chromatography. Thin-layer chromatograms [silica, $CHCl_3$:-MeOH:H_2O (95:36:6)] of I revealed at least five components (R_f 0.11, 0.24, 0.36, 0.64, 0.75) with major spots at R_f 0.24 and 0.36; all components gave positive color tests (ammonium molybdate–stannous chloride) for phosphorus. Elemental analysis of multicomponent I showed it to contain phosphorus (3.73%) and nitrogen (2.11%). Chromatography of 500 mg of I on a silicic acid column (0.5 × 30 cm) with $CHCl_3$:MeOH (4:1) as the eluent gave 81 mg of a homogeneous fraction II, R_f 0.38, which gave positive tests for phosphorus (ammonium molybdate–stannous chloride), unsaturation (fluorescein–bromine), and amine (ninhydrin). The R_f value of II was identical in two tlc systems with the main ninhydrin spot of crude phosphoglyceride obtained from hog kidney and with commercial bovine phosphatidylethanolamine standard.

The ir spectrum (neat) of II included bands at 3000, 1626 (C=C), 1709 (C=O), 1212 (P=O), 1053 (POC), and 900 cm^{-1} (POH) and several absorptions characteristic of polar head NH and OH stretching and deformation vibrations of phosphatidylethanolamines:[24] pmr (100 MHz) δ 0.96 (CH_3), 1.35 (CH_2), 1.80 (CH=$CHCH_2CH_2CH_2CO$), 2.14 (CH=$CHCH_2$), 2.45 (CH_2CO), 2.96 (CH=$CHCH_2CH$=CH), 3.26 (CH_2N), 3.87–4.75 (glyceryl protons, CH_2OP), 5.54 (CH=CH), and 8.24–8.68 [(O)P(O*H*)$OCH_2CH_2NH_2$ and/or (O)$P(O^-)OCH_2CH_2NH_3^+$].

Several milligrams of phospholipid II were dissolved in 3 ml of methanol–benzene (1:1), 1 ml of methanolic 0.5 *N* KOH was added, and the mixture was heated (100°) for 5 min in a Teflon-lined screw-cap centrifuge tube flushed under N_2; after cooling, 2 ml of 12% BF_3–methanol[25] then was added followed by heating (100°) under the same conditions for another 5 min. Tlc of the lipid resulting from work-up of the organic phase[25] confirmed the presence of methyl esters as the major species (*ca.* 95%).

Qualitative and quantitative analysis of the fatty acid methyl esters was performed using flame-ionization gas–liquid chromatography. The relative retention times of the methyl esters of the natural sample, before and after hydrogenation (PtO_2–Adam's catalyst, MeOH, 1 atm, 1 hr), were compared with several authentic methyl ester standards on polar (DEGS) and nonpolar (OV-1) columns. Lipids I and II were treated with phospholipase A[1,2] and the corresponding lysophosphatides were incubated with dog renin in the presence of dog renin substrate; the amounts of angiotensin formed (Table II) were assayed in the pentolinium-treated vagotomized rat.[1,2]

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Absolute Configuration by Asymmetric Synthesis of (+)-1-(4-Acetamidophenoxy)-3-(isopropylamino)-propan-2-ol (Practolol)

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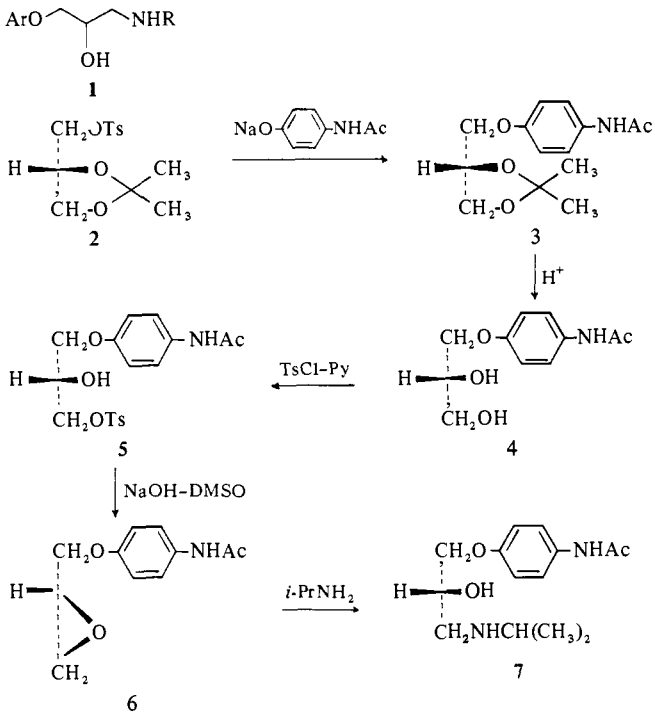
In recent years many substances based on the general structure 1-aryloxy-3-alkylaminopropan-2-ol (**1**) have been prepared in different laboratories in a search for compounds with β-adrenergic receptor blocking activity. To date, it has been found that the (−) isomers are the most effective in antagonizing the effects of isoproterenol and it has been of interest to relate the absolute configuration of these compounds to that of the natural agonists, epinephrine and norepinephrine. With this objective, Dukes and Smith have related (+)-propranolol (**1**, Ar = 1-naphthyl, R = isopropyl) to (+)-lactic acid and hence shown it to have the *R* configuration.[1] The configuration of other β-adrenergic receptor blocking substances, including the two enantiomers of practolol, were then in turn related to (*R*)-propranolol by Horeau's method of partial asymmetric synthesis, and it was thus inferred that all the active (−) isomers had the same *S* configuration, stereochemically equivalent to (*R*)-(−)-epinephrine.

During the course of our work on other cardiovascular drugs, we obtained (*R*)-(−)-1-(4-acetamidophenoxy)-2,3-epoxypropane (**6**) and the reaction of this substance with isopropylamine offered a convenient opportunity to prepare an isomer of practolol (**7**) with a known absolute configuration. The compound obtained showed a positive rotation both as the free base and as the hydrochloride salt and thus by direct evidence (+)-practolol was shown to have

the *R* configuration, in agreement with the result obtained earlier by Horeau's method.[1]

The synthetic route is shown in Scheme I. The starting

Scheme I



point was (*R*)-(−)-α-(4-toluenesulfonyl)acetone glycerol (**2**) which was obtained[2] from D-mannitol. Compound **2** was converted to the 4-acetamidophenoxy derivative **3** by treatment with sodium 4-acetamidophenoxide. The acetone-protecting group was removed by dilute acid hydrolysis, and the resulting diol **4** was treated with 1 mol equiv of TsCl in pyridine to give the primary tosyl derivative **5**. The selective tosylation was investigated on racemic material and demonstrated by ^{1}H nmr spectroscopy. Using DMSO-d_6 as solvent, primary and secondary hydroxyl groups were easily distinguished as a clear triplet and a (poorly resolved) doublet, respectively. Base treatment of compound **5** gave (*R*)-(−)-1-(4-acetamidophenoxy)-2,3-epoxypropane (**6**) which was then treated with isopropylamine to give (*R*)-(+)-1-(4-acetamidophenoxy)-3-isopropylaminopropan-2-ol (**7**).

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Specific rotations were measured on a Perkin-Elmer 141 polarimeter. Percentage yields are given for materials (pure by tlc) as used for subsequent reactions. In the cases where the analyses were done after a further crystallization, melting point and rotation did not change significantly. Analyses are indicated only by symbols of the elements analyzed and were within 0.4% of the theoretical values. Nmr spectra were taken with a Varian A-60 nmr spectrophotometer and ir spectra were taken as KBr disks with a Perkin-Elmer 257 spectrophotometer. Spectra for all substances not reported were consistent with the proposed structures.

(*S*)-(+)-α-(4-Acetamidophenyl)acetone Glycerol (3). Sodium (0.755 g) was dissolved in 2-methoxyethanol (12.5 ml), and 4-acetamidophenol (4.96 g) was added followed by (*R*)-(−)-α-(4-toluenesulfonyl)acetone glycerol[2] (**2**, 9.4 g) in 2-methoxyethanol (20 ml). The mixture was refluxed for 1.5 hr, cooled, added to water (150 ml), and shaken. The resulting precipitate was washed with water (4 × 25 ml) and dried under vacuum. The product (5.5 g) was crystallized from PhH to yield a white solid (4.0 g, 46%), mp 141–142°. Recrystallization raised the melting point to 142–143.5°, $[\alpha]^{25}_{365}$ +37.9° (*c* 1.0, EtOH). *Anal.* ($C_{14}H_{19}NO_4$) C, H, N.

(*R*)-(−)-α-(4-Acetamidophenyl)glycerol (4). Compound 3 (25.5 g) in aqueous 80% AcOH (125 ml) was heated at 50–75° for 0.5 hr; the solution was cooled and then added to ether (1250 ml). The precipitated product was washed with ether (5 × 50 ml) and dried under vacuum, yield 17.7 g (82%), mp 148–150°. Recrystallization (*i*-PrOH–Et_2O, charcoal) gave pure **4**: mp 153–155°; $[\alpha]^{25}_{365}$ −4.36° (*c* 5.0, pyridine). *Anal.* ($C_{11}H_{15}NO_4$) C, H, N. The known[3] racemic compound melts at 137.5–138°; its nmr spectrum (DMSO-d_6) shows a primary OH group, τ 4.64 (*J* = 5.5 Hz, triplet), and a secondary OH, τ 4.90 ($\nu_{1/2}$ = 6 Hz, rectangular singlet = unresolved doublet).

(*S*)-(+)-1-(4-Acetamidophenoxy)-3-(4-toluenesulfonoxy)propan-2-ol (5). The diol **4** (9.01 g) in dry pyridine (90 ml) was cooled to −10°, and pure TsCl (7.63 g) was added in one portion and shaken to dissolve. The mixture was allowed to warm to +5° over 16 hr and then diluted with EtOAc (100 ml) and added with cooling to H_2SO_4 (35 ml) in water (200 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 100 ml). The combined organic layers were dried (4Å molecular sieves) and the solvent was removed under vacuum. The residual oil (15.0 g) on trituration with ether (50 ml) yielded a pale pink solid (12.7 g) which on crystallization from 1,2-dichloroethane yielded a white solid (8.0 g, 53%), mp 118.5–120°. Recrystallization gave the pure tosylate: mp 120.5–121°; $[\alpha]^{25}_{365}$ +37.0° (*c* 2.0, EtOH). *Anal.* ($C_{18}H_{21}NO_6S$) C, H, N. The racemic isomer of **5**, mp 132–134° (*Anal.* C, H, N), was prepared similarly (yield 42%); its nmr spectrum (DMSO-d_6) shows a secondary OH group, τ 5.47 ($\nu_{1/2}$ = 6.5 Hz, rectangular singlet = unresolved doublet).

(*R*)-(−)-1-(4-Acetamidophenoxy)-2,3-epoxypropane (6). The tosylate 5 (5.0 g) in DMSO (10 ml) was treated with aqueous 20% NaOH (5 ml) for 10 min at room temperature. Water (50 ml) was added and the mixture was extracted with EtOAc (3 × 25 ml); on evaporation the extracts yielded an oil (2.79 g) which slowly crystallized, mp 92–95°. One crystallization from PhH yielded the pure compound (1.5 g, 55%): mp 104–106°; $[\alpha]^{25}_{365}$ −18.5° (*c* 2.0, EtOH). *Anal.* ($C_{11}H_{13}NO_3$) C, H, N. The known[4] racemic epoxide melts at 110°.

(*R*)-(+)-1-(4-Acetamidophenoxy)-3-(isopropylamino)propan-2-ol (7). The epoxide **6** (0.250 g) was dissolved in *i*-$PrNH_2$ (10 ml) and kept 3 days at ambient temperature. Evaporation under vacuum gave a white solid (0.328 g), mp 128–129°, which on crystallization from dioxane yielded pure (*R*)-(+)-practolol (**6**) (0.155 g, 48%): mp 130–131.5°; $[\alpha]^{25}_{365}$ +4.3°, $[\alpha]^{25}_{578}$ +3.5° (*c* 1.0, EtOH). *Anal.* ($C_{14}H_{22}N_2O_3$) C, H, N. The hydrochloride (prepared *in situ*) showed $[\alpha]^{25}_{436}$ +26.0° and $[\alpha]^{25}_{578}$ +14.0° (*c* 1.0, water). The racemic free base[4] melts at 134–136°.

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A Reinvestigation of the Structure of Chlorguanide Hydrochloride

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The structure of the antimalarial drug chlorguanide (proguanil; paludrine; 1-(*p*-chlorophenyl)-5-isopropylbiguanide) is usually depicted in the imino form **1a**. In some instances, however, an analogy has been drawn between the structures of chlorguanide and several of the diaminodiazines and triazines (*e.g.*, cycloguanil, **2a**) possessing similar drug activity,[1] by writing chlorguanide in the amino form, **1b**.

An X-ray crystallographic study[2] of chlorguanide hydrochloride (**1**·HCl) reported a structure which may be described as **3** or some resonance form thereof. The six biguanidinium C–N distances were sufficiently similar that no one of the resonance forms for this compound could be