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Crystal Structures of Polymorphs of α-[(*tert*-Butylamino)methyl]-2-chloro-4-hydroxybenzyl Alcohol Hydrochloride (HOKU-81)

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The crystal structures of the two crystalline forms (I and II) of α-[(*tert*-butylamino)-methyl]-2-chloro-4-hydroxybenzyl alcohol hydrochloride (HOKU-81), which is one of the metabolites of tulobuterol hydrochloride (C-78) and a potent β_2-adrenergic stimulant, have been determined by X-ray structure analysis. The structures were solved by direct methods and refined by the block-diagonal least-squares method including anisotropic thermal parameters to final R values of 0.051 and 0.050 for Forms I and II, respectively.

The molecular conformations in the two forms are similar, but nevertheless the crystal structures are very different. In Form I, independent hydrogen bonds of four types are formed, while three types of independent hydrogen bond are formed in Form II, producing characteristic molecular sheets in the crystals.

Comparison of the crystal structures of the polymorphs between HOKU-81 and C-78 indicates that some of the differences of physico-chemical properties are attributable to the differences of crystal packings. Furthermore, comparison of the molecular conformations of HOKU-81 and C-78 with those of the other adrenergic agents having an ethanolamine side chain shows that these compounds have homologous conformations in the aliphatic side chain.

Keywords——HOKU-81; metabolite of tulobuterol hydrochloride; β_2-adrenergic stimulant; polymorphism; crystal structure; molecular structure

α-[(*tert*-Butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol hydrochloride (HOKU-81), obtained from rat[1] or human[2] urine, is a hydroxylated metabolite of tulobuterol hydrochloride (C-78) with a prolonged and selective β_2-adrenergic stimulating activity.[3] It is expected to be more efficacious as a bronchodilator than C-78.

In the preceding paper,[4] it was shown that HOKU-81 takes two crystalline forms (Forms I and II), which are highly stable to heat, humidity and mechanical treatments such as grinding or compressing. On the other hand, it has been reported that C-78 also exhibits polymorphism with five different forms (three anhydrous forms, one amorphous form and one monohydrate) and that these forms can be interconverted by the physico-chemical treatments mentioned above.[5,6] Moreover, the phase transition mechanism of C-78 could be interpreted by using the results of the X-ray crystal structure analyses.[7]

We report here the crystal and molecular structures of the two crystalline forms of HOKU-81, and discuss the differences of physico-chemical properties between HOKU-81 and C-78 on the basis of their crystal and molecular structures.

Experimental

Materials——Forms I and II of HOKU-81 were prepared according to the methods reported previously.[4]

Crystal Data——Crystals ($0.2\times0.3\times0.3$ mm for Form I, $0.3\times0.4\times0.3$ mm for Form II) were used for the X-ray analyses, which were carried out with a computer-controlled, crystal-structure analysis system, Rigaku RASA-IIF, comprising a Cu-$K\alpha$ radiation source ($\lambda=1.5418$ Å) and a four-circle diffractometer with a graphite monochromator.

The crystal data are summarized in Table I. Intensity data were collected with an $\omega-2\theta$ scan mode

TABLE I. Crystallographic Parameters

	Form I	Form II
Formula	$C_{12}H_{18}ClNO_2 \cdot HCl$	
Formula weight	280.21	
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	10.349(1)	10.986(2)
b (Å)	7.520(1)	7.220(2)
c (Å)	20.108(5)	24.007(5)
β (°)	110.40(1)	132.34(2)
U (Å^3)	1466.7	1407.5
Z	4	4
D_x (gcm^{-3})	1.269	1.322
D_m (gcm^{-3})	1.268	1.310

TABLE II. Final Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^4$) with Their Estimated Standard Deviations for Non Hydrogen Atoms of Form I[a]

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	4515 (1)	9069 (2)	6524 (1)	277	365	197	−99	78	−103
Cl(2)	−480 (1)	9460 (1)	6047 (1)	241	168	220	14	55	21
C(1)	3402 (4)	7481 (4)	5234 (2)	229	136	159	− 9	47	6
C(2)	4595 (4)	8200 (5)	5729 (2)	236	181	167	−12	62	−21
C(3)	5830 (4)	8341 (5)	5626 (2)	201	182	220	−14	51	− 9
C(4)	5930 (4)	7713 (5)	4993 (2)	219	151	265	2	90	− 9
C(5)	4757 (4)	6988 (5)	4483 (2)	259	186	212	− 9	86	−36
C(6)	3547 (4)	6859 (5)	4611 (2)	233	168	197	−12	62	−21
C(7)	2079 (3)	7320 (4)	5381 (2)	182	151	159	−17	39	6
C(8)	2180 (4)	5771 (5)	5881 (2)	207	170	174	16	58	12
C(9)	1261 (4)	5066 (5)	6886 (2)	265	210	129	−19	43	24
C(10)	−145 (5)	4952 (7)	6962 (2)	315	430	182	−68	86	33
C(11)	2151 (5)	6478 (6)	7383 (2)	337	255	151	−22	31	−24
C(12)	1987 (5)	3274 (5)	6983 (2)	383	192	220	−17	12	60
N	958 (3)	5715 (4)	6120 (1)	197	178	121	−13	31	9
O(1)	7101 (3)	7826 (4)	4847 (1)	255	253	333	−20	136	−69
O(2)	909 (2)	6978 (3)	4754 (1)	211	171	174	−23	19	18

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

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	3542 (1)	2870 (2)	3442 (1)	169	133	148	6	80	−22
Cl(2)	−348 (2)	3407 (2)	1278 (1)	229	194	236	−93	139	−36
C(1)	4008 (4)	6529 (5)	3802 (2)	127	127	135	11	99	25
C(2)	4641 (5)	4749 (5)	4045 (2)	131	126	128	− 6	95	− 3
C(3)	6133 (5)	4376 (5)	4767 (2)	122	137	128	− 6	89	11
C(4)	7011 (4)	5843 (6)	5257 (2)	108	148	128	− 5	80	16
C(5)	6425 (5)	7637 (6)	5038 (2)	142	140	155	−21	83	0
C(6)	4944 (5)	7961 (6)	4315 (2)	156	140	162	13	105	33
C(7)	2435 (5)	6910 (6)	2992 (2)	127	142	128	21	83	27
C(8)	2917 (5)	6945 (7)	2527 (2)	117	259	108	4	71	33
C(9)	1846 (5)	7516 (6)	1215 (2)	134	199	135	3	102	19
C(10)	196 (5)	7472 (8)	398 (2)	176	309	121	1	92	16
C(11)	2941 (6)	5975 (8)	1333 (3)	212	315	236	63	166	33
C(12)	2635 (6)	9412 (8)	1408 (3)	224	277	202	−70	148	8
N	1457 (4)	7151 (5)	1705 (2)	108	153	121	5	80	22
O(1)	8489 (3)	5561 (4)	5983 (2)	122	173	135	6	49	19
O(2)	1738 (4)	8661 (4)	2893 (2)	198	187	169	70	95	52

(4° 2θ/min) in a 2θ range of less than 135°, giving 2175 and 2127 independent reflections with $F_o > 3\sigma(F)$ for Forms I and II, respectively. The observed intensities were corrected for Lorentz and polarization factors, but not for absorption.

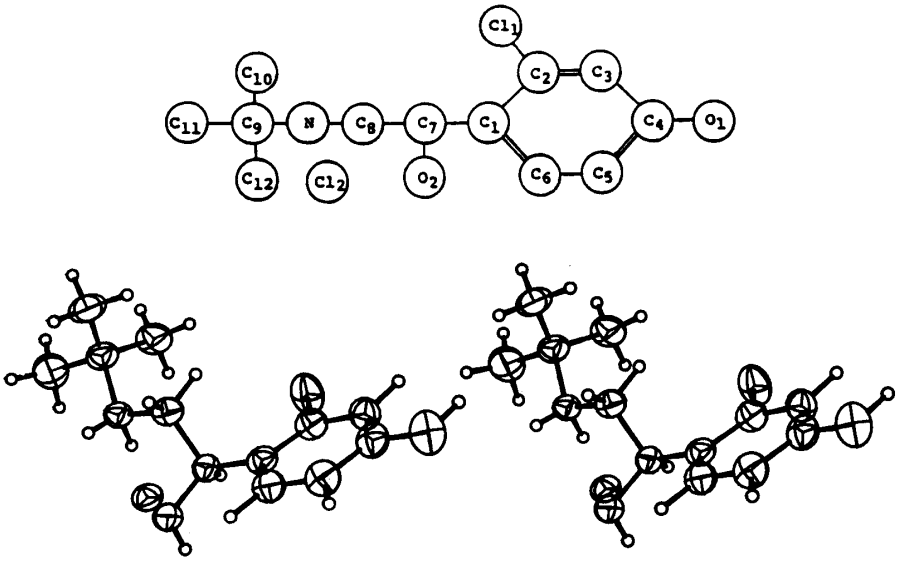
Structure Determination——The molecular structures were solved by the direct method with the computer program MULTAN.[8] The non-hydrogen atoms were first located on the E-map and the structures were refined by the block-diagonal least-squares method. The positions of hydrogen atoms were determined by difference-Fourier synthesis and further refinements of atomic parameters including anisotropic thermal parameters for nonhydrogen atoms and isotropic ones for hydrogen atoms (three cycles) led to final R factors of 0.051 and 0.050 for Forms I and II, respectively. The final atomic coordinates and thermal parameters are shown in Tables II and III.

Structure Description and Discussion

Molecular Structure

Numbering of the atoms in HOKU-81 and ORTEP[9] drawings of the molecules in the two crystalline forms for HOKU-81 are shown in Fig. 1. The valence bond lengths and angles are tabulated in Tables IV and V, respectively. All values are chemically reasonable and no significant difference in the molecular dimensions was found between the two crystalline forms.

The planarity of the benzene rings of the two forms is satisfactory, the mean deviations of atoms from the least-squares planes being 0.005 and 0.002 Å for Forms I and II, respectively.



Form I

Form II

Fig. 1. Numbering of the Atoms in HOKU-81 and Stereoscopic drawings of the Molecules for the Two Crystalline Forms of HOKU-81

The torsion angles about the C(1)–C(7) bond, *i.e.* τ[C(2)–C(1)–C(7)–C(8)], which determine the backbone conformation of the molecules, are ± 76.1 and $\pm 79.7°$ ($\pm$ is used because the crystals are composed of both optical enantiomers) for Forms I and II, respectively.

The *tert*-butylamino nitrogen atoms in the two forms are protonated and have tetrahedral configuration.

TABLE IV. Bond Lengths (Å) with Their Estimated Standard Deviations

Bond	Length	
	Form I	Form II
Cl (1)—C (2)	1.756 (4)	1.744 (4)
C (1)—C (2)	1.397 (10)	1.389 (5)
C (1)—C (6)	1.395 (6)	1.392 (5)
C (1)—C (7)	1.502 (6)	1.522 (4)
C (2)—C (3)	1.369 (6)	1.391 (4)
C (3)—C (4)	1.394 (6)	1.382 (5)
C (4)—C (5)	1.398 (10)	1.383 (6)
C (4)—O (1)	1.346 (6)	1.379 (4)
C (5)—C (6)	1.367 (7)	1.382 (4)
C (7)—C (8)	1.518 (5)	1.526 (9)
C (7)—O (2)	1.435 (11)	1.413 (5)
C (8)—N	1.501 (7)	1.491 (4)
C (9)—N	1.540 (5)	1.520 (8)
C (9)—C (10)	1.518 (7)	1.532 (4)
C (9)—C (11)	1.528 (8)	1.520 (8)
C (9)—C (12)	1.522 (6)	1.516 (7)

TABLE V. Bond Angles (°) with Their Estimated Standard Deviations

Bond	Angles	
	Form I	Form II
Cl (1)—C (2)—C (1)	118.8 (5)	120.0 (2)
Cl (1)—C (2)—C (3)	116.9 (6)	117.4 (3)
C (1)—C (2)—C (3)	124.2 (4)	122.7 (3)
C (1)—C (6)—C (5)	122.6 (6)	121.9 (4)
C (1)—C (7)—C (8)	109.6 (4)	106.4 (4)
C (1)—C (7)—O (2)	113.0 (4)	113.4 (3)
C (2)—C (1)—C (6)	115.1 (5)	116.9 (3)
C (2)—C (1)—C (7)	122.1 (4)	121.4 (3)
C (2)—C (3)—C (4)	118.8 (6)	118.3 (3)
C (3)—C (4)—C (5)	118.7 (5)	121.0 (3)
C (3)—C (4)—O (1)	122.5 (6)	121.0 (3)
C (4)—C (5)—C (6)	120.5 (4)	119.3 (4)
C (5)—C (4)—O (1)	118.8 (4)	118.0 (3)
C (6)—C (1)—C (7)	122.7 (6)	121.5 (3)
C (7)—C (8)—N	111.3 (4)	112.1 (4)
C (8)—C (7)—O (2)	106.6 (3)	106.1 (4)
C (8)—N—C (9)	115.4 (5)	115.3 (4)
C (10)—C (9)—N	104.6 (6)	106.3 (4)
C (10)—C (9)—C (11)	110.7 (5)	109.2 (4)
C (10)—C (9)—C (12)	112.7 (4)	110.5 (4)
C (11)—C (9)—N	107.5 (4)	109.2 (4)
C (11)—C (9)—C (12)	111.9 (5)	112.7 (5)
C (12)—C (9)—N	109.2 (4)	108.8 (4)

TABLE VI. Hydrogen Bond Lengths and Their Estimated Standard Deviations

Form I	d
I : Cl (2^{i})----H-N(1^{i})	3.16 (0)Å
II : Cl (2^{i})----H-O (1^{ii})	3.06 (2)
III : N (1^{i})-H----O (2^{iii})	2.93 (1)
IV : Cl (2^{i})----H-O (2^{iv})	3.08 (0)

(i) x, y, z; (ii) x-1, y, z ; (iii) $-x$, 1-y, 1-z ; (iv) $-x$, 2-y, 1-z

Form II	d
I : Cl (2^{i})----H-N (1^{i})	3.09 (1) Å
II : Cl (2^{i})----H-O (1^{ii})	3.02 (1)
III : Cl (2^{i})----H-O (2^{iii})	3.23 (2)

(i) x, y, z ; (ii) x-1, 1/2-y, z-1/2 ; (iii) $-x$, y-1/2, 1/2-z

The capital roman number attributed to each hydrogen bonding pair corresponds to that given in Figs. 2 and 3, and the small roman number in parentheses represents a symmetry operation applied to each atom.

Crystal Structure

Crystal packings of the two forms are shown in Figs. 2 and 3, respectively. In both crystalline forms, the hydrogen bonding systems make the frameworks of the crystal structures, but there is a distinct difference between the packing arrangements of the two forms, though there exists only a small conformational difference in the shapes of molecules. In Table VI, all crystallographically independent hydrogen bonds are summarized.

In Form I, as shown in Fig. 2, the stacking of benzene rings along the b axis is characteristic and there are four types of intermolecular hydrogen bonds in an asymmetric unit. Three of them, $Cl^{-}(2)....H-N^{+}$ (3.16 Å), $Cl^{-}(2)....H-O(2)$ (3.08 Å) and $N^{+}-H....O(2)$ (2.93 Å), successively link enantiomers related by a center of symmetry to form a columnar hydrogen bond network along the b axis. The fourth hydrogen bond, $Cl^{-}(2)....H-O(1)$ (3.06 Å), links the molecules along the a axis. These intermolecular hydrogen bond chains constitute an (001) molecular sheet.

Fig. 3 shows that, in Form II, the benzene rings are stacked to form a ($\bar{1}02$) molecular sheet, and there are three types of intermolecular hydrogen bonds in an asymmetric unit. Two of them, $Cl^{-}(2)....H-N^{+}$ (3.09 Å) and $Cl^{-}(2)....H-O(2)$ (3.23 Å), are formed between molecules having the same chirality related by the two-fold screw axis, and these bonds form a spiral column along the two-fold screw axis. The remaining hydrogen bond, $Cl^{-}(2)....H-O(1)$ (3.02 Å), connects the molecules along the a axis as in the case of Form I.

In both crystal forms, stacking of benzene rings and intermolecular hydrogen bonds might stabilize the crystal structure.

Comparison between HOKU-81 and C-78

In spite of the existence of an additional hydroxyl group in the benzene ring of HOKU-81 in comparison with C-78, there is little essential difference of molecular structure in the various crystal forms, and indeed, the torsion angles (τ_0, τ_1, τ_2) which determine the backbone conformation of the molecules have nearly the same values, as shown in Table VII.

However, the crystal structures of HOKU-81 polymorphs are quite distinct from those of C-78 polymorphs. In crystals of HOKU-81, not only the hydroxyl group in the benzene ring but also that in the ethanolamine side chain participate in the hydrogen bonding system to stabilize the crystal structure, whereas in crystals of C-78, the aliphatic hydroxyl group does not, notwithstanding its ability to do so, form a hydrogen bond.

This fact explains the following experimental results: (1) the melting points of HOKU-81 polymorphs (Form I, 179°; Form II, 181°) are higher than those of C-78 polymorphs (Form

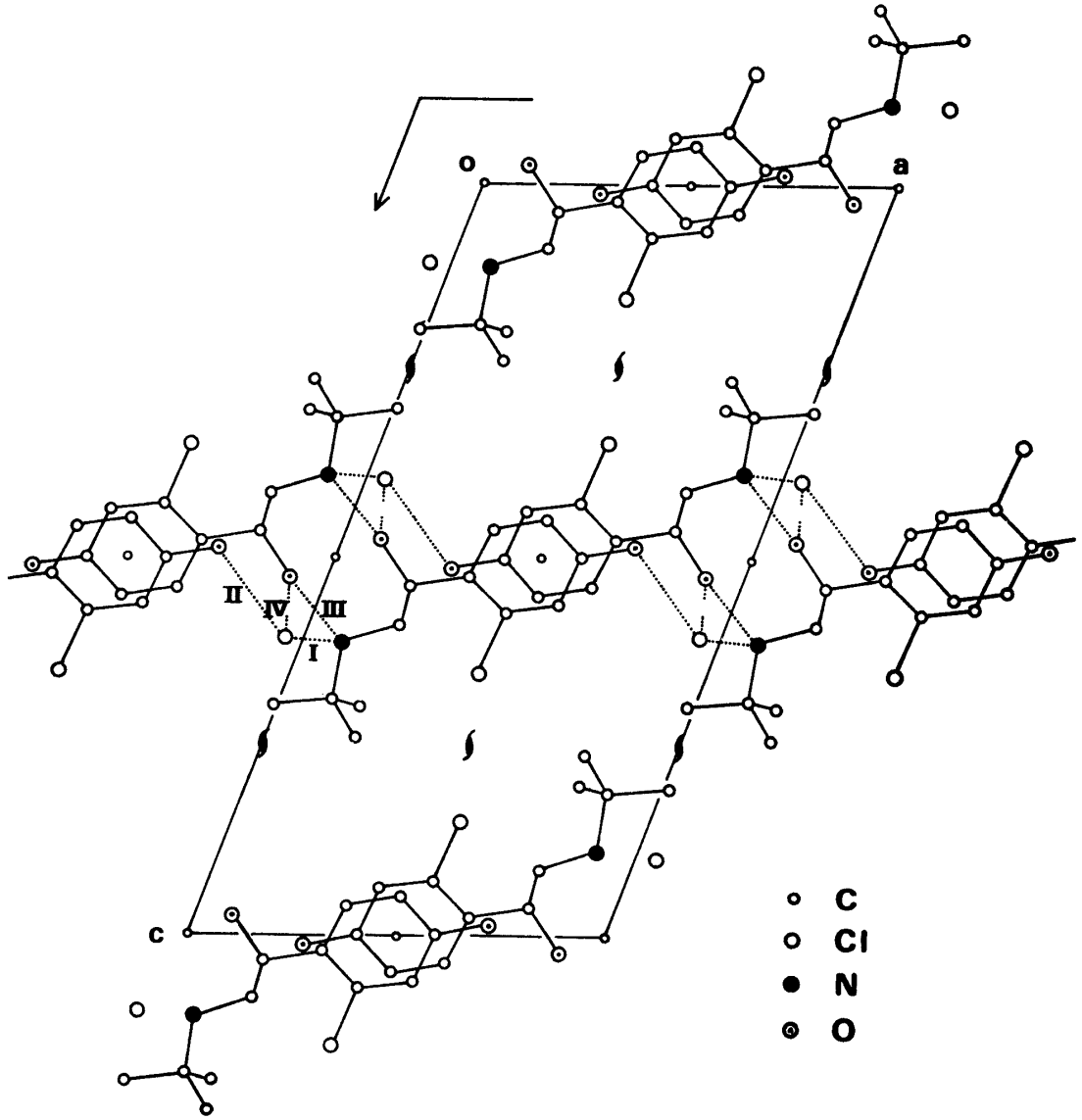


Fig. 2. The Crystal Structure of Form I viewed along the *b* Axis
Four independent hydrogen bonds are indicated by broken lines numbered I to IV.

I, 163°; Form II, 170°; Form III, 149°), (2) the heat of fusion of HOKU-81 polymorphs (Form I, 8.31 kcal/mol; Form II, 7.89 kcal/mol) are greater than those of C-78 polymorphs (Form I, 5.15 kcal/mol; Form II, 4.76 kcal/mol; Form III, 1.78 kcal/mol) and (3) polymorphs of HOKU-81 are more resistant than those of C-78 to humidity and mechanical treatments such as grinding or compressing.

Table VII also shows that common conformational features exist in the stereostructures of HOKU-81, C-78 and other adrenergic stimulants or blocking agents which have the ethanolamine side chain, such as *dl*-isoproterenol sulfate dihydrate[10] (β-stimulant), adrenaline hydrogen tartrate[11] (α- and β-stimulant), noradrenaline hydrochloride[12] (α-stimulant), propranolol and alprenolol hydrochlorides[13] and carteolol hydrochloride[14] (β-adrenergic blocking agent).

The aromatic group in adrenergic stimulants and the aryloxymethyl group in adrenergic blocking agents are *trans* to the amino nitrogen and the hydroxy group in the ethanolamine side chain is *gauche* to it. On the other hand, NMR studies of HOKU-81 and C-78 also suggested

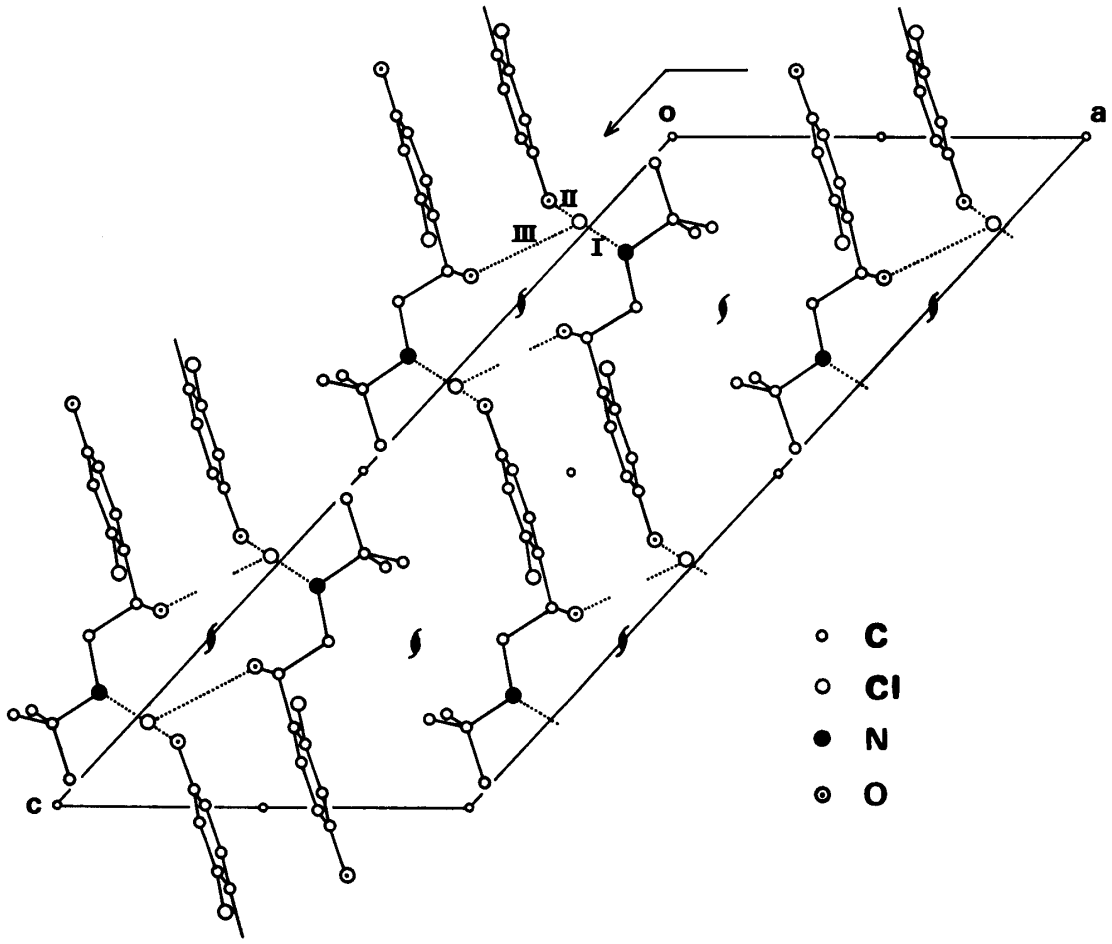
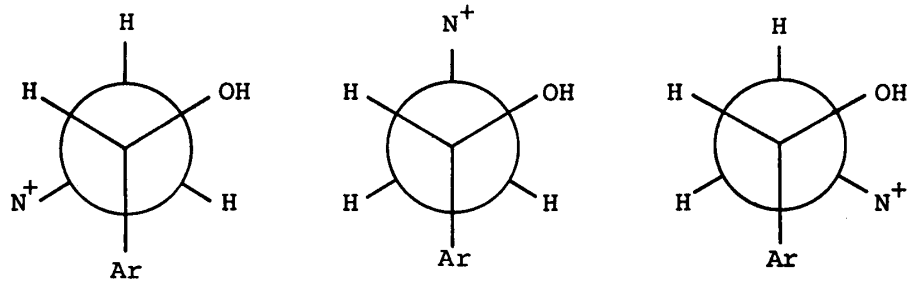


Fig. 3. The Crystal Structure of Form II viewed along the *b* Axis

Three independent hydrogen bonds are indicated by broken lines numbered I to III.



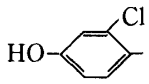
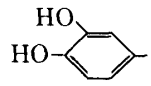
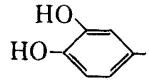
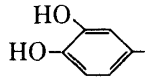
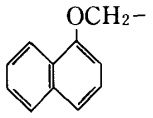
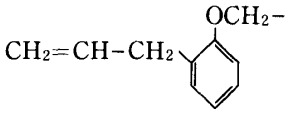
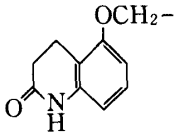
I II III

Chart 1

that the preferred conformation in solution is the rotamer II (Chart 1), as is case for catecholamines,[15] and this coincides with the conformation commonly observed in the crystalline state.

In conclusion, these stereostructural comparisons strongly support that the steric arrangement of the functional groups found in HOKU-81, C-78 and other adrenergic agents having the ethanolamine side chain is required for the elicitation of adrenoceptor-effecting activity.[16]

TABLE VII. Torsion Angles about C(7)-C(8) in Crystals of HOKU-81, C-78 and Other Adrenergic Agents having an Ethanolamine Side Chain

Compound	Chemical structure of base: R_1	R_2	Torsion angle[a] τ_0 (°) τ[C(2)-C(1)-C(7)-C(8)]	τ_1 (°) τ[R_1-C(7)-C(8)-N]	τ_2 (°) τ[O-C(7)-C(8)-N]
HOKU-81		$-C(CH_3)_3$			
Form I			± 76	∓172	±65
Form II			± 80	∓175	±64
C-78[b]		$-C(CH_3)_3$			
Form I[c]			± 91	∓171	±71
			± 97	∓170	±72
			± 84	∓170	±72
Form II			±108	∓172	±72
Form III			±103	∓174	±68
Hydrate			± 87	∓178	±62
dl-Isoproterenol sulfate dihydrate[d]		$-CH(CH_3)_2$		∓175	±62
				± 177	±50
Adrenaline hydrogen tartrate[e]		$-CH_3$		∓179	±58
Noradrenaline hydrochloride[f]		$-H$		∓176	±64
Propranolol hydrochloride[g]		$-CH(CH_3)_2$		±176	±50
Alprenolol hydrochloride[g]		$-CH(CH_3)_2$		∓170	±75
Carteolol hydrochloride[h]		$-C(CH_3)_3$		∓160	±97

a) ± and ∓ are used because the absolute configuration of the molecule is not determined. The upper signs in each row and the lower ones each describe one enantiomer.
b) See reference 7.
c) Three molecules exist in the asymmetric unit.
d) See reference 10. Two molecules exist in the asymmetric unit.
e) See reference 11.
f) See reference 12.
g) See reference 13.
h) See reference 14.

Further investigation on the structure-activity relationship, especially on the factor determining the medicinal specificity (α, β_1 or β_2-stimulant or blocking agent) is expected.

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