SAWADA, A. & TAKAGI, Y. (1972). *J. Phys. Soc. Jpn*, **33**, 1071–1075.
SHELDRICK, G. M. (1976). *SHELX76. Program for Crystal Structure Determination*. Univ. of Cambridge, England.
SHKURATOVA, I. G., KIOSSE, G. A. & MALINOVSKII, T. I. (1979). *Izv. Akad. Nauk SSSR Ser. Fiz.* **43**, 1685–1690.
STADNICKA, K. & BROŻEK, Z. (1991). *Acta Cryst.* B**47**, 484–492.
TAKAGI, Y. & MAKITA, Y. (1958). *J. Phys. Soc. Jpn*, **13**, 272–277.

Acta Cryst. (1994). B**50**, 68–71

Structure of the β-Blocker/Vasodilator Agent Prizidilol, DL-6-{2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl}-3-pyridazinylhydrazine Hemisulfate Monohydrate

BY KEITH PROUT AND KEITH BURNS

Chemical Crystallography Laboratory, Oxford University, 9 Parks Road, Oxford OX1 3PD, England

AND ANTHONY M. ROE

Smith Kline and French Research Ltd, The Frythe, Welwyn, Hertfordshire AL6 9AR, England

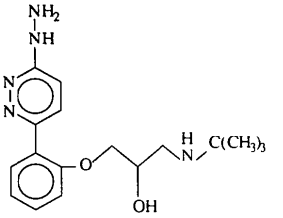
(*Received* 27 *January* 1993; *accepted* 19 *May* 1993)

Abstract

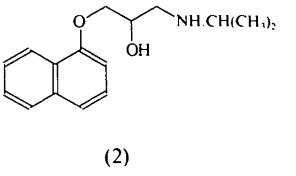
Prizidilol, a compound combining vasodilator and β-blocker functionalities in the same molecule, has been synthesized and characterized by Smith Kline and French Research Ltd. Crystal data: $C_{17}H_{25}N_5O_2.\frac{1}{2}H_2SO_4.H_2O$, $M_r = 398.47$, orthorhombic, $a = 10.722$ (2), $b = 11.635$ (6), $c = 34.105$ (3) Å, $V = 4254.61$ Å^3, *Pbnm* (non-standard form of *Pnma*) (D_{2h}^{16}, No. 62), $Z = 8$, $F(000) = 1704$, $D_x = 1.244$ Mg m^{-3}, μ(Cu $K\alpha$) = 11.673 cm^{-1}, $R = 0.064$ for 2432 independent reflections with $I > 3\sigma(I)$. Prizidilol shows strong conformational similarities to propranolol and is protonated at the secondary amine. The 6-phenyl-3-hydrazinopyridazine residue is not planar. The hydroxy group at the asymmetric carbon is disordered so that both enantiomers are found at each molecular site. The sulfate ions and disordered water molecules lie in the crystallographic mirror plane.

Introduction

Peripheral vasodilator agents are in clinical use to lower blood pressure: however, the reduction of blood pressure initiates the activation of β-adrenoceptors in the heart with a consequent undesirable increase in heart rate. These undesirable effects of vasodilators are inhibited by β-adrenoceptor antagonists with the result that the combined use of vasodilators and β-blockers has been widely adopted for the treatment of hypertension. An effort by Smith Kline and French Research Ltd to combine the vasodilator and β-blocker function in the one molecule led to the development of the hydrazinopyridazine, prizidilol (1) (Taylor, Cameron, Eden, Fielden & Owen, 1981; Taylor, Roe & Slater, 1979).



(1)



(2)

Although long-term toxicological effects prevented the completion of the development of prizidilol, substantial favourable clinical data established the therapeutic significance of the combination of vasodilator and β-blocker functions in the same molecule (Eggertsen, Andren & Hansson, 1983; Karlberg *et al.*, 1983). Here we present structural data with particular examination of the conformation of the vasodilator moiety and its β-blocker side chain.

Experimental

The needle-shaped orange crystal used for data collection (size 0.1 × 0.1 × 1.0 mm mounted on a CAD-4 diffractometer, Cu $K\alpha$ radiation) was obtained as the hemisulfate from dilute aqueous sulfuric acid solution. The unit-cell dimensions and orientation matrix were obtained from 25 carefully centred reflexions $27 < \theta < 36°$. The intensity data were collected by $\omega/2\theta$ scan, scan aperture 4 mm, graphite-monochromated Cu $K\alpha$ radiation. 4064

Table 1. *Positional parameters and equivalent isotropic temperature factors with e.s.d.'s in parentheses*

The equivalent isotropic temperature factor is calculated as $U_{eq} = (U_{11}U_{22}U_{33})^{\frac{1}{3}}$, where U_{11}, U_{22}, U_{33} are the mean-square displacements (Å^2) along each of the principal axes of the thermal ellipsoid.

	x	y	z	U_{iso}/U_{eq}
C(1)	0.2352 (4)	0.1481 (4)	0.1280 (1)	0.0568
C(2)	0.2900 (4)	0.2423 (4)	0.1092 (2)	0.0593
C(3)	0.2438 (5)	0.2813 (4)	0.0745 (2)	0.0599
C(4)	0.1447 (4)	0.2268 (4)	0.0576 (1)	0.0491
C(5)	0.0864 (3)	0.1324 (3)	0.0750 (1)	0.0376
C(6)	0.1335 (4)	0.0950 (3)	0.1106 (1)	0.0426
C(7)	0.0268 (3)	0.0834 (3)	0.0574 (1)	0.0348
C(8)	0.0504 (4)	0.0359 (3)	0.0535 (1)	0.0389
C(9)	0.1577 (4)	−0.0707 (3)	0.0361 (1)	0.0395
C(10)	0.2416 (4)	0.0138 (3)	0.0237 (1)	0.0407
N(11)	0.2163 (3)	0.1270 (3)	0.0277 (1)	0.0450
N(12)	0.1089 (3)	0.1590 (3)	0.0442 (1)	0.0425
N(13)	0.3529 (4)	0.0067 (3)	0.0066 (2)	0.0556
N(14)	0.4019 (4)	−0.1172 (3)	0.0006 (1)	0.0504
O(15)	−0.0697 (3)	0.0057 (2)	0.12852 (8)	0.0491
C(16)	0.0684 (5)	0.0031 (5)	0.1705 (1)	0.0640
C(17)	0.0435 (5)	−0.0646 (4)	0.1837 (1)	0.0543
O(18)	0.0233 (5)	−0.1824 (3)	0.1775 (1)	0.0634
O(19)	0.024 (2)	−0.083 (2)	0.2193 (6)	0.0880
C(20)	0.1579 (4)	−0.0277 (4)	0.1620 (1)	0.0499
N(21)	0.2735 (3)	−0.0740 (3)	0.18002 (9)	0.0433
C(22)	0.3896 (5)	−0.0744 (4)	0.1541 (1)	0.0573
C(23)	0.3736 (7)	−0.1678 (5)	0.1237 (2)	0.0784
C(24)	0.4055 (7)	0.0430 (5)	0.1346 (2)	0.0793
C(25)	0.4971 (7)	−0.1025 (8)	0.1812 (2)	0.0948
O(26)	0.2309 (6)	0.2065 (3)	0.2851 (1)	0.0918
O(27)	0.4205 (7)	0.2196 (6)	0.2500	0.1027
O(28)	0.3035 (5)	0.0452 (3)	0.2500	0.0503
S(29)	0.2927 (2)	0.1709 (1)	0.2500	0.0521
O(30)	0.939 (2)	0.172 (1)	0.2500	0.1261
O(31)	0.753 (1)	0.358 (2)	0.2500	0.1617
O(32)	0.670 (1)	0.078 (1)	0.2500	0.1772

Table 2. *Distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(1)—C(2)	1.399 (6)	N(13)—N(14)	1.405 (5)
C(1)—C(6)	1.386 (6)	O(15)—C(16)	1.431 (6)
C(2)—C(3)	1.359 (7)	C(16)—C(17)	1.505 (7)
C(3)—C(4)	1.365 (6)	C(17)—O(18)	1.404 (6)
C(4)—C(5)	1.396 (5)	C(17)—O(19)	1.25 (2)
C(5)—C(6)	1.386 (5)	C(17)—C(20)	1.495 (6)
C(5)—C(7)	1.470 (5)	C(20)—N(21)	1.484 (6)
C(6)—O(15)	1.386 (5)	N(21)—C(22)	1.526 (6)
C(7)—C(8)	1.417 (5)	C(22)—C(23)	1.512 (7)
C(7)—N(12)	1.323 (5)	C(22)—C(24)	1.529 (7)
C(8)—C(9)	1.355 (6)	C(22)—C(25)	1.513 (8)
C(9)—C(10)	1.398 (5)	O(26)—S(29)	1.430 (4)
C(10)—N(11)	1.351 (4)	O(27)—S(29)	1.483 (7)
C(10)—N(13)	1.349 (5)	O(28)—S(29)	1.468 (4)
N(11)—N(12)	1.334 (4)		
C(6)—C(1)—C(2)	118.9 (4)	C(16)—O(15)—C(6)	117.5 (3)
C(3)—C(2)—C(1)	120.4 (4)	C(17)—C(16)—O(15)	108.6 (4)
C(4)—C(3)—C(2)	119.8 (4)	O(18)—C(17)—C(16)	110.0 (5)*
C(5)—C(4)—C(3)	122.3 (4)	O(19)—C(17)—C(16)	104.3 (10)*
C(6)—C(5)—C(4)	117.1 (4)	O(19)—C(17)—O(18)	87.5 (12)*
C(7)—C(5)—C(4)	120.1 (3)	C(20)—C(17)—C(16)	110.8 (4)
C(7)—C(5)—C(6)	122.5 (3)	C(20)—C(17)—O(18)	109.4 (4)*
C(5)—C(6)—C(1)	121.4 (4)	C(20)—C(17)—O(19)	131.7 (13)*
O(15)—C(6)—C(1)	122.3 (4)	N(21)—C(20)—C(17)	112.1 (3)
O(15)—C(6)—C(5)	116.2 (3)	C(22)—N(21)—C(20)	116.3 (3)
C(8)—C(7)—C(5)	124.5 (3)	C(23)—C(22)—N(21)	107.9 (4)
N(12)—C(7)—C(5)	115.4 (3)	C(24)—C(22)—N(21)	109.8 (4)
N(12)—C(7)—C(8)	120.1 (3)	C(24)—C(22)—C(23)	110.9 (5)
C(9)—C(8)—C(7)	119.0 (3)	C(25)—C(22)—N(21)	105.6 (4)
C(10)—C(9)—C(8)	117.9 (3)	C(25)—C(22)—C(23)	110.5 (5)
N(11)—C(10)—C(9)	121.7 (4)	C(25)—C(22)—C(24)	111.9 (5)
N(13)—C(10)—C(9)	125.1 (3)	O(26)—S(29)—O(26)	113.8 (5)
N(13)—C(10)—N(11)	113.2 (3)	O(27)—S(29)—O(26)	108.5 (3)
N(12)—N(11)—C(10)	119.2 (3)	O(28)—S(29)—O(26)	108.9 (2)
N(11)—N(12)—C(7)	122.1 (3)	O(28)—S(29)—O(27)	107.9 (4)
N(14)—N(13)—C(10)	123.8 (3)		

Relevant intermolecular contact distances (Å) and angles ( )

N(14)···N(13^{i})	3.008 (5)	O(28)···N(21^{ii})	2.78 (4)
O(26)···N(21^{iv})	2.83 (4)	O(18)···O(27^{iii})	2.79 (6)
O(19)···O(27^{iii})	2.61 (8)		

Symmetry codes: (i) $1-x, -y, -z$; (ii) x, y, z; (iii) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iv) $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$.

* O(18) and O(19) are disordered.

independent reflections were measured (h − 1 to 13, k − 1 to 14, l − 1 to 41, θ 0 to 70°) which, after data reduction (merging $R = 2.32\%$), gave 4064 unique reflections. Lorentz and polarization corrections were applied but no absorption correction was made.

The structure was solved using *MULTAN*80 (Main *et al.*, 1980) and refined by least squares, minimizing $\sum w(|F_o| - |F_c|)^2$. A difference Fourier synthesis at $R = 14.3\%$ revealed three peaks lying at $z = 0.25$ which were interpreted as being water O atoms disordered over three sites each of occupancy 0.667. H atoms were found in a difference Fourier map and then placed geometrically. Blocked anisotropic refinement, with 'riding' H atoms, converged at 9.7%. When the structure was fully refined isotropically a difference synthesis revealed a peak larger than those corresponding to H atoms, lying about 1.25 Å from C(17). This was interpreted in terms of a disordered hydroxyl group represented by O(18) and O(19) with occupancies of 0.80 and 0.20, respectively. For both the water molecules and the hydroxyl groups no attempt was made to place the H atoms. The possibility of space group $Pna2_1$ was examined and rejected. A two-term Chebyshev weighting scheme (Carruthers & Watkin, 1979) applied with $w = [88.3t_0(x) + 85.4t_1(x)] - 1$, $x = F_o/F_{max}$, was used. At convergence (maximum parameter shift 0.02), the final residuals were $R = 6.44$ and $wR = 8.84\%$ for 2432 reflections with $I > 3\sigma(I)$, 341 parameters, 23 restraints and the sum of (shift/e.s.d.)$^2 = 2.8$. During the last stages of refinement corrections were made for extinction effects. A final difference map revealed maximum and minimum electron densities of 0.6 and −0.4 e Å^{-3}. Scattering factors were taken from Cromer & Waber (1974). Unless otherwise stated calculations were performed with the *CRYSTALS* program (Watkin, Carruthers & Betteridge, 1985).

Results and discussion

Atomic coordinates are given in Table 1, bond lengths and angles together with their standard deviations in Table 2 and torsion angles in Table 3. The numbering of the atoms corresponds to Fig. 1 which shows the least-squares best-plane view of prizidilol. There are eight prizidilol cations in the unit cell (one per asymmetric unit) as well as four sulfate anions and approximately eight water molecules disordered over 12 sites in the unit cell, lying on mirror planes at $y = \frac{1}{4}$ and $\frac{3}{4}$.

Prizidilol consists of a side chain similar to that in propranolol (2) attached to a biaryl system. Bond

Table 3. *Torsion angles (°) different from 0 or 180° by more than ±2°*

C(2)—C(1)—C(6)—O(15)	176.1 (5)	C(6)—O(15)—C(16)—C(17)	−156.5 (5)
C(3)—C(4)—C(5)—C(7)	−174.5 (5)	O(15)—C(16)—C(17)—O(18)	−74.1 (7)
C(6)—C(5)—C(7)—C(8)	47.9 (5)	O(15)—C(16)—C(17)—O(19)	−166 (1)
C(6)—C(5)—C(7)—N(12)	−132.7 (5)	O(15)—C(16)—C(17)—C(20)	46.9 (5)
C(4)—C(5)—C(6)—O(15)	−176.3 (5)	O(18)—C(17)—C(20)—N(21)	−70.7 (4)
C(7)—C(5)—C(6)—C(1)	175.5 (5)	O(19)—C(17)—C(20)—N(21)	34 (1)
C(4)—C(5)—C(7)—C(8)	−137.7 (5)	C(16)—C(17)—C(20)—N(21)	167.4 (5)
C(4)—C(5)—C(7)—N(12)	41.8 (5)	C(17)—C(20)—N(21)—C(22)	161.5 (3)
C(1)—C(6)—O(15)—C(16)	−29.1 (5)	C(20)—N(21)—C(22)—C(23)	−72.4 (4)
C(5)—C(6)—O(15)—C(16)	148.2 (5)	C(20)—N(21)—C(22)—C(24)	48.2 (5)
N(11)—C(10)—N(13)—N(14)	177.7 (5)	C(20)—N(21)—C(22)—C(25)	169.1 (4)
C(9)—C(10)—N(13)—N(14)	−3.0 (5)		

lengths and angles in both the phenyl ring and the pyridazine ring are in close agreement with those found in these ring systems in other structures in the Cambridge Structural Database (1992). Both rings are planar with the ring planes at a dihedral angle of 45° to minimize steric interaction between the pyridazine ring and propranolol side chain. The side-chain hydroxyl group on asymmetric carbon C(17) is disordered as in propranolol hydrochloride (Ammon *et al.*, 1977) and the crystal therefore contains both enantiomorphs (*ca* 0.8 of one, 0.2 of the other). The apparent shortening of the C—OH bond length compared to, for example, that found in dichloroisoproterenol (1.416 Å), is not considered significant. The crystal structure of propranolol hydrochloride shows similar apparently short bond lengths.

Protonation of prizidilol occurs at N(21) producing a C(20)—N(21)—C(22) angle of 116.3 (3)° similar to that found in the propranolol hydrochloride structure (116.5°) which is protonated at the same N atom (Ammon *et al.*, 1977). Similar large C—N—C angles are also found in dichloroisoproterenol hydrochloride [117.75 (3)°; Gadret, Goursolle, Leger & Colleter, 1975*a*] and bupranolol hydrochloride [117.28 (4)°; Gadret, Goursolle, Leger & Colleter, 1975*b*] which are presented as trigonal planar unprotonated secondary amines. When compared to the unprotonated dichloroisoproterenol [115.3 (3)°] and propranolol [112.5 (3)°; Ammon *et al.*, 1977], it is clear that these hydrochlorides are protonated at the secondary N atom.

The overall conformation of the side chain in prizidilol is similar to that found in most other β-blockers with the exception of the O(15)—C(16)—C(17)—C(20) torsion angle which appears to vary considerably. In other propranolol-like β-blockers the crystal structures of which have been determined, the displacement of C(16) from the plane of the adjacent aromatic ring is small, varying from 0.056 in pindolol (Gadret, Goursolle, Leger & Colleter, 1976) to 0.235 Å in propranolol.HCl. In prizidilol, however, the C(1)—C(6)—O(15)—C(16) torsion angle is −29.1° and C(16) is 0.773 Å from the aromatic ring plane.

N(14)···N(12) hydrogen bonds link the molecules of prizidilol as dimers across symmetry centres. N(21) acts as a hydrogen-bond donor to two sulfate anions. This produces two columns of molecules parallel to the *b* axis and related by a mirror plane. Hydrogen bonding may also occur between O(19) and O(27) as well as between the prizidilol cation and the water molecules present in the mirror plane. Pairs of O(19) atoms related by a mirror plane appear to be 2.10 Å apart; it is assumed that these two sites are never simultaneously occupied [site occupancy of O(19) was found as 0.20].*

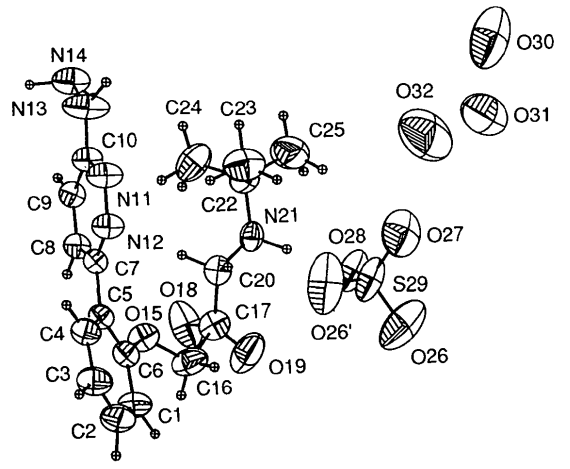


Fig. 1. A view of the molecule with the numbering scheme; the O(18) and O(19) sites with occupancies 0.8 and 0.2, respectively, represent a single disordered hydroxyl group. O(26)′ is related to O(26) by a mirror plane in which O(27), O(28), S(29), O(30), O(3) and O(32) lie.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71243 (26 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HA0119]

References

AMMON, H. L., HOWE, D.-B., ERHARDT, W. D., BALSAMO, A., MACCHIA, B., MACCHIA, F. & KEEKE, W. E. (1977). *Acta Cryst.* B33, 21–29.

Cambridge Structural Database (1992). Version 4.6. Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, England.

CARRUTHERS, J. R. & WATKIN, D. J. (1979). *Acta Cryst.* A35, 698–699.

CROMER, D. T. & WABER, J. T. (1974). *International Tables for X-ray Crystallography*, Vol. IV, edited by J. A. IBERS & W. C. HAMILTON. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

EGGERTSEN, R., ANDREN, L. & HANSSON, L. (1983). *Curr. Ther. Res. Clin. Exp.* **34**, 10233–10238.

GADRET, M., GOURSOLLE, M., LEGER, J. M. & COLLETER, J. C. (1975*a*). *Acta Cryst.* B31, 1942–1946.

GADRET, M., GOURSOLLE, M., LEGER, J. M. & COLLETER, J. C. (1975*b*). *Acta Cryst.* B31, 2780–2783.

GADRET, M., GOURSOLLE, M., LEGER, J. M. & COLLETER, J. C. (1976). *Acta Cryst.* B32, 17–20.

KARLBERG, B. E., LARSSON, R., OHMAN, K. P., NORLANDER, B., WIRSEN, A., HED, J., LUNDH, B. L. & FLOCK, A. (1983). *Eur. J. Clin. Pharmacol.* **25**, 179–186.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

TAYLOR, E. M., CAMERON, D., EDEN, R. J., FIELDEN, R. & OWEN, D. A. A. (1981). *J. Cardiovasc. Pharmacol.* **3**, 337–354.

TAYLOR, E. M., ROE, A. M. & SLATER, R. A. (1979). *Clin. Sci.* **57**, 433S-436S

WATKIN, D. J., CARRUTHERS, J. R. & BETTERIDGE, P. W. (1985). *CRYSTALS User Guide.* Chemical Crystallography Laboratory, Univ. of Oxford, England.

Acta Cryst. (1994). **B50**, 71–85

Crystal and Molecular Structures of Pyridazinone Cardiovascular Agents

BY KEITH PROUT,* COLIN BANNISTER, KEITH BURNS AND MINGQIN CHEN

Chemical Crystallography Laboratory, Oxford University, 9 Parks Road, Oxford OX1 3PD, England

AND BRIAN H. WARRINGTON AND J. G. VINTER†

SmithKline Beecham, The Frythe, Welwyn, Herts AL6 9AR, England

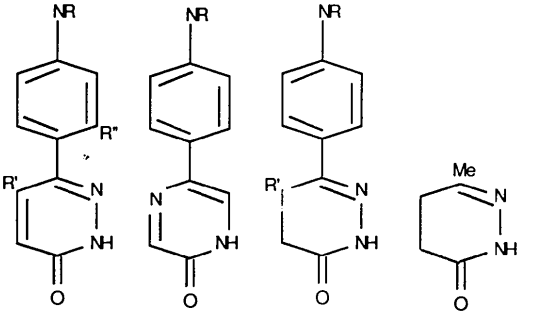
(*Received* 6 *April* 1993; *accepted* 7 *June* 1993)

Abstract

The crystal and molecular structures of 11 6-substituted pyridazinone derivatives: 6-phenyl-3(2*H*)-pyridazinone–acetic acid (1/1) (1), 6-(4-aminophenyl)-3(2*H*)-pyridazinone (2), 6-(4-aminophenyl)-5-methyl-3(2*H*)-pyridazinone (3), 6-(4-acetamidophenyl)-3(2*H*)-pyridazinone (4), 6-(4-acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone (5), 6-(2-aminophenyl)-3(2*H*)-pyridazinone (6), 6-phenyl-3(2*H*)-pyrazinone (7), 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (8), (*R*)-(−)-6-[4-(3-bromopropionamido)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (9), (*R*)-(−)-6-(4-ammoniophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (−)-tartrate–dichloromethane–methanol (1/1/1) (10), 4,5-dihydro-6-methyl-3(2*H*)-pyridazinone (11) have been determined as part of a study to determine the relationship between their cardiovascular properties and molecular structure and dimensions. For the two optically resolved chiral derivatives (9) and (10) the absolute configuration has been determined.

Introduction

The crystal and molecular structures of compounds (1)–(11) were determined as part of an investigation into quantitative structure–activity relationships in pyridazinone derivatives as antiaggregatory, antihypertensive and inotropic agents.



Peripheral vasodilator agents are in clinical use to lower blood pressure; however, the reduction of blood pressure initiates the activation of β-adrenoceptors in the heart with a consequent undesirable increase in heart rate. These undesirable effects of vasodilators are inhibited by β-adrenoceptor antagonists with the result that the combined use of vasodilators and β-blockers has been widely adopted for the treatment of hypertension. An effort by SmithKline Beecham Research to combine the vasodilator and β-blocker function in the one molecule

* Author for correspondence.

† Present address: Baylays Glen, Weston, Hitchin, Herts SG4 7AS, England.