methoxyethylamine and ethyl acrylate using a 3-step procedure described by Balyard and McElvain[2] for the synthesis of 1-alkyl-4-piperidones. The intermediate *N,N*-bis(β-carboxethoxyethyl)-β-methoxyethylamine boiled at 111° (0.05 mm). The last 2 steps, the cyclization and decarboxylation, were done consecutively without isolation of the intermediate 3-carbethoxy-1-(2-methoxyethyl)-4-piperidone. The final product, a colorless liquid, boiled at 72–73° (0.5 mm). *Anal.* ($C_8H_{15}NO_2$) C, H, N.

α-[1-(1-Alkyl-4-piperidylamino)alkyl]benzyl Alcohols (3–11).—$NaBH_4$ (0.125 mole) was added in small portions over 2 hr to a stirred mixt of *dl*-α-(1-aminoalkyl)-4-hydroxybenzyl alcohol·HCl (0.025 mole), KOH (0.025 mole), and 1-alkyl-4-piperidone (0.177 mole) in 100 ml of MeOH. The reaction mixt was maintained at about 5° by means of an ice bath during the addn. After the addn the mixt was stirred for 1 hr at 20° and then acidified to pH 4 with 4 *N* HCl in EtOH. The mixt was filtered to remove pptd inorg salts and then evapd to an oil. The residual oil was triturated with boiling *i*-PrOH. The resulting white cryst prod was filtered off and recrystd (see Table I).

α-[1-(4-Piperidylamino)alkyl]benzyl Alcohols (12 and 13).—A soln of α-[(1-benzyl-4-piperidylamino)methyl]benzyl alcohol·2HCl (4 or **6**) (0.085 mole) in 125 ml of aq 80% EtOH was hydrogenated for 6 hr at 3 atm using 5 g of 10% Pd/C as catalyst. The catalyst was removed by filtration, and the filtrate was evapd. The residue was recrystd (Table I).

Pharmacology Assay Method.—The test substances were assayed in anesthetized dogs on the vascular bed supplied by the carotid artery. In this prepn a constant flow (peristaltic) blood pump was interposed between the proximal and distal segments of the right carotid artery. Prior to drug treatment blood flow rate was set to result in a mean perfusion pressure approximately equal to systemic arterial blood pressure. Perfusion pressure was measured distal to the pump. Drug injections were made into the blood stream distal to the pump. Vasodilation was indicated by a decrease in perfusion pressure. Potency comparisons with papaverine were determined from plots of log molar dose *vs.* decrease in perfusion pressure. In this assay isoxsuprine was approximately 10 times more active than papaverine. The results reported in Table I are based upon the arbitrary assignment of papaverine potency at 100.

(2) N. W. Bolyard and S. M. McElvain, *J. Amer. Chem. Soc.*, **51**, 922 (1929).

Absolute Configuration of the Optical Isomers of Salbutamol

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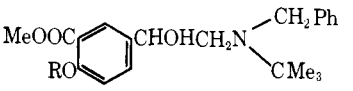
The synthesis and biological properties of the β-sympathomimetic amine, salbutamol (**4**), have been described.[1] This compound is more selective for β_2 receptors than previously known drugs and therefore it was of interest to test each enantiomer to ascertain if the activity resided mainly in the (*R*)-(−) configuration as is the case with other drugs which act at adrenoreceptors.[2]

Attempted resolutions of salbutamol, or any phenolic precursor, were unsuccessful.[3] However, when the phenolic group of the intermediate ester **1** was protected as the benzyl ether **2** then resolution was efficiently achieved with either (+)- or (−)-di-*p*-toluoyltartaric acid. In each case only one isomer formed a crystalline



1, R = H
2, R = $PhCH_2$

3, R_1 = $PhCH_2$
4, R_1 = H

salt and the antipode was recovered from the mother liquors in good yield and reasonable optical purity.

Neutralization of the purified salts liberated the resolved bases **2** which on reduction with LAH followed by catalytic debenzylation gave the required isomers **4**. The (+) and (−) forms were both characterized as their acetate salts.

The β-adrenoreceptive activities of these isomers were compared with those of the racemic compound on the β_1 receptors[4] of the isolated atria of the guinea pig and on the β_2 receptors[4] of the intact trachea of the guinea pig (Table I). In the latter test[5] the (−) isomer was approximately equiactive with the racemate and 80 times more potent than the (+) isomer. A similar pattern was shown in the much weaker effects on the force of contraction of the electrically driven left atrium.[6] However, both isomers were much less active than the racemate in increasing the rate of contraction of the spontaneously beating right atrium.[7] Although this result has been verified on several occasions, the very low order of activity precludes any useful interpretation of the apparent synergism in the racemate.[8]

TABLE I
BIOLOGICAL ACTIVITY OF THE ENANTIOMERS OF SALBUTAMOL

	Biological test[a]		
Compound	Trachea (β_2)	Left atrium (β_1)	Right atrium (β_1)
Racemate	4.3	15,000[b]	1,000
(−) Isomer	6.6	15,000[b]	10,000[b]
(+) Isomer	423	Inactive	100,000[b]

[a] These results represent the ratio of the amount of drug required to produce an equivalent response to a unit of isoprenaline. [b] Denotes partial agonist activity.

Comparison of the CD spectra of the salbutamol isomers with that of (*R*)-(−)-octopamine[9] showed that (−)-salbutamol had the *R* configuration. Both levorotatory compounds showed a clear negative Cotton effect at 276–280 nm. At lower wavelengths, 220–230 nm, the curves tended toward a further negative peak although this is somewhat masked by the high aromatic absorption.

(1) D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. C. Press, A. C. Ritchie, and P. Toon, *J. Med. Chem.*, **13**, 674 (1970).

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," Methuen and Co., London, 1964, pp 282–343.

(3) Similar difficulties in resolving phenolic amines have been described see A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta*, **52**, 678 (1969).

(4) (a) A. M. Lands, A. Arnold, J. P. McAuliff, F. P. Luduena, and T. G. Brown, Jr., *Nature (London)*, **214**, 597 (1967); (b) A. M. Lands, F. P. Luduena, and H. J. Buzzo, *Life Sci.*, **6**, 2241 (1967).

(5) For pharmacological method see J. B. Farmer and R. A. Coleman, *J. Pharm. Pharmacol.*, **22**, 46 (1970).

(6) For pharmacological method see J. R. Blinks, *J. Pharmacol. Exp. Ther.*, **151**, 221 (1966).

(7) For pharmacological method see J. W. Black, W. A. M. Duncan, and R. G. Shanks, *Brit. J. Pharmacol. Chemother.*, **25**, 577 (1965).

(8) A more detailed pharmacological evaluation of these isomers will be submitted for publication elsewhere by J. B. Farmer and R. J. Marshall.

(9) (a) V. Erspamer, *Nature (London)*, **169**, 375 (1952); (b) T. Kappe and M. D. Armstrong, *J. Med. Chem.*, **7**, 569 (1964).

Experimental Section

Melting points were determined on a Mettler FP 1 apparatus and the microanalyses on an F and M 185 C, H, and N analyzer. Where anal. are indicated only by the symbols of the elements anal. values obtained were within ±0.4% of the calcd values. Compds gave satisfactory uv, ir, and nmr spectral data obtained, resp, on Perkin-Elmer Model 137, Unicam SP 100, and Varian Associates A60A spectrometers. Optical rotations were measured in MeOH at 25°. Circular dichroism curves were measured in MeOH at 25° with a Roussel Jouan Dichrograph 185 and are expressed in mol ellipticity units $[\theta]$.

Methyl 5-[2-(Benzyl-*tert*-butylamino)-1-hydroxyethyl]-2-benzyloxybenzoate (2).—This compound was prepared by condensing methyl 2-benzyloxy-5-bromoacetylbenzoate[1] with *tert*-butylbenzylamine in EtCOMe and reducing the crude product with $NaBH_4$ in EtOH by the general procedures already described.[1] The product, mp 96° [from C_6H_6–petr ether (bp 60–80°)], was obtd in 43% yield from the bromo ketone. *Anal.* ($C_{25}H_{33}NO_4$) C, H, N.

Resolution of Methyl 5-[2-(benzyl-*tert*-butylamino)-1-hydroxyethyl]-2-benzyloxybenzoate.—The racemic ester (30 g, 0.064 mole) and (−)-di-*p*-toluoyltartaric acid (25.6 g, 0.064 mole)[10] in EtOAc (350 ml) at 70° were allowed to cool to room temp to give (*R*)-(+)-methyl 5-[2-benzyl-*tert*-butylamino)-1-hydroxyethyl]-2-benzyloxybenzoate (−)-di-*p*-toluoyltartrate (1:1): 27 g; mp 139.9°; $[\alpha]_D$ −48° (*c* 1.0). Two recrystns from EtOAc gave material of constant mp and rotation: 16 g; mp 148.2°; $[\alpha]_D$ −47° (*c* 1.5). *Anal.* ($C_{48}H_{51}NO_9$) C, H, N.

This salt (11 g) in EtOAc was extd several times with $NaHCO_3$ soln, dried (Na_2SO_4), and filtered through a small quantity of basic alumina. The eluate was evapd under reduced pressure and the residue crystd from petr ether (bp 60–80°) to give (*R*)-(+)-(**2**) as colorless needles: 4.5 g; mp 87°, $[\alpha]_D$ + 18.3° (*c* 0.35). *Anal.* ($C_{25}H_{33}NO_4$) C, H, N.

(*R*)-(+)-α¹-(Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-*m*-xylene-α,α′-diol (3).—A soln of (*R*)-(+)-(**2**) (2.5 g, 0.005 mole) in dry THF (25 ml) was added with stirring to LAH (0.5 g, 0.0125 mole) in dry THF (50 ml). The mixt was heated to reflux and then cooled, and the excess hydride was decompd by cautious addn of H_2O. The THF soln was filtered through Hyflo, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O, dried ($MgSO_4$), and evapd to give the diol as a colorless oil: 2.1 g; $[\alpha]_D$ +7.9° (*c* 0.45). *Anal.* ($C_{26}H_{33}NO_3$) C, H, N.

(*R*)-(−)-α¹-(*tert*-Butylaminomethyl)-4-hydroxy-*m*-xylene-α,α′-diol Acetate (Salt) Monomethanolate (4).—A soln of (*R*)-(+)-(**3**) (2 g) in EtOH was hydrogenated at room temp and atm pressure in the presence of 10% Pd/C (0.7 g). Uptake of H_2 ceased after 6 min. The catalyst and solvent were removed, and the residue was converted into an acetate salt with 10% HOAc in EtOAc. Recrystn from MeOH-Et_2O gave (*R*)-(−)-salbutamol acetate (salt) monomethanolate: mp 144.3°; $[\alpha]_D$ −36.9° (*c* 0.27); CD (*c* 0.37) $[\theta]_{260}$ 0, $[\theta]_{280}$ −569 (max), $[\theta]_{295}$ 0. *Anal.* ($C_{16}H_{29}NO_6$) C, H, N.

(*S*)-(+)-α¹-(*tert*-Butylaminomethyl)-4-hydroxy-*m*-xylene-α,α′-diol acetate (salt) monomethanolate (4) was obtd by a procedure similar to that described above for the (R)-(−) isomer but using (+)-di-*p*-toluoyltartaric acid.[11] Thus (*S*)-(−)-(**2**), (+)-di-*p*-toluoyltartrate, had mp 150.7°, $[\alpha]_D$ +47° (*c* 1.2). *Anal.* ($C_{48}H_{51}NO_{12}$) C, H, N. This was converted into (*S*)-(−)-(**2**), free base: mp 87°; $[\alpha]_D$ −18.4° (*c* 0.38). *Anal.* ($C_{26}H_{33}NO_3$) C, H, N. Reduction with LAH gave the diol (*S*)-(−)-(**3**) as an oil, $[\alpha]_D$ −8.18° (*c* 0.48). *Anal.* ($C_{27}H_{33}NO_3$) C, H, N. Hydrogenation of (*S*)-(−)-(**3**) then gave (*S*)-(+)-salbutamol which was purified as its acetate (salt) monomethanolate: mp 145.7°; $[\alpha]_D$ +36.9° (*c* 0.23); CD (*c* 0.23) $[\theta]_{260}$ 0, $[\theta]_{278}$ +683 (max), $[\theta]_{295}$ 0. *Anal.* ($C_{16}H_{29}NO_6$) C, H, N.

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(10) From (+)-tartaric acid see (a) D. A. A. Kidd, *J. Chem. Soc.*, 4675 (1961); (b) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922 (1943).

(11) From (−)-tartaric acid: see J. H. Hunt, *J. Chem. Soc.*, 1926 (1957).

Synthesis and Local Anesthetic Activity of *N*-Diethylaminoacetyl Derivatives of Naphthylalkylamines

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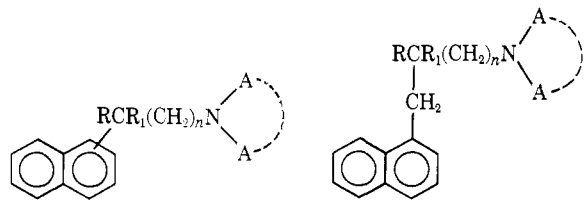
Our finding[1] that some α-naphthylalkylamines possess marked local anesthetic activity has led us to synthesize an extensive series of *N*-diethylaminoacetyl derivatives of naphthylalkylamines of the general structures I–III, in which R was H, or alkyl, or aminoalkyl; R_1 was $NHCOCH_2NEt_2$ or $CH_2NHCOCH_2NEt_2$; NAA was a tertiary amino group; n = 2–4.



I, substituted at position 1
II, substituted at position 2

III

The new substances (Table I) were obtained by allowing the corresponding amines to react in $CHCl_3$ with $(BrCH_2CO)_2O$ and subsequently treating the bromoacetyl derivatives with excess Et_2NH. To prevent the tertiary amino groups from quaternization, the bromoacetylation was accomplished in the presence of 1 or 2 equiv of AcOH.

Many of the compds displayed a marked local anesthetic activity. In particular, **22**, **27**, **28**, **31**, and **46** were as active as lidocaine, but irritant.

Experimental Section[2]

The intermediate amines were prepd as previously described.[3] **The *N*-diethylaminoacetyl derivatives of naphthylalkylamines** are listed in Table I, and their prepn is well illustrated by the following example.

***N*-[4-Diethylaminoacetamidomethyl-4-(α-naphthyl)-5-methylheptyl]piperidine (38).**—A soln of $(BrCH_2CO)_2O$ (14.35 g, 0.055 mole) in $CHCl_3$ (30 ml) was dropped at 5° into a stirred soln of *N*-[4-aminomethyl-4-(α-naphthyl)-5-methylheptyl]piperidine (15 g, 0.042 mole) and AcOH (2.56 g, 0.042 mole) in $CHCl_3$ (50 ml). The mixt was stirred for 1 hr at room temp, poured into excess Et_2NH (44.5 g), and stirred for an addnl 1 hr. The soln was then evapd to dryness, and the residue was taken up in Et_2O, washed (H_2O), and dried ($MgSO_4$). The solvent was evapd and

(1) S. Casadio, G. Pala, T. Bruzzese, C. Turba, and E. Marazzi-Uberti, *J. Med. Chem.*, **13**, 418 (1970).

(2) Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

(3) G. Pala, A. Donetti, C. Turba, and S. Casadio, *J. Med. Chem.*, **13**, 668 (1970).