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Crystal Structure of (±)-*trans*-2-Cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol Hydrobromide

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The crystal structure of (±)-*trans*-2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol hydrobromide, a potent β-adrenergic stimulant, has been determined by X-ray diffraction techniques. The compound crystallizes from water in the triclinic space group $P\bar{1}$ with $a=9.198$ (1), $b=10.472$ (2), $c=8.020$ (1) Å, $\alpha=109.09$ (2), $\beta=78.20$ (1), $\gamma=102.55$ (2)°.

The structure was solved by the heavy atom method, and the final R for 1300 independent reflections measured with a four circle diffractometer was 5.0%. The cyclohexene moiety of the compound is in a half-chair conformation, with both the benzylic hydroxyl and the substituted amino groups occupying diequatorial positions. Comparison of the crystal structure with that of *dl*-isoproterenol sulfate shows that both compounds have similar conformations of the aliphatic side chain moiety, including the alkyl amino side chain.

Keywords——X-ray analysis; crystal structure; amino tetralol; catecholamine; β-adrenergic stimulant; half-chair conformation

Epinephrine, an endogeneous adrenoceptor-stimulating compound, has an aminoethanol side chain in its molecule and may exist in various conformations. On the other hand, the drug receptor in the organism is composed of macromolecules and may have a sterically restricted conformation. Therefore, a particular conformation should be required for a chemical mediator such as epinephrine to be able to bind with the receptor to cause development of β-adrenergic activity. In the nature of things, the required conformation should be one of the stable conformations of the mediator compound. If we can obtain an epinephrine derivative which has a rigid structure and shows potent biological activity, it should be possible to deduce very important information about the stereochemical structure of the epinephrine receptor.

Two of the present authors (M.M. and M.N.) and their co-workers have reported the synthesis of potent β-adrenoceptor-stimulating 2-amino- and 2-substituted amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**), which are cyclic analogs of catecholamines, such as norepinephrine, epinephrine and isoproterenol.[2–4] As compounds **1** have two asymmetric centers in their tetrahydronaphthalene skeleton, at least four optical isomers can theoretically exist regardless of the chemical structure of the side chain, R. We have prepared both O,N-*cis* and *trans* isomers stereoselectively and found that the latter has 10 to 100 times more potent β-adrenoceptor-stimulating action than the former. Furthermore, unexpectedly, the cyclic analog (**1**, R=H) of α-adrenoceptor-directing norepinephrine exhibited a strong β-adrenergic activity while being practically devoid of α-activity. These results suggest that the steric arrangement of the functional groups in **1** is well fitted to the β-adrenoceptor. It

1) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
2) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975).
3) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.*, **25**, 632 (1977).
4) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.*, **25**, 2917 (1977).

was therefore desirable to obtain information about the orientation of the benzylic hydroxyl and substituted amino groups and the conformation of the cyclohexene part of the tetralin skeleton, as an aid to elucidating the structure-activity relationship of these cyclic analogs. This paper describes the crystal structure analysis of (±)-*trans*-2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**1**, R=cyclobutyl, *trans* isomer) hydrobromide (**1a**), which has the most potent β_2-adrenergic activity among the compounds **1** prepared; it is about twenty-four times more active than *l*-isoproterenol in an *in vitro* assay.

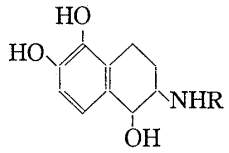

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Chart 1

Experimental

Material——(±)-*trans*-2-Cyclobutylamino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol[4] was hydrogenated and the resulting product was converted into the hydrobromide to give (±)-*trans*-2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol hydrobromide (**1a**). mp 193—196° (dec.). *Anal.* Calcd for $C_{14}H_{19}NO_3 \cdot HBr$: C, 50.92; H, 6.10; N, 4.24. Found: C, 50.58; H, 6.08; N, 4.18.

Crystal and Reflection Data——Colorless prisms of **1a** with dimensions of $0.5 \times 0.4 \times 0.4$ mm were obtained by recrystallization from water in a sealed ampule filled with oxygen-free nitrogen gas. On the basis of Weissenberg photographs, the crystals were assigned to the triclinic system, and from the optical nature and the unit cell volume, the space group was judged to be $P\bar{1}$. Intensity data were collected with a four-circle diffractometer, model AFC-5 (Rigaku Co.) using graphite-monochromated Cu $K\alpha$ radiation. Of 1416 independent reflections measured ($2 \leqq 2\theta < 95°$), 1300 reflections were usable [$F \geqq 3\sigma(F)$]. Unit cell parameters were determined by least-squares analysis of 25 high-angle reflections measured with the diffractometer. Crystal data are listed in Table I. Computation in this study was carried out with IBM 370/48 and JEC-6 (JEOL Co.) computers, mainly with the XRAY76 program.[5]

Table I. Crystal Data

Crystal system	Triclinic
Space group	$P\bar{1}$
Cell dimensions	a = 9.198±0.001 Å
	b =10.472±0.002
	c = 8.020±0.001
	α =109.09±0.02°
	β = 78.20±0.01
	γ =102.55±0.02
Cell volume	712.5±0.2 Å^3
Number of molecules in the unit cell	2
Composition of asymmetric unit	$C_{14}H_{19}O_3N \cdot HBr$
Formula weight	330.2
Calculated density	1.539 g/cm^3

Structure Determination——The heavy atom method was applied to the structure determination. The three-dimensional Patterson map indicated the position of the heavy atom without ambiguity. Electron density synthesis using phase angles of the bromine atoms revealed peaks for all non-hydrogen atoms. After five cycles of block-diagonal least-squares refinement with isotropic temperature factors, the difference Fourier synthesis indicated all peaks due to hydrogen atoms, and no other significant peaks were found. Block-diagonal least-squares refinement was carried out, with isotropic temperature factors for hydrogen atoms and anisotropic ones for the other atoms, until the shift values of parameters became smaller than the standard deviations. A final R value of 0.05 was obtained.

Results and Discussion

The final atomic coordinates and temperature factors are given in Tables II and III. The bond lengths and angles calculated from these atomic coordinates are listed in Table IV.

5) The X-ray system-Version of 1976, J.M. Stewart, Editor, Technical Reports TR-446 of The Computer Science Center, Univ. of Maryland.

Crystal structure, the atomic numbering system and intermolecular hydrogen bondings are shown in Fig. 1.

The planarity of the benzene ring is satisfactory, the deviation from the least-squares plane being less than 0.02 Å (Table V). The substituents on the benzene ring, C(1), C(4), O(2) and O(3), are also in the plane and the deviations are less than 0.07 Å. The atoms C(2) and C(3) are located on opposite sides of the plane, indicating that the cyclohexene ring in the

Table II. Fractional Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^3$) with Their Estimated Standard Deviations for Non Hydrogen Atoms[a)]

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C (1)	2133(9)	9126(8)	3657(10)	30(5)	25(5)	21(5)	6(4)	−0(4)	2(4)
C (2)	1244(9)	7724(8)	2939(11)	18(5)	23(5)	32(5)	−2(4)	5(4)	4(4)
C (3)	2196(10)	6629(8)	2606(12)	34(6)	20(5)	51(6)	3(4)	3(5)	5(4)
C (4)	3482(10)	6809(8)	1098(12)	28(5)	22(5)	41(6)	−4(4)	8(4)	−3(4)
C (5)	5825(9)	8497(8)	0669(11)	31(5)	27(5)	24(5)	6(4)	−1(4)	−2(4)
C (6)	6700(9)	9788(9)	1071(11)	21(5)	36(5)	26(5)	1(4)	4(4)	7(4)
C (7)	6080(10)	10834(9)	2304(11)	32(5)	29(5)	34(5)	−5(4)	−1(4)	−0(4)
C (8)	4624(10)	10593(8)	3153(11)	34(5)	24(5)	33(5)	1(4)	0(4)	−2(4)
C (9)	3744(9)	9310(8)	2743(10)	25(5)	25(5)	22(5)	5(4)	3(4)	2(4)
C (10)	4378(9)	8240(8)	1513(10)	22(5)	29(5)	21(5)	3(4)	1(4)	2(4)
C (11)	−1357(10)	6384(9)	3577(12)	35(6)	24(6)	42(6)	2(4)	7(5)	−3(4)
C (12)	−2356(12)	6675(12)	2474(14)	60(7)	83(8)	38(6)	−17(6)	−17(6)	19(6)
C (13)	−2741(10)	6099(10)	4912(12)	32(6)	43(6)	43(6)	−6(5)	2(5)	15(5)
C (14)	−3703(12)	5918(11)	3466(14)	43(7)	68(8)	48(7)	−8(6)	−4(5)	2(6)
O (1)	1361(6)	10146(5)	3538(7)	32(4)	24(3)	32(3)	9(3)	7(3)	3(2)
O (2)	6421(6)	7454(6)	−0578(8)	31(4)	32(4)	37(4)	5(3)	5(3)	−12(3)
O (3)	8136(6)	9946(6)	0158(8)	28(3)	35(4)	38(4)	1(3)	7(3)	2(3)
N	−0144(7)	7521(6)	4269(8)	21(4)	22(4)	27(4)	1(3)	1(3)	1(3)
Br	0121(1)	7087(1)	8065(1)	37(1)	36(1)	38(1)	−0(0)	−4(0)	5(0)

a) Anisotropic temperature factors are expressed as $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$.

Table III. Fractional Atomic Coordinates ($\times 10^3$) and Thermal Paramers ($\times 10^2$) with Their Estimated Standard Deviations for Hydrogen Atoms

	Bonded to	x	y	z	U
H (1)	C (1)	213(9)	920(8)	499(10)	3(2)
H (2)	C (2)	078(10)	770(9)	180(11)	4(3)
H (3eq)	C (3)	171(13)	588(12)	256(15)	8(4)
H (3ax)	C (3)	266(10)	670(10)	375(12)	5(3)
H (4ax)	C (4)	304(11)	676(10)	−007(13)	7(3)
H (4eq)	C (4)	428(14)	614(12)	107(16)	10(4)
H (7)	C (7)	666(12)	1171(11)	243(14)	8(3)
H (8)	C (8)	422(10)	1144(9)	400(12)	8(3)
H (11)	C (11)	−091(10)	561(9)	316(12)	5(3)
H (121)	C (12)	−218(14)	657(13)	144(17)	11(5)
H (122)	C (12)	−236(12)	771(11)	256(14)	9(4)
H (131)	C (13)	−281(11)	693(10)	593(13)	8(3)
H (132)	C (13)	−272(10)	529(9)	550(12)	6(3)
H (141)	C (14)	−384(14)	493(13)	306(16)	11(4)
H (142)	C (14)	−476(12)	629(11)	378(14)	8(4)
H (15)	O (1)	158(12)	1027(11)	238(14)	8(4)
H (16)	O (2)	730(13)	764(11)	−081(15)	9(4)
H (17)	O (3)	839(13)	1056(11)	019(15)	8(4)
H (181)	N	050(10)	744(9)	530(11)	6(3)
H (182)	N	−049(9)	824(8)	468(11)	6(3)

tetalin takes a half-chair conformation. A similar conformation has been reported for *trans*-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene.[6]

Figure 1 shows that the benzylic hydroxyl and the cyclobutylamino groups are orientated pseudo-di-equatorially. Around the C(1)—C(2) bond, the aromatic group is *trans* (167°) to

Table IV. Bond Lengths (Å) and Angles (degree) with Their Estimated Standard Deviations

Atoms	Length	Atoms	Angle	Atoms	Angle
C (1)-C (2)	1.51(2)	C (9)-C (1)-C (2)	114.1(6)	C (7)-C (8)-C (9)	122.0(7)
C (1)-C (9)	1.51(1)	C (9)-C (1)-O (1)	110.1(7)	C (1)-C (9)-C (8)	119.5(7)
C (1)-O (1)	1.44(2)	C (2)-C (1)-O (1)	109.2(7)	C (1)-C (9)-C (10)	122.4(7)
C (2)-C (3)	1.51(2)	C (1)-C (2)-C (3)	110.4(7)	C (8)-C (9)-C (10)	118.1(7)
C (2)-N	1.51(1)	C (1)-C (2)-N	109.0(6)	C (4)-C (10)-C (5)	121.0(7)
C (3)-C (4)	1.54(2)	C (3)-C (2)-N	110.4(7)	C (4)-C (10)-C (9)	119.8(7)
C (4)-C (10)	1.51(2)	C (2)-C (3)-C (4)	107.1(8)	C (5)-C (10)-C (9)	119.1(7)
C (5)-C (6)	1.39(2)	C (3)-C (4)-C (10)	112.4(6)	C (12)-C (11)-C (13)	90.3(8)
C (5)-C (10)	1.38(1)	C (6)-C (5)-C (10)	122.4(7)	C (12)-C (11)-N	116.1(9)
C (5)-O (2)	1.35(2)	C (6)-C (5)-O (2)	118.7(7)	C (13)-C (11)-N	117.3(7)
C (6)-C (7)	1.35(2)	C (10)-C (5)-O (2)	118.8(7)	C (11)-C (12)-C (14)	87.1(9)
C (6)-O (3)	1.38(1)	C (5)-C (6)-C (7)	118.2(7)	C (11)-C (13)-C (14)	87.3(8)
C (7)-C (8)	1.38(1)	C (5)-C (6)-O (3)	118.3(7)	C (12)-C (14)-C (13)	89.6(8)
C (8)-C (9)	1.38(2)	C (7)-C (6)-O (3)	123.5(7)	C (2)-N -C (11)	115.9(6)
C (9)-C (10)	1.38(2)	C (6)-C (7)-C (8)	120.0(7)		
C (11)-C (12)	1.53(2)				
C (11)-C (13)	1.53(2)				
C (11)-N	1.49(2)				
C (12)-C (14)	1.54(2)				
C (13)-C (14)	1.54(2)				

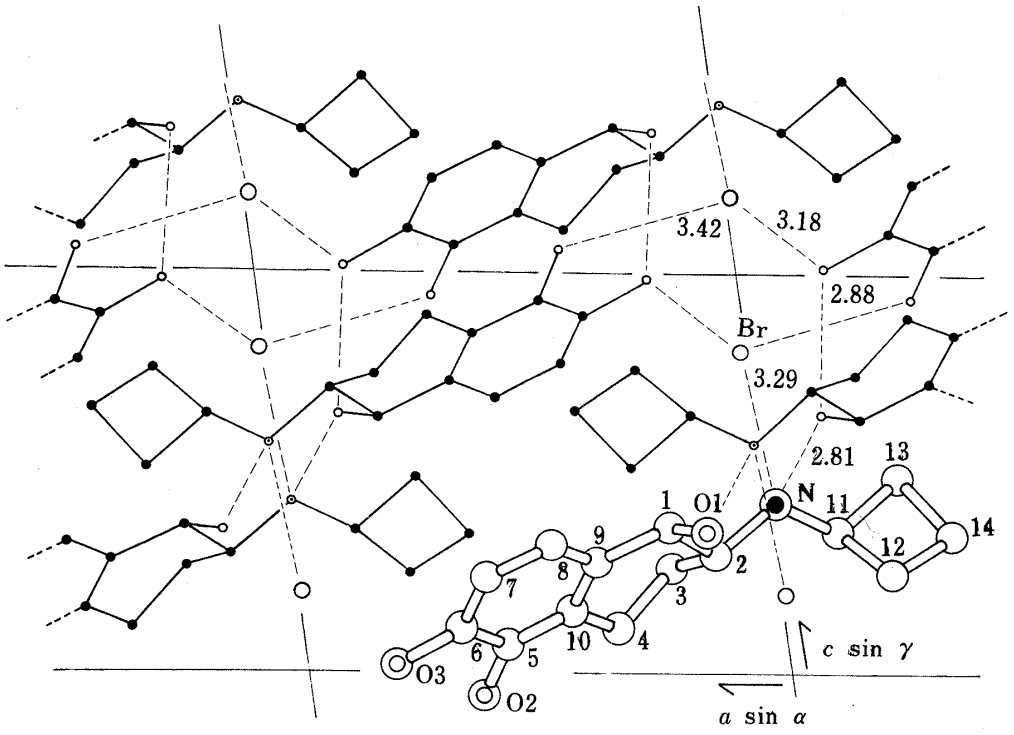


Fig. 1. Crystal Structure of **1a**

Thin dashed lines indicate hydrogen bonds.

6) M.C. Brianso, *C. R. Acad. Sci.*, **t283**, Ser. C, 457 (1976).

Table V. Deviation from the Least-Squares Plane of the Aromatic Ring

Atom	Deviation (Å)	Atom	Deviation (Å)
C (1)	−0.07	C (8)[a]	0.01
C (2)	−0.26	C (9)[a]	−0.02
C (3)	0.62	C (10)[a]	0.01
C (4)	0.06	O (1)	−1.14
C (5)[a]	−0.01	O (2)	−0.03
C (6)[a]	0.00	O (3)	−0.02
C (7)[a]	−0.00	N	0.13

a) These atoms were used to define the plane.

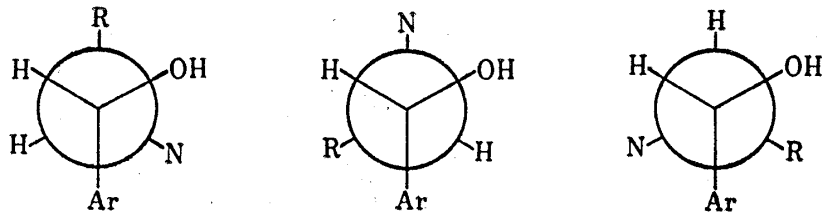
the cyclobutylamino group and the benzylic hydroxy group is *gauche* (−75°) to it (Table VI). This orientation is also observed in the crystals of *dl*-isoproterenol sulfate,[7] norepinephrine hydrochloride[8] and ephedrine hydrochloride.[9]

Table VI. Torsional Angles of **1a** and Isoproterenol[7]

		1a	ISOP-A[b]	ISOP-B[b]
θ_1	C (8)-C (9)-C (1)-O (1)	+51		
	C (2)-C (1)-C (7)-O (3)[a]		−19	+129
θ_2	O (1)-C (1)-C (2)-N	−75		
	O (3)-C (7)-C (8)-N[a]		−62	−50
θ_3	C (9)-C (1)-C (2)-N	+167		
	C (1)-C (7)-C (8)-N[a]		+175	−177
θ_4	C (1)-C (2)-N-C (11)	+168		
	C (7)-C (8)-N-C (9)[a]		−156	+172
θ_5	C (2)-N-C (11)-H (11)	+59		
	C (8)-N-C (9)-H (7)[a]		+52	−62

a) See reference 7.
b) Two different molecules in the asymmetric unit.

Conformational studies of catecholamines by the nuclear magnetic resonance (NMR) technique[10] or (PCILO) method[11] have shown that the rotamer II (Chart 2) is the most stable among the classical staggered rotamers I—III, and the population of the rotamer II was estimated to be about 80%. That the orientation of the three functional groups in **1a** around the C(1)—C(2) bond in the crystal structure coincides with that of the rotamer V afforded further strong support for the view that this conformation, II or V, plays an important role in the biological activity.



I: R=H II: R=H III: R=H
IV: R=C3 V: R=C3 VI: R=C3

Chart 2

7) M. Mathew and G.J. Palenik, *J. Am. Chem. Soc.*, **93**, 497 (1971).
8) D. Carlström and R. Bergin, *Acta Cryst.*, **23**, 313 (1967).
9) D.C. Phillips, *Acta Cryst.*, **7**, 159 (1954).
10) R.R. Ison, P. Partington, and G.C.K. Roberts, *Mol. Pharmacol.*, **9**, 756 (1973).
11) B. Pullman, J.L. Coubeils, Ph. Courrière, and J.P. Gervois, *J. Med. Chem.*, **15**, 17 (1972).

Torsional angles around several single bonds were compared between the (*R*)-isomer (*l*-isomer) of *dl*-isoproterenol[7] and the (1*R*,2*R*)-isomer of **1a** in their crystal structures. The angles were calculated according to Hearn's definition[12] and are listed in Table VI. As regards θ_2, θ_3 and θ_4, there is no significant difference between **1a** and two molecules of *dl*-isoproterenol (ISOP-A and ISOP-B), showing that they have similar conformations in this part of the molecule. Angle θ_5 is similar for **1a** and ISOP-A but differs considerably from that of ISOP-B. This result indicates that the side-chain conformation of ISOP-A very closely resembles that of **1a**, including the orientation of the N-alkyl group, though the alkyl substituents, isopropyl and cyclobutyl groups, are different. The methine proton of the cyclobutyl group [H(11)] in **1a** is located near the equatorial proton [H(3eq)] attached to C(3). The torsional angle, $\theta_5 = -62°$, in ISOP-B is not allowable for **1a** due to the interatomic interaction between C(3) and C(13) methylene groups. A wide variation in θ_1 seems to be of little importance. The construction of a space-filling model showed that the aromatic ring of ISOP-A or ISOP-B can freely rotate around its benzylic bond and take the torsional angle of **1a** (+51°) without affecting θ_2—θ_5. The rotation does not seem to result in a significant change in the total energy of the molecule. These considerations suggest that the steric arrangement of the functional groups found in **1a** is the one actually required for the elicitation of β-adrenoceptor-stimulating activity. We consider that **1** will serve as a useful tool for analyzing the interactions between β-agonists and receptors, and as an aid in the development of new, effective drugs.

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12) R.A. Hearn, G.R. Freeman, and C.E. Bugg, *J. Am. Chem. Soc.*, **95**, 7150 (1973).