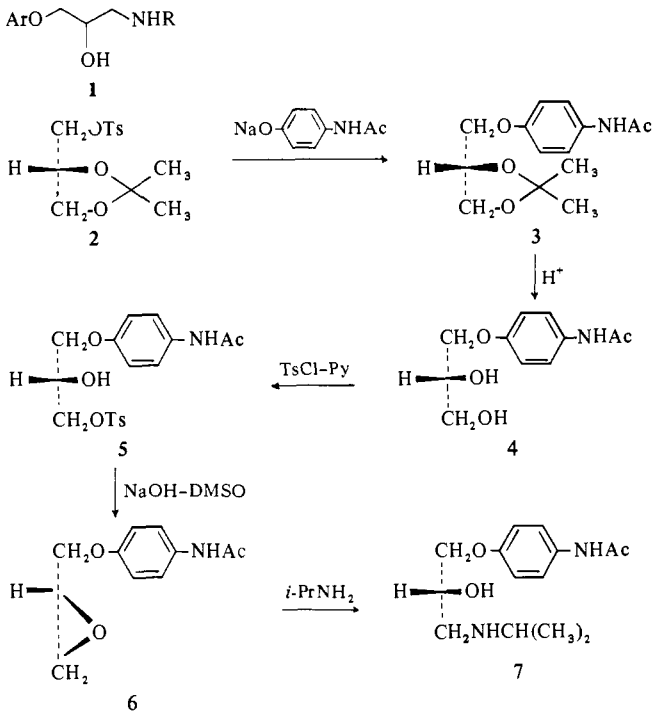
the *R* configuration, in agreement with the result obtained earlier by Horeau's method.[1]

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°.

Acknowledgment. The authors wish to thank Dr. M. J. Sewell and his staff for microanalyses and spectra.

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A Reinvestigation of the Structure of Chlorguanide Hydrochloride

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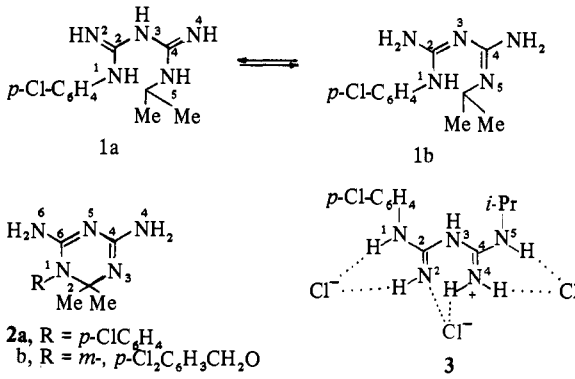
The structure of the antimalarial drug chlorguanide (proguanil; paludrine; 1-(*p*-chlorophenyl)-5-isopropylbiguanide) is usually depicted in the imino form **1a**. In some instances, however, an analogy has been drawn between the structures of chlorguanide and several of the diaminodiazines and triazines (*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



selected as the single, "best" structure, nor had the author[2] attempted to do this. In the crystal, N(1), N(2), N(4), and N(5) were involved in a total of six N···Cl⁻ contacts ranging from 3.22 to 3.32 Å: one each for N(1) and N(5) and two each for N(2) and N(4). The hydrogen atoms were not located from a difference electron density map but rather placed in assumed positions. The hydrogen attached to N(3) was positioned to give equal H-N(3)-C(2) and H-N(3)-C(4) angles, and the remaining five nitrogen H's were placed on the several N···Cl⁻ lines, presumably to simulate the N-H···Cl⁻ hydrogen bond. Since N(2) was connected to a single H atom, one of the N(2)···Cl⁻ contacts did not have an H interposed between the N and Cl⁻. The Cl⁻···N and Cl⁻···H contacts are illustrated in structure **3**. Indeed, the author mentions that "there are insufficient hydrogen atoms for one to lie on each of the Cl-N bonds."

A recent X-ray investigation of the hydrochloride salt of **2b** in our laboratory† has established the structure as a 4,6-diamino-1,2-dihydrotriazinium chloride. The H atoms were located in a difference electron density map; the extra hydrochloride proton was found on N(3) of **2b**. This atom is expected to be the preferred site for ring protonation because the + charge can be delocalized over the entire biguanide moiety, whereas charge delocalization arising from protonation at N(5) would be formally restricted to the N(1)-N(5)-C(6)-N(6) area. It seemed unlikely that the biguanidinium tautomers in **2b**·HCl and **1**·HCl should differ in structure beyond the obvious geometrical differences inherent in the cyclic and open forms. In this communication, we present the results from a reinvestigation of the crystal structure of chlorguanide hydrochloride.

Experimental Section

Crystals of 1·HCl were grown from DMF and preliminary X-ray photographs revealed the same space group and cell dimensions given in the literature.[2] Our data were measured on a Picker FACS-I diffractometer employing monochromatic Mo Kα radiation. The crystal data are: monoclinic $P2_1/a$; a = 18.830 (8), b = 6.387 (2), c = 13.945 (5) Å; β = 114.44 (3)°; Z = 4. The 2686 unique intensity data were measured to 2θ = 50° using a 0.5° min⁻¹ 2θ-θ scan with 40-sec background counts; 1867 of these data were more than 3σ above background. The structure was refined by the method of least squares starting with the literature[2] positions for the C and N atoms. All calculations were performed on a UNIVAC 1108 using the *X-ray System* of programs.[3] Using anisotropic temperature factors for C and N, the structure refinement converged at an agreement index ($R = \Sigma|F_o - F_c|/\Sigma F_o$) of 0.075. A difference map was calculated to locate the hydrogen atoms, all of which were found in the map with the exception of the six methyl H's. In subsequent calculations, the located H's were refined with individual isotropic temperature factors, whereas the two sets of three methyl H's were each approximated using a fixed circle of twelve ¼ weight H's. The function minimized in the structure refinement was $\Sigma[1/\sigma(F)]^2[F_o - F_c]^2$.

†H. L. Ammon, L. A. Plastas, and J. M. Stewart, unpublished results.

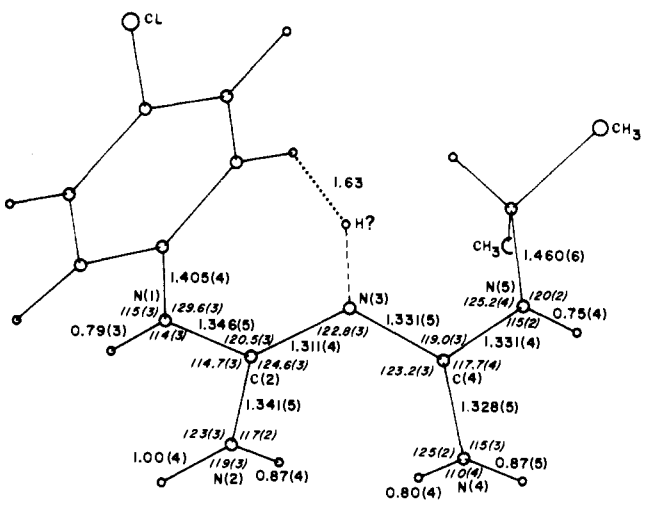


Figure 1. Bond lengths (Å) and angles (deg) for the biguanidinium portion of chlorguanide hydrochloride; estimated standard deviations are given in parentheses. The figure was drawn looking down $-b$. The smallest circles represent hydrogens atoms. H? indicates the hypothetic hydrogen on N(3) (see text).

The final R and weighted R indices ($R_w = [\Sigma w(F_o - F_c)^2/\Sigma w F_o^2]^{1/2}$, $w = [1/\sigma(F)]^2$) were 0.054 and 0.066, respectively.‡

Discussion

With the exception of the H atom locations, our structure of chlorguanide hydrochloride is essentially identical with that reported earlier.[2] The molecule contains three distinct atomic planes: (a) the benzene ring; (b) N(1)-C(2)-N(2)-N(3); (c) N(3)-C(4)-N(4)-N(5). The angles between the least-squares planes of these moieties are: (a)-(b) = 22.3° and (b)-(c) = 58.7°. Bond lengths and angles for the biguanidinium cation are given in Figure 1. As we found in the case of **2b**·HCl,† the close similarity between the six biguanidinium C-N lengths does not permit one resonance form to be chosen as the most representative structure for the cation. In **1**·HCl, however, the overall C-N bond distance similarity is surprising because the 58.7° angle between the planes (b) and (c) should restrict π-orbital interactions across N(3).

The positions of the six biguanidinium H atoms determined in the study are indicated in Figure 1. The principal differences between this arrangement and the one reported earlier[2] are the absence of an H on N(3) and the presence of two H's on N(2). It is now clear that all of the close N···Cl⁻ contacts are N-H···Cl⁻ contacts. Although the H's were located from a three-dimensional difference map, the biguanidinium H positions were checked using electron density difference maps evaluated in the planes[4] of (b), (c), and C(2)-N(3)-C(4). The six H peaks in the maps ranged from 0.45 to 0.57 e Å⁻³ in height. The largest "spurious" peak, 0.23 e Å⁻³, was located in the middle of a C-N bond. The largest peak in the vicinity of the N(3) H atom in question was only 0.12 e Å⁻³.

Additional evidence for the absence of the H on N(3) was obtained from the H···H? interaction illustrated in Figure

‡A table of atomic coordinates and temperatures factors for the C, H, N, and Cl atoms will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-73-169

1. The atom labeled "H?" was placed at an approximate position for the hypothetical N(3) hydrogen atom [1 Å from N(3) along the bisector of the C(2)-N(3)-C(4) angle]. This is a very improbable location for a H atom because the 1.6-Å H···H? approach illustrated in Figure 1 is *ca.* 0.8 Å shorter than the sum of the H van der Waals radii (2.4 Å).

The structure of chlorguanide hydrochloride has been clarified by the experimental determination of the six biguanidinium hydrogen atoms Because of the extensive delocalization in the cation, it was not possible to locate the two C-N double bonds shown in structure **1b**. However, the structure of chlorguanide hydrochloride can be thought of as the resonance hybrid of the cation formed by protonation of **1b** at N(5).

Finally, the expected structural similarity between the conjugate acids of chlorguanide (**1b**·HCl) and the cycloguanil analog (**2b**·HCl) has been verified.

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Synthesis and Biological Activity of (6a*S*)-10,11-Dihydroxyaporphine, the Optical Antipode of Apomorphine

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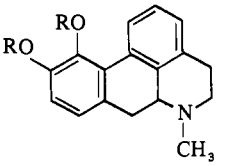
Apomorphine, (−)-**1**, has been shown to stimulate the dopaminergic system in the rat corpus striatum[1] and to produce a dopamine-like renal vasodilation in dogs.[2] On the basis of its dopamine receptor-stimulating properties, apomorphine has been investigated for the treatment of Parkinson's disease.[3,4] We have now prepared the previously undescribed optical antipode of apomorphine and have compared it with apomorphine in these dopaminergic systems.

The dimethyl ether of racemic apomorphine, **2**, prepared essentially by the method of Neumeyer, *et al.*[5] (for other syntheses of the racemic dimethyl ether, see ref 6), was resolved using the tartaric acid enantiomers. The dextrorotatory tartrate salt of **2**, which precipitated when the unnatural (−)-tartaric acid was used, was recrystallized until resolution was judged complete by comparison with a sample of authentic levorotatory dimethyl ether **2**. Levorotatory **2** was prepared by the action of diazomethane on apomorphine.[6d] It could also be obtained from *rac*-**2** through the use of natural (+)-tartaric acid as the resolving agent. Demethylation of (+)-**2** with a mixture of hydriodic acid and acetic anhydride gave (+)-**1** in 49% yield. Since apomorphine, (−)-**1**, has been shown to have an absolute stereochemistry designated as 6a*R*,[7-9] the newly prepared dextrorotatory isomer, (+)-**1**, as well as (+)-**2**, must have 6a*S* absolute configuration.



1, R = H
2, R = CH_3

Biological Results. The dihydroxyaporphine, (+)-**1**, its dimethyl ether, (+)-**2**, and the dimethyl ether of apomorphine, (−)-**2**, were examined for both apomorphine-like activity and as apomorphine antagonists using the caudate brain lesioned mouse preparation described by Lotti.[10] In this preparation apomorphine produces characteristic postural asymmetries which can be specifically blocked by apomorphine antagonists. The compounds were administered intraperitoneally, at a minimum of four dose levels, to groups of at least ten mice per dose and the mice observed for postural asymmetries 10, 20, and 60 min later. The highest dose of each compound tested was in excess of 25 times the dose of apomorphine (0.96 mg/kg ip) necessary to produce postural asymmetries in 50% of the lesioned mice.

Unlike apomorphine, none of the compounds were effective in producing postural asymmetries in caudate-lesioned mice. Similarly, when administered 1 hr prior to apomorphine, they were ineffective in antagonizing the response to apomorphine (4.0 mg/kg ip) in this preparation.

The dihydroxyaporphine (+)-**1** was additionally examined for its ability to induce emesis in dogs. Emesis was not observed in a group of six dogs administered (+)-**1** (0.14 mg/kg iv), whereas apomorphine was 100% effective when administered at $^1/_{10}$ this amount. When (+)-**1**, at doses of 1.0 and 100 μg/kg/min, was infused directly into a renal artery of an anesthetized dog, no increases in renal blood flow and no effect on blood pressure or heart rate were observed.

The results suggest that the optical antipode of apomorphine, (+)-**1**, its dimethyl ether, (+)-**2**, and the dimethyl ether of apomorphine,† (−)-**2**, do not possess significant apomorphine-like activity nor are they effective apomorphine antagonists.

Experimental Section

All melting points were obtained on a calibrated Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4 % of the theoretical values. Nmr spectra were recorded with Varian A-60A and HA-100D spectrophotometers (Me_4Si) and uv spectra with a Cary recording spectrophotometer, Model 11MS, in O_2 free EtOH. Optical rotations were determined with a Zeiss photoelectric precision polarimeter or a Perkin-Elmer polarimeter, Model 141. Tlc's

†The conclusion that the dimethyl ether of apomorphine, (−)-2, does not possess significant apormorphine-like activity is supported by the observation of Bergell and Pschorr[11] that this compound is "free of emetic action."