The Structure of Celiprolol

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Received April 28, 1991; accepted September 4, 1991

The crystal structure and nuclear magnetic resonance (NMR) spectra and assignments of celiprolol, *N'*-[3-acetyl-4[3-[*N*-t-butylamino-2-hydroxypropoxy]phenyl]-*N,N*-diethylurea, are reported. Celiprolol crystallizes in the monoclinic space group, $P2_1/a$, with a = 9.081(2), b = 13.800(4), and c = 17.471(5) Å and β = 95.04(2)°. Structure was solved by direct methods; structure refinement to R of 0.058. Intermolecular hydrogen-bonding in the crystal is discussed. The ^1H, ^{13}C, and two-dimensional (2D) NMR spectra of the hydrochloride have been obtained and definitive signal assignments made.

KEY WORDS: celiprolol; crystal structure; two-dimensional nuclear magnetic resonance (2D NMR).

INTRODUCTION

Celiprolol · hydrochloride (Fig. 1) is a long-acting cardioselective β-adrenergic receptor blocking agent which also possesses α2-adrenergic receptor blocking properties (1–5). The compound induces vasodilatory and cardiostimulatory effects (6,7) but is devoid of local anesthetic activity (8). Celiprolol had been thought to show mild intrinsic sympathomimetic activity (9), which additional studies have failed to confirm (5). The structure of celiprolol is unique among the classical β-blockers in having a diethylurea substituent para to the propanolamine side chain. The substance is highly hydrophilic and does not penetrate into the central nervous system (5). These properties make celiprolol a desirable β-blocker.

Commercially celiprolol is synthesized from phenetidine (10,11). The position of the acyl function in celiprolol, was based on the IR frequency (12) of the acetyl carbonyl group (1670 cm^{-1}) and the chemical shift of the hydroxyl proton (3.53–3.60 ppm) in the PMR spectrum by analogy to *o*-hydroxyacetophenone (13). Both these values could be susceptible to concentration effects which were not addressed in deriving the above conclusion.

We have studied celiprolol by two-dimensional nuclear magnetic resonance (2D NMR) and single-crystal X-ray analysis to address above concerns and to study its crystal packing and conformation. This paper deals with the results of these studies.

MATERIALS AND METHODS

Celiprolol · hydrochloride (Rhône Poulenc Rorer Central Research R&D No. 6109) was synthesized by the Zölss method. Solvents were obtained from Fischer Scientific. 2D NMR spectra were recorded in deuterated methanol on a VXR-200-FT-NMR spectrometer. The proton and COSY spectra were referenced to TMS and the carbon and HETCOR spectra were referenced to the methanol peak (49 ppm). The single-crystal X-ray data were measured on an Enraf-Nonius CAD4 diffractometer.

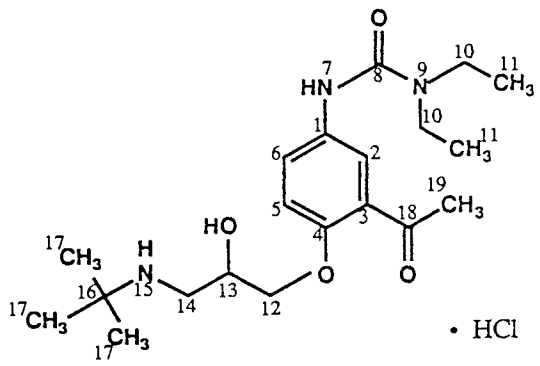

Fig. 1. Structure of celiprolol · hydrochloride.

Preparation of Celiprolol Single Crystals

Attempts to prepare single crystals of celiprolol·hydrochloride were unsuccessful. The free base was obtained by dissolving 500 mg of the hydrochloride salt in 10 ml of 0.5 *N* NaOH, extracting the solution with ethylacetate (3 × 15 ml), washing the ethyl acetate extract with water

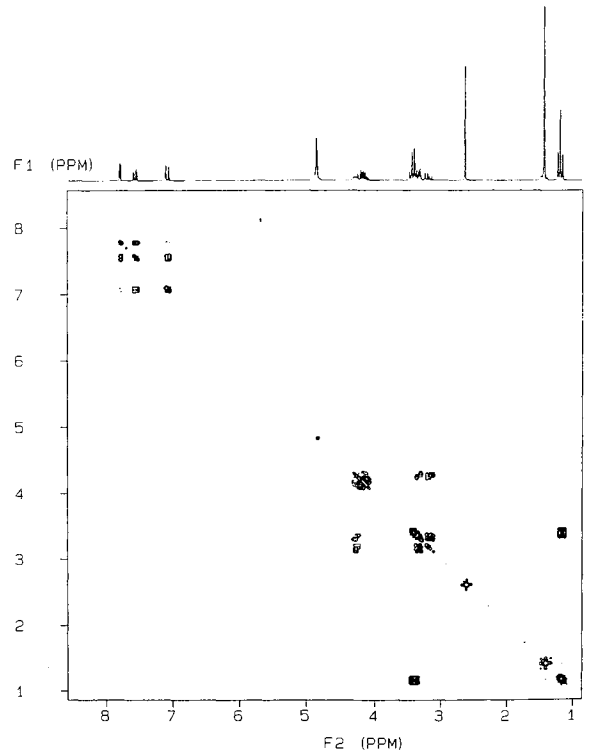

Fig. 2. Proton–proton homonuclear correlated spectrum of celiprolol · hydrochloride.

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0724-8741/92/0300-0365$06.50/0

Table I. Proton Assignment of Celiprolol

Proton	Chemical shift (ppm)
H-2	7.79
H-5	7.08
H-6	7.57
H-10	3.41
H-11	1.19
H-12, H-13	4.08–4.34
H-14	3.13–3.38
H-17	1.44
H-19	2.63

(5 ml), and drying over anhydrous Na_2SO_4. The solvent was evaporated and the residue dissolved in acetone (5 ml); hexane (1 ml) was added to this solution. The solution was then seeded, and the crystals were collected after 4 hr at room temperature.

Crystallographic Study of Celiprolol

Conditions were as follows: 0.10 × 0.26 × 0.46-mm crystals for X-ray measurements; Enraf-Nonius CAD-4 diffractometer; Cu radiation with incident beam monochromator (Cu Kα λ = 1.5418 Å); T = 293 K; cell parameters from 25 reflections centered in the range $8.6 < \theta < 22.0°$; monoclinic space group $P2_1/a$; a = 9.081(2), b = 13.800(4), and c = 17.471(5) Å, β = 95.04(2)°, V = 2181(2) Å^3, $\rho_{calc.}$ = 1.15 g cm^{-3}, Z = 4 (M_r = 387.49); intensity data measured with $2\theta - \theta$ scan at variable θ scan speed of 8.24–0.66° min^{-1}; θ scan range of $1.5(0.7 + 0.14\tan\theta)$, scan recorded as 96 steps with two outermost 16 step blocks for background determination; nine standard reflections measured every 1 hr of X-ray exposure; 3839 data (includes 199 standards) measured from θ = 2–60°; index range for h, k, and l of 0 to 10, 0 to 15, and −19 to 19; 3401 unique data; 2335 reflections with $I > 3\sigma(I)$; R_{sym} = 0.009 for 239 reflection pairs; average change in standard intensities of 0.5% with range of −0.9 to +2.9%; all crystallographic calculations performed with the TEXSAN program system (14) on a Digital Equipment Corp. MicroVax II computer; structure solved with the MITHRIL (15) direct methods link; refinement by full-matrix least-squares with anisotropic temperature factors for C, N, and O and isotropic terms for H, methyl-group H atom coordinates not refined; hydroxyl H atom could not be located in difference map and positioned on basis of strong intermolecular C=O. . .H−O interaction, these parameters not refined; $\Sigma[1/\sigma(F_o)]^2 (F_o - F_c)^2$ minimized; secondary extinction (16) refined; 319 variables; absorption correction with the Walker and Stuart procedure (17), final R, R_w, and goodness of fit = 0.058, 0.079, and 1.74; maximum Δ/σ =

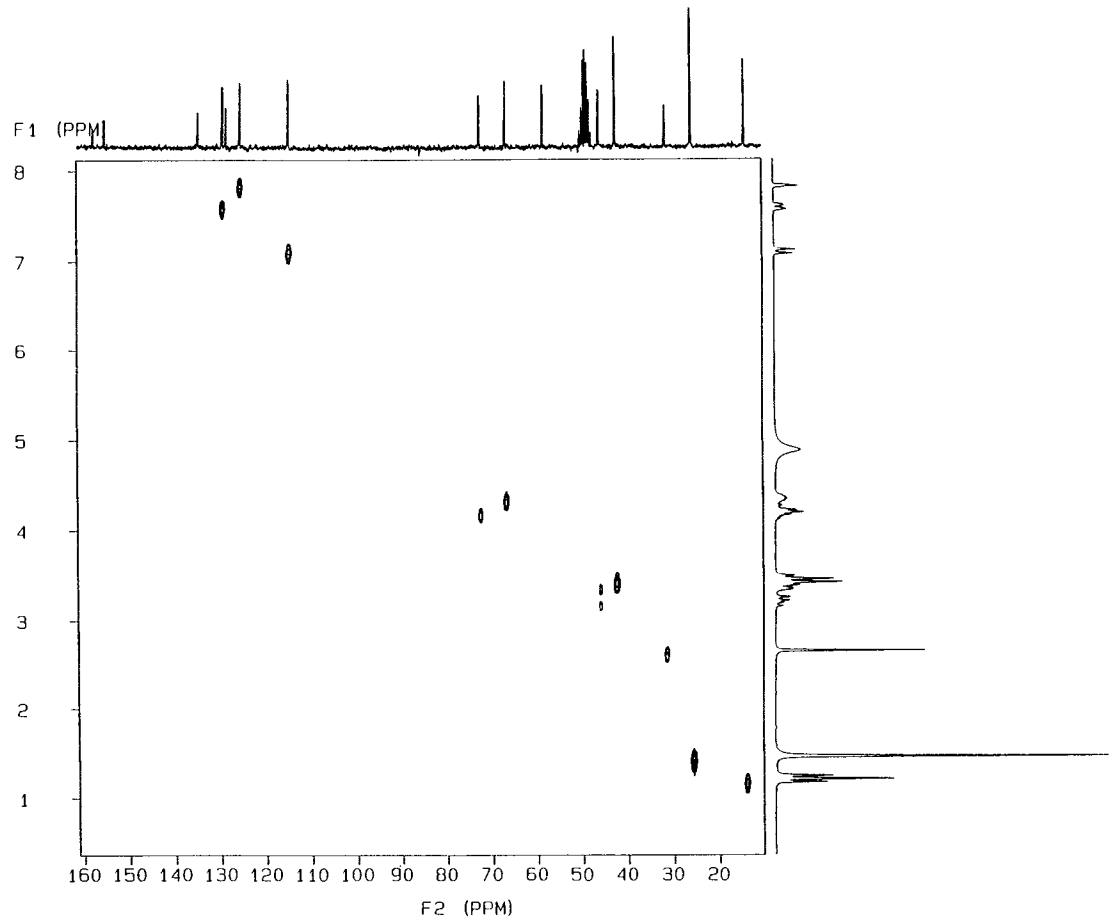

Fig. 3. Proton-^{13} heteronuclear correlated spectrum of celiprolol · hydrochloride.

Table II. Carbon Assignments of Celiprolol

Carbon No.	Chemical shift (ppm)
1	134.57
2	125.36
3	128.43
4	157.57
5	114.65
6	129.18
8	155.01
10	42.42
11	14.12
12	72.52
13	66.76
14	46.04
16	58.49
17	25.79
18	201.38
19	31.41

0.12; maximum and minimum values in final difference map of 0.13 and -0.18 e $Å^{-3}$. Tables of atomic coordinates, temperature factors, bond length and angles, and hydrogen bond characteristics are given below. Tables of hydrogen atom coordinates and temperature factors and structure factors are included as well. ORTEP drawings (18) are shown in Figs. 4 and 5; the PLOTMD program (19) was used to display the drawings on a DEC VaxStation II monitor, introduce atom labels, and prepare a plot file for a Hewlett-Packard Laserjet II printer.

2D NMR Data Acquisition

The proton–proton homonuclear correlated (COSY) spectrum was acquired with an initial delay of 1 sec and an observe pulse of 60° to deemphasize peaks on the diagonal. Zero filling was employed for Fourier transform of the raw data and the spectrum was symmetrized along the diagonal after transformation. The spectral width in both the dimensions was 1542 Hz. The proton–heteronuclear correlated spectrum was acquired along the *f2* axis with a ^{13}C spectral width of 7391 Hz and a spectral width of 1586.8 Hz along the proton dimension. Pseudo echo-shaped weighting and zero filling were used in Fourier transform of the interferogram.

RESULTS AND DISCUSSION

The proton–proton homonuclear correlated (COSY) spectrum of celiprolol · hydrochloride is shown in Fig. 2. All the protons were definitively assigned from the correlation peaks in the COSY spectrum and the assignments are listed in Table I. The proton–^{13}C heteronuclear correlated (HETCOR) spectrum is shown in Fig. 3. The assignment of ^{13}C signals based on the HETCOR spectrum is given in Table II. The NMR data allow the assignments of all the proton and ^{13}C resonances and agree with the structure (1). It should, however, be noted that the above data do not prove the location of the acetyl function at the position meta to the ureido group as opposed to the ortho position.

Crystal Structure of Celiprolol

Atomic coordinates and temperature factors for the carbon, nitrogen, and oxygen atoms are listed in Table III; an ORTEP drawing of a single molecule is shown in Fig. 4. The determination confirms the substitution pattern of the aromatic ring and overall structure. Table IV lists bond lengths, angles, and selected torsion angles; these parameters are normal. The urea and O3 of the propoxy chain are essentially coplanar with the aromatic ring. The acetyl is twisted approximately 16° from the ring, presumably as a result of the intramolecular contact between the acetyl methyl group (C13) and the adjacent propoxy substituent (O3). The observed C13. . .O3 nonbonded distance of 2.743(4) Å is substantially shorter than the 3.4 Å sum of the van der Waals radii of O and methyl. This crowding also can be seen in the substantial differences between the exocyclic bond angles at C2 of C12–C2–C3 = 117.1(2)° and C12–C2–C1 = 124.8(3)°.

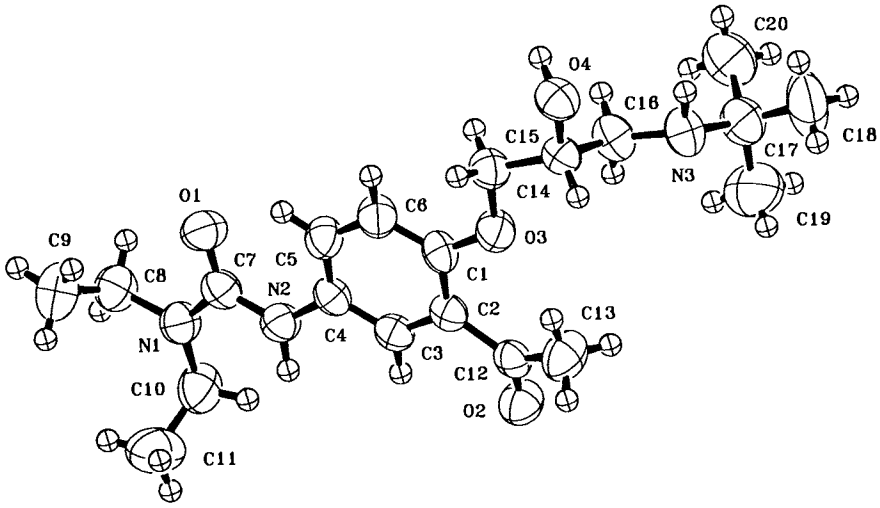

Fig. 4. ORTEP drawing of celiprolol. The C, N, and O atoms are shown as 50% ellipsoids and the H atoms as spheres with *B* of 1.5 $Å^2$.

Table III. Fractional Coordinates, Anisotropic Temperature Factors,[a] and Estimated Standard Deviations (in Parentheses) for Celiprolol

Atom	x	y	z
O1	0.6319(3)	0.3361(1)	−0.2063(1)
O2	0.3707(3)	0.0425(1)	0.0746(1)
O3	0.2756(3)	0.3285(1)	0.0986(1)
O4	0.1463(2)	0.5327(1)	0.2022(1)
N1	0.6922(3)	0.1933(2)	−0.2586(1)
N2	0.5511(3)	0.1975(2)	−0.1545(1)
N3	0.2583(3)	0.4050(2)	0.3261(2)
C1	0.3374(3)	0.3010(2)	0.0341(1)
C2	0.3650(3)	0.2014(20)	0.0253(1)
C3	0.4383(3)	0.1722(2)	−0.0375(2)
C4	0.4812(3)	0.2360(2)	−0.0921(2)
C5	0.4484(4)	0.3338(2)	−0.0834(2)
C6	0.3792(4)	0.3648(2)	−0.0209(2)
C7	0.6262(3)	0.2462(2)	−0.2060(2)
C8	0.7710(4)	0.2455(3)	−0.3152(2)
C9	0.6729(5)	0.2909(3)	−0.3788(2)
C10	0.7100(5)	0.0872(3)	−0.2572(2)
C11	0.6257(6)	0.0382(3)	−0.3235(3)
C12	0.3183(4)	0.1234(2)	0.0780(2)
C13	0.2039(5)	0.1412(3)	0.1326(2)
C14	0.2477(4)	0.4292(2)	0.1107(2)
C15	0.1944(4)	0.4357(2)	0.1901(2)
C16	0.3170(4)	0.4081(3)	0.2515(2)
C17	0.3586(4)	0.3699(3)	0.3907(2)
C18	0.2791(7)	0.3933(6)	0.4626(2)
C19	0.3782(8)	0.2611(4)	0.3818(4)
C20	0.5079(5)	0.4203(4)	0.3974(3)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	0.076(2)	0.065(1)	0.086(1)	−0.009(1)	0.020(1)	−0.006(1)
O2	0.086(2)	0.062(1)	0.083(2)	0.008(1)	0.016(1)	0.004(1)
O3	0.097(2)	0.057(1)	0.060(1)	0.010(1)	0.018(1)	−0.0017(9)
O4	0.069(2)	0.064(1)	0.072(1)	0.008(1)	0.006(1)	0.007(1)
N1	0.067(2)	0.066(1)	0.065(2)	−0.001(1)	0.017(1)	−0.004(1)
N2	0.068(2)	0.059(1)	0.065(2)	−0.005(1)	0.016(1)	−0.007(1)
N3	0.075(2)	0.091(2)	0.058(2)	0.009(2)	−0.001(1)	0.001(1)
C1	0.057(2)	0.064(2)	0.046(1)	0.011(1)	−0.001(1)	−0.001(1)
C2	0.044(2)	0.056(1)	0.051(1)	0.003(1)	−0.008(1)	−0.001(1)
C3	0.048(2)	0.056(2)	0.057(2)	0.002(1)	−0.004(1)	−0.006(1)
C4	0.048(2)	0.065(2)	0.051(2)	0.001(1)	−0.002(1)	−0.005(1)
C5	0.075(2)	0.061(2)	0.059(2)	0.009(2)	0.008(2)	0.005(1)
C6	0.090(3)	0.056(2)	0.061(2)	0.015(2)	0.011(2)	0.001(1)
C7	0.047(2)	0.069(2)	0.058(2)	−0.002(2)	−0.002(1)	−0.003(1)
C8	0.062(2)	0.084(2)	0.074(2)	0.000(2)	0.017(2)	0.000(2)
C9	0.018(4)	0.115(3)	0.079(2)	0.005(3)	0.022(3)	0.021(2)
C10	0.013(4)	0.077(2)	0.076(2)	0.014(2)	0.029(2)	0.001(2)
C11	0.122(5)	0.093(3)	0.132(4)	−0.023(3)	0.044(3)	−0.032(3)
C12	0.052(2)	0.060(2)	0.050(2)	−0.002(1)	−0.009(1)	−0.003(1)
C13	0.087(3)	0.081(2)	0.092(3)	0.005(2)	0.034(2)	0.009(2)
C14	0.076(3)	0.057(2)	0.060(2)	0.011(2)	0.006(2)	−0.004(1)
C15	0.056(2)	0.057(1)	0.054(2)	0.007(2)	0.002(1)	−0.002(1)
C16	0.060(2)	0.083(2)	0.0063(2)	0.008(2)	0.003(2)	−0.005(2)
C17	0.079(3)	0.096(3)	0.072(2)	−0.006(2)	−0.019(2)	0.007(2)
C18	0.131(5)	0.200(6)	0.061(3)	−0.020(4)	−0.003(3)	0.017(3)
C19	0.162(6)	0.100(3)	0.335(5)	0.000(4)	−0.046(4)	0.030(3)
C20	0.094(4)	0.135(4)	0.099(3)	−0.013(3)	−0.038(3)	0.004(3)

[a] The form of the anisotripic temperature factors is $\exp[-2\Pi^2 (U_{11}h^2a^* + \ldots 2U_{23}hlb * c^*)]$.

Table IV. Bond Distances (Å), Angles (°), Selected Torsion Angles (°), and Estimated Standard Deviations (in Parentheses) for the C, N, and O Atoms in Celiprolol

Bond distances					
Atoms		Distance	Atoms		Distance
O1	C7	1.242(3)	C2	C3	1.393(4)
O2	C12	1.217(3)	C2	C12	1.501(4)
O3	C1	1.356(3)	C3	C4	1.379(4)
O3	C14	1.432(3)	C4	C5	1.393(4)
O4	C15	1.429(3)	C5	C6	1.376(4)
N1	C7	1.354(4)	C8	C9	1.498(5)
N1	C8	1.461(4)	C10	C11	1.494(6)
N1	C10	1.472(4)	C12	C13	1.492(5)
N2	C7	1.355(4)	C14	C15	1.513(4)
N2	C4	1.413(3)	C15	C16	1.524(4)
N3	C16	1.452(4)	C17	C20	1.520(6)
N3	C17	1.468(4)	C17	C19	1.522(6)
C1	C6	1.381(4)	C17	C18	1.537(6)
C1	C2	1.407(4)			

Atoms			Angle	Atoms			Angle
Bond angles							
C1	O3	C14	119.1(2)	O1	C7	N2	121.5(3)
C7	N1	C8	117.8(3)	N1	C7	N2	117.5(3)
C7	N1	C10	125.4(3)	N1	C8	C9	114.4(3)
C8	N1	C10	116.2(3)	N1	C10	C11	112.9(4)
C7	N2	C4	127.8(3)	O2	C12	C13	118.6(3)
C16	N3	C17	116.6(3)	O2	C12	C2	119.7(3)
O3	C1	C6	123.9(3)	C13	C12	C2	121.6(3)
O3	C1	C2	117.0(2)	O3	C14	C15	105.5(2)
C6	C1	C2	119.0(3)	O4	C15	C14	108.5(2)
C3	C2	C1	118.1(3)	O4	C15	C16	110.2(2)
C3	C2	C12	117.1(2)	C14	C15	C16	111.0(3)
C1	C2	C12	124.8(3)	N3	C16	C15	109.6(3)
C4	C3	C2	122.9(3)	N3	C17	C20	113.4(3)
C3	C4	C5	117.9(3)	N3	C17	C19	108.6(3)
C3	C4	N2	117.8(3)	N3	C17	C18	104.7(3)
C5	C4	N2	124.3(3)	C20	C17	C19	110.4(4)
C6	C5	C4	120.3(3)	C20	C17	C18	108.7(4)
C5	C6	C1	121.8(3)	C19	C17	C18	110.9(5)
O1	C7	N1	121.0(3)				

Selected torsion angles									
O1	C7	N1	C8	.3(6)	C1	C2	C12	C13	16.5(5)
O1	C7	N1	C10	171.1(3)	C2	C1	O3	C14	179.0(3)
O1	C7	N2	C4	−5.5(5)	C3	C4	C5	C6	1.8(5)
O2	C12	C2	C3	15.3(4)	C3	C4	N2	C7	−166.4(3)
O2	C12	C2	C1	−166.0(3)	C3	C2	C12	C13	−162.2(3)
O3	C1	C6	C5	176.6(3)	C5	C4	N2	C7	15.8(5)
O3	C14	C15	O4	−172.6(2)	C6	C1	O3	C14	1.6(5)
O3	C14	C15	C16	66.2(3)	C7	N1	C8	C9	−76.7(4)
O4	C15	C16	N3	65.8(4)	C7	N1	C10	C11	115.0(4)
N1	C7	N2	C4	176.0(3)	C8	N1	C10	C11	−74.1(5)
N2	C7	N1	C8	178.8(3)	C9	C8	N1	C10	111.7(4)
N2	C7	N1	C10	−10.4(5)	C15	C16	N3	C17	174.0(3)
N2	C4	C3	C2	−178.1(3)	C16	N3	C17	C20	51.0(5)
N2	C4	C5	C6	179.6(4)	C16	N3	C17	C19	−72.1(5)
N3	C16	C15	C14	−174.0(3)	C16	N3	C17	C18	169.3(4)
C1	O3	C14	C15	−174.3(3)					
C1	C6	C5	C4	−1.4(6)					

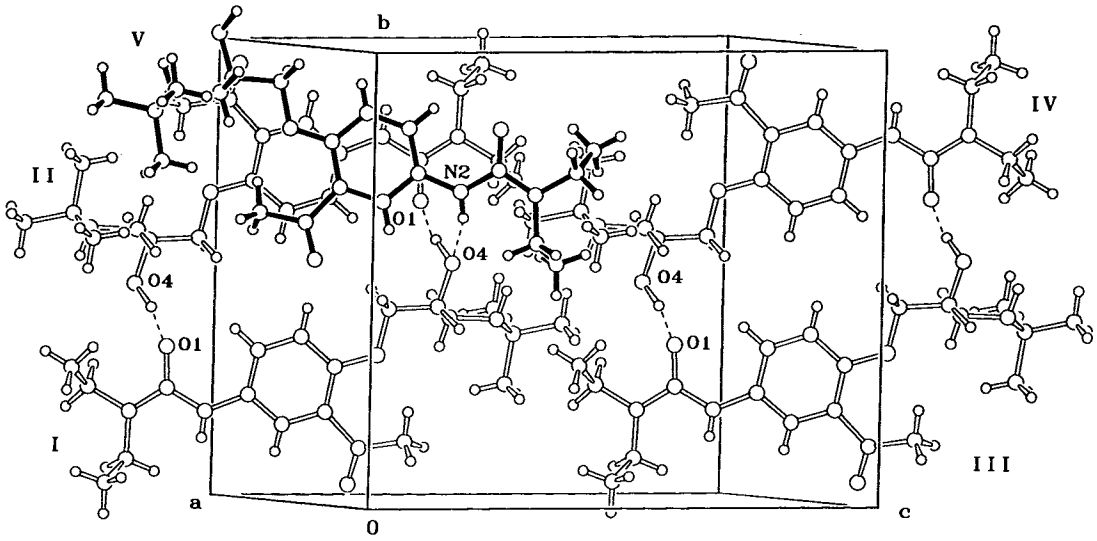

Fig. 5. Packing diagram of celiprolol. One of the molecules is shown with filled-in bonds to clarify molecular overlap. The symmetry operations indicated by the Roman numerals are I = x,y,z; II = $1-x, 1-y, -z$; III = $x,y, 1+z$; IV = $1-x, 1-y, 1-z$; V = $\frac{1}{2}-x, \frac{1}{2}+y, -z$. The O and N atoms involved in O–H. . .O=C and N–H. . .O intermolecular hydrogen-bonding are labeled and the contacts are shown with dashed lines. Intermolecular bond distances and angles are given in Table V.

A similar difference in exocyclic angles is found at C4, with C3–C4–N2 = 117.8(3)° and C5–C4–N2 = 124.3(3)°. The O1. . .C5 distance is 2.831(4) Å. The exocyclic bond angle differences at C1 of O3–C1–C6 = 123.9(3°) and O3–C1–C2 = 117.0(2)° cannot be rationalized on the basis of an intramolecular crowding effect.

The 3-*N*-t-butylaminopropoxy chain has a staggered conformation with dihedral angles, starting at O3–C14, of C1–O3–C14–C15 = −174.3(3), O3–C14–C15–C16 = 66.2(3), C14–C15–C16–N3 = −174.0(3), and C15–C16–N3–C17 = 174.0(3)°. The two oxygen substituents linked to C14–C15 show an anticonformation, with O3–C14–C15–O4 = −172.6(2)°.

A crystal packing diagram is shown in Fig. 5, and various characteristics of the two intermolecular hydrogen bonds are listed in Table V. The principal intermolecular contact is of the O–H. . .O=C type (O4–H22. . .O1=C7) between molecules related by a crystallographic center of symmetry. In Fig. 5, the pairs of molecules which have this relationship are (I, II) and (III, IV). This is a strong interaction, with O4. . .O1 = 2.694(3) Å. The hydroxyl oxygen atom (O4) also serves as a hydrogen bond acceptor from the urea group as O. . .H–N (O4. . .H2–N2). In Fig. 5, the hydroxyl acceptor and urea donor molecules (I, V) are related by a crystallographic screw dyad. This contact, with O4. . .N2 = 2.970(4) Å, is weaker than the hydroxyl. . .carbonyl interaction. The acetyl oxygen atom (O2) is not involved in any significant intermolecular contacts. All other intermolecular contacts are equal to or larger than the sums of the appropriate van der Waals radii.

The ends of the molecule, represented by the *N,N*-diethylurea and t-butylamino moieties, are hydrophobic and in contact with similar groups in neighboring molecules. In the solid-state conformation, the dispositions of acetyl and hydroxyl groups do not allow intramolecular hydrogen bonding between these groups.

^{13}C NMR studies employing solution of celiprolol containing calcium ions indicated that a 1:1 complex is formed involving acetyl carbonyl and hydroxyl group (20). Whether this has any effect on adenylcyclase and phospholipase inhibition remains to be determined. Structures of several other β-blockers appear to lack such structural features.

ACKNOWLEDGMENTS

This work was supported in part at the University of Maryland by equipment grants for a diffractometer (NSF, CHE-84-02155) and a computer/graphics system (NIH, RR-03354).

Table V. Intermolecular Hydrogen Bond Characteristics for Celiprolol

Atoms	X–H (Å)	X–H . . . O (Å)	X . . . O (Å)	X–H . . . O (°)
O4–H . . . O1 (II)[a]	0.96[b]	1.75[b]	2.694(3)	169[b]
O4 . . . H–N2 (V)	0.83(4)	2.30(4)	2.970(4)	140(1)

[a] Roman numerals refer to symmetry operations listed in Fig. 5.
[b] Values based on an assumed position for H.

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