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Resolution of Terbutaline, a New β-Sympathomimetic Amine

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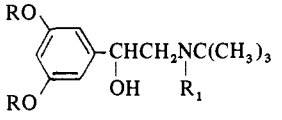
A recent article published in this Journal,[1] describing the resolution of salbutamol, prompts us to report an investigation[2] on the resolution of terbutaline, 1-(3',5'-dihydroxyphenyl)-2-(*tert*-butylamino)ethanol, where benzyl groups have been used for protection of the phenolic groups during the resolution.

The preparation[2] and pharmacological properties[3] of terbutaline have recently been described and it has been shown that this compound is a potent adrenergic β receptor stimulating agent, predominantly acting on the β_2 receptors.

Chemistry. Similar compounds, *e.g.*, orciprenaline,[4] have been resolved with unprotected phenolic groups, but owing to the unfavorable pK_a values of the hydroxyl groups and the ammonium group, it is difficult to extract the free base with an organic solvent in a good yield. Thus, after resolution of the racemic base, the salt with the optically active acid is dissolved in a suitable solvent and an optically inactive acid is added. The salt with this acid is then precipitated from the mixture with ether. The possibility of coprecipitation of the other salt makes this procedure less attractive. However, such problems can be completely eliminated as described below for terbutaline (1).



1, R = H; R_1 = H
2, R = $C_6H_5CH_2$; R_1 = $C_6H_5CH_2$

Compound **2** (racemic base) was treated with (−)-dibenzoyltartaric acid and formed a well-crystallized salt. After six recrystallizations to get reasonable optical purity, the salt was suspended in water, aqueous ammonia added, and the amine easily extracted with ether. A salt with a suitable optically inactive acid can then be prepared and isolated in the usual way. The protecting groups are then easily removed by catalytic hydrogenation to give one of the enantiomers of **1**. The salt of the other enantiomer can be prepared from the residual base from the mother liquors of the first resolution procedure. Two recrystallizations were found to give a reasonable optical purity.

Pharmacology. In 1966 and 1967, Lands, *et al.*,[5-7] showed, by means of rank order technique, that the adrenergic β receptors in the heart and the bronchi were not identical and classified them as β_1 and β_2 receptors. According to this theory, functions associated with β_1 stimulation are: myocardial excitation, relaxation of small intestine, and lipolysis in adipose tissue, whereas β_2 stimulation is associated with bronchodilatation, vasodilatation, and glycogenolysis. Since the racemate of terbutaline shows a very good selectivity for the β_2 receptors, investigation on the β-stimulating effect of each enantiomer on bronchi and heart muscle was carried out to see if a still better selectivity could be achieved in this way.

Table I. Biological Activity of the (−) and (+) Isomers of Terbutaline

Compound	Biological test[a]	
	Trachea	Left auricle
Racemate	0.8	0.09[c]
(−) isomer	1.6 ± 0.3	0.034 ± 0.003[c]
(+) isomer	0.0071[b]	Inactive[d]

[a] Effect relative (−)-adrenaline. The weight comparisons for the compounds are made on the base forms. [b] Partial agonist. [c] See ref 10. [d] Guinea pig heart. See ref 11.

The β-adrenoceptor-stimulating effect was tested on the left auricle (electrically driven) and on spirally cut trachea of the guinea pig[8-10] (Table I).

The (−) isomer has been found to be about 200 times more potent than the (+) isomer for the β_2 receptors. Since the latter was found to be a partial agonist, this value is uncertain.

Experimental Section

The melting points were observed with a microscope and are corrected. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter in MeOH at 20°. The compounds gave satisfactory uv and ir spectral data, obtained with a Beckman DK2 and a Unicam SP 200 G instrument, respectively.

1-(3',5'-Dibenzyloxyphenyl)-2-(benzyl-*tert*-butylamino)ethanol (2). This compd was prepared by condensing 3,5-dibenzyloxy-ω-bromoacetophenone with benzyl-*tert*-butylamine in EtOH and dry C_6H_6. The product was then reduced with $NaBH_4$ in EtOH and worked up in the usual way.[12] The product, mp 78–79°, was obtained in 86% yield from the amino ketone.

Resolution of 1-(3',5'-dibenzyloxyphenyl)-2-(benzyl-*tert*-butylamino)ethanol (2). To a hot soln of racemic **2** (25.0 g, 0.05 mole) in MeOH (375 ml) was added (−)-dibenzoyltartaric acid monohydrate[13-15] (19.0 g, 0.05 mole) in MeOH (125 ml). The mixture was refluxed for 30 min. After evaporation, the residual oil was dissolved in boiling *i*-PrOH and H_2O added until turbidity appeared, followed by a few ml of *i*-PrOH to get a clear soln. The soln was left overnight, and a white cryst product was obtained. This product was recrystd (6 times) from EtOH until the rotation remained const: [α]D −34.2° (*c* 1.0); yield 4.5 g (10%).

(−)-1-(3',5'-Dihydroxyphenyl)-2-(*tert*-butylamino)ethanol Hydrobromide (1). The above-mentioned salt (4.0 g, 0.005 mole) was suspended in H_2O and after addition of NH_4OH, the extraction of the base was performed with Et_2O. HBr (10%) was then added to the Et_2O phase followed by stirring for 1.5 hr. The white cryst product formed was filtered and washed with H_2O and Et_2O to give the hydrobromide of **2**: [α]D +33.3° (*c* 1.0).

This product was dissolved in EtOH (75 ml), 10% Pd/C (0.15 g) was added, and the hydrogenation was performed at room temp for 4 hr and 70 psig. The catalyst was filtered off, and the residue evaporated to dryness. A small amount of EtOH was added to dissolve the product, and then Et_2O was added until turbidity appeared. The cryst ppt was collected and dried (boiling toluene) for 7 hr: [α]D −34.6° (*c* 1.0); yield 1.2 g (86%); mp 241–242°. *Anal.* ($C_{12}H_{19}NO_3 \cdot HBr$) C, H, Br, N.

(+)-1-(3',5'-Dihydroxyphenyl)-2-(*tert*-butylamino)ethanol Hydrobromide (1). The base of **2** (23.7 g, 0.048 mole), derived from the collected supernatants from the preparation of the (−)-**2**, was dissolved in MeOH (250 ml), (+)-dibenzoyltartaric acid (18.2 g, 0.048 mole) in MeOH (250 ml) was added, and the mixture was refluxed for 60 min. The product was then worked up in the same way as described above and recrystd twice from EtOH to give the (+)-dibenzoyltartrate of **2**: [α]D +34.3° (*c* 1.0); yield 10.5 g (25%). The HBr of **2** was prepared from the tartrate in the same way as described above: [α]D −33.0° (*c* 1.0); yield 6.2 g (89%). The hydrogenation of the HBr of **2** (5.5 g, 0.010 mole) was performed as earlier described. Crystallization was from EtOH–Et_2O: [α]D +34.2° (*c* 1.0); yield 2.7 g (93%); mp 241–243°. *Anal.* ($C_{12}H_{19}NO_3 \cdot HBr$) C, H, Br, N.

Pharmacological Assay Methods. Isolated Guinea Pig Trachea. The male guinea pig trachea was prepared according to the procedure of Persson and Olsson.[10] Initial tension was adjusted to 2 g. Relaxations in the muscle were recorded by means of a Grass force displacement transducer (FT 03) and a Grass polygraph. The effect of the racemate, (−) isomer, and (+) isomer was compared to that of adrenaline. Dose–response curves were obtained and concentrations causing 50% relaxation were determined (EC 50).

Isolated Guinea Pig Auricle. Isolated left auricles were prepared from guinea pigs (0.5–0.7 kg) according to the method of Persson and Olsson.[10] Initial tension was adjusted to 1 g. Contractions in the muscle were recorded by means of a force displacement transducer and a Grass polygraph. Dose–response curves were obtained and the concentration causing 20% increase in the force of contraction was graphically determined. The effect of the compounds was compared to that of (−)-adrenaline.

Acknowledgment. The author wishes to thank Dr. H. Persson for the pharmacological tests, Miss L. Knutsson for preparing (+)- and (−)-dibenzoyltartaric acids, and Miss. E. Larsson for measuring the optical rotations.

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Syntheses and Pharmacological Actions of 2-[(2-Chloroethyl)methylamino]ethyl Acetate and Some of Its Derivatives on the Isolated Guinea Pig Ileum†

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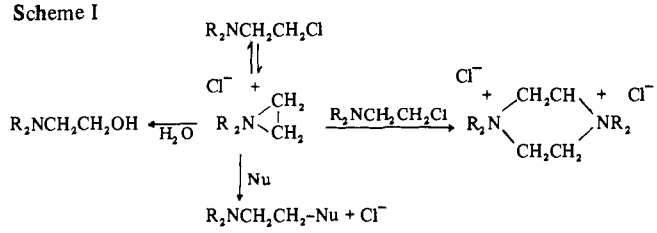
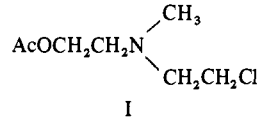
Aziridinium ions, formed from the internal SN2 reaction of tertiary β-haloethylamine precursors, have been shown to be consumed by four reactions:[1-3] reconversion to starting material by reaction with chloride ion; dimerization by reaction with starting material to a piperazinium derivative; hydrolysis to the corresponding alcohol and reaction with other nucleophiles present (Scheme I).

We recently reported[4] that aqueous solutions of 2-[(2-chloroethyl)methylamino]ethyl acetate consume sodium thiosulfate[5] and liberate chloride ion. These observations

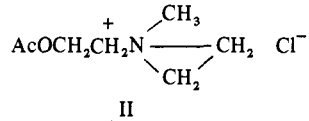
Scheme I



imply that this compound is capable of isomerizing to 1-(2-hydroxyethyl)-1-methylaziridinium chloride acetate II, an aziridinium analog of acetylcholine. As solutions of I are potent spasmogens of the guinea pig ileum,[4,6] we have suggested that the species II is of importance to the stimulant action of I.

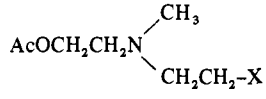


I

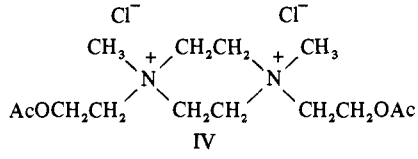


II

In order to confirm this proposal we have examined the potencies of the degradation products of II and some related compounds. By analogy with Scheme I the aziridinium ion may be hydrolyzed to 2,2′-(methylimino)diethanol acetate IIIa or dimerized to 1,4-bis(2-hydroxyethyl)-1,4-dimethylpiperazinium dichloride diacetate IV. The potencies of these compounds were investigated. As a means of indirectly assessing the activity of the uncyclized 2-chloroethylamine I, the methiodide salt Va was prepared and bioassayed. Also examined were 2,2′-(methylimino)diethanol diacetate IIIb and its methiodide salt Vb, the methiodide salt of IIIa, Vc, and 1-aziridineethanol acetate VI, the nor derivative of II.



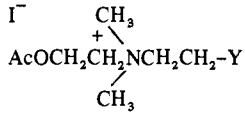
IIIa, X = OH
IIIb, X = OAc



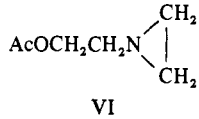
IV

Results and Discussion

Table I summarizes the activity of the compounds tested on the guinea pig ileum in the form of equipotent molar ratios (EPMR), against acetylcholine iodide as the standard drug.



Va, Y = Cl
Vb, Y = OAc
Vc, Y = OH



VI

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