envelope and OH), 3.75 (s over a multiplet, 2, $ArCH_2$), 7.47 (s, 5, aromatic). The hydrochloride was prepared in the normal manner and recrystallized from EtOH-Et_2O, mp 203–205°. *Anal.* ($C_{14}H_{20}ClNO$) C, H, N.

Further elution with petroleum ether-Et_2O (1:1) afforded the trans alcohol (0.3 g): mp 75–76°; ir (0.002 *M* CCl_4) 3620 cm^{-1} (free OH); nmr ($CDCl_3$) δ 1.1–2.2 (broad signals, 6, bicyclic envelope), 2.2–3.0 (broad signals, 4, H-1, H-3, and H-4), 3.75 (s, 2, NCH_2Ar), 4.0–4.4 (m, 1, H-6), 7.45 (s, 5, aromatic). *Anal.* ($C_{14}H_{19}NO$) C, H, N.

6-*trans*-Hydroxy-2-azabicyclo[2.2.2]octane. A solution of 2-benzyl-6-*trans*-hydroxy-2-azabicyclo[2.2.2]octane (13.0 g, 0.06 mol) in EtOH (100 ml) was hydrogenated (3.15 kg/cm^2) over 10% Pd/C (1.5 g) for 24 hr. The catalyst was removed by filtration and the solvent evaporated to yield a white solid. Recrystallization from $CHCl_3$–hexane gave 6.0 g (78%) of a white solid: mp 229–231°; ir (1% $CHCl_3$) 3620 (OH), 3350 cm^{-1} (NH); nmr (DMSO-d_6) δ 1.0–2.4 (broad signals, 9, bicyclic envelope), 2.5–2.75 (m, 1, H-1), 2.8 (broad singlet, 1, NH), 3.4 (broad singlet, 1, OH), 3.75–4.2 (m, 1, H-6). *Anal.* ($C_7H_{13}NO$) C, H, N.

2-Methyl-6-*trans*-hydroxy-2-azabicyclo[2.2.2]octane (7). A solution of 6-*trans*-hydroxy-2-azabicyclo[2.2.2]octane (5.0 g, 0.04 mol) and CH_2O (5 ml of 37%) in EtOH (70 ml) was hydrogenated (3.15 kg/cm^2) over 10% Pd/C (0.3 g) for 12 hr. The catalyst was removed by filtration and the solvent evaporated to yield a yellow oil which upon distillation gave 7 (4.5 g, 80%): bp 125–128° (20 mm); picrate mp 230–231°; ir (CCl_4, 0.002 m) 3640 cm^{-1}. This alcohol is identical with the alcohol obtained in Scheme II.

6-*cis*-Hydroxy-2-azabicyclo[2.2.2]octane. A solution of 2-benzyl-6-*cis*-hydroxy-2-azabicyclo[2.2.2]octane (1.7 g, 0.008 mol) in EtOH (80 ml) was hydrogenated (3.15 kg/cm^2) over 10% Pd/C (0.2 g) for 3 hr. The catalyst was removed by filtration and the EtOH evaporated. The crude product was recrystallized from Et_2O to yield a white solid (0.5 g, 50%): mp 193–195° dec; ir (1% $CHCl_3$) 3645, 3620, and 3380 cm^{-1} (OH and NH).

2-Methyl-6-*cis*-hydroxy-2-azabicyclo[2.2.2]octane (5). A solution of 6-*cis*-hydroxy-2-azabicyclo[2.2.2]octane (1.0 g, 0.008 mol) and CH_2O (1 ml of 37%) in EtOH (50 ml) was hydrogenated (3.15 kg/cm^2) over 10% Pd/C (0.2 g) for 6 hr. The catalyst was removed by filtration and the EtOH evaporated. The residue was distilled to give a clear oil (0.7 g, 63%): bp 106–110° (20 mm); ir (0.002 *M* CCl_4) 3450 cm^{-1} (associated OH); picrate mp 259–260°.

General Procedure for the Synthesis of *p*-Aminobenzoate Esters 1–4. A solution of the amino alcohol (0.014 mol) and TEA (0.021 mol) in 60 ml of C_6H_6 was added dropwise to a cooled solution of *p*-nitrobenzoyl chloride (0.014 mol). The mixture was refluxed for 24 hr, cooled, and extracted with 10% HCl (3 × 50 ml). The acid extracts were combined, made basic with K_2CO_3, and extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ was combined, dried ($MgSO_4$), and evaporated to yield a solid which was taken up in 100 ml of EtOH and added to a Parr flask. The solution was hydrogenated (3.15 kg/cm^2) over 0.2 g of 10% Pd/C for 12 hr and filtered through Celite and the solvent was evaporated to yield an orange solid. The solid was recrystallized from the indicated solvent (Table I) to yield the desired *p*-aminobenzoate ester.

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Notes

Relative Potency of (−)- and (±)-Salbutamol on Guinea Pig Tracheal Tissue†

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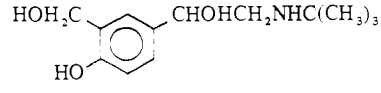
The two enantiomers of the various asymmetric β-sympathomimetic drugs are usually found to have significantly different potencies. Studies with guinea pig tracheal tissue have shown that, where the absolute configuration is known, the *R* isomer is the more active and the racemate's activity lies between those of the two enantiomers. Recently, however, it was reported that racemic salbutamol (**1**) was 1.5 times as active as the more active (laevo) of the two enantiomers.[1,‡]



1

This result is unique for this type of drug interaction and warranted further investigation especially as salbutamol's marked β_2 selectivity[2] has made it an important bronchodilator for the treatment of asthma.

This paper describes the results of relaxation studies with the isomers of salbutamol using guinea pig tracheal chains. Each tissue was tested by cumulative drug-response tests using adrenaline prior to study with salbutamol. The results are presented in Figure 1. The mean log ED_{50} values with their associated standard errors are as follows: isomer with $[\alpha]^{20}D$ −32.2°, −7.8 ± 0.06 (96.9 ± 4.2); (±), −7.61 ± 0.04 (101.2 ± 5.5); isomer with $[\alpha]^{20}D$ +30.8°, −7.50 ± 0.03 (98.9 ± 3.7). The mean slopes of the log dose-response curves with their standard errors are presented in parentheses. As the (+) isomer was not fully resolved, it would have somewhat less activity than that indicated by the above ED_{50}

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‡Hartley and Middlemiss in the text of their paper[1] considered the two to be approximately equiactive.

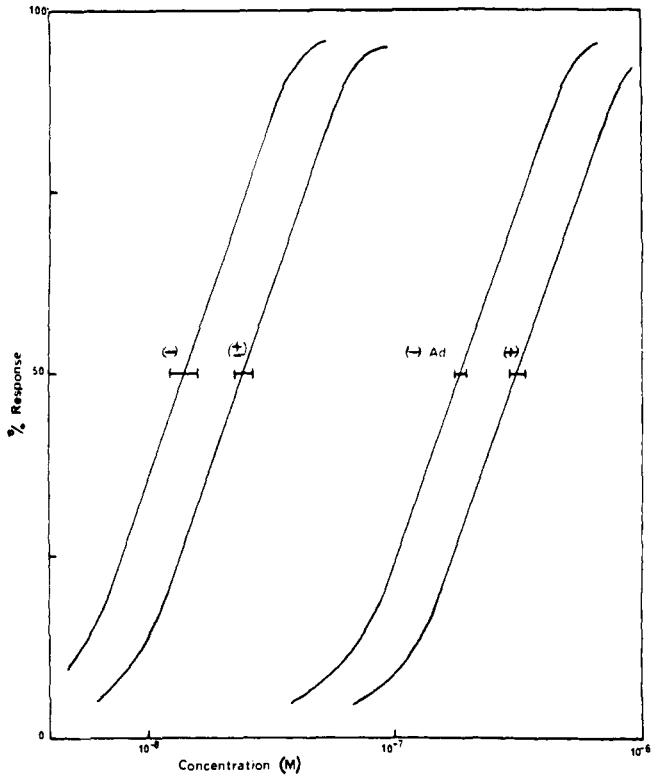

Figure 1. The mean log dose–response lines for (−), (±), and (+)-salbutamol and (−)-adrenaline. Doses are given as molar concentration in the tissue bath. The error bars represent the standard error of the mean log ED_{50}'s.

value due to contributions from the more active (−) isomer. These results, in contrast to those of Hartley and Middlemiss,[1] show that the (−) isomer is significantly more active than the racemic in agreement with the general finding that a racemic drug's activity lies between those of the two enantiomers.[3,4] From a comparison of the response curves for a set of tissues, it was found that (−)- and (±)-salbutamol are 12.6 and 5.6 times, respectively, more active than (−)-adrenaline.

The technique used in the present investigation, which is a standard method for studying the relaxation of smooth muscle,[5] differs from that used by Hartley and Middlemiss.[1] Their method, which was developed in their own laboratory,[6] is an intraluminal pressure technique. The two techniques and preparations might be expected to give small differences in the absolute values of the ED_{50}'s but the different techniques should not yield such large variations in the relative potencies of the isomers as observed.

Experimental Section

Melting points were observed on a Büchi oil-bath melting point apparatus and microchemical analyses were performed by the Australian Microanalytical Service, Melbourne, Australia. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter in H_2O at 20°. The compounds gave satisfactory uv and ir spectral data obtained with a Cary 14 and a Perkin-Elmer 225 instrument, respectively.

Resolution of 2-*tert*-Butylamino-1-(4′-hydroxy-3′-hydroxymethylphenyl)ethanol (Salbutamol). To a warm solution of racemic salbutamol[§] (0.8 g, 0.0034 mol) in dilute H_2SO_4 (4 ml) was added $(+)_{546}$-Ba[CoEDTA]$_2$·$4H_2O$ (0.76 g, 0.0008 mol), $[\alpha]^{20}_{546}$ +890° (*c* 0.05, H_2O),[#] which was prepared from the resolved potassium salt.[7] The precipitated $BaSO_4$ was filtered off and the diastereoisomer (1.2 g) obtained by the addition of EtOH and Et_2O to the solution while cooling in ice.

(−)-2-*tert*-Butylamino-1-(4′-hydroxy-3′-hydroxymethylphenyl)ethanol Hydrochloride Monohydrate. To the diastereoisomer (1.0 g) in H_2O (4 ml) was added $BaCl_2$ (0.22 g). The $(+)_{546}$-Ba[CoEDTA]$_2$·$4H_2O$ was recovered by the addition of EtOH and Et_2O while cooling in ice. (−)-Salbutamol was precipitated as the HCl salt from the oil formed on evaporation of the filtrate at reduced pressure. The recrystallized product yielded 0.24 g, $[\alpha]^{20}D$ −32.2° (*c* 0.10, H_2O). The compound changed crystalline form at 175° and decomposed over the range 185–195°. *Anal.* ($C_{13}H_{24}NO_4Cl$) C, H, N.

(+)-2-*tert*-Butylamino-1-(4′-hydroxy-3′-hydroxymethylphenyl)ethanol Hydrochloride Monohydrate. A HCl salt of (+)-salbutamol was prepared from the oil obtained on reducing the volume of the filtrate remaining after diastereoisomer removal. The recrystallized product yielded 0.15 g, $[\alpha]^{20}D$ +30.8° (*c* 0.10, H_2O). The compound changed crystalline form at 175° and decomposed over the range 185–195°. *Anal.* ($C_{13}H_{24}NO_4Cl$) C, H, N.

Relaxation Studies. The drugs were tested by a cumulative dose method on guinea pig tracheal chain at a tension of 300 mg in Krebs physiological salt solution. Linear regression lines were obtained by a least-squares method. Mean log ED_{50} and the standard error of the mean were found for each drug and tested at the 10% significance level for differences between the drugs using a student's t test. The mean log dose–response curves were obtained from approximately 20 tissue experiments for each drug. The tissue responses were recorded on a Hewlett-Packard 680M recorder using a Sanborn FTA-1-1 microforce transducer with a Sanborn Model 311A amplifier.

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[§] Kindly supplied by Allen and Hanburys Ltd., England.

[#] EDTA is ethylenediaminetetraacetate.

A Synthesis of Noformycin

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Noformycin (**5**) was isolated from a culture of *Nocardia formica* and was identified as the active constituent of this microorganism.[1-3] This material was unusual in that it exhibited a wide range of antimicrobial activity. Of particular interest was its *in vivo* activity in mice against swine influenza and SK poliomyelitis. Subsequent to its isolation and identification, noformycin was tested against a wide variety of plant and animal viruses[4-9] and found to possess very potent activity. However, this material appeared to possess considerable toxicity, which was confirmed in our laboratories.

In view of the broad spectrum of activity, we became interested in synthesizing homologs of noformycin with the expectation of reducing toxicity while retaining activity. Specifically, we were interested in developing a versatile synthesis which would adapt itself to a variety of transformations. A detailed synthesis of noformycin itself has not been published although it has been reported that the synthetic racemic material possesses half the activity of the isomer obtained from the culture.[2] Consequently, we wish to report a facile synthesis of both racemic and (+)-norformycin which