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Conformational Analysis of *Beta*$_2$-Adrenoceptor-Stimulating Agents

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SUMMARY

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The conformation of 2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol, a very potent *beta*-adrenoceptor-stimulating agent, was analyzed in solution by proton relaxation techniques. This compound seems to take two equilibrium conformations, one of which corresponds to that of the crystalline state. Furthermore, the conformational analysis of isoetharine and several *beta*$_2$-adrenergic-stimulating agents made it possible to restrict three dihedral angles so that the molecule was *beta*$_2$-active. Restricting these three dihedral angles unequivocally settles the stereochemical arrangement of all functional groups involved in *beta*$_2$-stimulants, two catechol hydroxyls, benzylic hydroxyl, and two N^+—H bonds.

INTRODUCTION

The authors and their co-workers (1-3) have recently reported the syntheses of potent *beta*-adrenoceptor-stimulating 2-amino- or 2-substituted amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**1**) and have shown that the *N,O-trans* isomer was more active than the *N,O-cis* isomer. Crystal structure analysis of the *N,O-trans*-2-cyclobutylamino derivative (**1b**) (4) and NMR study of the *N,O-trans*-2-isopropylamino derivative (**1a**) in solution (5) indicated that the cyclohexene portion of their tetralin skeleton takes a half-chair conformation and that the benzylic hydroxy and the alkylamino groups are orientated pseudo-diequatorially in both solid and solution states. This evidence implies that this conformation is preferred by the *N,O-trans* isomer of **1** regardless of the environment around the molecule (Fig. 1).

Crystal structure analysis of **1b** led to additional interesting information about the conformational requirement for the elicitation of *beta*$_2$-adrenoceptor-stimulating activity. Comparison of the crystal structure with that of catecholamines such as isoproterenol (**3**) and norepinephrine showed that the orientation of the three functional groups of **1b**, the catechol moiety, benzylic hydroxy, and alkylamino groups, was the same around the C-1—C-2 or C-β—C-α bond. This result supports the hypothesis of Patil *et al.* (6) that the steric arrangement of functional groups plays an important role in producing the pharmacological effect. Furthermore, the cyclobutylamino group of **1b** and the isopropylamino group of one of the two conformers[1] of **3** (7) had similar conformations around the C-2—N^+ bond and the N^+—C-11 bond, the bond between the protonated nitrogen atom and the methine carbon atom of the cyclobutyl or isopropyl group. Because of the potent *beta*$_2$-adrenergic-stimulating activity of these two compounds, the common feature around the three bonds C-1—C-2, C-2—N^+, and N^+—C-11 was assumed to be needed for their access to the receptor. However, conformational analysis of the isopropylamino derivative of **1** (**1a**), also a potent *beta*$_2$-agonist, based on measurement of the proton relaxation time (5) suggested that in solution the alkylamino side chain was in two equilibrium conformations; one of these conformations resembled that of **1b** or those of two conformers of **3** (A and B) with respect to the C-1—C-2 and C-2—N^+ bonds but were somewhat different around the N^+—C-11 bond.

There arises another question concerning the orientation of the side chain at C-2. Mardle *et al.* (8) have reported on the optical resolution and biological activity of the isomers of isoetharine, which has an ethyl substituent on the α-carbon atom, C-2, of isoproterenol. According to their study, racemic *erythro*-isoetharine (**2a**) was approximately 100 times more potent than racemic *threo*-isoetharine (**2b**) in *beta*$_2$-adrenoceptor-stimulating action. The absolute configuration at the *beta*- and *alpha*-positions of the *erythro* isomer is (*R,S*) or (*S,R*), and that of the *threo* isomer is (*R,R*) or (*S,S*). Although *beta*- and *alpha*-positions in **2** correspond with positions 1 and 2 (C-1 and C-2), respectively, of **1**, the (*R,R*) or (*S,S*) isomer, the *N,O-trans* isomer of **1**, has 10 to 100 times more potent *beta*$_2$-activity than the *N,O-cis*, (*R,S*), or (*S,R*) isomer, presenting an apparently conflicting result. The present research was undertaken to solve these problems. As the conformational analyses of the solid state and that of the solution state described above were performed on different compounds, **1b** and **1a**, respectively, conformational analysis of the solution state of **1b**

[1] Two molecules of **3** existed in an asymmetrical unit and were defined as A and B, respectively, according to ref. 7.

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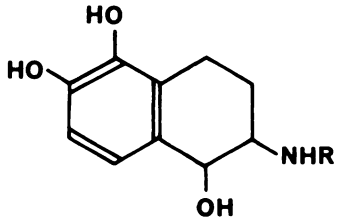

FIG. 1. *2-Alkylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol*

1a, *R* = isopropyl(*N,O-trans*); **1b**, *R* = cyclobutyl(*N,O-trans*); **1c**, *R* = *tert*-butyl(*N,O-trans*).

as determined by X-ray diffraction techniques may afford information to help solve the first problem. For insight into the second problem, conformational investigation of **2** should yield the most information. However, isoetharine, **2**, does not afford a suitable crystal for X-ray analysis; furthermore, it has too many flexible portions to be analyzed by NMR relaxation time method (5). Therefore, we checked the possible conformations of **2** with a hard-sphere molecular model and obtained some interesting information.

MATERIALS AND METHODS

Proton relaxation time (T_1) measurements were carried out in Fourier transform by the inversion recovery method at 100 MHz with a Varian XL-100-12 spectrometer. The sample was lyophilized twice in ^2H_2O and dissolved in dimethyl sulfoxide-d_6 (0.2 M). The solution was degassed on a vacuum line to eliminate the effect of dissolved oxygen, and the measurement tube was then sealed under oxygen-free nitrogen gas. T_1 values were deduced by least-squares fit of a semilogarithmic plot of the recovery of the proton longitudinal magnetization as a function of the time separation between the 180° and 90° pulses; temperature was 40°.

Data were calculated with IBM-360/48 and JEC-6 (JEOL Company) computers.

RESULTS

Conformation of 2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (1b). Conformational analysis of **1b** [absolute configuration: (1*R*,2*R*)] was done by measuring the proton relaxation time as reported in a previous paper (5). The atoms and the torsional angles were numbered as in previous papers (4, 5) (Fig. 2A). The absolute value of the torsional angle was defined according to the definition of Hearn et al. (9).[2] Because of the low solubility of **1b** in water, dimethylsulfoxide-d_6 was used as the solvent. In the NMR spectrum of **1b**, the signals of H-3 and H-4 appeared to overlap those of cyclobutyl protons, and accurate measurement of the relaxation time (T_1) for H-3 and H-4 was impossible. Comparison of the structure of **1b** with that of **1a** showed that the difference was only at the terminal of the alkylamino group and should have little influence on the T_1 values for H-3 and H-4. Thus, their T_1 values were estimated by multiplying the T_1 values for H-3 and H-4 in **1a** with the ratio of the T_1 values of **1b** to **1a** concerning H-1, H-7, and H-8, which were obtainable for both compounds.

[2] For the molecular structure of *beta*-stimulants, the molecule having the (*R*) configuration at C-1 was used throughout the present study.

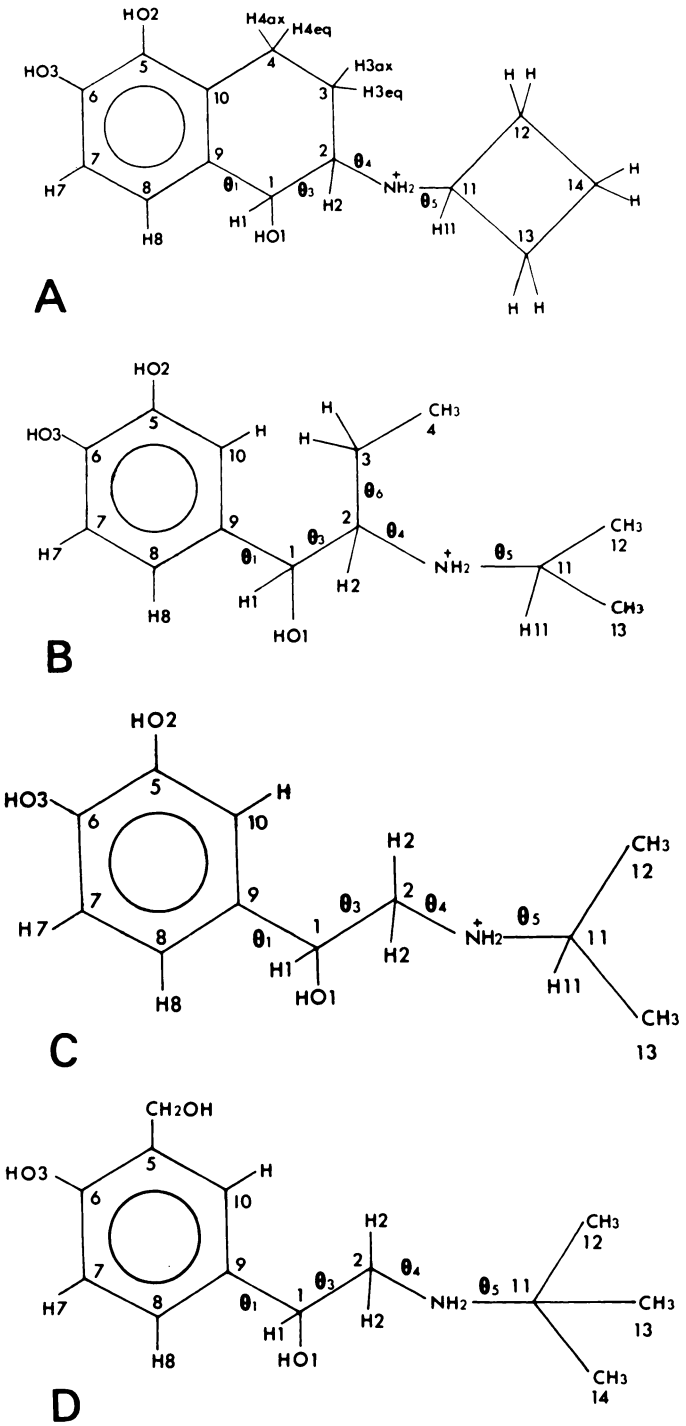

FIG. 2. *Atomic numbering systems and torsional angles*

A. Molecule **1b**: θ_1, C-8—C-9—C-1—O-1; θ_3, C-9—C-1—C-2—N^+; θ_4, C-1—C-2—N^+—C-11; θ_5, C-2—N^+—C-11—H-11.

B. Molecule **2**: θ_1, C-8—C-9—C-1—O-1; θ_3, C-9—C-1—C-2—N^+; θ_4, C-1—C-2—N^+—C-11; θ_5, C-2—N^+—C-11—H-11; θ_6, C-1—C-2—C-3—C-4.

C. Molecule **3**: θ_1, C-8—C-9—C-1—O-1; θ_3, C-9—C-1—C-2—N^+; θ_4, C-1—C-2—N^+—C-11); θ_5, C-2—N^+—C-11—H-11.

D. Salbutamol: θ_1, C-8—C-9—C-1—O-1; θ_3, C-9—C-1—C-2—N^+; θ_4, C-1—C-2—N^+—C-11; θ_5, C-2—N^+—C-11—C-12.

The coupling pattern of H-2 in the NMR spectrum of

TABLE 1

Two minimial points of R values[a]

Conformer	θ_4	θ_5	R
A	155°	45°	0.19
B	70	−30	0.17

[a] Reference 5. R represents the degree of coincidence between the calculated and the observed relaxation times.

1b in dimethyl sulfoxide-d_6 closely resembled that in **1a** in ^2H_2O. Consequently, the cyclohexene portion of the tetralin ring was assumed to have a similar half-chair conformation, with both the benzylic hydroxy and the substituted amino groups occupying diequatorial positions. Therefore, for calculation of τ_c, the coordinates of the carbon atoms, a nitrogen atom, and the oxygen atoms were determined according to those of the crystal data of **1b** (4). The coordinates of the hydrogen atoms were also rationally estimated mainly on the basis of the crystal data. The coordinates of two hydrogen atoms bonded to C-3 were corrected to have a normal C—H bond length (1.09 A) and bond angle (109.5°). As for the other hydrogen atoms, the crystal data were employed. The torsional angles with respect to C-2—N^+ (θ_4) and N^+—C-11 (θ_5) bonds connecting the tetralin portion with the cyclobutyl ring were rotated independently with an increment of 5°, as was done in the case of **1a**, and τ_c values were calculated for the protons on the tetralin ring. An R map, which expresses the degree of coincidence between the calculated and the observed relaxation times, was drawn with respect to these angles. Two minima were located on the map, as in the case of **1a** (5) (Table 1).

As **1a** and **1b** have very similar alkylamino side chains, **1b** is probably in equilibrium between two conformers, A and B, by analogy with **1a**. The observed and calculated spin-lattice relaxation times of the two conformers are listed in Table 2. Table 3 shows the conformation of **1a** (5) and **1b** in solution and of **1b** (4) and **3** (7) in the crystalline state with respect to the three torsional angles, θ_3, θ_4, and θ_5. The θ_3 angle of **3** is not very different from that of **1**. As for the θ_4 angle, a good coincidence was observed for **1a** (A) and **1b** (A) in solution and for **1b**

TABLE 2

Calculated and observed spin-lattice relaxation time and correlation time

Proton	$(T_1)^{-1}_{obs}$	$(T_1)^{-1}_{calcd}$	
		Conformer A	Conformer B
	sec	*sec*	*sec*
H-1	2.02	1.64	1.96
H-2	2.47	3.53	3.70
H-3ax	8.12[a]	10.03	8.61
H-3eq	7.70[a]	8.78	8.53
H-4ax	6.62[a]	5.95	5.82
H-4eq	6.62[a]	6.04	5.92
H-7	1.54	1.22	1.21
H-8	1.48	1.59	1.59
τ_c ($\times 10^{-10}$)		2.34	2.30

[a] Calculated from $(T_1)^{-1}$ value of **1a** (5).

TABLE 3

Conformation of 1 and 3

Compound	Conformer	θ_3	θ_4	θ_5
1a	A (solution)	167°[a]	160°	10°
1a	B (solution)	167[a]	70	−10
1b	A (solution)	167[a]	155	45
1b	B (solution)	167[a]	70	−30
1b	(crystal)	167	168	59
3	A (crystal)	175	−156	52
3	B (crystal)	−177	172	−62

[a] The torsional angles, θ_3, of **1a** and **1b** are the same because the crystal datum of **1b**, 167°, was used for the calculation of **1a** and **1b** in solution.

and **3** (B) in the crystal state, although some differences with the other molecules represented in Table 3 were observed. With respect to θ_5, **1a** (A) and **1b** (A) were different, but **1b** (A) very closely resembled **1b** and **3** (A) in the crystal state. As a whole, the conformer A of **1b** was very similar to that of **1b** in the crystal state.

Conformation of erythro (2a) and threo (2b) isoetharine. A small degree of freedom for molecule **1** enabled us to calculate the atomic coordinates for all possible conformations by changing the two single bonds. In contrast, many variables are involved in the side chain of **2**, and obtaining a conclusive result is difficult from conformational analysis using the spin-lattice relaxation time as discussed for **1a** and **1b**. However, as the hydroxy, ethyl, and isopropylamino groups are clustered on the side chains of **2a** and **2b**, there will be a number of improbable conformations from the view of steric hindrance. Thus, by using a hard-sphere molecular model constructed with a computer program, we examined whether **2a** and **2b** could take conformations similar to those which are assumed to be important for elicitating *beta*$_2$-stimulating activity.

The atomic numbering system and torsional angles of **2** correspond to those previously reported (4, 5) and to **1b** as shown in Fig. 2B. The minimum-pair contact distances of Barry *et al.* (10) were adopted to evaluate steric interactions. The protons in the three *methyl* groups were fixed in the staggered form. With respect to the torsional angle, θ_3, the phenyl and the alkylamino groups were *trans* around the C-1—C-2 bond in all *beta*-adrenergic-stimulants analyzed thus far by X-ray techniques (4, 9, 11, 12). The NMR study of epinephrine and **3** have also indicated that this conformation is preferential in solution (13). In the case of **2a**, the coupling constant between H-1 and H-2 has been reported to be 3 Hz (8), indicating the *gauche* orientation of these

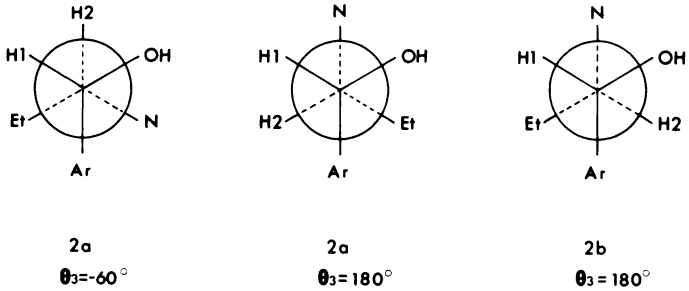

FIG. 3. *Newman projections of 2a and 2b about the C-α—C-β bond*

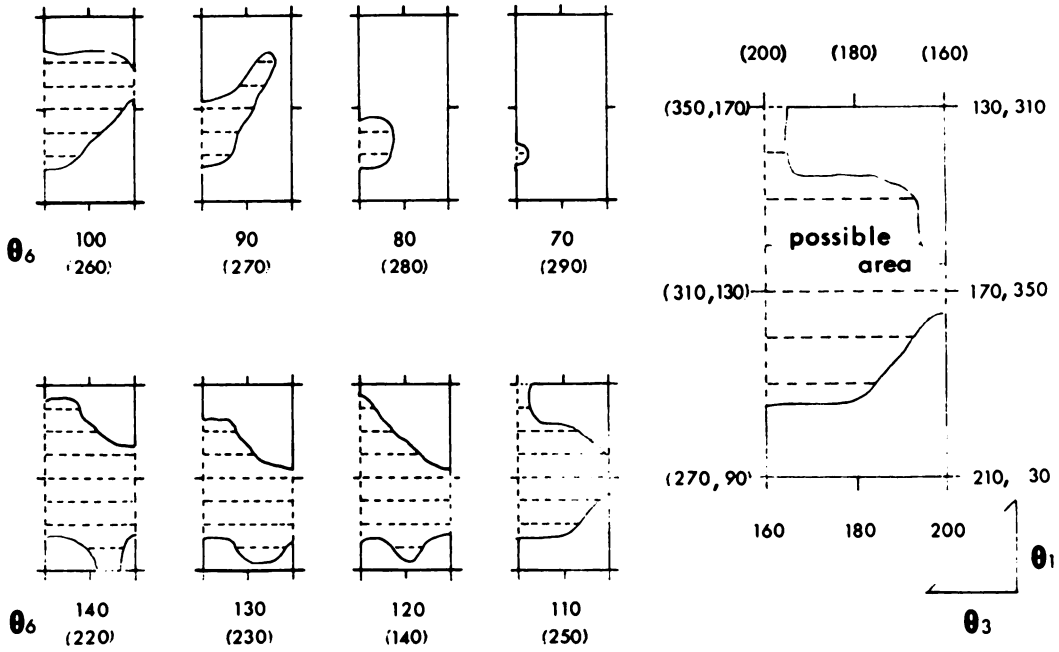

FIG. 4. *Possible areas of conformations for* **2a** *and* **2b**
Numbers in parentheses indicate the torsional angles (degrees) of **2b**.

TABLE 4
Possible conformers of **2**

Compound	θ_1	θ_3	θ_4	θ_5	θ_6
2a	150–200° 330–0–20	160–200°	180–210°	290–0–20°	90–130°
2b	100–150 280–330	160–200	150–180	340–0–70	230–270°

protons. Here the phenyl and alkylamino groups may be *gauche* ($\theta_3 = -60°$) or *trans* ($\theta_3 = 180°$) (Fig. 3), but the former conformation will be unfavorable because the phenyl group is crowded between the ethyl and bulky isopropylamino groups. The corresponding coupling constant of **2b** has been reported to be 8 Hz (8), indicating that H-1 and H-2 are *trans* ($\theta_3 = 180°$) and that the phenyl and alkylamino groups are *trans*. Thus, both **2a** and **2b** seem to take a similar conformation around C-1—C-2, with θ_3 being approximately 180°. Therefore, by limiting θ_3 to 180 ± 20°, θ_4 and θ_5 were changed in the range of 150–210° and 290–70°, respectively, to find the sterically possible conformations.[3] No restriction was imposed on θ_1 and θ_6. In **2a**, however, for θ_6, angles of 0–60°, 150–300°, and 300–360° were found to be impossible because of collision of the ethyl group with the aromatic, isopropyl, and benzylic hydroxy groups, respectively, regardless of θ_1, provided that θ_3, θ_4, and θ_5 were within the limited range given above. On setting θ_6 to 70–140°, the possible areas with regard to θ_1 and θ_3 and to θ_4 and θ_5 are shown in Figs. 4 and 5, respectively. Similarly, for **2b** the same values were obtained from θ_1, θ_3, θ_4, and θ_5; the θ values are given in parentheses. On the basis of these figures, the regions of θ angles within which **2a** and **2b** molecules were thought to exist favorably and energetically were chosen and are listed in Table 4.

[3] The θ angles were changed in increments of 10° for **2**.

DISCUSSION

Figure 6 shows θ_4 and θ_5 of molecules **1b** (4), **3** (7), and salbutamol (12) in the crystal state and of **1a** (5) and **1b** in solution. In the case of salbutamol, the substituent on the nitrogen atom is a *tertiary* butyl group having no C-11—H bond. Therefore, one of the three C-11—CH_3 bonds was used to estimate θ_5 as a substitute for C-11—H. The two equilibrium conformers of **1a** and **1b** in solution, determined by measurement of the proton relaxation time, and the two different molecules constructing an asymmetrical unit in crystals of **3** and salbutamol are shown as *A* and *B* in Fig. 6. Disorder of salbutamol molecule *A* is shown by *A* and *A'*.

The so-called antiperiplanar orientation (11), θ_3, $\theta_4 \simeq 180°$, which the strong $beta_2$-agonists **3** and **1b** preferably take in both solid and solution form, is accessible to both **2a** and **2b** without any steric hindrance. However, in this orientation, $beta_2$-active **2a** cannot take $\theta_5 \simeq 60°$, at which most of the other $beta_2$-stimulants shown in Fig. 6 exist. In contrast, this angle is feasible for the $beta_2$-inactive isomer **2b**. These results suggest that θ_5 plays a small role in the elicitation of $beta_2$ activity. In fact, the replacement of the isopropyl group on the nitrogen atom by *tertiary* butyl, in which no C-11—H bond exists, enhances the $beta_2$ activity, leading to a more $beta_2$-selective agonist. From these considerations, the difference in $beta_2$ activity between **2a** and **2b** was not explainable by the conformations of θ_3, θ_4, and θ_5.

Figure 7 shows the torsional angle between the plane of the catechol ring and that formed by C-9—C-1—O-1 (θ_1). Crystallographic data for **1b** are also given in Fig. 6. The symbol ◉ represents *meta* (O-2) and *para* (O-3) oxygen atoms on the catechol ring. *Broad circles* illustrate the possible areas taken by *meta* oxygen atoms of **2a** and **2b**. Open-chain catecholamines, such as isoproterenol and epinephrine, or salbutamol can rotate freely around their benzylic bonds (no limitation on θ_1). Since

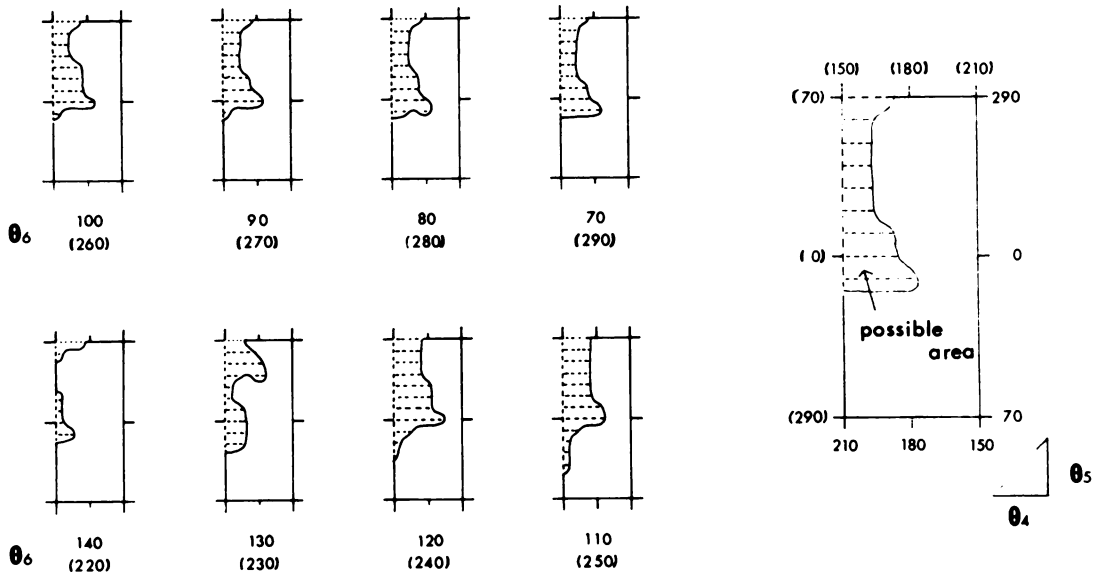

FIG. 5. *Possible areas of conformations for* **2a** *and* **2b**
Numbers in parentheses indicate the torsional angles (degrees) of **2b**.

1b has very potent *beta*$_2$ activity, racemic **1b** being about 24 times stronger than *l*-isoproterenol, and since it has a rigid structure with respect to θ_1, the plane angle of this compound, $\theta_1 \simeq 50°$, will be assumed to fit exactly on the receptor. If we suppose, therefore, that θ_1 is an important factor in the elicitation of *beta*$_2$ activity and is required to be within the range from 0 to 60°, the *beta*$_2$ activity of **2a**, which can take θ_1 within this range despite an absolute configuration at C-2 which is different from that of the active isomer of **1b**, may be convincingly explained. On the other hand, **2b** will be judged to be inactive because its θ_1 is out of this range even though the configuration at C-2 is the same as that of the active isomer of **1b**. The condition for θ_1 assumed here is further supported by the following evidence. 2-Alkylamino-6,7-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols, synthesized by Thrift (14), have a rigid tetralin ring and fixed benzylic hydroxy and alkylamino groups similar to those of **1b**. The only difference from **1b** is in the position of the *meta* hydroxy group, which is located on C-7 in place of C-5 in **1b**. The difference compels θ_1 to be approximately 230°, and the compounds were reported to have no noticeable *beta*$_2$ activity.

There is another difference concerning the structure-activity relationship between *beta*$_2$-stimulants having a tetralin skeleton like **1** and those of open-chain analogues, e.g., *N*-alkyl norepinephrine. The *tert*-butyl group as a substituent on the amino group usually potentiates the *beta*$_2$ activity and increases *beta*$_2$ selectivity in *beta*$_2$-stimulants of an open-chain structure (15). However, the same group reduces the activity to one-twelfth when it replaces the isopropyl group of **1a**.[4] Since such phenomena were also observed in other *beta*-stimulants having a similar tetralin ring (16), the cause of this discrepancy may be attributed to the stereochemical interaction of the *tert*-butyl group with a tetralin skeleton, most probably the hydrogen atoms on C-3, deviating the N^+—H bond direction from the position required to elicit *beta*$_2$ activity ($\theta_4 \simeq 180°$). To confirm this idea, a Van der Waals contact check was conducted for the *N-tert*-butyl derivative of **1**, **1c**. The method used was the same as that used for the analogues **2a** and **2b**, and the possible combinations of θ_4 and θ_5 obtained as a result are shown

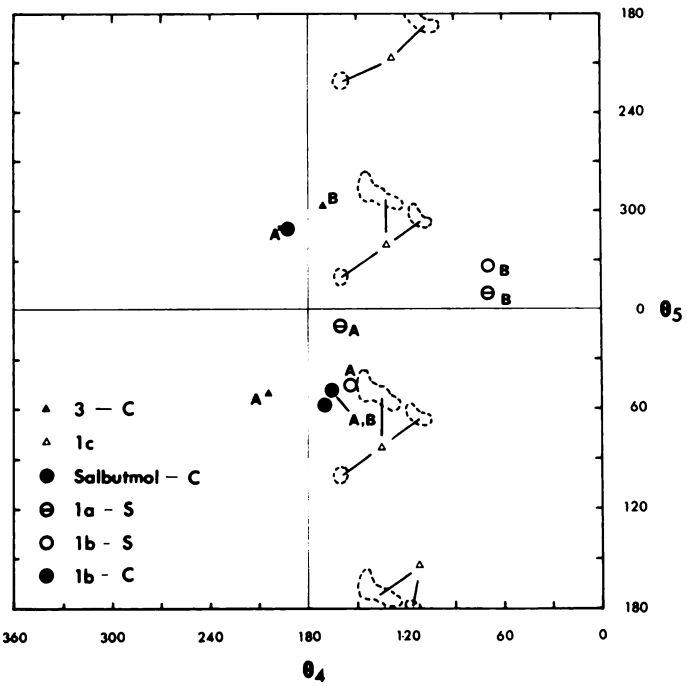

FIG. 6. *Conformation of some adrenergic agonist with respect to* θ_4 *and* θ_5
A (*A'*) and *B* represent the two equilibrium conformers in solution (**1a** and **1b**), or different molecules forming an asymmetrical unit in the crystalline state. *C* and *S* represent crystalline and solution states, respectively. Possible areas for **1c** are also shown.

[4] H. Kuriki, unpublished data.

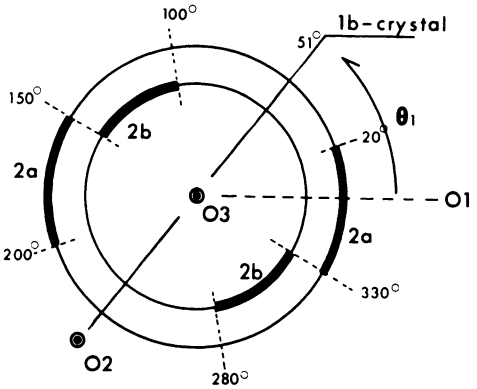

FIG. 7. *Correlation of the torsional angle (θ_1) between the benzylic C-1—O-1 bond and the aromatic ring*

The *center* of two *large circles* represents the C-9—C-1 bond.

in Fig. 6 as *contours* encircled by *broken lines*.[5] In this case also, θ_5 was defined by using a C-11—CH_3 bond instead of a C-11—H bond as in the case of salbutamol. A small area at $\theta_4 = 160°$ and $\theta_5 = 100°$ (or 220° or 340°) was severely limited, and any change of more than 5° in θ_4 or θ_5 led to an impossible structure. Thus the existence of **1c** in this area is improbable. The remaining possible areas were situated more than 30° apart from 180° with regard to θ_4. When $\theta_4 = 180°$, one of the N^+—H bonds was coplanar with C-1—O-1 and the other with C-1—H-1. Such orientation may be important for interaction of the molecule with the $beta_2$-receptor.

In conclusion, in order for the molecule to be $beta_2$-active, θ_1 should be 0-60°, preferably near 50°, and θ_3 and θ_4 should be around 180°. Restricting these three dihedral angles unequivocally settles the stereochemical arrangement of all functional groups involved in $beta_2$-stimulants, two catechol hydroxyls, benzylic hydroxyl, and two N^+—H bonds. We believe that these results provide valuable insight into the structure of the $beta_2$-receptor.

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[5] The θ angles were changed in increments of 5° for **1c**.

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