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The Crystal Structures of Dichloroisoproterenol, Propranolol and Propranolol Hydrochloride*

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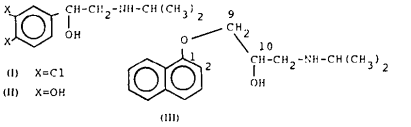
The crystal structures of three β-adrenergic antagonists have been determined with three-dimensional Mo $K\alpha$ X-ray diffraction data. The space groups and unit-cell parameters are: dichloroisoproterenol, monoclinic, $P2_1/a$, $a = 7{\cdot}948$, $b = 16{\cdot}778$, $c = 9{\cdot}826$ Å, $\beta = 101{\cdot}70°$; propranolol, monoclinic, $P2_1/a$, $a = 11{\cdot}760$, $b = 4{\cdot}807$, $c = 26{\cdot}509$ Å, $\beta = 99{\cdot}89°$; propranolol hydrochloride, monoclinic, $P2_1/n$, $a = 14{\cdot}017$, $b = 8{\cdot}285$, $c = 14{\cdot}005$ Å, $\beta = 98{\cdot}76°$. The structures were solved with direct methods and refined with full-matrix least-squares techniques to R indices of 0·048, 0·046 and 0·057 respectively. The H—C(10)—OH region of propranolol.HCl is disordered; previous work on the structure reported no evidence of disorder. The $-CH(OH)-CH_2-NH-$ sections of the side chains show the typical *gauche* conformation. The overall conformation of dichloroisoproterenol is quite similar to that of the hydrochloride, but different side-chain conformations occur in the case of propranolol, propranolol.HCl and (+)-propranolol.HCl.

Introduction

Dichloroisoproterenol (DCI, I) is the first selective adrenergic β-receptor blocking agent reported in the literature, and the discovery of its pharmacological activity (Powell & Slater, 1958) brought the full acceptance of Ahlquist's (1948) concept of α and β-receptors. DCI has been used extensively to investigate the adrenergic effects mediated by β-receptors, but the compound is too toxic to be used clinically to treat physiological disorders because of its great intrinsic β-sympathomimetic action. Propranolol (III; Black, Crowther, Shanks, Smith & Dornhorst, 1964) is another specific β-antagonist, but unlike DCI it is non-toxic and used clinically throughout the world to treat angina pectoris, various cardiac arrhythmias, hypertension, and other cardiovascular disorders (Crowther & Smith, 1968). Both compounds compete in a direct manner with β-agonists, such as isoproterenol (II), and effectively antagonize their adrenergic effects.



The common structural units in propranolol and DCI are an aromatic ring and an aminoethanol, $CH(OH)CH_2NHCH(CH_3)_2$, side chain. In DCI, the

* Studies of the Relationships between Molecular Conformation and Pharmacological Activity by X-ray Diffraction, Part II. Part I of this series: Ammon, Balsamo, Macchia, Macchia, Howe & Keefe (1975).

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dichlorobenzene and aminoethanol units are directly linked, whereas in propranolol the naphthalene nucleus and side chain are separated by an oxymethylene, $O-CH_2$, bridge. The structural basis for the similar activity of these two drugs has recently been suggested (Ammon, Balsamo, Macchia, Macchia, Howe & Keefe, 1975), with the proposal that the C(2)–C(1)–O–CH_2 portion of propranolol can electronically and sterically simulate a portion of the aromatic ring in catecholamines in the drug-receptor interaction.

We have investigated the crystal structures of the racemic forms of dichloroisoproterenol (I), propranolol (III) and propranolol hydrochloride (III.HCl) to clarify structural similarities and differences between these and other adrenergic compounds. Whereas the structure of III.HCl was reported (Dangoumau, Barrans & Cotrait, 1973; Barrans, Cotrait & Dangoumau, 1973; hereinafter BCD) when our work essentially had been completed, we have reason to believe that the OH group in their structure is disordered, and that the disorder was not detected (see *Discussion*). The structures of (+)-propranolol hydrochloride (Gadret, Goursolle, Leger & Colleter, 1975*a*), and dichloroisoproterenol hydrochloride (Gadret, Goursolle, Leger & Colleter, 1975*b*), pronethanol hydrochloride (Gadret, Goursolle, Leger & Colleter, 1975*c*), bupranolol hydrochloride (Gadret, Goursolle, Leger & Colleter, 1975*d*) and pindolol (Gadret, Goursolle, Leger & Colleter, 1976) have been published recently.* It is probable that the protonated forms of these drugs are responsible for the sympathetic response, since the compounds should be extensively protonated in the physiological environment (Perrin, 1965; Sinistri & Villa, 1962). However, the possibility that the free-base form could interact with a receptor (Serrano & Hardman, 1968) cannot be totally ignored and, therefore, a knowledge of the three-dimensional structures of both the free base and HCl salt forms of the drugs and the possibility of comparing them is of interest.

Experimental

The specific techniques used for the measurement of X-ray diffraction data have been previously detailed (Ammon, 1973). The final cell parameter and intensity measurements were made with a Picker FACS-I automatic diffractometer, equipped with a Mo X-ray source, and graphite-crystal monochromator (Mo $K\alpha$ $\lambda = 0{\cdot}71069$ Å, monochromator $2\theta = 12{\cdot}16°$). The cell constants were refined by the method of least squares from the Bragg angles obtained from manual measurements of $\pm 2\theta$ for each of 12 reflections. The θ–2θ scan method was used for data collection, and background measurements were made at the beginning and end of each reflection scan. Three standard reflections were monitored at intervals of 50–100 reflections to correct for intensity fluctuations.

The crystal and intensity measurement data are summarized in Table 1. The data were corrected for intensity fluctuations, Lorentz and polarization factors, but not for absorption. The three structures were solved in a routine manner with the X-RAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) direct methods subprogram *PHASE*. *E* maps revealed the locations of all of the C, N, O and Cl atoms. In the case of propranolol.HCl, two maxima were found in the region expected for the hydroxyl O atom, suggesting that the OH group was disordered (see below). Initial positions for H atoms connected to aromatic rings and CH_2 groups were calculated with a C–H distance of 1·0 Å; all of the other H atoms were located in difference maps with the exception of the atoms associated with the disordered CH–OH region of propranolol.HCl.

The structures were refined by full-matrix least squares with anisotropic temperature factors for C, N, O, Cl and isotropic terms for H. The function minimized for propranolol and dichloroisoproterenol was $\Sigma\,\mathrm{Wt}(|F_o| - |F_c|)^2$ where $\mathrm{Wt} = 1/\sigma^2(F)$; for propranolol.HCl, $\mathrm{Wt} = 1$ when $F \le 30$ and $\mathrm{Wt} = (30/F_o)^2$ when $F > 30$ (Hughes, 1941). Propranolol.HCl was refined with 0·5 population parameters assigned to the disordered OH oxygen atoms, and two 0·5 weight H atoms linked to the chiral C atom, C(10), were included in the calculations with $U = 0{\cdot}10$ Å^2 at a fixed C–H distance of 1·0 Å. The hydroxyl H atoms were omitted.

The F_c's were corrected for isotropic secondary extinction [equation (22) in Larson (1970)] assuming the crystals were 0·3 mm spheres. The scattering factors for C, O, N and Cl were generated from the analytical expressions of Cromer & Mann (1968); the scattering factors for H were those of Stewart, Davidson & Simpson (1965).

The final R $(\Sigma\,|F_o - F_c|/\Sigma\,F_o)$ and weighted R $\{[\Sigma\,\mathrm{Wt}\,(F_o - F_c)^2/\Sigma\,\mathrm{Wt}\,F_o^2]^{1/2}\}$ values were 0·046 and 0·021 for propranolol, 0·057 and 0·064 for propranolol.HCl, and 0·048 and 0·037 for dichloroisoproterenol. Refinement of the propranolol.HCl population parameter, $P_{O(2A)}$, with all other variables fixed, gave a value of 0·515 (5) ($P_{O(2B)} = 0{\cdot}485$); the R and weighted R values were 0·058 and 0·064.

The atomic parameters for dichloroisoproterenol and propranolol are listed in Tables 2 and 3, while only

* The levorotatory isomers are the more potent forms of the adrenergic β-receptor antagonists. The active dichloroisoproterenol-like compounds have the (*R*)-configuration, whereas the active configuration of the propranolol-like molecules is (*S*) (Howe & Rao, 1968; Dukes & Smith, 1971). The atomic coordinates reported for these molecules provide the following configurational information: (*R*)-dichloroisoproterenol.HCl, (*R*)-pronethanol.HCl, (*R*)-pindolol, (*S*)-bupranolol.HCl, (*R*)-propranolol.HCl and (*S*)-(+)-propranolol. Note that the (*S*)-configuration reported for (+)-propranolol is incorrect; the structure should have the (*R*)-configuration [*i.e.* it should be (*R*)-(+)-propranolol].

Table 1. *Crystal and intensity-measurement data*

	Dichloroisoproterenol	Propranolol	Propranolol.HCl
Molecular formula	$C_{11}H_{15}ONCl_2$	$C_{16}H_{21}O_2N$	$C_{16}H_{22}O_2NCl$
Crystallization solvent	Ethyl ether/60–80° petroleum spirit	Ethyl ether/60–80° petroleum spirit	Ethanol
Space group	Monoclinic $P2_1/a$	Monoclinic $P2_1/a$	Monoclinic $P2_1/n$*
Unit-cell parameters	$a = 7{\cdot}9483\ (9)$ Å	$a = 11{\cdot}7599\ (18)$ Å	$a = 14{\cdot}017\ (2)$ Å
	$b = 16{\cdot}7776\ (11)$	$b = 4{\cdot}8068\ (6)$	$b = 8{\cdot}285\ (1)$
	$c = 9{\cdot}8263\ (4)$	$c = 26{\cdot}5086\ (27)$	$c = 14{\cdot}005\ (1)$
	$\beta = 101{\cdot}70\ (6)°$	$\beta = 99{\cdot}89\ (2)°$	$\beta = 98{\cdot}76(2)°$
Z	4	4	4
Reciprocal-lattice vector parallel to diffractometer φ axis	[100]	[102]	[400]
2θ scan rate	2° min^{-1}	0·5° min^{-1}	2° min^{-1}
Reflection width (W)†	1·9°	1·4°	1·8°
Time for each background	10 s	40 s	10 s
Maximum 2θ	50°	40°	50°
Instability factor (D; Stout & Jensen, 1968)	0·00012	0·00006	0·00009
Total data measured	2360	1770	3293
Total unique data	2264	1611	2890
Data with $I > 3\sigma(I)$	1486	775	2071

* The space group reported by BCD was $P2_1/c$. Our choice of $P2_1/n$ was dictated by the 98·8° β. The matrix for the n to c unit-cell transformation is 001/010/101, which provides $P2_1/c$ lattice constants of $a = 14{\cdot}005$, $b = 8{\cdot}285$, $c = 18{\cdot}243$ Å, $\beta = 130{\cdot}59°$. The BCD parameters are $a = 13{\cdot}931$, $b = 8{\cdot}327$, $c = 18{\cdot}240$ Å, $\beta = 130{\cdot}81°$.

† 2θ scan range $= W + 0{\cdot}692 \tan\theta$.

Table 2. *Fractional coordinates* ($\times 10^4$; *for* H $\times 10^3$), *temperature factors* ($\times 10^3$; *for* H $\times 10^2$) (Å^2) *and e.s.d.'s (in parentheses) for dichloroisoproterenol*

$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \cdots 2U_{23}klb^*c^*)]$; extinction factor = 0·0125 (2).

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	7737 (4)	8210 (2)	4216 (3)	48 (2)	53 (2)	47 (2)	1 (2)	16 (1)	−1 (1)
C(2)	7009 (5)	7803 (2)	3020 (3)	76 (3)	82 (3)	59 (2)	−32 (2)	21 (2)	−7 (2)
C(3)	7435 (5)	7979 (2)	1760 (3)	83 (3)	97 (3)	44 (2)	−19 (2)	15 (2)	−13 (2)
C(4)	8591 (4)	8564 (2)	1674 (3)	57 (2)	70 (2)	47 (2)	10 (2)	20 (2)	7 (2)
C(5)	9333 (4)	8973 (2)	2849 (3)	58 (2)	55 (2)	63 (2)	−8 (2)	22 (2)	2 (2)
C(6)	8905 (4)	8792 (2)	4116 (3)	67 (2)	59 (2)	49 (2)	−10 (2)	19 (2)	−8 (2)
C(7)	7202 (4)	8030 (2)	5576 (3)	58 (2)	54 (2)	50 (2)	−4 (2)	20 (2)	−1 (2)
C(8)	5795 (5)	8592 (2)	5785 (4)	59 (2)	75 (3)	52 (2)	−1 (2)	21 (2)	6 (2)
C(9)	3984 (5)	8980 (2)	7448 (4)	65 (3)	85 (3)	73 (2)	12 (2)	28 (2)	−6 (2)
C(10)	3296 (9)	8643 (4)	8675 (6)	118 (5)	126 (5)	104 (4)	5 (4)	76 (4)	−16 (4)
C(11)	4760 (8)	9808 (3)	7740 (6)	108 (4)	88 (4)	143 (5)	31 (3)	47 (4)	−15 (3)
O	8581 (3)	8125 (2)	6728 (2)	66 (2)	75 (2)	47 (1)	76 (2)	16 (1)	−2 (1)
N	5156 (4)	8393 (2)	7037 (3)	54 (2)	76 (2)	52 (2)	3 (2)	19 (2)	0 (1)
Cl(1)	9109 (1)	8769·6 (6)	81·8 (8)	95·6 (8)	133·4 (5)	54·4 (5)	4·9 (7)	34·3 (5)	17·3 (5)
Cl(2)	10791 (2)	9720·8 (7)	2773 (1)	163 (1)	139 (1)	100·1 (8)	89·3 (9)	58·0 (8)	−10·3 (7)

	x	y	z	U		x	y	z	U
H(2)	626 (4)	740 (2)	312 (3)	9 (1)	H(9)	291 (3)	912 (1)	657 (2)	5·2 (8)
H(3)	699 (4)	771 (2)	95 (3)	8 (1)	H(10A)	418 (6)	865 (3)	939 (4)	14 (3)
H(6)	935 (3)	908 (1)	485 (3)	4·7 (9)	H(10B)	250 (6)	901 (3)	886 (5)	16 (2)
H(7)	681 (3)	749 (1)	561 (2)	3·4 (7)	H(10C)	278 (6)	802 (3)	832 (4)	18 (2)
H(O)	905 (4)	771 (2)	681 (3)	9 (2)	H(11A)	398 (5)	1011 (2)	799 (4)	12 (2)
H(8A)	491 (3)	853 (2)	506 (3)	5·2 (9)	H(11B)†	490 (10)	1001 (4)	645 (6)	37 (4)
H(8B)	625 (3)	917 (2)	573 (3)	6·4 (9)	H(11C)	570 (6)	967 (3)	855 (4)	16 (2)
H(N)	591 (3)	837 (2)	753 (2)	3 (1)					

† The position of H(11B) is unreliable: note the large e.s.d.'s and U. The C(11)–H(11B) distance is 1·34 (6) Å.

those parameters associated with the disordered region of propranolol.HCl are given for space group $P2_1/c$ in Table 4.*

All calculations were performed at the University of Maryland Computer Science Center on a Univac 1108 computer with the X-RAY system of crystallographic programs (Stewart *et al.*, 1972), the molecular drawings were made with *ORTEP*-II (Johnson, 1971) and the *VDO2S* system (Lenhert, 1975) was used for diffractometer control.

* A list of structure factors, a complete set of atomic parameters for both the $P2_1/n$ and $P2_1/c$ space groups, and complete lists of bond lengths and angles for propranolol.HCl and tables of lengths and angles involving H for I and III have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32013 (38 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Discussion

Our structure for propranolol.HCl is virtually identical to that reported by BCD with the exception of the previously indicated hydroxyl disorder; the largest differences between the two sets of fractional coordinates

Table 3. *Fractional coordinates (for* H × 10^3), *temperature factors* (× 10^3; *for* H × 10^2) (Å^2) *and e.s.d.'s (in parentheses) for propranolol*

$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \cdots 2U_{23}klb^*c^*)]$; extinction factor = 0·0006 (1).

	x (×10^4)	y (×10^3)	z (×10^4)	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	1761 (4)	129 (1)	8252 (2)	59 (4)	60 (5)	49 (4)	8 (3)	26 (3)	9 (3)
C(2)	1178 (4)	−1 (1)	7824 (2)	72 (4)	77 (5)	44 (3)	7 (3)	4 (3)	−1 (4)
C(3)	1516 (4)	69 (1)	7341 (2)	84 (4)	85 (5)	48 (4)	19 (4)	13 (3)	6 (4)
C(4)	2368 (5)	258 (1)	7315 (2)	89 (4)	85 (5)	66 (4)	24 (4)	25 (4)	18 (4)
C(4*A*)	2977 (4)	393 (1)	7758 (2)	66 (4)	63 (5)	69 (4)	25 (4)	30 (4)	15 (4)
C(5)	3862 (5)	592 (1)	7749 (2)	77 (5)	64 (5)	110 (5)	8 (5)	51 (4)	39 (5)
C(6)	4416 (5)	719 (1)	8186 (3)	86 (4)	84 (6)	113 (5)	12 (4)	43 (4)	18 (6)
C(7)	4128 (4)	649 (1)	8668 (2)	63 (4)	66 (5)	118 (5)	−12 (4)	27 (3)	5 (4)
C(8)	3275 (4)	455 (1)	8699 (2)	58 (4)	64 (5)	63 (4)	5 (3)	4 (3)	−4 (4)
C(8*A*)	2670 (4)	328 (1)	8251 (2)	52 (3)	44 (4)	71 (4)	12 (3)	30 (3)	12 (4)
C(9)	584 (3)	−103 (1)	8797 (2)	56 (3)	68 (5)	53 (3)	−20 (3)	19 (3)	2 (3)
C(10)	570 (4)	−97 (1)	9376 (1)	54 (3)	59 (4)	50 (3)	−8 (3)	16 (3)	6 (3)
C(11)	1641 (3)	−236 (1)	9670 (2)	56 (3)	65 (4)	50 (3)	3 (3)	16 (2)	3 (3)
C(12)	2759 (4)	−312 (1)	10535 (2)	63 (3)	68 (5)	69 (3)	16 (3)	−4 (3)	4 (3)
C(13)	2607 (4)	−309 (1)	11096 (2)	105 (4)	139 (6)	52 (3)	−1 (4)	−6 (3)	3 (4)
C(14)	3766 (4)	−130 (1)	10441 (2)	61 (3)	142 (7)	160 (5)	−22 (4)	−2 (4)	40 (5)
O(1)	1514 (2)	84·7 (7)	8739 (1)	76 (2)	75 (3)	49 (2)	−20 (2)	24 (2)	−4 (2)
O(2)	−438 (2)	−244·1 (6)	9461·7 (9)	55 (2)	57 (2)	68 (2)	−14 (2)	23 (2)	1 (2)
N	1663 (3)	−210·1 (8)	10229 (1)	55 (3)	58 (3)	52 (2)	−5 (2)	12 (2)	−1 (3)
	x	y	z	U		x	y	z	U
H(2)	35 (2)	−134 (7)	781 (1)	12 (1)	H(11*A*)	171 (2)	−461 (7)	957 (1)	11 (1)
H(3)	109 (3)	−47 (9)	700 (1)	15 (1)	H(11*B*)	238 (2)	−119 (6)	958·0 (9)	7 (1)
H(4)	262 (2)	321 (7)	695 (1)	12 (1)	H(N)	110 (2)	−304 (6)	1028 (1)	7 (1)
H(5)	409 (2)	669 (7)	738 (1)	11 (1)	H(12)	308 (2)	−522 (7)	1043 (1)	9 (1)
H(6)	529 (4)	853 (12)	822 (2)	30 (3)	H(13*A*)	194 (3)	−406 (8)	1117 (1)	13 (1)
H(7)	463 (4)	777 (12)	906 (2)	26 (3)	H(13*B*)	337 (3)	−391 (8)	1132 (1)	14 (1)
H(8)	312 (2)	392 (7)	909 (1)	13 (1)	H(13*C*)	261 (3)	−89 (9)	1121 (1)	16 (2)
H(9*A*)	−37 (2)	−28 (7)	857 (1)	10 (1)	H(14*A*)	449 (3)	−240 (10)	1071 (2)	21 (2)
H(9*B*)	73 (2)	−317 (8)	869 (1)	14 (1)	H(14*B*)	403 (3)	−160 (10)	1006 (2)	23 (2)
H(10)	55 (2)	117 (7)	951 (1)	9 (1)	H(14*C*)	368 (4)	10 (10)	1059 (2)	29 (3)
H(O2)	−96 (3)	−158 (8)	953 (1)	16 (2)					

Table 4. *Fractional coordinates* (× 10^4; *for* H × 10^3) *and temperature factors* (× 10^3; *for* H × 10^2) (Å^2) *for the disordered section of propranolol*.HCl *in space group* $P2_1/c$

$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \cdots 2U_{23}klb^*c^*)]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(10)	3670	233	5532	97	38	50	8	35	3
O(2*A*)†	3784	−406	6245	187	44	44	−2	62	−2
O(2*B*)†	4637	−692	5755	87	44	80	5	41	−6
H(10*A*)†‡	438	−94	569	10					
H(10*B*)†‡	375	−26	607	10					

† 0·5 weight.
‡ Not refined.

are of the order of 3σ. The temperature factors reported by BCD for the hydroxyl O atom [their O(14)] are substantially larger than these terms observed for the two half-weight oxygens, O(2*A*) and O(2*B*). For example, the thermal ellipsoid r.m.s. displacements are 0·325, 0·366, 0·471 Å* for O(14), 0·189, 0·209, 0·353 Å for O(2*A*) and 0·202, 0·229, 0·328 Å for O(2*B*). The scattering of BCD's O(14) compared to our half-weight O(2*A*) and O(2*B*) was estimated in the following manner. The three r.m.s. displacements for the atom were averaged to obtain an approximate value of u, the r.m.s. displacement of an isotropic atom, and the temperature factor exponential (TFE) was calculated for a $\sin\theta/\lambda$ of 0·3 from TFE = $\exp[-8(\pi u \sin\theta/\lambda)^2]$. In the case of O(2*A*) and O(2*B*), the TFE's were multiplied by 0·5 to account for the scattering by the half-weight oxygens. The similar values of the TFE's for O(14) and the two half-weight atoms, *viz* O(14) = 0·345, O(2*A*) = 0·316 and O(2*B*) = 0·319, indicate that the site occupancy of BCD's O(14) should be close to the 0·5 assumed for O(2*A*) and O(2*B*). Refinement of our data with O(2*B*) and both C(10)-linked H atoms deleted, and with a site occupancy of 1·0 for O(2*A*), gave r.m.s. displacements for O(2*A*) of 0·292, 0·368 and 0·436 Å (TFE = 0·387), and an R index of 0·142. A difference map revealed a maximum of 3·6 e Å^{-3} at the original location of O(2*B*).

The C(10)—O distances in the two propranolol.HCl structures are substantially smaller than normal C(sp^3)—O lengths: *e.g.* 1·416 Å in dichloroisoproterenol. Our lengths and angles for the disordered region are given in Table 5.† The short distances for C(13)—O(14) of 1·30 (BCD), C(10)—O(2*A*) of 1·315 and C(10)—O(2*B*) of 1·368 Å are presumably associated with the disorder at C(10).

The C—C, C—N and C—O bond lengths and angles in I, III and III.HCl are within normal ranges. Tables 6 and 7 list the C, N, O and Cl length and angle data for I and III.† Although there appear to be significant differences between distances in the free base and protonated forms of dichloroisoproterenol and propranolol, there are no obvious trends in the data which appear to be related to N-protonation with the exception of an increase in the C—N—C angle. These angles in dichloroisoproterenol and the hydrochloride are 115·3 and 117·7° (Gadret *et al.*, 1975*b*) respectively, and the angles in propranolol, the hydrochloride and (+)-propranolol.HCl are 112·5, 116·3 and 116·5° (Gadret *et al.*, 1975*a*) respectively. This increase in the angle with protonation presumably reflects the larger effective size of an electron pair on N compared to H. Surprisingly, in none of the hydrochloride structures of

* The form of the anisotropic temperature factors reported by BCD was not specified, but we have determined it to be $\exp[-(h^2\beta_{11} \cdots + kl\beta_{23})]$.

† See footnote on p. 24.

Table 5. *Bond lengths* (Å), *angles* (°) *and e.s.d.'s (in parentheses) for the disordered region of propranolol*.HCl

C(9)—C(10)	1·514 (5)	C(9)—C(10)—C(11)	110·8 (3)
C(10)—C(11)	1·510 (4)	C(9)—C(10)—O(2*A*)	109·9 (3)
C(10)—O(2*A*)	1·315 (5)	C(9)—C(10)—O(2*B*)	114·9 (3)
C(10)—O(2*B*)	1·368 (6)	O(2*A*)—C(10)—O(2*B*)	91·3 (3)
C(10)—H(10*A*)	1·0	H(10*A*)—C(10)—H(10*B*)	92
C(10)—H(10*B*)	1·0		

Table 6. *Bond lengths* (Å), *angles* (°) *and e.s.d.'s (in parentheses) for the* C, O, N *and* Cl *atoms in dichloroisoproterenol*

C(1)—C(2)	1·380 (4)	C(2)—C(1)—C(6)	117·7 (3)
C(1)—C(6)	1·366 (5)	C(2)—C(1)—C(7)	120·6 (3)
C(1)—C(7)	1·512 (4)	C(6)—C(1)—C(7)	121·6 (3)
C(2)—C(3)	1·380 (5)	C(1)—C(2)—C(3)	121·5 (3)
C(3)—C(4)	1·359 (5)	C(2)—C(3)—C(4)	120·1 (3)
C(4)—C(5)	1·371 (4)	C(3)—C(4)—C(5)	119·4 (3)
C(4)—Cl (1)	1·731 (3)	C(3)—C(4)—Cl(1)	119·2 (2)
C(5)—C(6)	1·389 (5)	Cl(1)—C(4)—C(5)	121·4 (3)
C(5)—Cl(2)	1·719 (3)	C(4)—C(5)—C(6)	120·3 (3)
C(7)—C(8)	1·509 (5)	C(4)—C(5)—Cl (2)	120·5 (3)
C(7)—O	1·416 (4)	Cl(2)—C(5)—C(6)	119·2 (2)
C(8)—N	1·461 (5)	C(1)—C(6)—C(5)	121·0 (3)
C(9)—N	1·468 (5)	C(1)—C(7)—C(8)	110·1 (3)
C(9)—C(10)	1·530 (8)	C(1)—C(7)—O	111·9 (3)
C(9)—C(11)	1·524 (7)	C(8)—C(7)—O	107·1 (3)
		C(7)—C(8)—N	111·4 (3)
		C(8)—N—C(9)	115·3 (3)
		C(10)—C(9)—C(11)	112·6 (4)
		C(10)—C(9)—N	108·5 (4)
		C(11)—C(9)—N	114·1 (4)

Table 7. *Bond lengths* (Å), *angles* (°) *and e.s.d.'s (in parentheses) for the* C, O *and* N *atoms in propranolol*

C(1)—C(2)	1·371 (6)	C(2)—C(1)—C(8*A*)	124·6 (5)
C(1)—C(8*A*)	1·435 (7)	C(2)—C(1)—O(1)	123·1 (4)
C(1)—O(1)	1·386 (6)	C(8*A*)—C(1)—O(1)	112·3 (4)
C(2)—C(3)	1·444 (7)	C(1)—C(2)—C(3)	116·9 (4)
C(3)—C(4)	1·364 (8)	C(2)—C(3)—C(4)	121·1 (4)
C(4)—C(4*A*)	1·423 (7)	C(3)—C(4)—C(4*A*)	122·1 (5)
C(4*A*)—C(8*A*)	1·448 (8)	C(4)—C(4*A*)—C(5)	124·1 (5)
C(4*A*)—C(5)	1·419 (8)	C(4)—C(4*A*)—C(8*A*)	118·5 (5)
C(5)—C(6)	1·369 (8)	C(5)—C(4*A*)—C(8*A*)	117·3 (5)
C(6)—C(7)	1·418 (7)	C(4*A*)—C(5)—C(6)	121·9 (6)
C(7)—C(8)	1·383 (7)	C(5)—C(6)—C(7)	120·4 (5)
C(8)—C(8*A*)	1·416 (7)	C(6)—C(7)—C(8)	120·0 (5)
O(1)—C(9)	1·446 (5)	C(7)—C(8)—C(8*A*)	120·5 (5)
C(9)—C(10)	1·539 (6)	C(1)—C(8*A*)—C(4*A*)	116·6 (4)
O(2)—C(10)	1·432 (5)	C(1)—C(8*A*)—C(8)	123·6 (5)
C(10)—C(11)	1·519 (6)	C(4*A*)—C(8*A*)—C(8)	119·8 (5)
C(11)—N	1·484 (5)	C(1)—O(1)—C(9)	118·5 (3)
C(12)—N	1·482 (5)	C(10)—C(9)—O(1)	103·4 (3)
C(12)—C(13)	1·527 (6)	C(9)—C(10)—C(11)	110·7 (4)
C(12)—C(14)	1·526 (7)	C(9)—C(10)—O(2)	107·4 (3)
		C(11)—C(10)—O(2)	109·6 (4)
		C(10)—C(11)—N	112·2 (4)
		C(11)—N—C(12)	112·5 (3)
		C(13)—C(12)—C(14)	110·2 (3)
		C(13)—C(12)—N	107·0 (4)
		C(14)—C(12)—N	110·4 (4)

(+)-propranolol, dichloroisoproterenol, pronethanol or bupranolol recently published by Gadret *et al.* (1975*a*,*b*,*c*,*d*) is more than one H on N reported. No rationale is given for the missing H atoms, and in the dichloroisoproterenol.HCl and bupranolol.HCl papers (Gadret *et al.*, 1975*b*,*d*), the suggestion is made that the C–N–C angles of 117·7 and 117·3°, respectively, show sp^2 hybridization for N. Additionally, the bond angle standard deviations quoted by these workers are too small by an order of magnitude.

In III and III.HCl, the hydroxyl O–N distances of 2·92 (III), 2·85 [III.HCl; O(2*A*)···N] and 2·90 Å [III.HCl; O(2*B*)···N] are typical of those found in other adrenergic compounds, 2·65–3·04,* and there is no evidence for hydrogen-bond formation between these nuclei. Dichloroisoproterenol, however, contains a weak hydrogen bond from N to O: the O···N and O···H(N) distances are, respectively, 2·84 and 2·42 Å, and the O···H(N)–N angle is 118° (Fig. 1). Intermolecular hydrogen bonds between N and the hydroxyl O in I and III, and between Cl, N and the hydroxyl O in III.HCl are the main determinants of crystal packing (Figs. 1–3).

The two structural regions, the aromatic ring–oxygen bridge and aminoethanol side chain, of I and III are essentially planar (see Tables 8–10). The hydroxyl O–N torsion angles of −66° in III, −55° in III.HCl and −62·5° in I are in agreement with the −50 to −75°

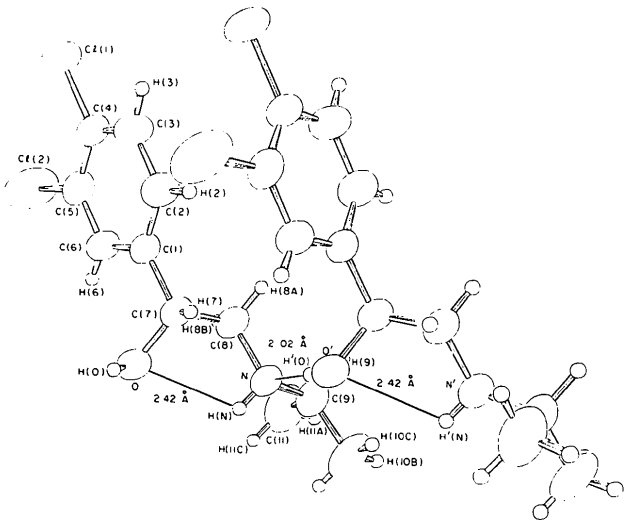

Fig. 1. *ORTEP*-II drawing of dichloroisoproterenol showing inter- and intramolecular contacts (Å). The two molecules plotted have the relative positions of x,y,z (unprimed) and $\frac{1}{2}+x, \frac{1}{2}-y, z$. 45% probability ellipsoids are shown for C, N, O and Cl; H atoms are drawn as 0·1 Å spheres.

* Norepinephrine hydrochloride (Carlström & Bergin, 1967); epinephrine hydrotartrate (Carlström, 1973); isoproterenol hydrosulfate (Mathew & Palenik, 1971); ephedrine hydrochloride (Phillips, 1954; Bergin, 1971); ephedrine monohydrogen phosphate (Hearn, Freeman & Bugg, 1973); Th1165a (Beale, 1972; Beale & Stephenson, 1972); salbutamol (Beale & Grainger, 1972; Beale & Stephenson, 1972); alprenolol (Barrans, Cotrait & Dangoumau, 1973); pronethanol hydrochloride (Gadret, Goursolle, Leger & Colleter, 1975*c*); bupranolol hydrochloride (Gadret, Goursolle, Leger & Colleter, 1975*d*); pindolol (Gadret, Goursolle, Leger & Colleter, 1976).

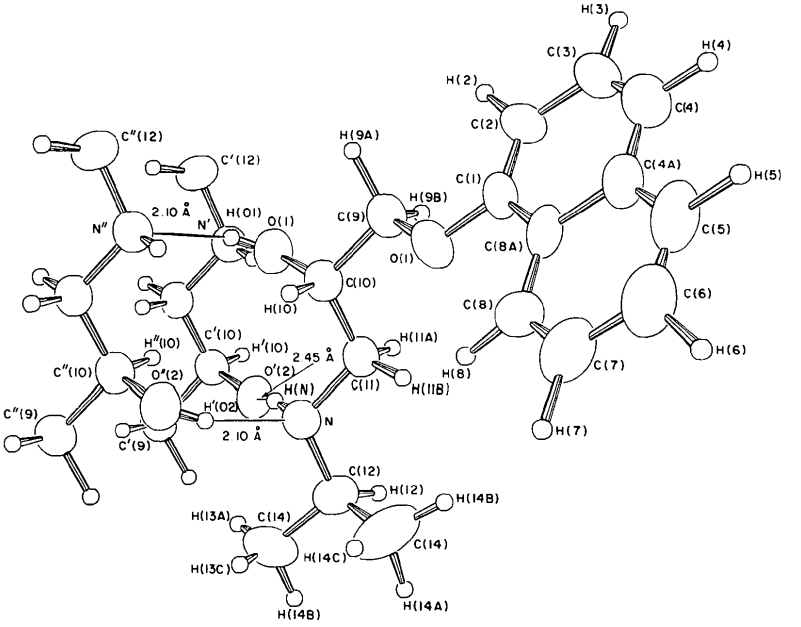

Fig. 2. *ORTEP*-II drawing of propranolol illustrating intermolecular contacts (Å). A complete molecule is shown along with the side chains from two others. The relative positions of the three molecules are x,y,z (unprimed), $-x, -y, 2-z$ (′) and $-x, -1-y, 2-z$ (″). 45% probability ellipsoids are shown for C, N and O; H atoms are drawn as 0·1 Å spheres.

values found in other adrenergic compounds (see footnote on p. 26).

The angle between the C—CH_2—NH—CH side chain and aromatic ring in I is 84·1°, and the side chain/pseudo-aromatic ring [C(2)—C(1)—O—C(9)] angles in III and III.HCl are 70·0 and 56·6° respectively. The corresponding angles in I.HCl, pronethanol.HCl, (+)-propranolol.HCl, bupranolol.HCl and pindolol are 82·8, 62·6, 6·3, 12·2 and 20·9 respectively. We had observed (Ammon *et al.*, 1975) previously that the ring/side chain angles in a series of α,β-adrenergic stimulating and β-blocking drugs were in the range of 56–87°, with the one exception of epinephrine hydrotartrate (2·8°); three more exceptions are now known.

The overall molecular conformations of dichloroisoproterenol free base and hydrochloride are very similar (Fig. 4). The largest difference arises from rotation about the C(8)—N bond, which results in a displacement of the isopropyl groups.

The crystal conformations of four propranolols, drawn with (*S*)-chirality, are illustrated in Fig. 5; the middle two diagrams were obtained from our propranolol.HCl since the disorder, in effect, reveals two conformations for the active (*S*)-enantiomer. The four molecules are virtually identical from C(1) to C(10), at which point differences occur in the side

Table 8. *Least-squares planes and deviations* (Å) *for dichloroisoproterenol*

Plane 1 $-5{\cdot}701x + 11{\cdot}277y - 0{\cdot}341z = 0{\cdot}534$
Plane 2 $4{\cdot}733x + 10{\cdot}528y + 3{\cdot}641z = 5{\cdot}035$

	Plane 1	Plane 2
C(1)	−0·002*	0·026*
C(2)	0·000*	
C(3)	0·002*	
C(4)	−0·002*	
C(5)	0·000*	
C(6)	0·003*	
C(7)	−0·058	−0·026*
C(8)	−1·487	−0·028*
C(9)	−2·901	−0·185
C(10)	−2·871	0·048
C(11)	−3·382	
N	−1·585	0·027*
O	0·659	−1·198
Cl(1)	0·007	
Cl(2)	−0·015	

* Used for plane definition.

Table 9. *Least-squares planes and deviations* (Å) *for propranolol*

Plane 1 $-7{\cdot}846x + 3{\cdot}537y + 0{\cdot}008z = -0{\cdot}932$
Plane 2 $-5{\cdot}776x - 4{\cdot}183y + 1{\cdot}212z = 1{\cdot}186$
Plane 3 $-7{\cdot}482x + 3{\cdot}648y - 0{\cdot}711z = -1{\cdot}440$

	Plane 1	Plane 2	Plane 3
C(1)	0·013*		0·005*
C(2)	0·010*		−0·003*
C(3)	−0·008*		
C(4)	−0.007*		
C(4*A*)	−0·007*		
C(5)	0·004*		
C(6)	0·016*		
C(7)	−0·003*		
C(8)	−0·020*		
C(8*A*)	−0·003*		
C(9)	0·117	−0·026*	0·002*
C(10)	0·151	0·026*	−0·006
C(11)	−1·183	0·027*	−1·337
C(12)	−2·326	−0·198	−2·510
C(13)	−2·196	−0·055	−2·425
C(14)	−2·474	−1·550	−2·595
N	−1·107	−0·027*	−1·298
O(1)	0·051	−1·355	−0·005*
O(2)	0·420	1·235	0·205
H(2)	0·193		0·137
H(9*A*)	1·132	0·186	1·006
H(9*B*)	−0·750	0·774	−0·876

* Used for plane definition.

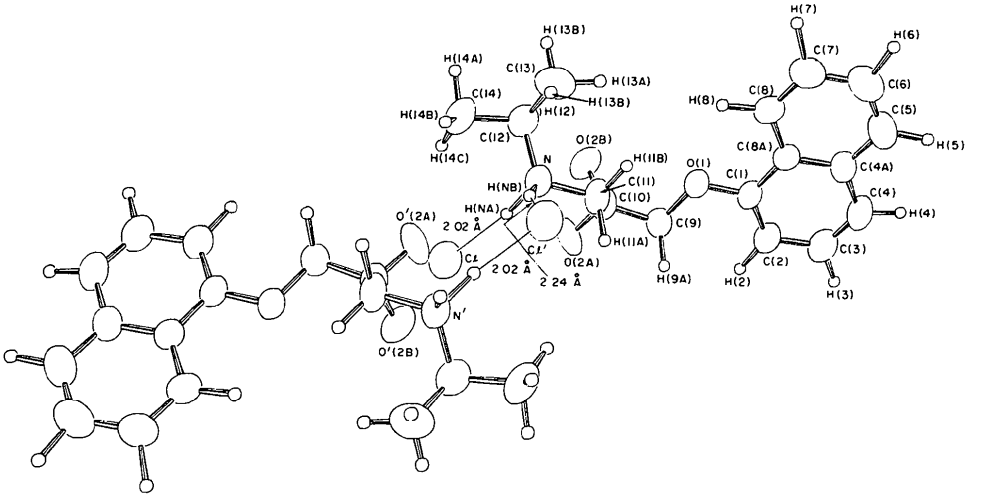

Fig. 3. *ORTEP*-II drawing of propranolol hydrochloride. Two complete molecules related by a twofold screw axis are shown along with several intermolecular contacts (Å). Both of the disordered hydroxyl O atoms, O(2*A*) and O(2*B*), have been included. 45% probability ellipsoids are shown for C, N, O and Cl; H atoms are drawn as 0·1 Å spheres.

chains. The three possible staggered conformations of the C(9)–C(10) bond are represented by the arrangements of the C(10)-substituents in the propranolols. Beginning with (–)-propranolol (bottom of Fig. 5), a *ca* 137° clockwise rotation of C(10) viewed along the C(10)–C(9) bond yields the C(10) arrangement in propranolol.HCl [with O(2*B*)], and a second rotation of *ca* 114° gives the conformations observed in both propranolol (top of Fig. 5) and propranolol.HCl [with O(2*A*)].

Table 10. *Least-squares planes and deviations* (Å) *for propranolol hydrochloride*

Plane 1 $-7{\cdot}517x - 6{\cdot}889y - 0{\cdot}861z = -5{\cdot}945$
Plane 2 $-12{\cdot}806x - 0{\cdot}735y - 3{\cdot}544z = -4{\cdot}157$
Plane 3 $-6{\cdot}922x - 7{\cdot}189y + 0{\cdot}274z = -5{\cdot}664$

	Plane 1	Plane 2	Plane 3
C(1)	0·016*		0·031*
C(2)	0·012*		–0·016*
C(3)	–0·005*		
C(4)	–0·012*		
C(4*A*)	–0·009*		
C(5)	0·010*		
C(6)	0·019*		
C(7)	0·009*		
C(8)	–0·013*		
C(8*A*)	–0·009*		
C(9)	0·235	0·024*	0·014*
C(10)	0·348	–0·024*	0·050
C(11)	1·496	–0·025*	1·249
C(12)	0·796	–1·296	0·511
C(13)	1·085	–2·221	0·946
C(14)	1·045	–0·970	0·651
N	1·698	0·025*	1·369
O(1)	0·045	–1·107	–0·030*
O(2*A*)	0·420	0·950	–0·013
O(2*B*)	–0·830	–0·966	–1·136
H(2)	0·017		–0·128
H(9*A*)	1·208	1·062	0·955
H(9*B*)	–0·671	0·042	–0·936

* Used for plane definition.

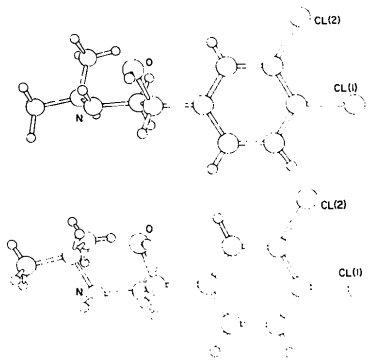

Fig. 4. *ORTEP*-II drawing of dichloroisoproterenol free base (upper) and hydrochloride [lower; from coordinates of Gadret, Goursolle, Leger & Colleter (1975*b*)] normal to the benzene rings. Both molecules have the active (*R*)-configuration. H atoms are drawn as 0·1 Å spheres; C atoms are 0·2 Å spheres. Only one of the two H atoms on N in the hydrochloride is shown.

In the free base and hydrochloride forms of propranolol, the side chain curves in such a way as to bring the isopropyl group relatively close to the C(8) region of the naphthalene ring, in contrast to the extreme side-chain extension in (–)-propranolol. The C(7)

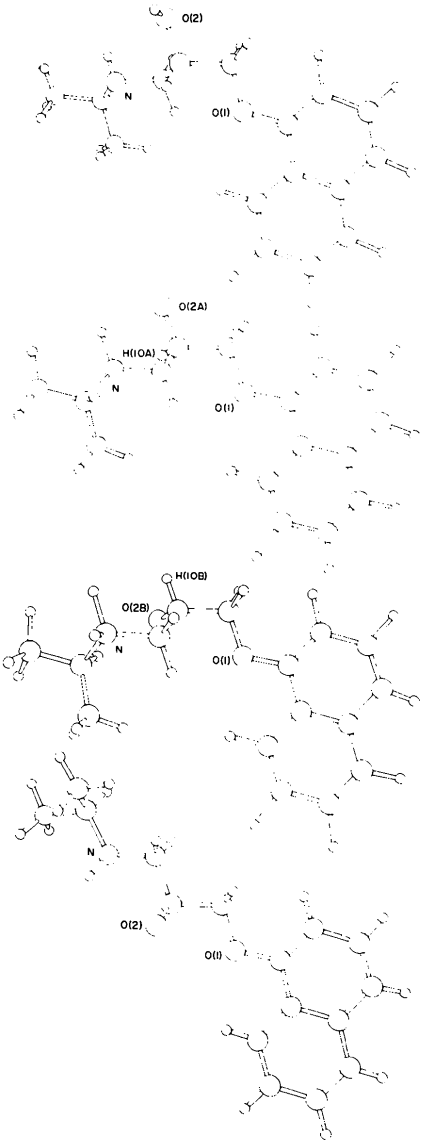

Fig. 5. *ORTEP*-II drawings of propranolol (upper), propranolol hydrochloride (middle two) and (–)-propranolol hydrochloride [lower; from the coordinates of Gadret, Goursolle, Leger & Colleter (1975*a*) for the (+)-isomer] normal to the pseudo-aromatic rings. All molecules are drawn in the most active (*S*)-configuration. One of the propranolol.HCl drawings was made with O(2*A*) and H(10*A*), while the other included O(2*B*) and H(10*B*). The $\bar{x},\bar{y},\bar{z}$ molecule was plotted with O(2*A*) and H(10*A*) to achieve the *S*-chirality. H atoms are drawn as 0·1 Å spheres; C atoms are depicted as 0·2 Å spheres. In the case of (–)-propranolol.HCl, only one of the two H atoms on N is shown. The coordinates reported by BCD for propranolol.HCl are for the (*R*)-configuration.

conformations in the two dichloroisoproterenols are closest to the C(10)-conformations in propranolol. In propranolol, the hydroxyl oxygen atom, O(2), is 0·20 Å out of the C(2)–C(1)–C(1)–C(9) plane compared to 0·66 Å for the distance of O from the aromatic ring plane in dichloroisoproterenol. These differences presumably reflect the larger steric requirements of the benzene nucleus in the latter, and also that the C(10)–O(2) bond in propranolol must essentially bisect the H–C(9)–H angle.

The crystal structures of six propranolol-like adrenergics (*i.e.* compounds in which an aromatic ring is linked to an oxypropanolamine chain) are known, and in all cases the C(2)–C(1)–O(1)–C(9) is approximately coplanar with the adjacent aromatic ring. With reference to the least-squares planes of the aromatic ring, for example, the deviations of C(9) from the plane ranged from 0·056 Å in pindolol to 0·235 Å in propranolol.HCl. This arrangement is just the opposite of that observed in the CNDO/2-determined minimum energy conformation of practolol (Germer, 1973), in which the C(1)–O(1)–C(9) plane was virtually perpendicular to the aromatic ring. We must conclude, on the basis of the six crystal structures, that the CNDO conformation is incorrect.

The commonly measured parameters of planarity, O–N distances and torsion angles seem to show that there are several well established similarities between adrenergically active compounds. What remains unclear is the relative importance of chemical and structural differences necessary to define a compound's unique activity.

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