(0.87 g, 5.7 mmol) in dry ether were treated with *n*-butyllithium (1 equiv) at reflux for 1 h. The solution of 2-lithio-*N*-methylpyrrole was stirred with copper(I) bromide (1.2 g) for 90 min at room temperature to give a brown suspension of 2-cuprio-*N*-methylpyrrole. This was treated with the iodoacetylene 7 (X = I, 5.0 g, 6.5 mmol) in THF (20 mL) and stirred at room temperature overnight. The mixture was diluted with benzene, the solids were removed by centrifugation, and the supernatant solution was concentrated and then chromatographed to give the pyrrolylacetylene 7 (X = 1-methyl-2-pyrrolyl) (28%): ν_{max} ($CHCl_3$) 2980, 1750, and 1630 cm^{-1}. Refluxing in piperidine for 12 h, followed by the usual aqueous work-up, gave the ketone 8 (X = 1-methyl-2-pyrrolyl, 59%): ν_{max} ($CHCl_3$) 2980, 1760, and 1635 cm^{-1}. Cyclization by refluxing in dioxane for 30 h gave the cephem 37 (Table IV) in 83% yield.

***tert*-Butyl 7β-Amino-3-(1-methyl-2-pyrrolylmethyl)-ceph-3-em-4-carboxylate (38).** For this acid-sensitive compound the following exceptionally mild detritylation procedure was preferred. The trityl derivative 37 in redistilled MeOH was stirred with an equal weight of pyridine hydrochloride for 4 days; then the solvent was evaporated and the residue dissolved in EtOAc. The solution was washed with aqueous $NaHCO_3$, dried, and evaporated, and the residue was chromatographed to give the primary amine 38 (81%).

***tert*-Butyl 3-(2-Acetoxyethyl)-7β-(*N*-*tert*-butoxycarbonyl-D-α-phenylglycyl)aminoceph-3-em-4-carboxylate (46).** The *O*-tetrahydropyranyl derivative 45 (106 mg, 0.17 mmol, synthesized according to Scheme I) was treated with toluene-*p*-sulfonic acid (35 mg, 0.2 mmol) in isopropenyl acetate (4 mL) at 0 °C for 4 h and then at room temperature for a further 4 h. EtOAc was added and the solution washed with dilute aqueous $NaHCO_3$, followed by brine. Evaporation of the dried solution, followed by chromatography, gave the cephem 46 (Table IV) in 25% yield.

Supplementary Material Available: High-resolution mass spectral data, NMR data, and elemental composition data (4 pages). Ordering information is given on any current masthead page.

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Notes

Structure and Biological Activity of (−)-[^{3}H]Dihydroalprenolol, a Radioligand for Studies of β-Adrenergic Receptors

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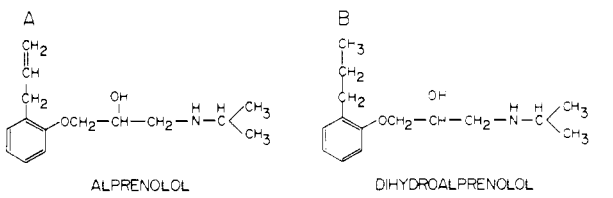
(−)-Alprenolol is a potent competitive β-adrenergic antagonist. "(−)-[^{3}H]Alprenolol", a radioactive form of this agent produced by catalytic reduction with tritium, has recently been used successfully as a radioligand for direct studies of β-adrenergic receptors. In this communication it is documented that the compound formed by catalytic reduction of (−)-alprenolol with tritium gas is the saturated product (−)-[^{3}H]dihydroalprenolol in which tritium is added across the double bond and exchanged into the adjacent benzylic position. No exchange into the aromatic ring was observed. These conclusions were substantiated by results obtained on hydrogenation and deuteration of (−)-alprenolol. The biological activity of (−)-[^{3}H]dihydroalprenolol, dihydroalprenolol, and alprenolol was also shown to be identical as assessed by direct ligand binding and inhibition of catecholamine-stimulated adenylate cyclase.

Recently reports from several laboratories have indicated the feasibility of directly studying β-adrenergic receptors by radioligand binding techniques. Several agents have been used. These have included [^{3}H]-(±)-propranolol,[2,3] "(−)-[^{3}H]alprenolol",[4-13] and (±)-[^{125}I]hydroxybenzylpindolol.[14-16] (−)-Alprenolol [1-(2-allylphenoxy)-3-isopropylamino-2-propanol] contains an olefinic bond in the hydrocarbon side chain on the benzene ring. Since the radioligand is produced by catalytic reduction of the molecule with tritium, it has seemed likely that "(−)-[^{3}H]alprenolol" was in all probability (−)-[^{3}H]dihydroalprenolol [[*propyl*-2,3-^{3}H(N)]-1-(2-propylphenoxy)-3-isopropylamino-2-propanol]. This has not previously been documented.

In this communication we present data which (1) verify that the structure of tritiated "(−)-alprenolol" formed by catalytic reduction with tritium is in fact (−)-[^{3}H]dihydroalprenolol and (2) document that the biological activity of (−)-alprenolol and (−)-dihydroalprenolol is identical.

Chart I



Discussion

(−)-Alprenolol (see Chart I) has been catalytically reduced with hydrogen, deuterium, and tritium to yield the corresponding saturated derivatives. The reduced materials have indistinguishable UV spectra and are homogeneous and indistinguishable by TLC. The R_f values

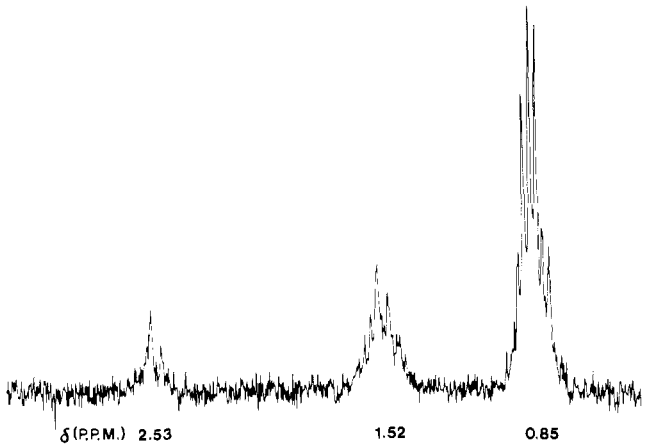


Figure 1. Triton magnetic resonance spectrum of (−)-[^{3}H]dihydroalprenolol.

determined by argentation chromatography are higher than (−)-alprenolol and this is indicative that saturation of the double bond has occurred. We have assumed that the integrity of the center of optical activity has been maintained during the reduction process and this was further indicated when the biological activity of (−)-alprenolol and (−)-dihydroalprenolol was found to be identical.

The ^{1}H NMR spectrum of (−)-alprenolol (free base in $CDCl_3$) integrates as expected for the known structure. The well-defined doublet at δ 1.1 is due to the *N*-isopropyl group methyls coupling to the methine proton. The multiplets at δ 4.9, 5.15, and 6.0 are due to the three vinylic protons on the propene moiety, and the four aromatic protons occur as a multiplet at δ 7.06.

Catalytic hydrogenation of (−)-alprenolol gave (−)-dihydroalprenolol. The ^{1}H NMR of the hydrochloride salt in D_2O integrates as expected for the postulated structure (Figure 1, b). The spectrum is similar to that of propylbenzene in the aliphatic region with the *N*-isopropyl moiety superimposed upon the methylene group signals. Thus the three-proton triplet at δ 1.0 is due to the terminal methyl group. The signals under the *N*-isopropyl signals (δ 1.48) at δ 1.5 must be due to the methylene group and the two-proton triplet at δ 2.68 must be due to the benzylic methylene protons. As expected, the vinylic protons at (−)-alprenolol at δ 4.9, 5.15, and 6.0 are removed in the spectrum of (−)-dihydroalprenolol. The four aromatic protons appear at δ 7.15.

The ^{1}H NMR spectrum of dideuterioalprenolol (free base in $CDCl_3$) shows signals at δ 0.95 corresponding to the propyl methyl group (δ 1.0) in (−)-dihydroalprenolol, δ 1.25 (*N*-isopropyl group) compared to δ 1.48 in the hydrogenated product, and a broad multiplet centered at δ 1.58. There are no vinylic protons in the spectrum, which is comparable to the spectrum of (−)-dihydroalprenolol. Integration of the spectrum does not balance if deuterium has added exclusively to the double bond. This suggests that catalytic exchange of carbon–hydrogen bonds by deuterium has accompanied the reduction process.

Investigation of the hydrogenated derivative by high-resolution mass spectroscopy gave the expected molecular ion peak at mass 251.1880. This is two mass units higher than (−)-alprenolol and the observation is in accord with the expected saturation of the double bond. Investigation of the deuterated material by high-resolution mass spectroscopy showed several molecular ion peaks between 251.1890 and 256.2212, the most abundant peak appearing at 253.2015 which represents the molecular ion of the dideuterated compound. The molecular ions at 254.2086, 255.2153, and 256.2212 must be formed by scrambling of several hydrogen atoms and the additional incorporation of deuterium. Investigation of the tritiated material by low-resolution mass spectroscopy showed several molecular ion peaks between 251 and 256, the most abundant peaks occurring at ca. 252, 253, 254, 255, and 256. These ions must be formed by scrambling of several hydrogen atoms and the additional incorporation of tritium. This process obviously remains undetected in the hydrogenation of (−)-alprenolol. Similar observations have been previously reported by Bieman.[17]

In order to gain further insight into the structure of these products and to obtain information on the tritium distribution in the molecule, we investigated the triton magnetic resonance spectrum of the tritiated product.

Recent reports in the literature[18,19] have discussed the uses of triton magnetic resonance techniques in order to determine the specificity of tritium-labeling procedures. Proton noise decoupling has been used in order to simplify the spectra and observe only triton–triton coupling.

The triton magnetic resonance spectrum (Figure 1) confirmed the mass spectral information on the protonated, deuterated, and tritiated dihydroalprenolol. Three signals were obtained with chemical shifts consistent with terminal methyl (δ .85), aliphatic methylene (δ 1.52), and benzylic triton atoms (δ 2.53). No aromatic tritons were observed. These chemical shifts are comparable with those of (−)-dihydroalprenolol (δ 1.0, 1.5, and 2.68). Each signal was comprised of several lines which were caused by coupling with tritons on adjacent carbon atoms as well as the presence of polytritiated species. This implies that there are several species in the sample such as C^3H_3, $C^1H^3H_2$, and $C^1H_2{}^3H$ representing the terminal methyl group. Similar polytritiated species may also exist for the benzylic and methylene groups, thus accounting for the multiplet nature of the signals associated with these positions. Integration of the spectrum indicates that most tritium is attached to the terminal methyl group with the least amount being attached to the benzylic position. The latter observation is not unexpected since the benzylic position was allylic to the original double bond and, therefore, the tritium has become attached by a process of exchange on the catalyst. The most surprising observation is that the tritium is unevenly distributed across the original double bond, most tritium being attached to the terminal methyl position. At the present time we have no satisfactory explanation for this observation; however, similar observations have been recorded with other olefinic reductions.

Biological Activity Studies. The biological activity of (−)-[^{3}H]dihydroalprenolol as a β-adrenergic antagonist was assessed by (1) direct binding experiments and (2) experiments in which its ability to antagonize isoproterenol activated adenylate cyclase in frog erythrocyte membranes was studied. Figure 2 depicts results obtained when increasing concentrations of (−)-[^{3}H]dihydroalprenolol were added to frog erythrocyte membranes. One-half maximal specific binding occurs at a concentration of 3 nM (−)-[^{3}H]dihydroalprenolol which provides an estimate of the equilibrium dissociation constant of the radioligand for the β-adrenergic receptor binding sites in the membranes.

Dissociation constants of unlabeled ligands for the receptors can be determined from the concentrations of agents which 50% inhibit the specific binding of (−)-[^{3}H]dihydroalprenolol. In Figure 3 are shown displacement curves for (−)-dihydroalprenolol and (−)-alprenolol. It can be seen that the displacement curves obtained with the two agents are essentially identical. In each case one-half

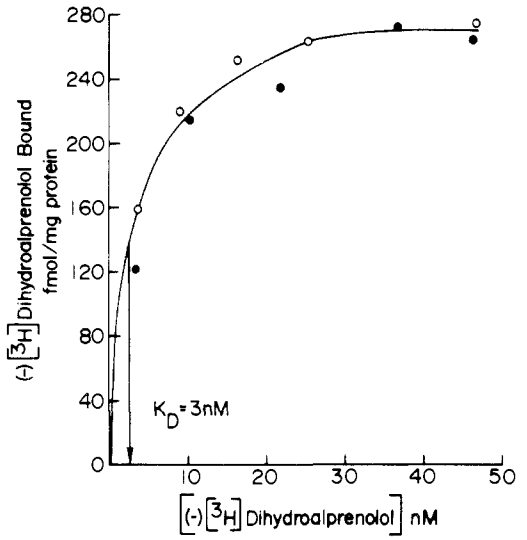


Figure 2. Binding of (−)-[^{3}H]dihydroalprenolol to frog erythrocyte membranes as a function of (−)-[^{3}H]dihydroalprenolol concentration. Closed and open circles represent the results of two separate experiments each determined in duplicate. "Specific" binding is plotted and was 95% of the total binding in these experiments.

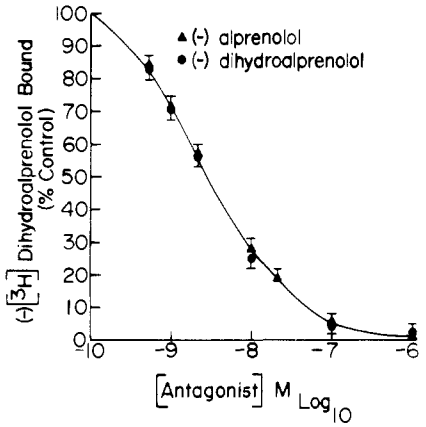


Figure 3. Inhibition of (−)-[^{3}H]dihydroalprenolol binding to frog erythrocyte membranes by (−)-alprenolol and (−)-dihydroalprenolol. In these assays relatively low (−)-[^{3}H]dihydroalprenolol (0.6 nM) and receptor (0.1 nM) concentrations were used. Results shown are mean ± SEM of three experiments determined in duplicate.

maximal displacement occurs at a concentration of 3 nM. From the EC_{50} K_D's may be calculated according to the equation

$$K_D = EC_{50}/(1 + S/K_m)$$

In the equation S = the concentration of (−)-[^{3}H]dihydroalprenolol in the assay and K_m = the dissociation constant of (−)-[^{3}H]dihydroalprenolol for the binding sites.[20] In these experiments S = 0.6 nM and K_D = 3 nM (from Figure 2). Thus, the calculated K_D's for (−)-alprenolol and (−)-dihydroalprenolol are 2.5 nM which is in good agreement with the value determined from the direct experiments with (−)-[^{3}H]dihydroalprenolol (Figure 2).

The biological activity of (−)-alprenolol and (−)-dihydroalprenolol was also assessed by measuring their ability to competitively antagonize (−)-isoproterenol stimulated adenylate cyclase in frog erythrocyte membranes. The results of these studies are presented in Figure 4. It can be observed that at 10^{-7} M (−)-alprenolol, (−)-dihydroalprenolol, and (−)-[^{3}H]dihydroalprenolol all produced essentially identical rightward *displacement* of

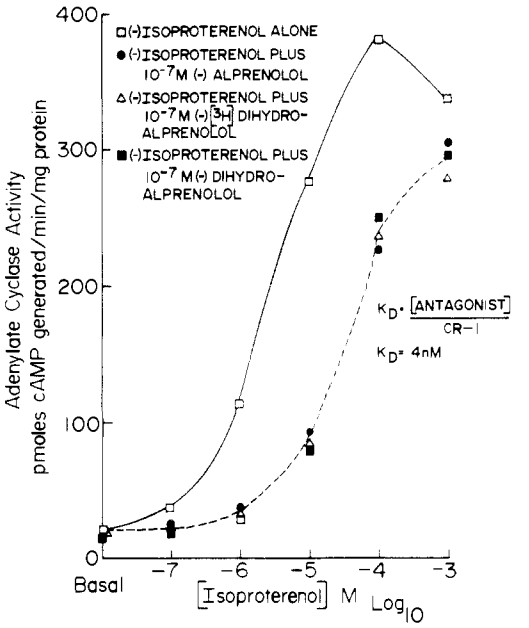


Figure 4. Inhibition of (−)-isoproterenol stimulated frog erythrocyte membrane adenylate cyclase by several β-adrenergic antagonists. (−)-Isoproterenol and antagonists were added to membranes simultaneously at the beginning of assays. Results of a typical experiment determined in duplicate are shown. The experiment was replicated with comparable results three times. Results with the three antagonists did not differ significantly from each other.

the (−)-isoproterenol enzyme stimulation curve. The extent of rightward displacement can be used to calculate the dissociation constants of the antagonists. The equation is

$$K_D = [\text{antagonist}]/(CR - 1)$$

where CR = the ratio of equiactive concentrations of (−)-isoproterenol in the presence and absence of the antagonist.[21]

Our studies demonstrate that the biological activity of (−)-[^{3}H]dihydroalprenolol is indistinguishable from that of native (−)-alprenolol as assessed by (1) direct binding studies, (2) competitive displacement experiments, and (3) competitive antagonism of (−)-isoproterenol stimulated adenylate cyclase. In all cases the K_D for the β-adrenergic receptors in frog erythrocyte membranes is 2–4 nM.

The specific radioactivity of (−)-[^{3}H]dihydroalprenolol (~33 Ci/mmol) is not as high as that of (±)-[^{125}I]-hydroxybenzylpindolol (up to 1000–2000 Ci/mmol),[14-16] another radioligand which has been used recently to study the β-adrenergic receptors. (−)-[^{3}H]Dihydroalprenolol does, however, possess several advantageous features. These are (1) it is a pure (−) stereoisomer; (2) it has great stability, hence it need not be repeatedly prepared; (3) it has accurately defined specific radioactivity; and (4) it has documented utility in receptor studies in a wide variety of tissues from mammalian (including human) and non-mammalian sources.[4-13]

Experimental Section

General Procedures. (−)-Alprenolol [1-(2-allylphenoxy)-3-isopropylamino-2-propanol] was purchased from AB Hassle, Molndal 1, Sweden, as the tartrate salt. Preparative thin-layer chromatography was carried out using Analtech 250-μ silica gel plates with irrigation by 1-butanol–acetic acid–water (25:4:10). Analytical thin-layer chromatography was carried out using Analtech silica gel plates and three solvent systems were used: A, 1-butanol–acetic acid–H_2O (25:4:10); B, methanol–benzene–

water (15:2:3); and C, acetone–benzene–acetic acid (70:24:5). Argentation chromatography was carried out using silver nitrate impregnated silica gel plates. The UV spectra were obtained on ethanol solutions using a Beckman Model 25 recording spectrophotometer. Optical rotations were measured using a Model 241 Perkin-Elmer polarimeter. Radioactivity was measured using a Packard Tricarb Model 3320 liquid scintillation counter with Aquasol as the liquid scintillation counting cocktail. Mass spectra were obtained using a MS 902 mass spectrometer, with probe temperature 140 °C and electron energy 70 eV, or an AET Model MS-30 with probe temperature 150–250 °C and electron energy 70 eV. ^{1}H NMR spectra were measured with a Varian A-60 spectrometer. The ^{3}H NMR spectrum was measured (using a deuterated dimethyl sulfoxide solution of the hydrochloride salt) with a Varian XL 100 FT spectrometer operating at 106.7 MHz. Approximately 6000 transients were taken at intervals of 4 s using a pulse width of 44 μs (90 °C) under conditions of noise-modulated proton decoupling. Tritium chemical shifts were calculated using external monotritiated methyl iodide and are reported relative to "monotritiated tetramethylsilane" by assuming that the tritium chemical shift of monotritiated methyl iodide is identical with the proton chemical shift of methyl iodide.

(−)-Alprenolol [1-(2-Allylphenoxy)-3-isopropylamino-2-propanol]. (−)-Alprenolol tartrate (100–200 mg) was dissolved in water (5 mL) and Na(OH) added until the product oiled out. After extraction with ether and drying ($MgSO_4$) the oily free base was obtained by concentration of the solvent. The ^{1}H NMR spectrum of the free base in $CDCl_3$ using tetramethylsilane as internal standard gave δ 1.1 (doublet, J = 6 Hz, isopropyl, 6 protons), 2.5–3.2 (multiplet, 5 protons), 3.28–3.5 (broad doublet, 2 protons), 4.0 (multiplet, 3 protons), 4.9 (multiplet, vinylic, 1 proton), 5.15 (multiplet, vinylic, 1 proton), 6.0 (multiplet, vinylic 1 proton), 7.06 (multiplet, aromatic, 4 protons). Conversion of (−)-alprenolol to the hydrochloride salt gave a crystalline compound which on recrystallization from ethanol–ether gave mp 89–91 °C; $[\alpha]^{25}_D$ −25° (c 0.4, water). Anal. ($C_{15}H_{24}NO_2Cl$) C, H, N. The mass spectrum gave the molecular ion peak at 249.1730 compared to the calculated value of 249.1728.

(−)-Dihydroalprenolol [[*propyl*-2,3-^{3}H(N)]-1-(2-Propylamino)-2-propanol]. A measured tritium uptake was carried out on (−)-alprenolol tartrate (0.025 g) dissolved in water (0.5 mL) using 10% palladium on carbon as the catalyst. After removal of volatile tritiated products the crude material was dissolved in ethanol and purified by preparative thin-layer chromatography. The desired band was detected by UV light and after scraping it off the plate the product was eluted with ethanol–water (1:1). Concentration of the aqueous ethanol solution yielded product as the free base which was converted to an ethanolic solution of (−)-dihydroalprenolol hydrochloride (3.3 Ci) by the addition of HCl, concentration to dryness, and dissolution in ethanol. The product was investigated by thin-layer chromatography and was found to be homogeneous in system A, B, and C and had the same mobility as starting material. Argentation chromatography using system B and C also showed the product to be homogeneous but with a higher mobility than starting material. The UV spectrum showed three bands at 220 nm (ϵ_{max} 4998), 272 (1145), and 278 (1025). The specific activity as determined by UV was 32.65 Ci/mmol.

The low-resolution mass spectrum showed the following multiple molecular ions in the region of 251–257 mass units, m/e (rel intensity) 251 (2), 252 (7), 253 (2), 254 (6), 255 (2), 256 (3), 257 (1).

The triton NMR (Figure 1) (using a deuterated dimethyl sulfoxide solution of the hydrochloride) showed three aliphatic type tritons which on integration on an undecoupled spectrum using 2292 transients and a pulse width of 35 μs (71 °C) were in the ratio 1:3.6:10. The triton signal at lowest field was the minor component and occurred at δ 2.53 (benzylic CH_2). The intermediate triton signal occurred at δ 1.52 (CH_2) downfield from the high-field signal at δ 0.85 (CH_3).

(−)-Dihydroalprenolol [1-(2-Propylphenoxy)-3-isopropylamino-2-propanol]. The product was obtained using the techniques described for the tritiated material except that hydrogen was used.

The crude hydrochloride salt was recrystallized from ethanol–ether to afford (−)-dihydroalprenolol: mp 86–87 °C; $[\alpha]^{25}_D$ −23° (c 0.46, water). Anal. ($C_{15}H_{26}NO_2Cl$) C, H, N. The material was homogeneous in the TLC systems described and was indistinguishable from the tritiated product. Investigation of the product by high-resolution mass spectrometry gave the molecular ion peak at 251.1880 compared to the calculated value of 251.1885. The ^{1}H NMR spectrum of the hydrochloride salt in D_2O using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard gave δ 1.0 (triplet, CH_3, 3 protons), 1.48 (doublet, J = 7 Hz, isopropyl, 6 protons) superimposed on signal at 1.5 (CH_2, 2 protons), 2.68 (triplet, benzylic CH_2, 2 protons), 3.1–3.8 (multiplet, 3 protons), 4.0–4.6 (unresolved multiplet, 3 protons), 4.9 (H_2O), 7.15 (multiplet, aromatic, 4 protons).

(−)-Dideuterioalprenolol [[*propyl*-2,3-^{2}H(N)]-1-(2-Propylphenoxy)-3-isopropylamino-2-propanol]. The product was obtained using the techniques described for the tritiated material except that deuterium was used. The material was homogeneous in the TLC systems described and was indistinguishable from the tritiated and the hydrogenated products.

Investigation of the product by high-resolution mass spectrometry gave the following multiple molecular ion peaks and relative intensities: 251.1890 (1), 252.1967 (2.1), 253.2015 (2.5), 254.2086 (2.4), 255.2153 (2.0), 256.2212 (1.1).

The ^{1}H NMR spectrum of the free base in $CDCl_3$ with tetramethylsilane as internal standard showed δ 0.95 (broad unresolved peak), 1.25 (doublet, J = 7 Hz), 1.58 (broad signal), 1.98 (sharp singlet), 2.56 (unresolved signals), 3.08 (unresolved signals), 4.03 (unresolved signals), 7.02 (unresolved signals).

Biological Activity Studies. Preparation of frog erythrocyte membranes was as reported previously.[5,12]

Adenylate cyclase assays were performed as described previously[22,23] by following the production of [^{32}P]-cAMP from [α-^{32}P]-ATP. Labeled product was isolated by sequential chromatography on Dowex AG 50WX-4 and neutral alumina as described by Salomon et al.[24] Product recovery was monitored with [^{3}H]-cAMP and was generally about 70%.

(−)-[^{3}H]Dihydroalprenolol binding assays were performed by incubating radioligand and membranes with or without unlabeled ligands for 10 min at 37 °C in 75 mM Tris–HCl, pH 7.4, and 15 mM $MgCl_2$. Incubations were terminated by rapid vacuum filtration through glass fiber filters (Whatman GFC) followed by two 5-cm^3 buffer washes (0–4 °C). In all experiments "nonspecific" binding was determined by performing incubations in the presence of 10 μM (±)-propranolol which blocks all the β-adrenergic receptor binding sites. "Specific" binding was taken as total binding minus nonspecific binding and was generally 90% of total binding. Specific binding has been plotted in all figures. Additional experimental details are provided in the figure legends.

Proteins were determined as described by Lowry et al.[25]

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Pyrrole Esters of Tropanols and Related Structures as Analgesics[1]

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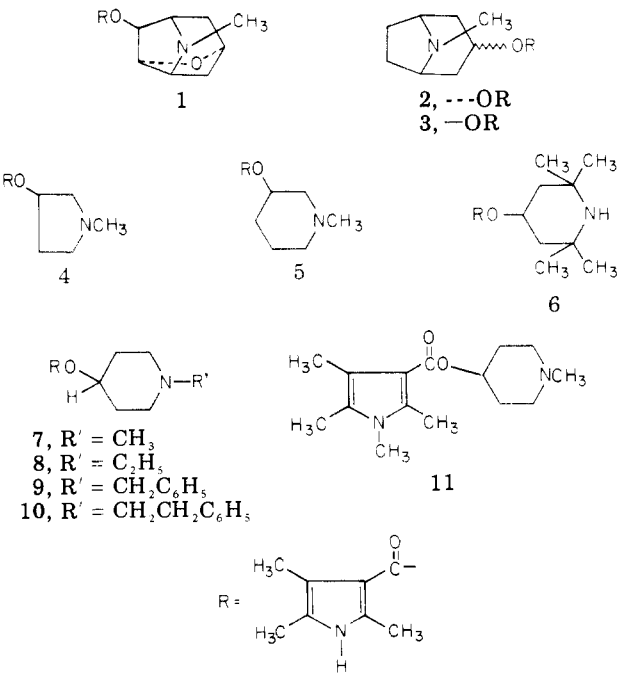
2,4,5-Trimethylpyrrole-3-carboxylic acid esters of tropanols and related monocyclic amino alcohols were synthesized and evaluated for analgesic activity by the mouse hot-plate and Nilsen methods. 1-Methyl-4-piperidinol 4-(2,4,5-trimethylpyrrole-3-carboxylate) (7) exhibited activity in the morphine–codeine range (mouse hot plate). In monkeys, 7 acted neither as a typical narcotic agonist nor as a typical antagonist and it showed no physical dependence liability of the morphine-type. Whereas the pethidine and prodine analgesics have quaternary phenyl substitution at C-4 of the piperidine ring, compound 7 does not.

In an effort to develop new analgesics that are devoid of undesirable side effects and to study their interactions with stereospecific receptors, it was of interest to prepare pyrrolecarboxylates of tropanols and monocyclic amino alcohols related to scopoline ester 1 [3α,6α-epoxy-7β-hydroxytropane 7-(2,4,5-trimethylpyrrole-3-carboxylate)].[2] The scopoline ester 1 was observed to have analgesic activity comparable to that of codeine by the mouse hot-plate method, whereas the unesterified scopoline was inactive. In this investigation, epimeric tropanol esters 2 and 3, pyrrolidinol ester 4, and piperidinol esters 5–11 (Chart I and Table I) were prepared by the mixed trifluoroacetic anhydride procedure,[2] the preferred method for the synthesis of these labile pyrrole compounds.

Chart I[a]



[a] These compounds were obtained as salts as indicated in Table I.

Pharmacological Results and Discussion. The 2,4,5-trimethyl- and 1,2,4,5-tetramethylpyrrole-3-carboxylates were assayed for analgesic activity by the mouse hot-plate[3] and Nilsen methods[4] (Table II). The 3β-tropanol ester 3 exhibited an ED_{50} of 21.3, whereas the 3α-epimer 2 was only marginally active at 50 mg/kg. The 3-pyrrolidinol ester 4, a partial structure of scopoline ester 1, was marginally active (ED_{50} 64.3), while the 3-piperidinol ester 5 was inactive. The 1-methyl-4-piperidinol pyrrolecarboxylate 7 showed an ED_{50} of 4.9 (hot plate) and an ED_{50} of 7.1 (Nilsen). It was the most active compound in this study, with potency in the codeine–morphine range (hot-plate assay). The *N*-benzyl 9 and *N*-phenethyl 10 analogues were somewhat less active than *N*-methyl 7. The tetramethylpyrrole compound 11, analogous to 7, was marginally active.

4-Piperidinol ester 7 showed no morphine-like dependence liability in monkeys.[5] In single dose suppression experiments, no suppression of the narcotic abstinence syndrome was indicated at 5.0 mg/kg. Compound 1 exhibited very mild CNS depression but it neither precipitated nor suppressed the withdrawl syndrome (3.0–24.0 mg/kg). In nonwithdrawn monkeys, 7 did not precipitate abstinence signs at 5.0 mg/kg.

A structure–activity comparison of the monocyclic amino alcohol esters 4, 5, and 7 indicates that the distance(s) between the heterocyclic pyrrole ring or the carbonyl bond (or conceivably both) and the protonated nitrogen of the piperidine ring in the more potent ester 7 is preferred for optimum receptor binding over those distances found in