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The Crystal Structure of Carteolol Hydrochloride [5-(3-*tert*-Butylamino-2-hydroxy)propoxy-3,4-dihydro-2-quinolone, OPC-1085]

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The crystal structure of carteolol hydrochloride ($C_{16}H_{24}N_2O_3 \cdot HCl$), a novel β-adrenergic blocking agent, was determined by X-ray diffraction analysis. The crystal is monoclinic and the space group is P $2_1/n$ with $Z=4$. The cell dimensions are $a=7.873(4)$, $b=26.435(19)$, $c=8.549(7)$ Å, and $\beta=105.67(6)°$. 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 0.054. Cl^- anion forms two hydrogen bonds with the cationic amino group and one with the hydroxy group. The amino and hydroxy groups are relatively close together, but no intramolecular hydrogen bond is formed. The C(3)—C(4) bond distance of the 3,4-dihydro-2-quinolone ring, 1.397 Å, is rather shorter than a normal single bond distance but it seems probable that the bond is actually single and that the C(3) and C(4) atoms deviate from the least-squares ring plane by 0.42 Å and 0.30 Å, respectively, to opposite sides.

Keywords——carteolol hydrochloride; β-adrenergic blocking agent; arylpropoxinolamine; 3,4-dihydro-2-quinolone; X-ray crystal structure analysis

According to various papers on the structure-activity relationship of adrenergic drugs,[1-4] the stereostructural requirement is relatively strict, even when the structures are chemically similar to each other. Beta-adrenergic blocking agents can be regarded as derivatives of arylethanolamines or arylpropoxinolamines with an aromatic ring, ethanol or propoxinol groups, and amino groups as substituents.

Carteolol hydrochloride [5-(3-*tert*-butylamino-2-hydroxy) propoxy-3,4-dihydro-2-quinolone hydrochloride, OPC-1085][5] (Chart 1) is a β-adrenergic blocking agent which belongs to the arylpropoxinolamine class. Its pharmaceutical action was reported by Yabuuchi *et al.*[6] to be 20—30 times more potent than that of propranolol. The structural specificity of carteolol hydrochloride is found in its ring moiety rather than in its side chain, but no detailed study on the conformation of the 3,4-dihydro-2-quinolone ring has been reported.

As a part of our studies on the pharmaceutical function of adrenergic drugs, X-ray crystal structure analysis of carteolol hydrochloride has been carried out.

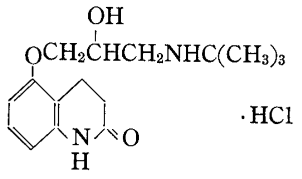


Chart 1

Experimental

Colorless, plate-like crystals of carteolol hydrochloride ($C_{16}H_{24}N_2O_3 \cdot HCl$) were obtained by slow evaporation of its aqueous solution at room temperature. *Anal.* Calcd for $C_{16}H_{24}N_2O_3 \cdot HCl$: C, 58.44; H, 7.66; N, 8.52. Found: C, 58.28; H, 7.80; N, 8.55, MS *m/z*: 292 (M^+, Calcd for $C_{16}H_{24}N_2O_3$ 292.1786, Found 292.1798); ^1H NMR δ: 1.44 (9H, s), 2.51 (2H, t, 7.9 Hz), 2.88 (2H, t, 7.9 Hz), 4.09 (1H, dd, 10.4 Hz, 5.1 Hz), 4.15 (1H, dd, 10.4 Hz, 4.5 Hz), 4.33 (1H, m), 6.56 (1H, d, 8.2 Hz), 6.74 (1H, d, 8.2 Hz), 7.20 (1H, dd, 8.2 Hz, 8.2 Hz). A crystal with dimensions of $0.1 \times 0.1 \times 0.2$ mm was used for the X-ray work. The cell dimensions were refined by a least-squares method, using 20 reflections measured on a Syntex R3 four-circle automated diffractometer with graphite-monochromated Mo $K\alpha$ radiation. The crystal data are summarized in Table I. Intensity data were collected on the diffractometer with an ω-scan mode (scan width of 1°) in a 2θ range of less than 40°. The scan speed was changed in accordance with the intensities of each reflection, and backgrounds were measured at both ends of the scan range. Three reflections monitored periodically showed no significant intensity fluctuations during the course of data collection. A total of 1604 independent reflections were collected, among which 1235 reflections ($I > 1.96\sigma(I)$) were used as observed; their intensities were corrected for Lorentz and polarization factors, but not for absorption.

TABLE I. Crystal Data

Molecular formula	$C_{16}H_{24}N_2O_3 \cdot HCl$
Molecular weight	328.84
Crystal system	Monoclinic
Unit cell a, Å	7.873(4)
b, Å	26.435(19)
c, Å	8.549(7)
β, degree	105.67(6)
Space group	$P2_1/n$
Z	4
Dm, Mg/m^3	1.28
Dx, Mg/m^3	1.28
μ(Mo $K\alpha$)/cm	2.4

Determination and Refinement of the Structure

The structure was solved by a direct method using the MULTAN program. The resulting E map revealed the positions of all non-hydrogen atoms. All the hydrogen atoms except for those bonded to C(3) or C(4) were found on a difference Fourier map. The refinement of atomic parameters was carried out by the block-diagonal least-squares method, minimizing $\sum w(|F_o| - |F_c|)^2$, where $w = 1.0$ for all the reflections. Thermal parameters were refined anisotropically for all the non-hydrogen atoms and isotropically for the hydrogen atoms. The final R-value was 0.054. The atomic scattering factors were taken from "International Tables for X-ray Crystallography".[7] The final atomic coordinates and thermal parameters are shown in Table II. The observed and calculated structure factors are listed in Table III.[8]

All the computations were made on a NOVA-3 computer using the Syntex XTL programs.

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

A) Atomic Coordinates ($\times 10^4$) and Anisotropic Temperature Factors for Non-Hydrogen Atoms

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	5223(3)	2609(1)	3608(2)	4.6(1)	6.0(1)	4.5(1)	−2.0(1)	1.8(1)	−1.8(1)
O(1′)	14124(7)	4400(2)	15231(5)	6.9(3)	4.2(3)	4.0(3)	−0.2(2)	0.8(2)	−0.0(2)
O(2′)	10569(6)	4070(2)	7839(5)	5.7(3)	3.2(2)	3.6(2)	−1.4(2)	0.1(2)	0.1(2)
O(3′)	7617(6)	3617(2)	4157(5)	6.0(3)	4.9(3)	3.6(2)	−1.4(2)	1.1(2)	−0.2(2)
N(1)	13714(7)	4807(2)	12839(6)	4.2(3)	3.4(3)	3.4(3)	−0.5(3)	0.5(3)	0.1(2)
O(2′)	6760(6)	3040(2)	7121(6)	2.8(3)	2.8(3)	3.6(3)	0.1(2)	1.2(2)	0.4(2)
C(2)	13528(9)	4404(3)	13723(8)	4.6(4)	4.9(4)	3.0(3)	0.8(3)	0.6(3)	0.4(3)

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(3)	12479(15)	3960(3)	12829(9)	17.0(9)	5.4(5)	4.1(4)	−6.2(6)	−0.2(5)	−0.5(4)
C(4)	11914(12)	3943(3)	11135(8)	10.5(6)	4.0(4)	3.2(4)	−2.3(4)	0.4(4)	1.7(3)
C(5)	11430(9)	4491(2)	8616(8)	2.8(4)	3.2(3)	4.4(4)	−0.6(3)	1.1(3)	−0.4(3)
C(6)	11620(9)	4938(2)	7794(8)	3.6(4)	3.6(4)	3.8(3)	−0.6(3)	0.9(3)	0.5(3)
C(7)	12551(9)	5338(2)	8720(8)	4.1(4)	3.6(4)	3.9(4)	−0.8(3)	1.4(3)	0.5(3)
C(8)	13222(9)	5292(2)	10361(8)	3.7(4)	2.9(3)	4.2(3)	−0.4(3)	1.3(3)	−0.5(3)
C(9)	12110(8)	4431(2)	10288(7)	3.1(4)	3.9(4)	2.9(3)	−0.4(3)	0.2(3)	−0.2(3)
C(10)	13012(8)	4847(2)	11149(7)	3.3(4)	3.1(3)	3.0(3)	0.3(3)	0.7(3)	0.0(3)
C(11)	9549(9)	4104(2)	6193(7)	4.6(4)	4.0(4)	2.8(3)	−1.0(3)	1.1(3)	−0.3(3)
C(12)	8528(9)	3608(2)	5857(7)	4.0(4)	3.3(3)	2.3(3)	−0.4(3)	0.8(3)	−0.0(3)
C(13)	7316(8)	3573(2)	6944(7)	3.2(4)	3.0(3)	3.9(4)	−0.1(3)	1.6(3)	0.4(3)
C(14)	5482(9)	2960(3)	8172(8)	3.6(4)	4.4(4)	4.0(4)	0.5(3)	1.6(3)	1.5(3)
C(15)	5240(10)	2386(3)	8221(9)	6.4(5)	4.5(4)	6.3(4)	−0.6(4)	3.2(4)	1.7(4)
C(16)	3746(9)	3227(3)	7323(9)	3.5(4)	6.1(4)	6.7(5)	0.4(4)	2.7(4)	1.7(4)
C(17)	6287(10)	3179(3)	9853(8)	6.8(5)	7.2(5)	3.6(4)	0.4(4)	2.4(4)	0.7(4)

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

B) Atomic Coordinates ($\times 10^3$) and Isotropic Temperature Factors for Hydrogen Atoms$^{a)}$

	x	y	z	B
H(O3′)	693(8)	330(2)	390(7)	7.5(17)
H(1)	1439(8)	504(2)	1354(7)	7.9(19)
H(N2′)-1	281(7)	220(2)	252(6)	4.6(14)
H(N2′)-2	609(7)	288(2)	593(6)	6.5(16)
H(6)	1109(7)	499(2)	656(6)	4.8(14)
H(7)	1268(7)	565(2)	810(6)	4.0(15)
H(8)	1387(7)	557(2)	1101(6)	4.2(14)
H(11)-1	1034(7)	412(2)	536(6)	4.2(14)
H(11)-2	857(7)	440(2)	600(6)	5.5(15)
H(12)	947(5)	331(2)	601(5)	0.6(10)
H(13)-1	626(7)	380(2)	641(6)	4.4(14)
H(13)-2	809(7)	368(2)	817(6)	6.6(16)
H(15)-1	510(7)	224(2)	708(6)	6.9(16)
H(15)-2	471(7)	233(2)	900(6)	6.8(16)
H(15)-3	647(8)	222(2)	903(6)	7.9(16)
H(16)-1	380(7)	363(2)	740(7)	6.6(15)
H(16)-2	294(7)	317(2)	787(6)	5.7(14)
H(16)-3	325(8)	308(2)	606(7)	8.6(16)
H(17)-1	625(8)	356(2)	992(7)	8.7(18)
H(17)-2	745(7)	303(2)	1035(7)	7.4(16)
H(17)-3	559(8)	308(2)	69(7)	9.4(18)

a) Hydrogen atoms are given the numbers of the atoms to which they are bonded.

Results and Discussion

The molecular structure with the atomic numbering of carteolol hydrochloride and the molecular packing are shown in Figs. 1 and 2, respectively. Bond distances and angles with their standard deviations are listed in Tables IV and V. No abnormal distance or angle was found in the structure except for the C(3)–C(4) bond which is significantly shorter than the normal C–C single bond. The *tert*-butylamino nitrogen, N(2′), is protonated and has a tetrahedral sp^3 hybrid bond, involving two N^+–H---Cl^- hydrogen bonds (3.133 and 3.181 Å). Since the distances of O(3′)–H(O3′), H(O3′)–Cl^-, and O(3′)–Cl^-, and the angle of O(3′)–H(O3′)–Cl^- are 1.00, 2.23, 3.22 Å and 172 °, respectively, it is clear that the O(3′)–H---Cl^- hydrogen bond is formed. The average C–C bond distance of the benzene ring is 1.392 Å. The ring systems of the two molecules related by a center of symmetry form a cyclic dimer with an

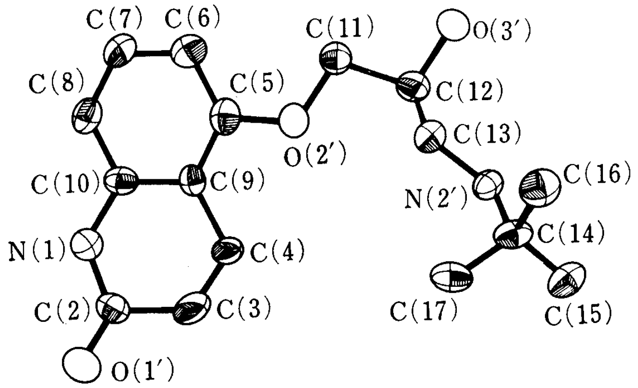


Fig. 1. Molecular Structure and Atomic Numbering of Carteolol Hydrochloride

Each atom is represented by a thermal ellipsoid at 50% probability.

N(1)–H---O(1′) hydrogen bond (2.915 Å) and these dimers stack with an interplanar distance of 3.50 Å. The side chain portions adopt a folded conformation and the polar groups form a hydrophilic region at y=1/4 and 3/4, connected by N$^+$–H---Cl$^-$ and O–H---Cl$^-$ hydrogen bonds.

The deviations of individual atoms from the least-squares plane of the 3,4-dihydro-2-quinolone ring are listed in Table VI. It appears that the average conformation of the 3,4-dihydro-2-quinolone ring is nearly planar. From the thermal parameters listed in Table II, however, the anisotropic motions of C(3) and C(4) atoms are characterized by abnormally large B_{11} values, and such an observation can hardly be explained only in terms of thermal vibrations. It seems likely that some sorts of conformational disorder are involved; the observed ring conformation could be interpreted as a result of the superposition of two or more different conformers. Now, let us consider two different conformers, N- and S-conformers, where the C(3) and C(4) atoms are symmetrically displaced to either side of the average ring plane as shown in Fig. 3. The extent of the displacement can be approximately evaluated by assuming that the observed thermal parameters perpendicular to the average ring plane, B_{11}, are equal to $8\pi^2(\sigma^2+t^2)$,[9,10] where σ^2 and t^2 are the mean-square amplitudes due to the conformational disorder and thermal vibration, respectively. If the value $8\pi^2t^2$ is taken to be equal

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

O(1′)-C(2)	1.248(8)	O(2′)-C(5)	1.376(8)
O(2′)-C(11)	1.422(7)	O(3′)-C(12)	1.437(7)
N(1)-C(2)	1.337(8)	N(1)-C(10)	1.404(8)
N(2′)-C(13)	1.496(8)	N(2′)-C(14)	1.533(8)
C(2)-C(3)	1.518(11)	C(3)-C(4)	1.397(10)
C(4)-C(9)	1.510(10)	C(5)-C(6)	1.403(9)
C(5)-C(9)	1.393(9)	C(6)-C(7)	1.403(9)
C(7)-C(8)	1.364(9)	C(8)-C(10)	1.390(9)
C(9)-C(10)	1.403(9)	C(11)-C(12)	1.526(9)
C(12)-C(13)	1.504(9)	C(14)-C(15)	1.532(10)
C(14)-C(16)	1.535(10)	C(14)-C(17)	1.520(9)
C(2)-N(1)-C(10)	124.6(6)	O(1′)-C(2)-N(1)	121.5(6)
O(1′)-C(2)-C(3)	121.0(7)	N(1)-C(2)-C(3)	117.4(6)
C(2)-C(3)-C(4)	121.6(8)	C(3)-C(4)-C(9)	115.1(7)
O(2′)-C(5)-C(6)	123.0(6)	O(2′)-C(5)-C(9)	114.0(6)
C(6)-C(5)-C(9)	123.0(6)	C(5)-C(6)-C(7)	117.5(6)
C(6)-C(7)-C(8)	120.8(6)	C(7)-C(8)-C(10)	120.6(6)
C(4)-C(9)-C(5)	121.9(6)	C(4)-C(9)-C(10)	121.4(6)
C(5)-C(9)-C(10)	116.8(6)	N(1)-C(10)-C(8)	119.8(6)
N(1)-C(10)-C(9)	119.0(6)	C(8)-C(10)-C(9)	121.2(6)
C(5)-O(2′)-C(11)	120.0(5)	O(2′)-C(11)-C(12)	105.1(5)
O(3′)-C(12)-C(11)	105.6(5)	O(3′)-C(12)-C(13)	113.5(5)
C(11)-C(12)-C(13)	109.0(5)	N(2′)-C(13)-C(12)	111.8(5)
C(13)-N(2′)-C(14)	116.4(5)	N(2′)-C(14)-C(15)	104.9(5)
N(2′)-C(14)-C(16)	107.5(5)	N(2′)-C(14)-C(17)	109.3(5)
C(15)-C(14)-C(16)	111.5(6)	C(15)-C(14)-C(17)	112.0(6)
C(16)-C(14)-C(17)	111.3(6)		

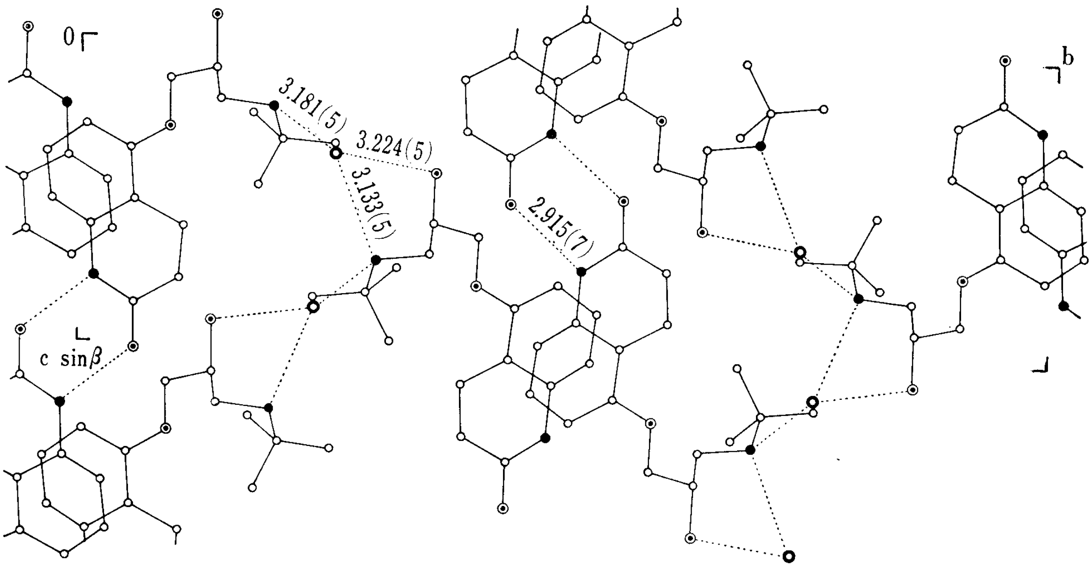


Fig. 2. The Molecular Packing of Carteolol Hydrochloride in the Crystal Projected Along the a-axis

The hydrogen bonds are shown by broken lines.
O: Cl⁻ ⊙: O ●: N ○: C

TABLE V. Bond Distances (Å) and Angles (°) Involving Hydrogen Atoms, with estimated Standard Deviations in Parentheses

H(O3′)-O(3′)	1.00(6)	H(1)-N(1)	0.92(6)
H(N2′)-1-N(2′)	1.03(5)	H(N2′)-2-N(2′)	1.09(5)
H(6)-C(6)	1.03(5)	H(7)-C(7)	0.99(5)
H(8)-C(8)	0.97(5)	H(11)-1-C(11)	1.07(5)
H(11)-2-C(11)	1.09(6)	H(12)-C(12)	1.07(4)
H(13)-1-C(13)	1.03(5)	H(13)-2-C(13)	1.10(5)
H(15)-1-C(15)	1.03(5)	H(15)-2-C(15)	0.88(6)
H(15)-3-C(15)	1.12(6)	H(16)-1-C(16)	1.08(5)
H(16)-2-C(16)	0.90(6)	H(16)-3-C(16)	1.12(6)
H(17)-1-C(17)	1.01(6)	H(17)-2-C(17)	0.98(6)
H(17)-3-C(17)	1.05(6)		
H(1)-N(1)-C(2)	107(4)	H(1)-N(1)-C(10)	128(4)
H(6)-C(6)-C(5)	123(3)	H(6)-C(6)-C(7)	119(3)
H(7)-C(7)-C(6)	115(3)	H(7)-C(7)-C(8)	124(3)
H(8)-C(8)-C(7)	121(3)	H(8)-C(8)-C(10)	118(3)
H(11)-1-C(11)-O(2′)	113(3)	H(11)-1-C(11)-C(12)	106(3)
H(11)-1-C(11)-H(11)-2	113(4)	H(11)-2-C(11)-O(2′)	113(3)
H(11)-2-C(11)-C(12)	106(3)	H(12)-C(12)-O(3′)	106(2)
H(12)-C(12)-C(11)	108(2)	H(12)-C(12)-C(13)	114(2)
H(13)-1-C(13)-N(2′)	112(3)	H(13)-1-C(13)-C(12)	105(3)
H(13)-1-C(13)-H(13)-2	117(4)	H(13)-2-C(13)-N(2′)	104(3)
H(13)-2-C(13)-C(12)	107(3)	H(15)-1-C(15)-C(14)	110(3)
H(15)-1-C(15)-H(15)-2	134(5)	H(15)-1-C(15)-H(15)-3	107(4)
H(15)-2-C(15)-C(14)	105(3)	H(15)-2-C(15)-H(15)-3	89(5)
H(15)-3-C(15)-C(14)	108(3)	H(16)-1-C(16)-C(14)	114(3)
H(16)-1-C(16)-H(16)-2	99(5)	H(16)-1-C(16)-H(16)-3	114(4)
H(16)-2-C(16)-C(14)	110(3)	H(16)-2-C(16)-H(16)-3	109(5)
H(16)-3-C(16)-C(14)	109(3)	H(17)-1-C(17)-C(14)	115(4)
H(17)-1-C(17)-H(17)-2	114(5)	H(17)-1-C(17)-H(17)-3	101(5)
H(17)-2-C(17)-C(14	111(3)	H(17)-2-C(17)-H(17)-3	102(5)
H(17)-3-C(17)-C(14)	113(3)	H(N2′)-1-N(2′)-C(13)	113(3)
H(N2′)-1-N(2′)-C(14)	108(3)	H(N2′)-1-N(2′)-H(N2′)-2	102(4)
H(N2′)-2-N(2′)-C(13)	111(3)	H(N2′)-2-N(2′)-C(14)	105(3)
H(O3′)-O(3′)-C(12)	107(3)		

Table VI. The Deviations of Atoms from the Least-Squares Plane (Å)

C (5)*	0.000	N (1)	−0.007
C (6)*	−0.004	C (2)	−0.061
C (7)*	0.005	C (3)	−0.136
C (8)*	−0.001	C (4)	0.033
C (9)*	0.003	O (1′)	−0.117
C (10)*	−0.003	O (2′)	0.013

The atoms indicated by an asterisk were included in the calculation of the least-squares plane.

$0.9273x-0.3480y-0.1378z=1.3916$

to the average thermal factor (B_{11}) of ring atoms, 3.43 Å^2, the resulting σ values are 0.42 Å for C(3) and 0.30 Å for C(4), respectively. After correction with the σ values the C(3)–C(4) bond distance is estimated to be 1.57 Å, which is a reasonable single bond distance. On the other hand, the observed displacements of C(3) and C(4) from the average ring plane were not zero but 0.136 Å on the O(1′) side and 0.033 Å on the opposite side, respectively (Table VI). This may be explained by assuming that the occupancies for N– and S–conformers are about 0.6 and 0.4,[11] respectively. The non-equal ratio is probably a result of the steric or electrostatic effect of O(1′).

The conformation about the C(12)–C(13) bond in carteolol hydrochloride is given in Fig. 4, together with that found in propranolol and alprenolol hydrochlorides.[12] As a common

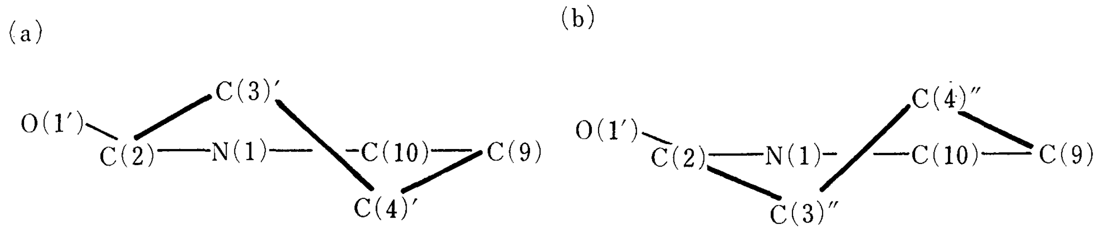
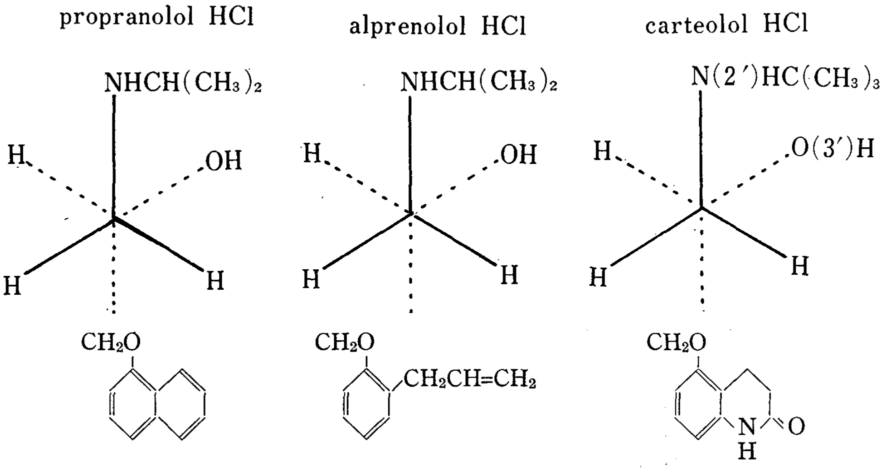


Fig. 3. Two Distinct Conformers of the 3,4-Dihydro-2-Quinolone Ring

a) N-conformer, b) S-conformer.



torsion angle (O(3′)-C(12)-C(13)-N(2′))	50°	75°	97°
distance (N(2′)-O(3′))	2.84 Å	2.95 Å	3.183 Å

Fig. 4. The Conformations about The C(12)–C(13) Bond of the Side Chain for Carteolol Hydrochloride, Propranolol Hydrochloride and Alprenolol Hydrochloride

feature in these three related compounds, the amino and hydroxy groups are specifically fixed; the torsion angle, O(3′)–C(12)–C(13)–N(2′), falls in the narrow range of 50 ° to 97 °, but there is no intramolecular O(3′)---N(2′) hydrogen bond. Such a fixed conformation may play an important role in the appearance of their activities. A possible reason why carteolol hydrochloride is more potent than the others in its pharmaceutical action may be its structural specificity, *i.e.*, the hydrogen bonding ability of the amide group in the 3,4-dihydro-2-quinolone ring, and this group may play a significant part in the interaction between carteolol base and the β-adrenergic receptor.

References and Notes

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11) The occupancies for N– and S–conformers may be calculated as follows.

$$O_N + O_S = 1 \qquad (1)$$

for the C(3) atom, $0.42\,O_N - 0.42\,O_S = 0.136$ (2)

for the C(4) atom, $0.30\,O_N - 0.30\,O_S = 0.033$ (3)

where O_N and O_S are the occupancies for N– and S–conformers, respectively. From (1), (2) and (1), (3), we obtain O_N values of 0.66 and 0.55, respectively, and the average O_N is 0.61.

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