24] The results appear in Table I.

o-Quinone **12** was a competitive β_1- and β_2-adrenoceptor antagonist, being approximately $^1/_{16}$th as potent as propranolol in both assays. Consistent with effects of propranolol (**1**) and 4-hydroxypropranolol (**2**), no selectivity for β_1- or β_2-adrenoceptors was noted. Since the conversion of propranolol to more polar compounds like **2** and **12** provides compounds retaining competitive antagonistic properties at β-adrenoceptors, it seems possible that catechol **3** would retain β-adrenoceptor antagonist activity. Our inability to test **3** precludes additional speculation on this point.

Additional work on the metabolism of propranolol is underway.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A or Perkin-Elmer 727B spectrophotometer. NMR spectra were recorded on a Varian T-60 or EM-360 spectrometers with Me_4Si as internal standard. Notations used in the NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded

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on the VG-7070H mass spectrometer operated in the EI and CI modes as noted. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

4-(Allyloxy)-1,2-naphthoquinone (5). 2-Hydroxy-1,4-naphthoquinone (4; 34.8 g, 0.20 mol) was added to 500 mL of hot water. Concentrated aqueous ammonium hydroxide was added until the quinone dissolved. The mixture was then neutralized with dilute aqueous nitric acid until a precipitate remained. Silver nitrate (33.9 g, 0.20 mol) in 300 mL of water was added to the mixture, and the resulting dark red salt was collected by filtration, washed with ethanol and ether, and dried to yield 44.2 g of the silver salt of 4, which was used without further purification.

Allyl bromide (24.2 g, 0.20 mol) was added to a suspension of 44.2 g of the silver salt of 4 in 300 mL of benzene. The mixture was then refluxed for 20 min, the precipitate was collected by filtration and washed with benzene, and the mother liquor was dried ($MgSO_4$) and evaporated, affording an orange solid. Crystallization from ethanol yielded 16.8 g (40%) of 5 as orange needles: mp 124–126 °C (lit.[16] mp 125 °C); IR (KBr), 3400, 3160, 1705, 1620, 1605, 1595, 1560, 1385, 1360, 1300, 1255, 1220, 1090, 985, 950, 860, 780, 735 cm^{-1}; NMR (Me_2SO-d_6) δ 7.80 (m, 4 H_5, H_6, H_7, and H_8 of Ar ring), 6.20 (m, 1, CH=CH_2), 6.10 (s, 1, H_3 of Ar ring), 5.60 and 5.50 (2 m, 2, HC=CH_2),[26] 4.80 (d, 2 Ar OCH_2, J = 6 Hz).

4-(Allyloxy)-1,2-bis(benzyloxy)naphthalene (7). 4-(Allyloxy)-1,2-naphthoquinone (5; 1.50 g, 7.0 mmol) was added to 150 mL of boiling water. Sodium dithionite was added in small amounts until a colorless solution was obtained. The mixture was filtered hot and then allowed to cool to room temperature, and the resulting precipitate was collected by filtration, washed with water, and dried to yield catechol 6, which was used without further purification.

Benzyl chloride (4.00 g, 32 mmol) and K_2CO_3 (4.20 g, 30 mmol) were added to crude 6 in 40 mL of DMF, and the mixture was heated under nitrogen at 50 °C for 24 h. The solution was then added to 70 mL of aqueous 5% NaOH and extracted with ether (2 × 70 mL). This ether extract was then washed with 5% aqueous NaOH (2 × 70 mL), dried ($MgSO_4$), and evaporated to yield a solid. Crystallization from ethanol and subsequent recrystallization from acetonitrile/water yielded 0.41 g (15%) of 7 as white needles: mp 114–114.5 °C; IR (KBr), 3400, 1625, 1600, 1455, 1405, 1355, 1275, 1175, 1100, 1050, 1025, 985, 770, 760, 705 cm^{-1}; NMR ($CDCl_3$) δ, 8.10 (m, 2, H_5 and H_8 of Ar ring), 7.30 (m, 12, H_6 and H_7 of Ar ring and benzyl Ar H), 6.55 (s, 1, H_2 of Ar ring), 6.10 (m, 1, HC=CH_2), 5.40 and 5.35 (2 m, 2, HC=CH_2), 5.15 and 5.05 (2 s, 4, benzyl CH_2), 4.55 (d, 2, Ar OCH_2, J = 6 Hz); CIMS (methane), m/z 397 (QM), 396 (M^+), 306 (QM – C_7H_7, 50), 305 (M^+ – C_7H_7, 100).

1-[3,4-Bis(benzyloxy)-1-naphthoxy]-2,3-propanediol (8). Under nitrogen, 95 mg (0.70 mmol) of *N*-methylmorpholine *N*-oxide was dissolved in 5 mL of distilled water and 2.5 mL of acetone, and as the solution was stirred, 1.5 mL of a 2.5% osmium tetroxide solution in *tert*-butyl alcohol stabilized with *tert*-butyl peroxide (Aldrich Chemical Co.) was added. 4-(Allyloxy)-1,2-bis(benzyloxy)naphthalene (7; 240 mg, 0.65 mmol) in 5 mL of THF was added, and then enough THF/acetone (1:1) was added to dissolve the precipitate. After the solution was stirred for 24 h, a slurry of 200 mg of sodium dithionite and 2.25 g of silica gel in 10 mL of water was added. After stirring for 20 min, the mixture was filtered through a Celite filter pad. The filter pad was washed with acetone, and the combined extracts were concentrated on the rotary evaporator. The concentrate was adjusted to pH 2 with 14 N H_2SO_4 and extracted with ether. The ether layers were combined, washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated on the rotary evaporator to give 8 as a white solid. Recrystallization from benzene/hexane (1:1) gave 200 mg (71%) of 8 as a white powder: mp 133–133.5 °C; IR (Nujol) 3400, 1600, 1575, 1080, 1025, 1000, 950, 785, 720, 710, 680 cm^{-1}; NMR (acetone-d_6) δ 8.20 (m, 2, H_5 and H_8 of Ar ring), 7.45 (m, 12, H_6 and H_7 of Ar ring and benzyl Ar H), 7.10 (s, 1, H_2 of Ar ring), 5.40 and 5.12 (2 s, 4, benzyl CH_2), 4.20 and 3.80 [m, 5, $(CH_2O)_2$ and $CHOH$].

1-[3,4-Bis(benzyloxy)-1-naphthoxy]-2,3-epoxypropane (10). Using oven dried glassware, we dissolved 1-[3,4-bis(benzyloxy)-1-naphthoxy]-2,3-propanediol (8; 1.07 g, 2.48 mmol) in 5 mL of freshly distilled, anhydrous pyridine under nitrogen (very dry pyridine is needed to obtain satisfactory yields). As the solution stirred in an ice bath, 0.587 g (3.08 mmol) of tosyl chloride in 20 mL of ice-cold, anhydrous pyridine was added dropwise over 45 min. The reaction was allowed to warm to room temperature and stirred for 48 h. The tosylate (9) was not isolated. The reaction mixture containing crude 9 was cooled in an ice bath, and a solution of 0.50 g (9.00 mmol) of KOH in 20 mL of MeOH was added. After stirring for 20 min, the mixture was poured into 200 mL of water and filtered. The precipitate was dissolved in 20 mL of EtOAc and washed with aqueous 5% H_2SO_4 (2 × 50 mL) and water and then dried ($MgSO_4$). After the solvent was removed, the white solid obtained was purified by column chromatography [45 g of 0.05–0.20-mm silica gel, with EtOAc/$CHCl_3$ (3:7) as eluent] to give 0.65 g (63%) of epoxide 10, mp 112–119 °C. Unreacted diol (0.25 g) was also recovered: NMR ($CDCl_3$) δ 8.20 (m, 2, H_5 and H_8 of Ar ring), 7.45 (m, 12, H_6 and H_7 of Ar ring and benzyl Ar H), 6.74 (s, 1, H_2 of Ar ring), 5.30 and 5.18 (2 s, 4, benzyl CH_2), 4.20 (m, 2, Ar OCH_2), 3.48 (m, 1, CHO), 2.90 (m, 2, CH_2O); EIMS, m/z 412 (M^+, 4.3), 321 (M^+ – C_7H_7, 100).

1-[3,4-Bis(benzyloxy)-1-naphthoxy]-3-(isopropylamino)-2-propanol Hydrochloride (11). Under nitrogen, 670 mg (1.62 mmol) of 1-[3,4-bis(benzyloxy)-1-naphthoxy]-2,3-epoxypropane (10) was suspended in 25 mL of isopropylamine, and sufficient tetrahydrofuran (THF) was aded until the epoxide had just dissolved. The mixture was stirred for 4 days, and the isopropylamine and THF were removed on a rotary evaporator, affording 620 mg of an orange solid. This solid was dissolved in a mixture of EtOAc and Et_2O, and HCl gas was bubbled through it for 10 min. The white precipitate that formed was removed by suction filtration and washed with Et_2O. The mother liquor was cooled in ice and additional precipitate was collected. The crude product (340 mg) was further purified by crystallization from acetonitrile, affording 250 mg (30%) of 11 as a white solid: mp 157–158 °C; IR (Nujol) 3350, 160, 1600, 1275, 1090, 1050, 1020, 760, 700 cm^{-1}; NMR (CD_3OD) δ 8.20 (m, 2, H_5 and H_8 of Ar ring), 7.45 (m, 12, H_6 and H_7 of Ar ring and benzyl Ar H), 6.95 (s, 1, H_2 of Ar ring), 5.32 and 5.08 (2 s, 4, benzyl CH_2), 4.25–3.50 (m, 6, Ar OCH_2, $CHOH$, CH_2NHCH), 1.42 [d, 6, $(CH_3)_2CH$, J = 6 Hz]; EIMS, m/z 471 (M^+, 2.5), 380 (M^+ – C_7H_7, 15), 116 ($C_6H_{14}NO^+$, 100), 91 ($C_7H_7^+$, 100), 72 ($C_4H_{10}N^+$, 42).

4-[2-Hydroxy-3-(isopropylamino)-1-propoxy]-1,2-naphthoquinone Hydrochloride (12). 1-[3,4-Bis(benzyloxy)-1-naphthoxy]-3-(isopropylamino)-2-propanol hydrochloride (11; 250 mg, 0.50 mmol) was dissolved in 20 mL of ethanol, and 10 mg of 10% Pd/C was added to the solution. Hydrogenolysis was performed at 1 atm at room temperature. The hydrogen uptake was stopped after 20 min when the calculated amount of hydrogen was taken up. After hydrogenolysis, the solution was colorless, but it rapidly became yellow when exposed to any air. After filtration, 20 mL of absolute Et_2O was added to the filtrate, and cooled below 0 °C overnight. Compound 12, as a yellow powder (142 mg, 88% yield), was obtained, mp 218 °C dec. The product was further purified by crystallization from acetonitrile/H_2O: IR (KBr), 3370, 3060, 2975, 2925, 2770, 1700, 1630, 1590, 1550, 1440, 1370, 1305, 1245, 1090, 980, 795 cm^{-1}; NMR (Me_2SO-d_6/D_2O) δ 8.00 (m, 2, H_5 and H_8 of Ar ring), 7.80 (m, 2, H_6 and H_7 of Ar ring), 5.98 (s, 1, H_3 of Ar ring); CIMS (methane), m/z 290 (QM, 11), 292 (QM of catechol 3, arising from reduction on the probe), 175 ($C_{10}H_7O_3^+$, 7), 116 ($C_6H_{14}NO^+$, 79), 72 ($C_4H_{10}N^+$, 100). Anal. ($C_{13}H_{12}O_3$) C, H, N.

Metabolism Experiments. Male Sprague–Dawley rats (145–155 g) were killed by cervical dislocation, and their lives were removed and homogenized at 0 °C in 4 vol of 0.01 M potassium phosphate buffer (pH 7.4) containing 1.15% KCl in a Potter-Elvehjem homogenizer with a Teflon pestle. The homogenates were centrifuged at 9000*g* for 30 min, and the supernatant fraction was removed by pipet. Suspensions containing 5 mL of the 9000*g* supernatant fraction (1.0 g of liver), 5 mL of 0.1 M potassium phosphate buffer (pH 7.4), $MgCl_2$ (51.0 mg, 250 μmol), glucose 6-phosphate (28.2 mg, 100 μmol), $NADP^+$ (1.25 mg, 1.5 μmol), and 0.25 mg of pseudoracemic propranolol [made up of equal molar amounts of (2*R*)-propranolol and (2*S*)-propranolol-3′,3-d_2[18]] were incubated in air for 60 min at 37 °C. After the addition of 20 mg of sodium bisulfite, the incubations were adjusted to pH

9.6 (Na_2CO_3) and extracted with 10 mL of EtOAc. The EtOAc extract was evaporated (N_2) and derivatized with 50 μL of *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) (60 °C, 15 min) just prior to GC–MS analysis. For comparisons, a standard (50–200 μg of **12**·HCl) was dissolved in 1 mL of H_2O. Sodium bisulfite was added (10 mg), and the sample was immediately extracted with 2 × 5 mL of EtOAc. The combined EtOAc extracts were evaporated (N_2) and derivatized with BSTA as described for the metabolic samples.

The propranolol metabolites were separated with a J&W DB-5 fused silica capillary column (30 m × 0.25 μm film). Separation was achieved with a 5710A Hewlett-Packard gas chromatograph interfaced with the VG-7070 mass spectrometer. Chromatographic conditions were as follows: injector temperature, 250 °C; helium flow rate, 60 mL/min; column head pressure, 15 psi; temperature programmed from 220–300 °C at 5 °C/min. The mass spectrometer was operated at 20 eV, and the ion source was maintained at 200 °C.

Pharmacological Testing. Affinity for β_1- and β_2-adrenoceptors was assessed in guinea pig atria and rat uterus, respectively. Studies in guinea pig atria were performed in Krebs' solution [composition (mM): NaCl, 118; KCl, 4.7; $MgCl_2$, 0.54; $CaCl_2$, 2.5, NaH_2PO_4, 1.0; $NaHCO_3$, 25; glucose, 11], while studies in rat uterus were performed in DeJalon's solution [composition (mM): NaCl, 154, KCl, 5.6, $CaCl_2$, 0.4; $NaHCO_3$, 6; glucose, 2.7]. All solutions were prepared with demineralized water and were continually gassed with a mixture of 95% O_2/5% CO_2. Studies for β_1-adrenoceptor antagonism activity in guinea pig atria were performed at 30 °C with norepinephrine as the agonist. All studies were performed in the presence of 10 nM ICI 118551, a potent β_2-adrenoceptor antagonist.[24] Studies for β_2-adrenoceptor antagonism activity in rat uterus were performed at 25 °C (to reduce spontaneous activity) with isoproterenol as the agonist. All tissues were attached to Grass FT-03 isometric transducers connected to a Beckman R4 Dynograph recorder and allowed to equilibrate for at least 2 h before drug addition. Dose–response curves were obtained by the method of stepwise cumulative addition of the agonist.[27] The concentration of agonist in the muscle chamber was increased approximately 3-fold at each step, with each addition being made only after the response to the previous addition had attained a maximum level and remained steady. Drugs were washed from the preparation at regular intervals by the overflow method after completion of a dose–response curve. Consecutive dose–response curves on a given tissue were spaced at least 1 h apart to ensure maximum washout of agonists and to minimize receptor desensitization. In all experiments, at least one uterine strip receiving no antagonist was run in parallel with the experimental strips to correct for time-dependent changes in agonist sensitivity.[28]

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Registry No. 1, 525-66-6; **3**, 89710-82-7; **4**, 83-72-7; 4 silver(I) salt, 36417-25-1; **5**, 42164-68-1; **6**, 89710-74-7; **7**, 89710-75-8; **8**, 89710-76-9; **9**, 89710-77-0; **10**, 89710-78-1; 11, 89710-79-2; **12**, 89710-81-6; **12**-HCl, 89710-80-5; $H_2C{=}CHCH_2Br$, 106-95-6.

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Synthesis, Characterization, and Properties of a Group of Platinum(IV) Complexes

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The synthesis, characterization, and antitumor properties of a group of platinum(IV) complexes is presented. The compounds, formed by oxidation of *cis*-dichlorodiammineplatinum(II) (1) or its *cis*-dihydroxo analogue, were characterized by elemental analysis and infrared and ^{195}Pt NMR spectroscopies. EPR studies of aqueous solutions containing the spin trap phenyl-*tert*-butylnitrone and various platinum(IV) complexes revealed that the compounds are incapable of producing radical species which may in turn cause DNA breakage. It appears that the antitumor activity of the compounds is either due to Pt(IV) binding via ligand displacement to important cellular components or through the ability of the compounds to undergo in vivo reduction to platinum(II) species, which in turn exert their cytotoxic effects in a manner analogous to 1. As a group, the platinum(IV) compounds were found to be significantly less active against L-1210 leukemia than the parent platinum(II) complex, 1.

The study of the mechanism of action of the anticancer drug *cis*-dichlorodiammineplatinum(II) (1) and its analogues is under active investigation.[1-3] The bulk of the evidence suggests that 1 exhibits its cytotoxic effects by direct interaction with cellular DNA. Although the interaction is site specific and involves platination at oligoguanine sequences of DNA,[4] 1 does not cleave DNA as does bleomycin[5] and neocarzinostatin.[6]

In addition to square planar platinum(II) compounds, a number of octahedral platinum(IV) complexes are known to be active as antitumor agents.[2,7-11] However, unlike

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