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X-ray analysis of Th 1165a* and salbutamol†

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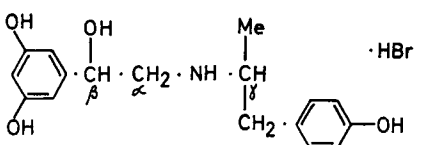
Two drugs, Th1165a* and salbutamol,† having a promising potential as bronchodilators and producing low cardiac stimulation, have been examined for their structural features. These were found to be similar and have been noted as possibly characteristic of the particular β_2-adrenoceptor site. Th1165 consists of two enantiomers possessing an (*R*–*R*) or (*S*–*S*) configuration about the two centres of asymmetry.

Sympathomimetic amines which stimulate the β-adrenoceptors in the respiratory smooth muscle producing bronchodilation are widely used in the treatment of asthma. Unfortunately these drugs, while acting as bronchial relaxants, also have the undesirable tendency to stimulate the cardiovascular system. Therefore, during the development of new bronchodilators for use in the treatment of asthma, it became necessary to obtain drugs that would retain the ability to act as bronchial relaxants (i.e. stimulate the β_2-adrenoceptors), but which had little effect on the cardiovascular system (i.e. β_1-adrenoceptors).

Two such drugs which have only recently been developed and satisfy both these requirements, are Th1165a and salbutamol.

(±)-1-(3,5-Dihydroxyphenyl)-2{[2-[3-(4-hydroxyphenyl)]propylamino]}ethanol hydrobromide was synthesized in the laboratories of C. H. Boehringer Sohn, Germany. The initially available hydrochloride (Th1165) was replaced by the hydrobromide (Th1165a) which exists as an odourless, bitter-tasting, white crystalline powder only slightly soluble in ethanol. This compound (I) was prepared as a derivative of orciprenaline and found to be a sympathomimetic agonist of much greater effectiveness than the parent compound (O'Donnell, 1970; Young, 1971, personal communication).

Crystals of Th1165a, (I), as rectangular prisms, were obtained from aqueous ethanol. The space group for (I) was determined from spectral absences as $P2_1/c$; Unit-cell dimensions are a = 0·8713 (3), b = 1·7347 (8), c = 1·3978 (6) nm and $\beta = 124{\cdot}93(6)^\circ$, Z = 4, $\rho_{obs} = 1{\cdot}48$ g cc^{-1}; $\rho_{calc} = 1{\cdot}47$ g cc^{-1}.



I

Intensity data and unit-cell dimensions were obtained on a Siemens automatic single crystal diffractometer using CuK_α radiation and nickel attenuators. The integrated intensities were recorded using the four value method (Hoppe, 1965;

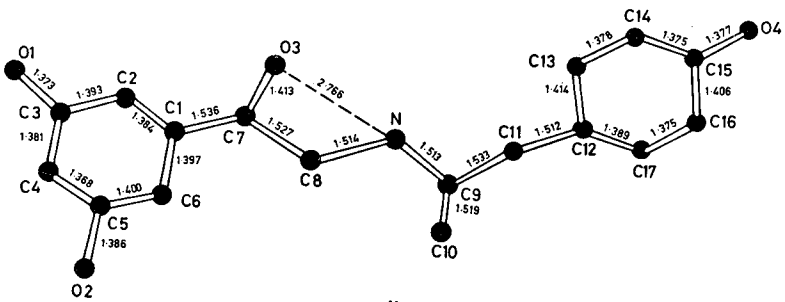
* (±)-1-(3,5-Dihydroxyphenyl)-2-{[2-[3-(4-hydroxyphenyl)]propylamino]}ethanol hydrobromide.

† (±)-α-[(t-Butyl(amino)methyl]-4-hydroxy-*m*-xylene-α^1,α^3-diol (AH 3365).

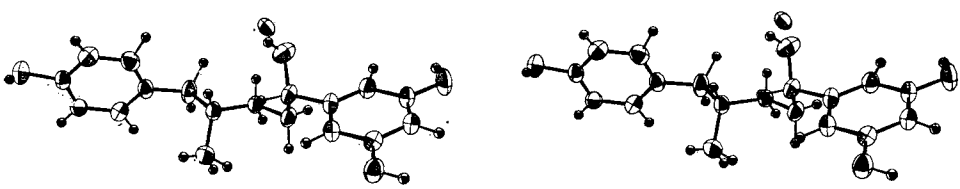
Craig, 1971, personal communication). The scanning procedure utilized the moving crystal-moving detector method ($\theta/2\theta$ scan) (Arndt & Willis, 1966), with the scan range varying between 1·0° at low θ to 3·0° at a θ of 70°, the limit of the diffractometer. The structure was solved using the Patterson and heavy atom methods and refined to a final discrepancy (R) factor of 0·050.

The molecule (I) has two asymmetric carbon atoms and four stereoisomers are possible. One racemic pair, designated as Th1165, is 9 to 20 times more active than the other racemate Th1179.

The results of the present structural study are depicted in (II) whilst the configuration about each of the asymmetric carbon atoms C(7) and C(9) is more clearly seen in the stereo diagram (III). Each configuration can be described as *R* (or *S*), depend-



II



III

ing upon which isomer of the racemic compound is referenced. This result is significant, since the *laevo* (−) isomers of adrenaline and noradrenaline, which are the active isomers when compared with the *dextro* (+) forms, each have an *R* configuration about the β-carbon atom. It may be implied that the active component of the Th1165 racemate is the isomer with an *R* configuration about each of the asymmetric carbon atoms C(7) and C(9), viz. the *R*–*R* isomer.

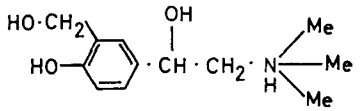
The other racemic form, Th1179, contains 50% of molecules with an *R* configuration about the β carbon atom. However, the other centre of asymmetry in these molecules has an *S* arrangement of substituent groups and the compound therefore contains *R*-*S* and *S*-*R* isomers in equal proportions.

A conformational feature which is common to ephedrine (Phillips, 1950) isoprenaline (Mathew & Palenik, 1971), noradrenaline (Carlstrom & Bergin, 1967) and Th1165 is the *cis* positioning of the amino and hydroxyl groups of the ethyl side chain. The N–O distances are short, indicating possible intramolecular hydrogen bonding or dipole interaction. This conformation may be of prime importance since all four compounds are strong β-adrenoceptor stimulants.

(±)-α-[(t-Butylamino)methyl]-4-hydroxy-*m*-xylene-α^1,α^3-diol (Salbutamol, AH3365) is one compound of a new series of β-adrenoceptor stimulants which have been found to have a considerably greater action on bronchial smooth muscle than on other

smooth muscles affected by β-stimulants, such as the catecholamines and their derivatives (Brittain, Farmer & others, 1968; Hartley, Jack & others, 1968).

Salbutamol (IV) is a white powder which is slightly soluble in water. Rectangular crystals were obtained by recrystallization of (IV) from water. The space group for

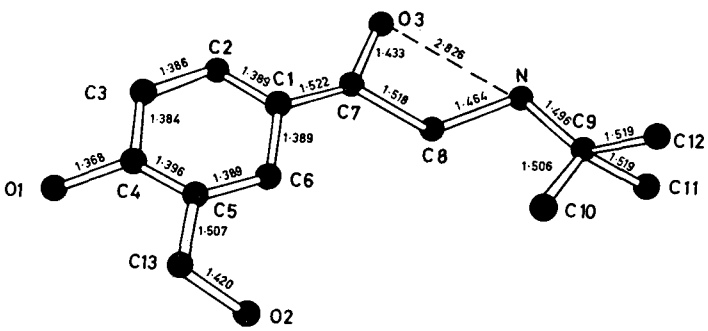


IV

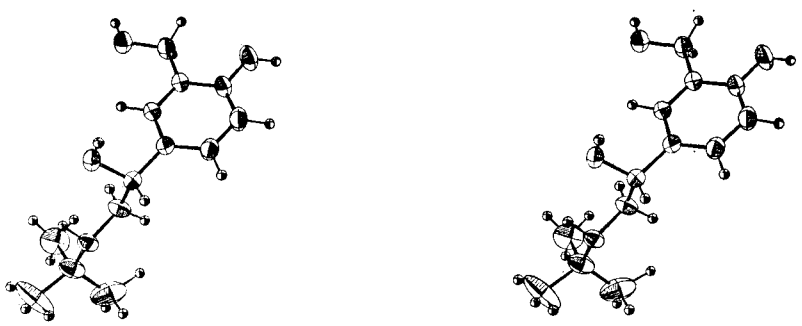
(IV) as determined from systematic spectral absences is Pbca; the unit-cell dimensions are a = 2·1654 (10), b = 0·8798 (4), c = 1·4565 (7) nm; Z = 8; ρ_{obs} = 1·15 g cc^{-1}, ρ_{calc} = 1·145 g cc^{-1}.

The intensity data for crystal structure analysis were collected using procedures similar to those employed in collecting data for Th1165. A total of 2644 independent reflections were measured and used in the final structure analysis. This structure was solved using direct phasing methods which employed a procedure only recently developed in this laboratory (Grainger, 1971: personal communication).

The results of this structural investigation are summarized in V and VI.



V



VI

Salbutamol molecules exhibit the same *cis* orientation of amino and hydroxyl groups as observed with Th1165. The N . . . O distance (0·2826 (2) nm) is in fact a little larger than the corresponding distance (0·2766 (3) nm) in Th1165. The benzene ring is inclined at 74·5 (2)° to the plane of the C(7)-C(8)-N-C(9) atoms, whilst in the Th1165 molecule this angle is 66·9 (3)°. The tertiary butyl group is on the *opposite* side of the salbutamol molecule to the amino and hydroxyl groups. The

Th1165 molecule has the substituent group on the nitrogen atom on the *same* side of the molecule as the amino and hydroxyl groups and therefore in closer proximity to the receptor site. The absolute configuration of this substituent group would be expected to have a direct bearing on the activity of the compound, and has been noted above.

An additional feature of salbutamol is the close planarity of the benzene ring and the substituted $-H_2C-O-H$ group. In the case of the catecholamines and their derivatives the hydroxyl groups and aromatic ring must form a planar arrangement. However, the substitution of the $-CH_2-OH$ group on the aromatic ring would normally favour a repulsion of this end hydroxyl group out of the plane of the aromatic system. Indeed, with salbutamol, close planarity is preserved even to the hydroxyl hydrogen.

Finally, and perhaps the most important feature of these compounds, is the orientation of the C–OH bond on the β-carbon atom with respect to the plane of the phenyl ring. It has been previously stated (Kier, 1968, 1969) that the α-adrenoceptor is stimulated when the C–OH bond is coplanar with the phenyl ring. From our results the C–OH bond is orientated at 48·3° and 45·2° to the phenyl ring in Th1165 and salbutamol respectively. It may therefore be inferred that β-stimulation is promoted when this C–OH bond is directed out of the molecular plane containing the catechol nucleus. However, the conditions for maximum β-stimulation and final confirmation of the relations presented above, must await further analyses.

The points developed in the foregoing discussion, while strictly confined to the solid state, have been interpreted with respect to the solution state. Such an interpretation has been shown to be valid for similar type compounds, such as ephedrine and noradrenaline (Kier, 1968, 1969). Moreover, it is to be anticipated that such comprehensive and systematic structural studies as described above, will lead not only to identification of those structural features necessary for activity, but eventually to the nature and the very identity of the receptor involved in initiating the response.

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