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2-Azabicyclo[2.2.2]octane Derivatives as Conformational Analogs of Local Anesthetics†

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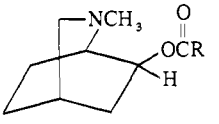
The importance of conformational factors in the production of local anesthesia by the *p*-aminobenzoate esters, particularly procaine, was examined through the synthesis of the *p*-aminobenzoate esters of the cis and trans isomers of 5- and 6-hydroxy-2-methyl-2-azabicyclo[2.2.2]octane. One of these isomers, the *p*-aminobenzoate ester of *trans*-6-hydroxy-2-methyl-2-azabicyclo[2.2.2]octane, produced three times the duration of action of procaine in the intradermal wheal assay in guinea pigs. The syntheses, stereochemical assignments, and pharmacological results are presented.

The concept that blockade of nerve impulses by local anesthetics is a consequence of interactions of the local anesthetic with a biological receptor site located in a structurally distinct area on the cell membrane has generated a significant degree of recent interest.[1,2] While attempts to correlate physicochemical properties of local anesthetics have been reported, it is only recently that the importance of conformational effects has been studied. It has been suggested that a gauche conformation of the ethanolamine linkage of procaine is an important feature in its ability to block conduction of the nerve impulse.[3] Quantum mechanical calculations have been performed by the method of perturbative configuration interaction using localized orbitals on model local anesthetics representing the methanolamine, ethanolamine, propanolamine, and anilide structures.[4] The stable conformations calculated for the ester anesthetics indicated an optimum separation of 4.1-4.2 Å between the basic nitrogen and carbonyl oxygen atoms. This observation did not hold true for the anilide series. In a recent study designed to clarify conformational aspects of local anesthetics, Boots and Boots reviewed previous efforts directed toward testing conformational isomers and reported their results of conformationally restricting the flexibility of the propanolamine chain through its incorporation, in part, into the norbornane ring system.[5] Differences in activity between the two epimers studied were observed, the most potent epimer being the one in which the amine and alcohol functions occupy the exo positions of the norbornane ring. More recently, a series of 1-alkyl-3-benzoyl-3-acyloxypiperidines was tested for local anesthetic activity and toxicity.[6] These derivatives can be formally considered as ethanolamines which are restricted in a preferred gauche conformation. The procaine analog of this series was eight times more active and 16 times more toxic than procaine.

We wish to report here the synthesis and local anesthetic activity of 2-azabicyclo[2.2.2]octane analogs of local anesthetics in order to examine conformational effects of both the ethanolamine and propanolamine series of local anesthetics within the same "conformationally rigid" ring framework. Compounds **1** and **3** can be considered as conformational analogs of procaine in which the N-C-C-O grouping is restricted in gauche and trans conformations, respectively. Compounds **2** and **4** represent similarly restricted conformers of the corresponding propanolamine series.



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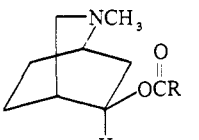

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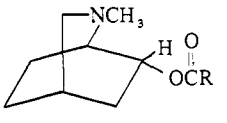

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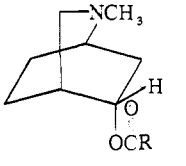

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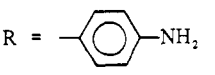

Chemistry. The key intermediates in the synthesis of the esters **1-4** were, of course, the corresponding alcohols **5-8**. While syntheses of several of these alcohols had been previously reported, we noted some inconsistencies in structural assignments on repetition of these reactions. Two basic approaches were utilized and are shown in Schemes I and II. The synthesis of **5**, **6**, and **8** was accomplished (Scheme I) through a modification of the procedure reported by DeGraw and Kennedy.[7] Oxidation of the olefin obtained from 1,3-cyclohexadiene and methylene bisurethane with *m*-chloroperoxybenzoic acid gave a mixture of epoxides which was not separated. Reduction of the epoxide mixture with Red-Al gave three different alcohols, **5**, **6**, and **8**, in a ratio of 1:4.5:4.5 based on glc. DeGraw and Kennedy reported only

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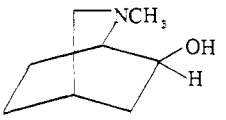

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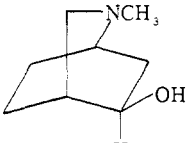

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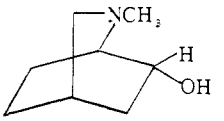

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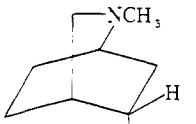

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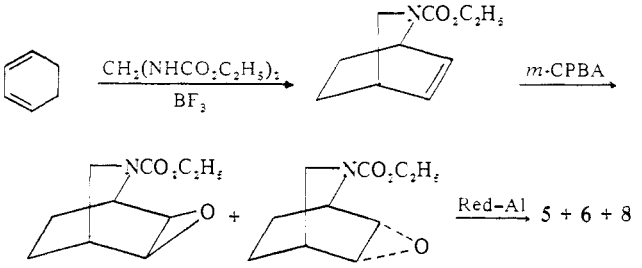
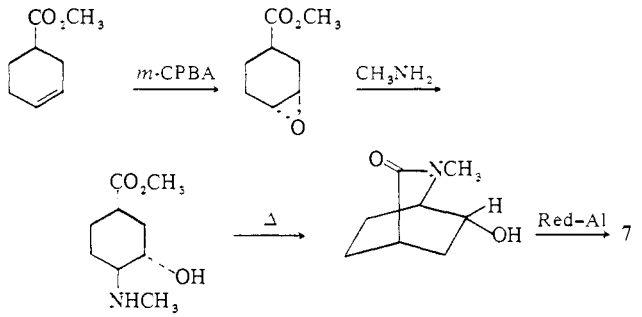
Scheme I

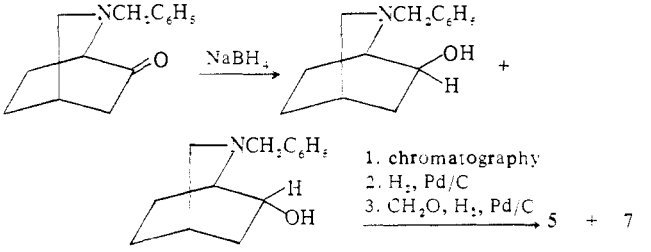


Scheme II



the isolation of **5** and **8** upon reduction of the purified epoxides with $LiAlH_4$. We obtained the same product ratio when the epoxide mixture was reduced with $LiAlH_4$ as we observed with Red-Al. The lower boiling alcohols **5** and **6** showed intramolecular hydrogen bonding absorption in 0.002 *M* CCl_4 indicative of a cis relationship of the hydroxyl group to the amino function. The higher boiling alcohol **8** showed only free hydroxyl absorption upon dilution. Structural assignments to **5** and **6** were based upon an unambiguous synthesis of **5** which is shown in Scheme III. The *N*-benzyl ketone **9**[8] was reduced with $NaBH_4$ to give a mixture of intramolecular and intermolecular hydrogen-bonded alcohols which were separated by column chromatography. Each alcohol was debenzylated by hydrogenolysis and reductively methylated. The cis alcohol obtained by this method was identical in all respects (ir, nmr, glc retention time) with the cis alcohol obtained in low yields in Scheme I. Because the

Scheme III



oxygen function of the cis alcohol obtained in Scheme III was defined by the starting ketone **9**, alcohol **5** must be the *cis*-6-hydroxy derivative. Therefore, the other cis alcohol obtained in Scheme I must be the *cis*-5-hydroxy derivative. The *trans*-6-alcohol **7** was obtained by a modification of the procedure described by Huffman, *et al.*,[9] using methylamine rather than benzylamine (Scheme II). Because of the stereospecificity of this synthesis, the alcohol obtained must possess the trans-6 configuration. This alcohol is identical in all respects (ir, nmr, glc retention time) with the trans alcohol obtained in Scheme III and different than the trans alcohol obtained in Scheme I. Therefore, alcohol **8** must possess the trans-5 configuration. All alcohols showed similar mass spectral fragmentation patterns with an *m/e* of 141.

The *p*-aminobenzoate esters **1–4** were synthesized in a straightforward manner by esterifying the corresponding alcohol with *p*-nitrobenzoyl chloride and subsequent catalytic reduction of the nitro group. Ir and nmr data were consistent with assigned structures. Appropriate physical data are presented in Table I.

Pharmacology. Compounds **1–4** were tested as their hydrochloride salts for local anesthetic activity using the rabbit corneal reflex[10] and guinea pig intradermal wheal[11] assays employing procaine as a standard in both assays. In the corneal reflex assay only **3** showed appreciable activity as a surface anesthetic at a 1% (w/v) concentration possessing an average duration of activity of 14 min. None of the other esters possessed activity at this concentration. Procaine itself at 1% (w/v) concentration did not produce topical anesthesia. The results of the intradermal wheal assay are shown in Figure 1. All compounds were tested at three different (w/v) concentrations: 0.25, 0.5, and 1%. All of the compounds were at least as active as procaine in this assay. Interestingly, **3** possessed a duration of action at least three times that of procaine.

Discussion

It is not surprising that the conformers tested lacked appreciable topical activity in view of the fact that procaine is not an efficient local anesthetic for topical application.[12] It is interesting, however, that **3** did possess some activity. Results from the intradermal wheal assay were more revealing. The general order of activity observed was **3** > **2** > **4** > **1** > procaine. The most active conformer possesses a trans

Table I

No.	% yield[a]	Mp, °C	Recrystn solvent	Partition coeff[b]	Formula	Analyses[c]
1	40	132–134	C_6H_6–hexane	1.3	$C_{15}H_{20}N_2O_2$	C, H, N
2	34	120–121	C_6H_6–hexane	1.1	$C_{15}H_{20}N_2O_2$	C, H, N
3	45	157–159	Et_2O–hexane	5.4	$C_{15}H_{20}N_2O_2$	C, H, N
4	33	174–176	C_6H_6	3.0	$C_{15}H_{20}N_2O_2$	C, H, N

[a] Overall yield from corresponding alcohol. [b] Determined in 1-octanol–pH 7.0 buffer by the method of Hansch: C. Hansch, R. M. Muir, T. Kujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Amer. Chem. Soc.*, 85, 2817 (1963). [c] Where analyses are indicated by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

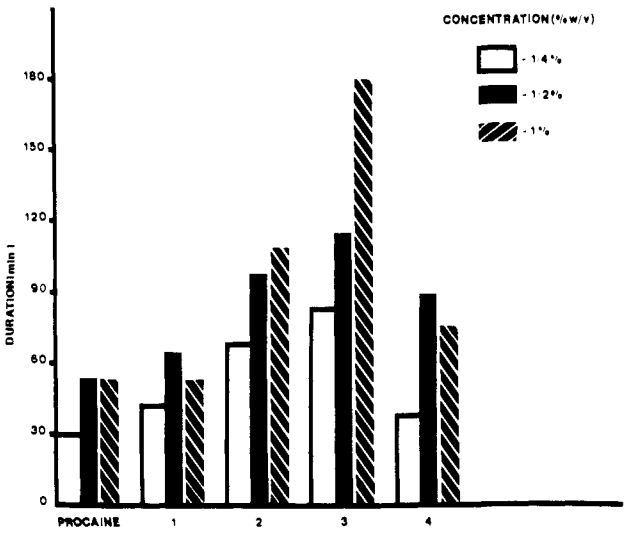


Figure 1. Effects of compounds 1-4 and procaine in the guinea pig intradermal wheal assay. Each bar represents the average of five determinations.

relationship between the ester oxygen and the amine function while the next most active conformer possesses a cis relationship. One is tempted to speculate, therefore, that a trans configuration may play an important role in the interaction of the ethanolamine-type local anesthetic with the "local anesthetic receptor" while a gauche configuration may be important among the propanolamines. This speculation gains further support when one views Drieding stereomodels of the conformers tested. The N to ester O bond distances calculated from these models are as follows: **3** = 3.7 Å, **2** = 3.6 Å, **4** = 4.2 Å, and **1** = 2.9 Å. Despite different configurations, this distance is strikingly similar in **3** and **2**. However, if differences in biological activity among conformers are proposed to reflect differences in abilities to interact with a biological receptor, it must then be a basic assumption of this proposal that these conformers reach the biophase of the receptor in equal concentrations. Thus, partition coefficients of **1-4** were measured between 1-octanol and pH 7.0 buffer (Table I). Unfortunately, large differences in partition coefficients were observed, thus discouraging any attempt to correlate the activities observed in the intradermal wheal assay to differences in conformational factors alone.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Ir data were recorded on a Perkin-Elmer 257 spectrophotometer and nmr data on a Jeolco C-60-HL spectrometer. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Mass spectra data were obtained on a Du Pont-CEC 492 spectrometer. Gas chromatographic data were obtained on a Varian Aerograph Model 600-D. The term Red-Al refers to sodium bis-2-methoxyethoxy aluminum hydride and is supplied commercially by Aldrich Chemical Co. *m*-Chloroperoxybenzoic acid (*m*-CPBA) was obtained from Columbia Organic Chemicals Co., Inc.

2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene. A modified procedure of Cava, *et al.*,[13] was used. A solution of BF_3 etherate (11.0 g, 0.07 mol) and methylene bisurethane (60.0 g, 0.31 mol) in 400 ml of C_6H_6 was refluxed. A solution of 1,3-cyclohexadiene (25.0 g, 0.31 mol) in 50 ml of C_6H_6 was added dropwise and the resulting mixture refluxed for 1 hr. The mixture was washed with a solution of $NaHCO_3$ (saturated) and then H_2O and dried ($MgSO_4$). The solvent was evaporated to yield an oil which was distilled [bp 130–134° (10 mm); lit.[13] bp 58–64° (3 mm)] to give 18.9 g (34%) of the olefin.

2-Carbethoxy-5,6-epoxy-2-azabicyclo[2.2.2]octane. A modified procedure of DeGraw and Kennedy[7] was used. A solution of 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (25.0 g, 0.14 mol) in $CHCl_3$ (600 ml) was added to a three-necked flask equipped with a mechanical stirrer and reflux condenser. *m*-CPBA (37.5 g, 0.21 mol) was added and the solution stirred for 48 hr. The solution was filtered, and the filtrate washed with 2% Na_2SO_4 until all the peroxy acid was destroyed, then with 2% NaOH (3 × 100 ml), and H_2O (2 × 50 ml). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to yield a liquid which was distilled [bp 112–116° (0.1 mm)] to give a mixture of epoxides (18.5 g, 68%) which was reduced without further purification.

Synthesis of 6 and 8. The epoxide obtained above (16.0 g, 0.08 mol) was dissolved in 70 ml of C_6H_6 and added, dropwise with stirring, to 100 ml of Red-Al (0.73 mol). The solution was refluxed for 4 hr and cooled to room temperature, and excess hydride was destroyed with EtOH and H_2O. The mixture was filtered and the filtrate dried ($MgSO_4$) and evaporated to give an oil which was shown by glc (SE-30 column) to be a mixture of **5**, **6**, and **8** in a ratio of 1:4.5:4.5 and was subsequently fractionally distilled. The lower boiling fraction [2.0 g, 18%, bp 96–99° (20 mm)] was shown to be **6**: ir (0.002 *M* CCl_4) 3640 (free OH) and 3500 cm^{-1} (associated OH); picrate mp 241–243°. *Anal.* (picrate $C_{14}H_{28}N_4O_8$) C, N; H: calcd, 4.86; found, 4.42.

An intermediate fraction contained a mixture of **5**, **6**, and **8**. The high-boiling fraction [2.0 g, 18% bp 131–133° (20 mm)] afforded pure **8**: ir (0.002 *M* CCl_4) 3640 cm^{-1} (free OH); picrate mp 264–266° (lit.[7] mp 260–262°).

3-Carbomethoxy-7-oxabicyclo[4.1.0]heptane. A solution of methyl 3-cyclohexene-1-carboxylate (100 g, 0.71 mol) in Et_2O (400 ml) was placed in a 3-l. three-necked flask and cooled to 0°. A solution of *m*-CPBA (150 g, 0.87 mol) in Et_2O (500 ml) was added dropwise and the resulting mixture stirred for 8 hr. The solution was washed with 2% Na_2SO_4 until no active oxygen remained (determined by KI oxidation). The Et_2O was evaporated and the resulting white solid washed with $CHCl_3$ (500 ml) and filtered. The $CHCl_3$ filtrate was extracted with 2% NaOH (5 × 100 ml) and H_2O and dried ($MgSO_4$). The solvent was evaporated to yield a yellow oil which was distilled to give 65.0 g (73% based on recovered starting material) of a clear liquid, bp 114–119° (20 mm) [lit.[14] bp 58–59° (0.9 mm)].

2-Methyl-6-*trans*-hydroxy-2-azabicyclo[2.2.2]octan-3-one. A solution of 3-carbomethoxy-7-oxabicyclo[4.1.0]heptane (25.0 g, 0.16 mol) in MeOH (150 ml) was added to 500-ml flask and stirred magnetically. The solution was cooled to 5°, $MeNH_2$ (30 g of 40% aqueous, 0.38 ml) was added, and the mixture was stirred at room temperature for 12 hr and refluxed for 2 hr. The solution was cooled, dried ($MgSO_4$), and evaporated to yield a yellow oil (26.0 g). The oil was taken up in MeCN (200 ml) and the solution added to a Parr reaction vessel containing an additional 200 ml of MeCN. The vessel was purged with N_2, sealed, and heated at 180–200° for 3 days. The vessel was cooled and the solvent evaporated to yield a yellow oil which solidified on standing. The solid was recrystallized from toluene to give 8.0 g (32%) of the lactam: mp 99–101°; ir (Nujol) 3300 (OH), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.2–2.7 (broad signals, 7, bicyclic envelope), 3.06 (s, 3, NCH_3), 3.5 (broad signal, 1, H-1), 4.0–4.4 (m, 1, H-6), 4.57 (s, 1, OH). *Anal.* ($C_8H_{13}NO_2$) C, H, N.

2-Methyl-6-*trans*-hydroxy-2-azabicyclo[2.2.2]octane (7). A solution of the above lactam (5.0 g, 0.032 mol) in C_6H_6 (100 ml) was added dropwise to Red-Al (36 ml, 0.27 mol) contained in a 500-ml three-necked flask. The solution was refluxed with stirring for 4 hr and cooled, and excess hydride was destroyed with EtOH and H_2O. The solution was filtered and the solvent dried and evaporated. The residue was distilled to give a clear oil (3.0 g, 67%): bp 125–128° (20 mm); picrate mp 230–231°; ir (CCl_4, 0.002 *M*) 3640 cm^{-1} (free OH); nmr ($CDCl_3$) δ 0.9–3.0 [broad signals, 13, bicyclic envelope and NCH_3 (s, 2.4)], 3.9–4.3 (m, 1, H-6), 4.5–4.95 (broad signal, 1, OH). *Anal.* (picrate $C_{14}H_{28}N_4O_8$) C, H, N.

2-Benzyl-6-*cis*- and -*trans*-hydroxy-2-azabicyclo[2.2.2]octanes. 2-Benzyl-2-azabicyclo[2.2.2]octan-6-one[8] (3.0 g, 0.015 mol) and $NaBH_4$ (1.2 g, 0.03 mol) were added to 100 ml of *i*-PrOH in a 250-ml flask and the mixture was stirred magnetically at room temperature for 24 hr, chopped ice was added until the solution cleared, and the solvent was evaporated to yield a white slurry which was taken up in Et_2O and H_2O. The Et_2O layer was washed with H_2O (3 × 50 ml), dried ($MgSO_4$), and evaporated to give 2.8 g of clear oil. A 1.0-g portion of the oil was chromatographed on 40 g of silica gel using petroleum ether–Et_2O (4:1) as eluent. The first fraction eluted as a clear oil and was the cis alcohol (0.6 g): ir (CCl_4) 3500 cm^{-1} (broad, OH associated); ir (0.002 *M* CCl_4) 3500 cm^{-1} (broad, OH associated intramolecular); nmr ($CDCl_3$) δ 1.0–4.0 (broad signals, 12, bicyclic

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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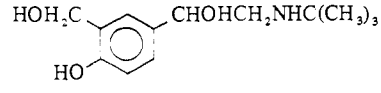
The two enantiomers of the various asymmetric β-sympathomimetic drugs are usually found to have significantly different potencies. Studies with guinea pig tracheal tissue have shown that, where the absolute configuration is known, the *R* isomer is the more active and the racemate's activity lies between 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.