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The Molecular Structure of Procaterol Hydrochloride Hemihydrate [5-(1-Hydroxy-2-isopropylaminobutyl)-8-hydroxy-2-quinolone Hydrochloride Hemihydrate, OPC-2009]

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The molecular structure of procaterol hydrochloride hemihydrate ($C_{16}H_{22}N_2O_3 \cdot HCl \cdot 1/2H_2O$) was determined by X-ray diffraction analysis. The crystal is orthorhombic with the space group $P22_12_1$ and $Z=4$. The cell dimensions are $a=7.247(2)$, $b=12.491(8)$, and $c=18.822(13)$ Å. The structure was solved by a direct method using the MULTAN program and refined by a block-diagonal least-squares method to give a final R-value of 0.069. The $N(2')^+$ cation of the side chain forms two hydrogen bonds with Cl^- anion and a water molecule but not with O(3′) atom, although O(3′)–C(11)–C(12)–N(2′) is *gauche*(53°) with a close intramolecular N(2′)–O(3′) distance of 2.679(7) Å. It was confirmed by proton magnetic resonance spectroscopic measurements that the molecular conformation found in the crystal is retained in solution as a preferred conformation.

Keywords——procaterol hydrochloride hemihydrate; bronchodilator; OPC-2009; β_2-adrenoreceptor stimulant; X-ray analysis; direct method; PMR

Conformational studies of biologically active molecules are important for elucidating the mechanism of drug action. In the past few years, X-ray structural studies of adrenergic agents have been reported,[1-3] in which the important question has been raised as to whether the conformation present in the crystal is unique or whether significant populations of some other conformations are also present in solution.[4-7] This problem could be solved by high resolution nuclear magnetic resonance spectroscopic measurements.

Procaterol hydrochloride hemihydrate [5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxy-2-quinolone hydrochloride hemihydrate, OPC-2009] (Chart 1) has been reported to be an entirely new type of long-lasting bronchodilator, with a selective binding to β_2-adrenoreceptors of the bronchial smooth muscles, and with a potent anti-allergic action, but little effect on the cardiovascular system.[8-12]

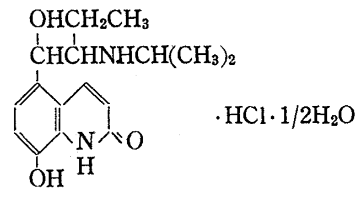


Chart 1

As a part of studies on the pharmaceutical function of adrenergic drugs, X-ray crystal structure analysis of procaterol hydrochloride hemihydrate was carried out, and its molecular conformation in solution was investigated by proton magnetic resonance (PMR) measurements.

Experimental

X-Ray Data Collection and Processing——Colorless, plate-like crystals of procaterol hydrochloride hemihydrate ($C_{16}H_{22}N_2O_3 \cdot HCl \cdot 1/2H_2O$) were obtained by slow evaporation of its aqueous solution at room temperature. A crystal with dimensions of 0.2×0.2×0.4 mm was used for the X-ray work. The cell dimensions were refined by a least-squares method, using 15 reflections measured on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation. The crystal data are summarized in Table I. Intensity data were collected on the diffractometer using an ω-scan mode (scan width of 1°) within 2θ less than 50°. The scan speed was changed in accordance with the intensity of each reflection, and backgrounds were measured at both sides of each peak position. Three reflections monitored periodically showed no significant intensity fluctuations during the data collection. In total, 1750 independent reflections were collected and their intensities were corrected for Lorentz and polarization factors, but not for absorption.

TABLE I. Crystal Data

Molecular formula	$C_{16}H_{22}N_2O_3 \cdot HCl \cdot 1/2\ H_2O$
Molecular weight	335.8
Crystal system	Orthorhombic
Unit cell	
a, Å	7.247(2)
b, Å	12.491(8)
c, Å	18.822(13)
Space group	$P22_12_1$
Z	4
Dx, Mg/m³	1.31
μ(Mo Kα)/cm	2.4

The observed structure factors were adjusted to their absolute values by Wilson's method. The distribution of E-values showed the crystal to be non-centrosymmetric and the overall temperature factor was estimated as 2.67 Å².

PMR Measurements——Procaterol hydrochloride hemihydrate and procaterol base were dissolved in D_2O and dimethylsulfoxide-d_6 (DMSO-d_6), respectively, and the PMR spectra of approximate 1% solutions were measured at 200 MHz and 22°C, using a Brueker WH-200 spectrometer. Rotamer populations were calculated by Ison's method.[5]

Determination and Refinement of the Structure——The structure was solved by a direct method using the MULTAN program.[13] The resulting E map revealed the positions of all non-hydrogen atoms and the oxygen atom of the water molecule could be located at approximately (0.25, 0, 0.5). All the hydrogen atoms were found on a difference Fourier map. The refinement of atomic parameters was carried out by a block-diagonal least-squares method, minimizing $\sum w(|Fo|-|Fc|)^2$ where w=1.0 for all reflections. Thermal parameters were refined anisotropically for all the non-hydrogen atoms and isotropically for the hydrogen atoms. The final R-value was 0.069. The atomic scattering factors were taken from "International Tables for X-ray Crystallography".[14] The final atomic coordinates and thermal parameters are shown in Table II.[15]

All the computations were made on a NOVA-3 computer coupled to the Syntex R3 diffractometer, using the Syntex XTL programs.

TABLE II. Atomic Coordinates and Thermal Parameters with Their Estimated Standard Deviations in Parentheses

A) Atomic coordinates (×10⁴) and anisotropic temperature factors for non-hydrogen atoms

Atom	*x*	*y*	*z*	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C1	4221(2)	2854(1)	4454(1)	2.52(6)	2.75(6)	2.57(6)	−0.12(6)	−0.17(6)	−0.05(6)
O(1′)	4942(7)	8978(4)	4048(2)	4.0(2)	3.2(2)	3.4(2)	−1.4(2)	0.4(2)	−0.9(2)
O(2′)	3868(9)	5266(3)	4268(2)	8.3(4)	2.3(4)	1.9(2)	−0.2(3)	−1.0(2)	−0.0(2)
O(3′)	1902(7)	5212(4)	985(2)	3.4(2)	2.9(2)	2.1(2)	−0.9(2)	−0.4(2)	0.8(2)
O(W)	2445(10)	10000	5000	3.1(3)	3.2(3)	3.1(3)			0.2(2)
N(1)	4224(8)	7266(4)	3783(2)	3.2(2)	1.9(2)	2.0(2)	−0.8(2)	0.2(2)	−0.2(2)
N(2′)	−347(7)	6789(4)	559(3)	2.4(2)	3.0(2)	2.1(2)	0.0(2)	−0.4(2)	−0.7(2)
C(2)	4415(9)	8303(5)	3609(3)	2.0(3)	3.3(3)	2.6(2)	−0.3(3)	0.7(2)	0.2(2)
C(3)	3965(10)	8573(5)	2877(3)	3.4(3)	2.0(2)	3.0(3)	−0.1(3)	−0.0(3)	0.5(2)
C(4)	3382(9)	7827(5)	2421(3)	2.7(3)	2.3(3)	2.8(2)	0.2(3)	−0.3(2)	0.4(2)
C(5)	2483(9)	5918(5)	2174(3)	2.2(3)	2.2(2)	2.2(2)	0.5(2)	−0.3(2)	0.1(2)
C(6)	2235(9)	4908(5)	2441(3)	3.1(3)	2.3(3)	2.1(2)	0.3(3)	−0.4(2)	−0.2(2)
C(7)	2668(11)	4663(5)	3152(3)	4.4(4)	2.1(3)	2.2(2)	0.4(3)	−0.1(3)	−0.1(2)
C(8)	3357(11)	5427(5)	3586(3)	3.9(3)	2.8(3)	1.6(2)	0.4(3)	0.2(2)	−0.2(2)
C(9)	3156(9)	6732(5)	2630(3)	2.2(3)	2.1(2)	2.4(2)	0.0(2)	0.2(2)	0.4(2)
C(10)	3574(9)	6484(5)	3332(3)	2.4(3)	2.1(2)	2.1(2)	−0.1(2)	0.2(2)	0.0(2)
C(11)	1999(8)	6158(5)	1401(3)	1.9(2)	2.3(2)	1.8(2)	−0.1(2)	−0.4(2)	−0.4(2)
C(12)	106(10)	6681(5)	1339(3)	3.0(3)	2.4(3)	2.0(2)	−0.3(2)	−0.2(2)	0.2(2)
C(13)	996(9)	7422(6)	107(3)	2.1(3)	3.9(3)	2.8(3)	−0.2(3)	0.2(2)	−1.1(2)
C(14)	372(11)	7276(7)	−666(3)	3.7(4)	7.1(5)	2.2(3)	0.3(4)	−0.3(3)	−0.7(3)
C(15)	1050(12)	8588(6)	319(4)	4.6(4)	3.2(3)	4.9(4)	0.6(3)	−0.2(4)	−1.0(3)
C(16)	−1448(9)	6083(6)	1695(3)	2.4(3)	3.5(3)	2.3(2)	−0.0(3)	0.3(2)	−0.3(2)
C(17)	−1818(11)	6470(7)	2461(4)	2.9(3)	5.8(4)	3.4(3)	−0.2(3)	1.0(3)	0.3(3)

B) Atomic coordinates ($\times 10^3$) and isotropic temperature factors for hydrogen atoms[a]

Atom	x	y	z	B
H(1)	420(13)	721(7)	411(4)	9.7(25)
H(3)	425(10)	944(5)	279(3)	3.4(16)
H(4)	318(8)	802(5)	198(3)	2.3(13)
H(6)	151(13)	431(7)	211(4)	6.3(24)
H(7)	258(11)	385(6)	335(4)	5.0(19)
H(11)	302(8)	670(4)	122(3)	1.4(11)
H(12)	15(7)	734(4)	152(2)	0.9(10)
H(13)	234(8)	713(5)	8(3)	2.3(12)
H(14)-1	145(12)	763(6)	−92(4)	5.4(21)
H(14)-2	−21(14)	638(7)	−80(5)	9.6(27)
H(14)-3	−116(13)	761(7)	−69(4)	7.7(26)
H(15)-1	219(9)	896(6)	−4(4)	4.1(16)
H(15)-2	−32(13)	896(7)	28(4)	8.6(26)
H(15)-3	176(11)	868(6)	75(4)	4.9(19)
H(16)-1	−235(10)	623(6)	149(3)	3.2(17)
H(16)-2	−119(6)	513(3)	156(2)	2.3(8)
H(17)-1	−82(10)	619(5)	271(3)	4.2(17)
H(17)-2	−337(15)	601(8)	260(5)	10.4(30)
H(17)-3	−215(13)	723(8)	242(4)	7.8(27)
H(O2′)	471(10)	473(5)	425(3)	4.2(18)
H(O3′)	364(18)	502(10)	79(7)	15.9(44)
H(N2′)-1	−173(9)	715(5)	54(3)	3.8(15)
H(N2′)-2	−118(10)	604(6)	35(3)	5.4(18)

The anisotropic temperature factors are in the form:
$\exp[-1/4(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$.
a) The numberings in parentheses indicate the atoms to which hydrogen atoms are bonded.

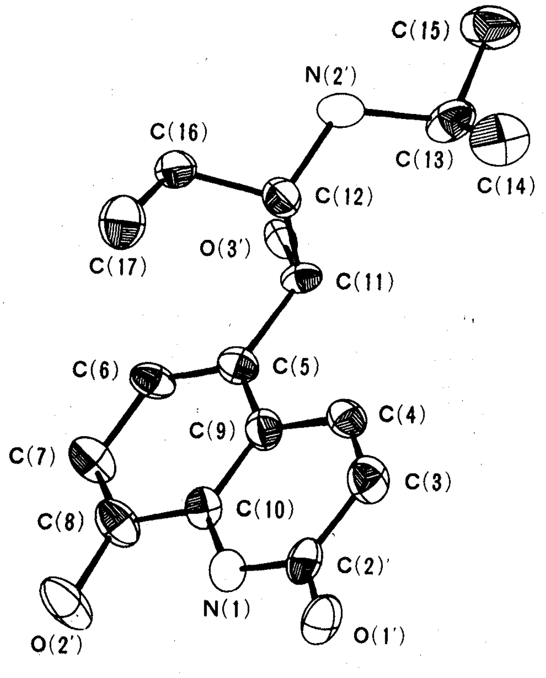


Fig. 1. Molecular Structure and Atomic Numbering of Procaterol Hydrochloride Hemihydrate

Each atom except for hydrogen is represented by thermal ellipsoids with 50% probability.

Results and Discussion

A perspective view of the molecule, together with the atomic numberings, is shown in Fig. 1. Figure 2 shows the molecular packing in the crystal. Bond distances and angles are listed in Tables III and IV. The O(1′)–C(2) bond distance, 1.240(8) Å, strongly indicates double bond character, and therefore, presumably the 2-quinolone ring takes completely the 2-one form and π-electrons in the ring atoms are rather localized on the C(3)–C(4), C(5)–C(6), C(7)–C(8) and C(9)–C(10) bonds in the crystals; such a structure might be retained in solution as in the case of α-pyridone.[16] The dihedral angles characterizing the side chain are τ_1[C(9)–C(5)–C(11)–C(12)] = 100° and τ_2[C(5)–C(11)–C(12)–N(2′)] = −174°. The protonated isopropylamino nitrogen, N(2′), is in a tetrahedral sp^3 hybrid state, forming two hydrogen bonds with Cl^- anion and a water molecule; N^+–H—Cl^-, 3.107(5) Å, and N^+–H—O(W), 2.900 (6) Å. It is clear that the N(2′) atom does not form an intramolecular hydrogen bond with the O(3′) atom, although O(3′)–C(11)–C(12)–N(2′)

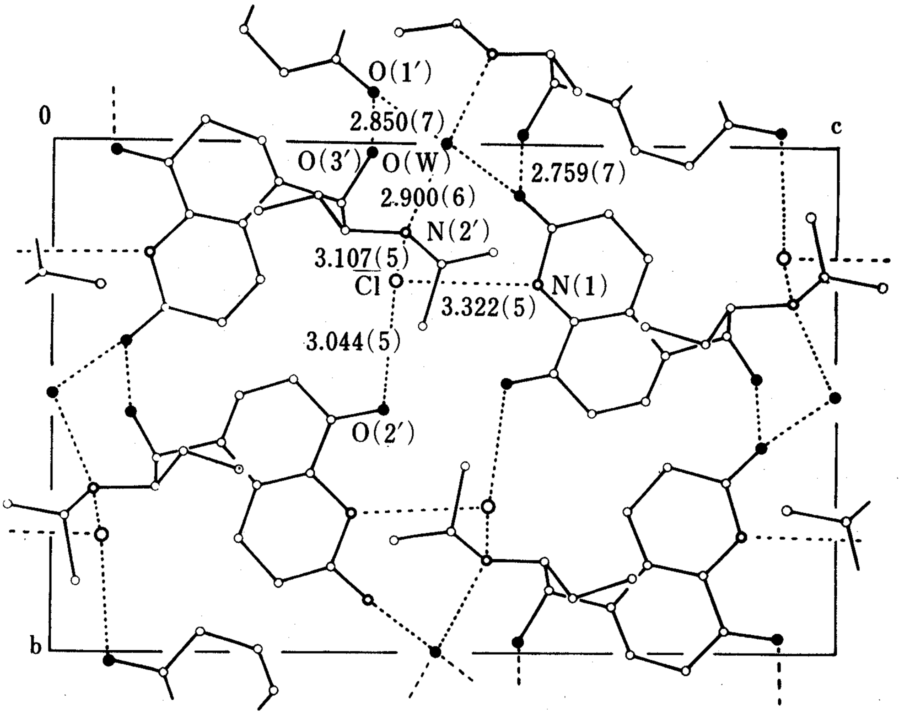


Fig. 2. The Molecular Packing of Procaterol Hydrochloride Hemihydrate in the Crystal Projected along the a-Axis

The hydrogen bonds are shown by broken lines.

Table III. Bond Distances (Å) and Angles (°) Involving Non-hydrogen Atoms, with Estimated Standard Deviations in Parentheses

O (1′)-C (2)	1.240(8)	O (2′)-C (8)	1.350(7)
O (3′)-C (11)	1.419(7)	N (1)-C (2)	1.343(8)
N (1)-C (10)	1.377(8)	N (2′)-C (12)	1.509(8)
N (2′)-C (13)	1.516(8)	C (2)-C (3)	1.455(9)
C (3)-C (4)	1.335(9)	C (4)-C (9)	1.433(9)
C (5)-C (6)	1.369(9)	C (5)-C (9)	1.417(8)
C (5)-C (11)	1.527(8)	C (6)-C (7)	1.409(8)
C (7)-C (8)	1.351(9)	C (8)-C (10)	1.414(9)
C (9)-C (10)	1.390(8)	C (11)-C (12)	1.524(9)
C (12)-C (16)	1.508(9)	C (13)-C (14)	1.535(9)
C (13)-C (15)	1.511(10)	C (16)-C (17)	1.544(10)
C (2)-N (1)-C (10)	124.6(5)	C (12)-N (2′)-C (13)	116.9(5)
O (1′)-C (2)-N (1)	121.6(6)	O (1′)-C (2)-C (3)	122.8(6)
N (1)-C (2)-C (3)	115.6(6)	C (2)-C (3)-C (4)	121.2(6)
C (3)-C (4)-C (9)	121.8(6)	C (6)-C (5)-C (9)	119.0(6)
C (6)-C (5)-C (11)	120.0(5)	C (9)-C (5)-C (11)	121.0(5)
C (5)-C (6)-C (7)	121.3(6)	C (6)-C (7)-C (8)	120.2(6)
O (2′)-C (8)-C (7)	124.8(6)	O (2′)-C (8)-C (10)	115.4(6)
C (7)-C (8)-C (10)	119.8(6)	C (4)-C (9)-C (5)	124.0(6)
C (4)-C (9)-C (10)	116.6(6)	C (5)-C (9)-C (10)	119.4(6)
N (1)-C (10)-C (8)	119.5(6)	N (1)-C (10)-C (9)	120.2(6)
C (8)-C (10)-C (9)	120.3(6)	O (3′)-C (11)-C (5)	111.9(5)
O (3′)-C (11)-C (12)	105.7(5)	C (5)-C (11)-C (12)	111.3(5)
N (2′)-C (12)-C (11)	108.0(5)	N (2′)-C (12)-C (16)	108.2(5)
C (11)-C (12)-C (16)	115.2(5)	N (2′)-C (13)-C (14)	106.4(5)
N (2′)-C (13)-C (15)	111.8(5)	C (14)-C (13)-C (15)	111.8(6)
C (12)-C (16)-C (17)	112.9(6)		

Table IV. Bond Distances (Å) and Angles (°) Involving Hydrogen Atoms, with Estimated Standard Deviations in Parentheses

H(1)-N(1)	0.62(8)	H(3)-C(3)	1.11(6)
H(4)-C(4)	0.87(5)	H(6)-C(6)	1.10(9)
H(7)-C(7)	1.08(7)	H(11)-C(11)	1.06(5)
H(12)-C(12)	0.89(5)	H(13)-C(13)	1.05(6)
H(14)-1-C(14)	1.02(8)	H(14)-2-C(14)	1.22(9)
H(14)-3-C(14)	1.18(9)	H(15)-1-C(15)	1.17(7)
H(15)-2-C(15)	1.10(9)	H(15)-3-C(15)	0.96(7)
H(16)-1-C(16)	0.78(7)	H(16)-2-C(16)	1.23(4)
H(17)-1-C(17)	0.93(7)	H(17)-2-C(17)	1.30(11)
H(17)-3-C(17)	0.99(10)	H(O′2)-O(2′)	0.90(7)
H(O3′)-O(3′)	1.34(13)	H(N2′)-1-N(2′)	1.10(7)
H(N2′)-2-N(2′)	1.19(7)		
H(1)-N(1)-C(2)	110(8)	H(1)-N(1)-C(10)	122(8)
H(3)-C(3)-C(2)	109(3)	H(3)-C(3)-C(14)	130(3)
H(4)-C(4)-C(3)	118(4)	H(4)-C(4)-C(9)	120(4)
H(6)-C(6)-C(5)	119(4)	H(6)-C(6)-C(7)	119(4)
H(7)-C(7)-C(6)	121(4)	H(7)-C(7)-C(8)	119(4)
H(11)-C(11)-O(3′)	113(3)	H(11)-C(11)-C(5)	106(3)
H(11)-C(11)-C(12)	109(3)	H(12)-C(12)-N(2′)	107(3)
H(12)-C(12)-C(11)	110(3)	H(12)-C(12)-C(16)	108(4)
H(13)-C(13)-N(2′)	117(3)	H(13)-C(13)-C(14)	101(3)
H(13)-C(13)-C(15)	109(3)	H(14)-1-C(14)-C(13)	100(4)
H(14)-1-C(14)-H(14)-2	124(6)	H(14)-1-C(14)-H(14)-3	123(6)
H(14)-2-C(14)-C(13)	114(4)	H(14)-2-C(14)-H(14)-3	89(6)
H(14)-3-C(14)-C(13)	106(4)	H(15)-1-C(15)-C(13)	105(3)
H(15)-1-C(15)-H(15)-2	115(6)	H(15)-1-C(15)-H(15)-3	93(5)
H(15)-2-C(15)-C(13)	112(5)	H(15)-2-C(15)-H(15)-3	120(6)
H(15)-3-C(15)-C(13)	110(4)	H(16)-1-C(16)-C(12)	106(5)
H(16)-1-C(16)-C(17)	104(5)	H(16)-1-C(16)-H(16)-2	105(5)
H(16)-2-C(16)-C(12)	106(2)	H(16)-2-C(16)-C(17)	121(2)
H(17)-1-C(17)-C(16)	102(4)	H(17)-1-C(17)-H(17)-2	114(6)
H(17)-1-C(17)-H(17)-3	126(7)	H(17)-2-C(17)-C(16)	102(8)
H(17)-2-C(17)-H(17)-3	104(7)	H(17)-3-C(17)-C(16)	106(5)
H(N2′)-1-N(2′)-C(12)	105(3)	H(N2′)-1-N(2′)-C(13)	111(3)
H(N2′)-1-N(2′)-H(N2′)-2	82(5)	H(N2′)-2-N(2′)-C(12)	112(3)
H(N2′)-2-N(2′)-C(13)	123(3)	H(O3′)-O(3′)-C(11)	105(5)

is *gauche* (53°) with a close N(2′)–O(3′) distance of 2.679(7) Å. The water molecule forms hydrogen bonds with N(2′) and O(1′), and the Cl^- anion is hydrogen-bonded to O(2′), N(1) and N(2′). The ring portions on neighboring molecules are linked by hydrogen bonds through the Cl^- anion. The hydrophilic side chain portions adopt a folded conformation and are connected to each other through hydrogen bonds.

The deviations of individual atoms from the least-squares planes of the benzene and hetero rings are listed in Table V. The results indicate that the 2-quinolone ring is slightly bent at the C(9)–C(10) bond; the dihedral angle between these planes is 177.5°.

The conformation about the C(11)–C(12) bond in procaterol hydrochloride hemihydrate is shown in Fig. 3, together with those found in isoproterenol sulfate,1) norepinephrine hydrochloride,3) and ephedrine hydrochloride.2) The common features in these four cases are that the amino and hydroxy groups are *gauche* and therefore the intramolecular N(2′)–O(3′) distances are similar (2.65 to 3.00 Å). Since all these compounds have strong activities in the central nervous system as β_2-adrenoreceptor stimulants, the above conformational similarities might correlate closely to their activities.

In order to determine whether the molecular conformation found in the crystal is retained in solution, a PMR study was carried out. The conformations of the side chain of catechol-

Table V. The Deviations (Å) of Atoms from the Least-squares Planes

Plane 1		Plane 2	
C (5)*	0.01	N (1)*	−0.02
C (6)*	−0.01	C (2)*	−0.01
C (7)*	−0.01	C (3)*	−0.00
C (8)*	0.02	C (4)*	0.01
C (9)*	−0.00	C (9)*	0.00
C (10)*	−0.01	C (10)*	−0.01
C (11)	0.01	O (1′)	−0.03
O (2′)	0.06		

The atoms indicated with an asterisk were included in the calculation of the least-squares planes.

Plane 1; $0.9340x-0.2297y-0.2736z=-1.1476$

Plane 2; $0.9437x-0.1882y-0.2721z=-0.7729$

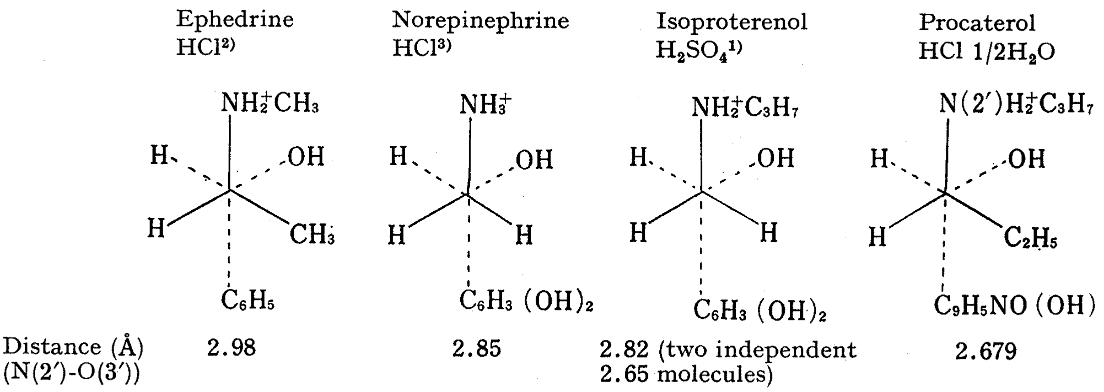
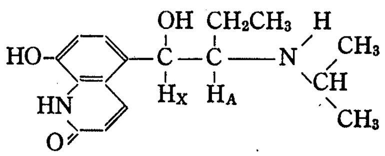


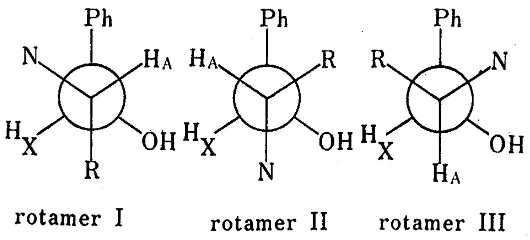
Fig. 3. The conformations about the C(11)-C(12) bond of the side chain for procaterol hydrochloride hemihydrate and related compounds

amines and related compounds were determined from PMR spectra by Ison *et al.*[5] The relative populations of the three possible staggered rotamers (I, II and III) about the C(11)–C(12) bond should be considered. The coupling constants were derived from the PMR spectra of procaterol salt or base and the calculated rotamer populations are given in Table VI. The procaterol salt in D_2O and DMSO-d_6 consisted mostly of rotamers II and III, while in DMSO-d_6 solution of procaterol base, the population of rotamer I was considerably increased. The

Table VI. The Coupling Constants (J_{AX}) Derived from PMR Spectra of Procaterol Salt or Base and the Rotamer Populations (P)

Compound	Solvent	δ(H(11))	J_{AX}	P_{I}	($P_{II}+P_{III}$)
Procaterol·HCl·1/2H_2O	D_2O	5.51 ppm	3.8 Hz	0.13	0.87
Procaterol·HCl·1/2H_2O	DMSO-d_6	5.61	3.1	0.04	0.96
Procaterol base	DMSO-d_6	4.91	5.3	0.37	0.63





population of each rotamer could be changed by protonation at the N(2′) atom. As a result of structural studies on many catecholamines in solution, it was found that the population of rotamer III is negligibly small in comparison with that of rotamer II, whereas the populations of norepinephrine P_{I}, P_{II} and P_{III} are 0.14, 0.76 and 0.10, respectively. Accordingly, both procaterol salt and base adopt rotamer II in solution as the preferred conformer.

In the crystals, the four compounds mentioned above were all observed to have similar molecular conformations corresponding to rotamer II. Therefore, β-adrenergic drugs presumably exert their pharmaceutical effects in this conformation.

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