Slight disorder is found in the hydrogen-bond chain, related to the partially occupied water-molecule site situated next to this chain. Its presence causes a slight displacement of O(2), keeping its H atoms roughly in place. In this way the disorder hardly influences the hydrogen-bond chain geometry. The distance of the displaced O(2) to O(3) [O(21)—O(3)] is 2·73 (2) Å, suggesting the presence of a hydrogen bond with a hydrogen of O(3) directed towards O(21).

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Structures of (S)-Timolol Hemihydrate* and (S)-Timolol O,O-Diacetyl-L-tartaric Acid Monoester†

By Jussi Kivikoski and Jussi Valkonen

Department of Chemistry, University of Jyväskylä, SF-40100 Jyväskylä, Finland

and Esko Pohjala

Huhtamäki Oy Leiras, Box 33, SF-33721 Tampere, Finland

Abstract. (S)-Timolol hemihydrate, $2C_{13}H_{24}N_4O_3S$. H_2O, $M_r = 650 \cdot 9$, monoclinic, C2, $a = 23 \cdot 435$ (3), $b = 6 \cdot 384$ (1), $c = 11 \cdot 591$ (1) Å, $\beta = 103 \cdot 08$ (1)°, $V = 1687$ (3) Å³, $Z = 2$, $D_x = 1 \cdot 28$ Mg m⁻³, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0 \cdot 20$ mm⁻¹, $F(000) = 700$, $T = 296$ K, final $R = 0 \cdot 035$ for 1369 unique observed reflections. The morpholine ring has a chair conformation. The thiadiazole ring is planar with the side-chain O and N atoms in the plane. The crystal water between the molecules is hydrogen bonded to the propanol O atom. (S)-Timolol O,O-diacetyl-L-tartaric acid monoester, $C_{21}H_{32}N_4O_{10}S$, $M_r = 532 \c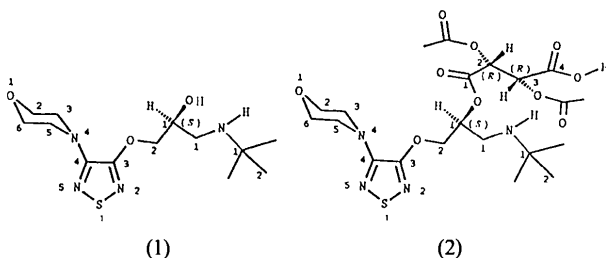dot 6$, monoclinic, $P2_1$, $a = 9 \cdot 670$ (4), $b = 8 \cdot 853$ (2), $c = 31 \cdot 053$ (7) Å, $\beta = 93 \cdot 49$ (2)°, $V = 2651$ (2) Å³, $Z = 4$, $D_x = 1 \cdot 33$ Mg m⁻³, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0 \cdot 17$ mm⁻¹, $F(000) = 1128$, $T = 296$ K, final $R = 0 \cdot 050$ for 3130 unique observed reflections. The asymmetric unit contains two molecules of differing conformation. There are intramolecular N···O hydrogen bonds in both molecules.

Introduction. Timolol (1) is a non-selective β-adrenergic blocker, whose 1:1 maleate salt is used for the treatment of glaucoma and cardiovascular diseases (Mazzo & Loper, 1987). The crystal structure of the maleate salt has been determined (Carpy, Colleter, Gadret, Coursolle & Leger, 1976). The racemic base (The Merck Index, 1983) crystallizes in anhydrous form, but the enantiomers of timolol contain crystal water (2:1) (Perälampi, 1988). The O,O-diacetyl-L-tartaric acid ester (2) is successfully

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* (S)-1-[(1,1-Dimethylethyl)amino]-3-{[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy}-2-propanol.

† (S)-[(1,1-Dimethylethyl)amino]methyl-2-{[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy}ethyl hydrogen (2R,3R)-2,3-bis(acetoxy) butanedioate.

used for the the industrial resolution of racemic timolol, giving quantitatively the crystalline (S)-form ester in one step (Hietaniemi & Nupponen, 1984). In order to explain these observations in detail and to elucidate the stereochemical requirements for the action of timolol at the receptor site, crystal and molecular structures were determined for the (S)-timolol base and its mono-O,O-diacetyl-L-tartaric acid ester.

(1)   (2)

Experimental. Single crystals of the title compounds, with m.p. = 325–326 K for (1) and m.p. = 489–490 K for (2) were crystallized from a solution of water and CH_2Cl_2. Intensity data were measured on a Enraf–Nonius CAD-4 diffractometer using graphite-monochromatized Mo $K\alpha$ radiation and the ω–2θ method. Cell parameters and orientation matrix for (1) were determined from a least-squares fit of 18 reflections $(6 < \theta < 10°)$ and for (2) from 25 reflections $(8 < \theta < 18°)$. Two standard reflections were measured every hour, no systematic variation was detected. The polar space groups were chosen because of the pure enantiomers of optically active compounds. No equivalent reflections were measured and no efforts to determine absolute configurations by X-ray diffraction were made.

Compound (1): The crystal size was $0.20 \times 0.20 \times 0.15$ mm. 1632 reflections $(h: 0\rightarrow27, \; k: 0\rightarrow7, \; l: -13\rightarrow13)$ with $\theta < 25°$ were measured, 1369 of which had $I > 3\sigma(I)$. An empirical absorption correction (Walker & Stuart, 1983) was made with correction factors: max. = 1.250 and min. = 0.631. The structure was solved by direct methods and refined by full-matrix least squares on F with all non-H atoms anisotropic. The positions of the H atoms bonded to C were calculated (C—H distance 1.025 Å) whereas the H atoms bonded to O and N atoms were found in $\Delta\rho$ maps. These H atoms were treated as riding atoms. The H atoms bonded to the water molecule were also found in $\Delta\rho$ maps and refined. The isotropic temperature factor was fixed at $B_{eq} = 5.0$ Å^2 for all H atoms. 197 parameters were refined. The results are $R = 0.035$, $wR = 0.034$, $w = 1/(\sigma F)^2$ (σF from counting statistics), max. shift/σ = 0.03 in final cycle, $S = 1.546$, max. and min. peaks 0.14 (4) and -0.25 (4) e Å^{-3} in final $\Delta\rho$ map.

Compound (2): The crystal size was $0.70 \times 0.40 \times 0.40$ mm. 5005 reflections $(h: 0\rightarrow11, \; k: 0\rightarrow10,$

Table 1. *Fractional coordinates and equivalent isotropic temperature factors for (S)-timolol hemihydrate with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)].$$

	x	y	z	B_{eq}(Å^2)
S	0.19294 (3)	0.157	0.17281 (8)	4.56 (2)
OW	0.500	0.6808 (7)	0.000	7.1 (1)
O1	0.44078 (8)	0.0560 (4)	0.0605 (2)	3.35 (5)
O2	0.33687 (7)	0.2748 (4)	0.1104 (2)	3.30 (4)
O3	0.3490 (1)	0.9630 (4)	0.3707 (2)	5.33 (6)
N1	0.45621 (9)	0.2552 (4)	−0.1693 (2)	2.87 (5)
N2	0.24495 (9)	0.1265 (4)	0.0987 (2)	3.55 (6)
N3	0.2221 (1)	0.3509 (5)	0.2596 (2)	3.93 (6)
N4	0.0381 (1)	0.5541 (5)	0.2945 (2)	3.30 (5)
C1	0.4578 (1)	0.2563 (6)	−0.2975 (2)	3.71 (7)
C2	0.5137 (1)	0.3765 (8)	−0.3051 (3)	5.6 (1)
C3	0.4613 (1)	0.0329 (7)	−0.3393 (3)	5.18 (9)
C4	0.4049 (2)	0.3669 (8)	−0.3748 (3)	6.3 (1)
C5	0.4028 (1)	0.1647 (7)	−0.1432 (2)	3.17 (6)
C6	0.4020 (1)	0.1959 (5)	−0.0142 (2)	2.76 (6)
C7	0.3408 (1)	0.1602 (7)	0.0054 (2)	3.15 (6)
C8	0.2857 (1)	0.2618 (5)	0.1451 (2)	2.82 (6)
C9	0.2727 (1)	0.3973 (6)	0.2348 (3)	3.13 (7)
C10	0.2819 (1)	0.6744 (7)	0.3775 (3)	4.83 (8)
C11	0.3256 (2)	0.8290 (7)	0.4454 (3)	5.6 (1)
C12	0.3776 (1)	0.8408 (6)	0.2990 (3)	4.37 (9)
C13	0.3368 (1)	0.6915 (6)	0.2214 (3)	3.98 (8)
HW	0.481 (1)	0.777 (7)	0.034 (3)	5.0
HN1	0.459	0.410	−0.139	5.0
HO1	0.471	0.119	0.082	5.0

$l: -37\rightarrow37$) with $\theta < 25°$ were measured, 3130 of which had $I > 3\sigma(I)$. An empirical absorption correction (Walker & Stuart, 1983) was made with correction factors: max. = 1.074 and min. = 0.764. The structure was solved by direct methods and refined by full-matrix least squares on F with all non-H atoms anisotropic. The positions of the H atoms bonded to N atoms were found in $\Delta\rho$ maps, other H atoms were calculated (C—H distance 1.025, O—H distance 1.000 Å). All H atoms were treated as riding atoms. The isotropic temperature factor was fixed at $B_{eq} = 5.0$ Å^2 for all H atoms. 648 parameters were refined. The results are $R = 0.050$, $wR = 0.044$, $w = 1/(\sigma F)^2$ (σF from counting statistics), max. shift/σ = 0.03 in final cycle, $S = 1.424$, max. and min. peaks 0.22 (4) and -0.29 (4) e Å^{-3} in final $\Delta\rho$ map.

Scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). The computer programs *MULTAN*11/82 (Main *et al.*, 1982), *SHELXS*86 (Sheldrick, 1986), *SDP* (Frenz, 1978) and *PLUTO* (Motherwell & Clegg, 1978) were used.

Discussion. The atomic coordinates and isotropic temperature factors are listed in Tables 1 and 2,* and

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* Lists of structure factors, anisotropic thermal parameters, least-squares planes and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53196 (41 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Fractional coordinates and equivalent isotropic temperature factors for (S)-timolol O,O-diacaetyl-L-tartaric acid monoester with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)[a^2 B(1,1) + b^2 B(2,2) + c^2 B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)].$$

	x	y	z	$B_{eq}(\text{Å}^2)$
S1	0·4576 (2)	1·200	0·80889 (7)	9·45 (6)
S1'	0·9836 (2)	0·6341 (3)	0·69825 (7)	11·23 (7)
O1'	0·6497 (3)	0·5377 (4)	0·5915 (1)	3·54 (8)
O1	0·8321 (3)	0·7867 (4)	0·9080 (1)	3·80 (8)
O2'	0·7023 (3)	0·8143 (4)	0·6318 (1)	4·59 (9)
O2	0·7698 (3)	1·0667 (4)	0·8713 (1)	4·56 (9)
O3	1·0562 (6)	1·0740 (7)	0·7349 (2)	12·9 (2)
O3'	0·3642 (5)	0·7496 (7)	0·7589 (1)	10·8 (2)
O4	0·6714 (3)	0·6969 (5)	0·9506 (1)	5·6 (1)
O4'	0·8228 (3)	0·4586 (5)	0·5531 (1)	5·2 (1)
O5	0·9231 (3)	0·3428 (4)	0·9624 (1)	4·63 (9)
O5'	0·5783 (3)	0·0950 (4)	0·5402 (1)	4·85 (9)
O6	1·0378 (4)	0·5539 (4)	0·9520 (1)	5·7 (1)
O6'	0·4521 (4)	0·2980 (4)	0·5491 (1)	6·2 (1)
O7	0·9671 (3)	0·5319 (4)	0·8642 (1)	4·33 (9)
O7'	0·5199 (3)	0·2870 (4)	0·6376 (1)	4·79 (9)
O8	1·1056 (4)	0·3265 (5)	0·8653 (1)	6·6 (1)
O8'	0·3926 (4)	0·0773 (5)	0·6388 (1)	6·9 (1)
O9'	0·8400 (3)	0·1916 (4)	0·5952 (1)	5·01 (9)
O9	0·6504 (3)	0·4365 (4)	0·9102 (1)	4·51 (9)
O10	0·4814 (4)	0·5723 (5)	0·8779 (1)	7·1 (1)
O10'	1·0090 (4)	0·3233 (5)	0·6289 (1)	6·9 (1)
N1'	0·3974 (4)	0·6051 (5)	0·5445 (1)	3·42 (9)
N1	1·0842 (4)	0·8653 (5)	0·9516 (1)	3·4 (1)
N2'	0·9160 (5)	0·7087 (7)	0·6538 (2)	7·3 (2)
N2	0·5412 (4)	1·1336 (6)	0·8529 (2)	5·8 (1)
N3'	0·8496 (5)	0·6439 (7)	0·7280 (2)	7·9 (2)
N3	0·5860 (5)	1·1999 (8)	0·7773 (2)	8·5 (2)
N4	0·8236 (5)	1·1399 (7)	0·7828 (1)	7·2 (1)
N4'	0·6248 (5)	0·7400 (6)	0·7219 (1)	5·9 (1)
C1'	0·2426 (5)	0·6165 (7)	0·5527 (2)	4·5 (1)
C1	1·2353 (5)	0·8840 (7)	0·9409 (2)	4·4 (1)
C2	1·2793 (6)	1·0434 (7)	0·9529 (2)	7·8 (2)
C2'	0·2218 (6)	0·5927 (9)	0·6009 (2)	7·8 (2)
C3	1·2514 (6)	0·853 (1)	0·8944 (2)	8·2 (2)
C3'	0·1932 (6)	0·7747 (8)	0·5386 (2)	8·2 (2)
C4'	0·1724 (5)	0·4953 (8)	0·5251 (2)	7·0 (2)
C4	1·3147 (5)	0·7680 (8)	0·9683 (2)	6·3 (2)
C5'	0·4860 (4)	0·7225 (6)	0·5664 (2)	3·8 (1)
C5	0·9873 (5)	0·9815 (6)	0·9316 (2)	3·9 (1)
C6'	0·6372 (5)	0·6778 (6)	0·5662 (2)	3·4 (1)
C6	0·8405 (5)	0·9253 (6)	0·9337 (2)	3·7 (1)
C7'	0·7341 (5)	0·7959 (6)	0·5870 (2)	4·3 (1)
C7	0·7338 (5)	1·0370 (6)	0·9148 (2)	4·3 (1)
C8	0·6658 (5)	1·1128 (7)	0·8429 (2)	4·8 (1)
C8'	0·7899 (6)	0·7432 (7)	0·6614 (2)	4·8 (1)
C9'	0·7482 (6)	0·7084 (7)	0·7045 (2)	5·8 (2)
C9	0·6950 (6)	1·1483 (7)	0·7994 (2)	5·9 (2)
C10	0·8334 (7)	1·193 (1)	0·7398 (2)	11·7 (3)
C10'	0·6064 (7)	0·677 (1)	0·7650 (2)	10·0 (2)
C11'	0·4845 (7)	0·727 (1)	0·7812 (2)	16·4 (4)
C11	0·9827 (8)	1·214 (1)	0·7317 (3)	14·6 (3)
C12	1·0511 (6)	1·029 (1)	0·7784 (2)	9·0 (2)
C12'	0·3832 (6)	0·816 (1)	0·7189 (2)	9·6 (2)
C13'	0·5029 (6)	0·760 (1)	0·6976 (2)	11·1 (3)
C13	0·9077 (7)	1·0065 (9)	0·7905 (2)	8·8 (2)
C14'	0·7457 (5)	0·4376 (6)	0·5804 (2)	3·5 (1)
C14	0·7439 (5)	0·6801 (6)	0·9216 (2)	3·9 (1)
C15'	0·7408 (4)	0·2978 (6)	0·6094 (2)	3·8 (1)
C15	0·7470 (5)	0·5382 (6)	0·8935 (2)	3·6 (1)
C16'	0·6041 (5)	0·2112 (6)	0·6077 (2)	3·9 (1)
C16	0·8881 (5)	0·4545 (6)	0·8950 (2)	3·5 (1)
C17'	0·5364 (5)	0·2020 (6)	0·5620 (2)	3·5 (1)
C17	0·9580 (5)	0·4518 (6)	0·9399 (2)	3·4 (1)
C18'	0·4164 (6)	0·2025 (8)	0·6523 (2)	5·6 (2)
C18	1·0756 (5)	0·4506 (8)	0·8509 (2)	5·2 (2)
C19	1·1498 (5)	0·5363 (8)	0·8179 (2)	6·9 (2)
C19'	0·3370 (5)	0·2828 (8)	0·6855 (2)	6·2 (2)
C20	0·5154 (5)	0·4726 (7)	0·9019 (2)	4·8 (1)
C20'	0·9730 (5)	0·2168 (7)	0·6069 (2)	5·6 (2)
C21'	1·0634 (6)	0·0994 (8)	0·5885 (2)	9·4 (2)
C21	0·4244 (5)	0·3778 (7)	0·9274 (2)	6·9 (2)
HN1	1·0820	0·7509	0·9379	5·0
HN1'	0·4159	0·5007	0·5622	5·0

Table 3. *Bond distances (Å) and angles (°) for (S)-timolol hemihydrate with e.s.d.'s in parentheses*

S—N2	1·654 (3)	N3—C9	1·315 (4)
S—N3	1·644 (3)	N4—C9	1·381 (4)
OW—HW	0·90 (4)	N4—C10	1·470 (5)
O1—C6	1·420 (3)	N4—C13	1·482 (4)
O1—HO1	0·795 (2)	C1—C2	1·539 (5)
O2—C7	1·440 (4)	C1—C3	1·514 (6)
O2—C8	1·352 (3)	C1—C4	1·527 (5)
O3—C11	1·414 (5)	C5—C6	1·513 (4)
O3—C12	1·414 (4)	C6—C7	1·518 (4)
N1—C1	1·494 (4)	C8—C9	1·436 (4)
N1—C5	1·471 (4)	C10—C11	1·507 (5)
N1—HN1	1·049 (3)	C12—C13	1·497 (5)
N2—C8	1·308 (4)		
N2—S—N3	98·7 (1)	N1—C5—C6	110·7 (2)
C7—O2—C8	116·8 (2)	O1—C6—C5	111·7 (2)
C11—O3—C12	109·2 (3)	O1—C6—C7	108·1 (2)
C1—N1—C5	114·8 (2)	C5—C6—C7	110·6 (2)
S—N2—C8	105·4 (2)	O2—C7—C6	107·1 (2)
S—N3—C9	107·8 (2)	O2—C8—N2	122·2 (3)
C9—N4—C10	114·4 (2)	O2—C8—C9	121·7 (3)
C9—N4—C13	116·2 (2)	N2—C8—C9	116·1 (3)
C10—N4—C13	112·1 (3)	N3—C9—N4	121·5 (3)
N1—C1—C2	105·8 (2)	N3—C9—C8	111·8 (3)
N1—C1—C3	109·2 (3)	N4—C9—C8	126·6 (3)
N1—C1—C4	112·7 (3)	N4—C10—C11	110·4 (3)
C2—C1—C3	110·0 (3)	O3—C11—C10	112·9 (3)
C2—C1—C4	108·9 (3)	O3—C12—C13	112·3 (3)
C3—C1—C4	110·1 (3)	N4—C13—C12	110·1 (2)
OW—HW—O1	156 (4)	C6—O1—HO1	105·4 (2)
C1—N1—HN1	108·6 (2)	C5—N1—HN1	106·9 (2)

the bond distances and angles in Tables 3 and 4. A view of compound (1) and its numbering scheme are shown in Fig. 1. A stereoscopic view of the packing is presented in Fig. 2. Views of compound (2) and its numbering scheme are shown in Figs. 3 and 4, and a stereoscopic view of the packing is presented in Fig. 5.

Compound (1): Bond distances and angles are normal. There is an intermolecular hydrogen bond $O1\cdots N1(1-x,y,-z)$ with $O—HO\cdots N = 167.5°$, $O\cdots N = 2.766\,(3)$ and $HO\cdots N = 1.984\,(2)$ Å. Other distances between the molecules shorter than the sum of van der Waals radii do not exist. The crystal water molecule is hydrogen bonded to $O1(1-x, 1+y,z)$ with $OW—HW\cdots O1 = 159.6°$. Because the distance $OW\cdots O1$ is long [2·932 (4) Å], this hydrogen bond is weak. This is supported by thermogravimetric measurements: the water is expelled at 323 K. The distance between atoms HW and O is 2·07 (4) Å. The thiadiazole ring is planar [max. deviation $-0.021\,(3)$ Å for C8]. The morpholine ring has a chair conformation. Atoms C10, C11, C12 and C13 are in the same plane [max. deviation 0·007 (4) Å], while O3 is 0·658 (3) Å above the plane and N4 $-0.595\,(3)$ Å below. The absolute configuration was not determined by X-ray diffraction since it had earlier been shown to be S by the manufacturer.

Compound (2): Bond distances and angles are mostly normal. Comparison of the skeletons of (1) and (2) shows that the only difference in the two

Table 4. Bond distances (Å) and angles (°) for (S)-timolol O,O-diacetyl-L-tartaric acid monoester with e.s.d.'s in parentheses

S1—N2	1·653 (5)	N1—C1	1·525 (6)
S1—N3	1·629 (6)	N1—C5	1·500 (6)
S1′—N2′	1·630 (5)	N2′—C8′	1·292 (7)
S1′—N3′	1·639 (6)	N2—C8	1·274 (7)
O1′—C6′	1·470 (6)	N3′—C9′	1·317 (8)
O1′—C14′	1·343 (6)	N3—C9	1·304 (8)
O1—C6	1·463 (6)	N4—C9	1·375 (7)
O1—C14	1·355 (6)	N4—C10	1·423 (9)
O2′—C7′	1·453 (6)	N4—C13	1·446 (9)
O2′—C8′	1·365 (6)	N4′—C9′	1·368 (7)
O2—C7	1·439 (6)	N4′—C10′	1·472 (8)
O2—C8	1·360 (6)	N4′—C13′	1·370 (7)
O3—C11	1·43 (1)	C1′—C2′	1·537 (8)
O3—C12	1·412 (9)	C1′—C3′	1·535 (9)
O3′—C11′	1·331 (8)	C1′—C4′	1·509 (9)
O3′—C12′	1·399 (9)	C1—C2	1·514 (9)
O4—C14	1·184 (6)	C1—C3	1·487 (8)
O4′—C14′	1·177 (6)	C1—C4	1·512 (8)
O5—C17	1·249 (6)	C5′—C6′	1·514 (6)
O5′—C17′	1·246 (6)	C5—C6	1·509 (6)
O6—C17	1·232 (6)	C6′—C7′	1·521 (7)
O6′—C17′	1·227 (6)	C6—C7	1·520 (7)
O7—C16	1·435 (6)	C8—C9	1·432 (8)
O7—C18	1·356 (7)	C8′—C9′	1·452 (8)
O7′—C16′	1·437 (6)	C10—C11	1·49 (1)
O7′—C18′	1·350 (7)	C10′—C11′	1·38 (1)
O8—C18	1·214 (8)	C12—C13	1·472 (9)
O8′—C18′	1·203 (8)	C12′—C13′	1·454 (9)
O9′—C15′	1·430 (6)	C14′—C15′	1·533 (8)
O9′—C20′	1·332 (6)	C14—C15	1·530 (7)
O9—C15	1·417 (6)	C15′—C16′	1·525 (6)
O9—C20	1·352 (6)	C15—C16	1·550 (6)
O10—C20	1·188 (7)	C16′—C17′	1·531 (6)
O10′—C20′	1·205 (8)	C16—C17	1·512 (6)
N1′—HN1′	1·084 (4)	C18′—C19′	1·501 (8)
N1′—C1′	1·536 (6)	C18—C19	1·493 (8)
N1′—C5′	1·485 (6)	C20—C21	1·479 (8)
N1—HN1	1·098 (4)	C20′—C21′	1·492 (9)

N2—S1—N3	98·4 (3)	O1—C6—C7	108·7 (4)
N2′—S1′—N3′	99·6 (3)	C5—C6—C7	112·7 (4)
C6′—O1′—C14′	117·0 (4)	O2′—C7′—C6′	108·9 (4)
C6—O1—C14	115·5 (4)	O2—C7—C6	106·5 (4)
C7′—O2′—C8′	115·8 (4)	O2—C8—N2	123·8 (4)
C7—O2—C8	117·0 (4)	O2—C8—C9	119·9 (4)
C11—O3—C12	105·3 (6)	N2—C8—C9	116·2 (5)
C11′—O3′—C12′	111·6 (5)	O2′—C8′—N2′	122·6 (5)
C16—O7—C18	113·7 (4)	O5′—C17′—O6′	125·6 (4)
C16′—O7′—C18′	114·8 (4)	O5′—C17′—C16′	114·2 (4)
C15′—O9′—C20′	117·4 (4)	O6′—C17′—C16′	120·2 (5)
C15—O9—C20	115·5 (4)	O5—C17—O6	125·5 (4)
C1′—N1′—C5′	114·7 (4)	O5—C17—C16	114·0 (4)
C1—N1—C5	114·6 (4)	O6—C17—C16	120·4 (5)
S1′—N2′—C8′	105·9 (4)	O7′—C18′—O8′	121·5 (5)
S1—N2—C8	105·8 (4)	O7′—C18′—C19′	112·9 (5)
S1′—N3′—C9′	107·2 (4)	O8′—C18′—C19′	125·6 (5)
S1—N3—C9	107·6 (4)	C5—N1—HN1	118·3 (3)
C9—N4—C10	116·5 (5)	O2′—C8′—C9′	121·5 (5)
C9—N4—C13	119·6 (5)	N2′—C8′—C9′	115·8 (5)
C10—N4—C13	110·8 (6)	N3′—C9′—N4′	120·4 (3)
C9′—N4′—C10′	115·9 (5)	N3′—C9′—C8′	111·4 (5)
C9′—N4′—C13′	123·4 (5)	N4′—C9′—C8′	128·1 (5)
C10′—N4′—C13′	113·7 (5)	N3—C9—N4	122·7 (5)
N1′—C1′—C2′	109·8 (4)	N3—C9—C8	112·0 (5)
O9—C15—C14	106·1 (4)	N4—C9—C8	125·1 (5)
O9—C15—C16	106·5 (4)	N4—C10—C11	108·6 (6)
C14—C15—C16	115·0 (4)	N4′—C10′—C11′	111·2 (6)
O7′—C16′—C15′	105·5 (4)	O3′—C11′—C10′	126·5 (7)
O7′—C16′—C17′	113·4 (4)	O3—C11—C10	111·4 (8)
C15′—C16′—C17′	112·2 (4)	O3—C12—C13	111·8 (5)
O7—C16—C15	104·8 (4)	O3′—C12′—C13′	114·2 (6)
O7—C16—C17	113·4 (4)	N4′—C13′—C12′	118·4 (6)
C15—C16—C17	112·2 (4)	N4—C13—C12	112·0 (6)
C1—N1—HN1	90·7 (3)	O1′—C14′—O4′	124·0 (5)
C5′—N1—HN1′	107·0 (3)	O1′—C14′—C15′	109·6 (4)
N1′—C1′—C3′	107·5 (4)	O4′—C14′—C15′	126·4 (5)
N1′—C1′—C4′	105·5 (4)	O1—C14—O4	124·1 (5)
C2′—C1′—C3′	110·3 (5)	O1—C14—C15	111·2 (4)
C2′—C1′—C4′	112·2 (5)	O4—C14—C15	124·7 (5)
C3′—C1′—C4′	111·4 (5)	O9′—C15′—C14′	107·8 (4)
N1—C1—C2	107·8 (4)	O9′—C15′—C16′	104·8 (4)
N1—C1—C3	110·4 (4)	C14′—C15′—C16′	116·3 (4)
N1—C1—C4	105·3 (4)	O7—C18—O8	122·7 (5)

Table 4 (cont.)

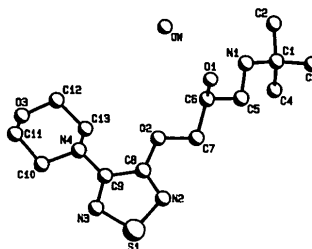|			
C2—C1—C3	111·4 (6)	O7—C18—C19	110·5 (5)
C2—C1—C4	111·7 (5)	O8—C18—C19	126·7 (5)
C3—C1—C4	110·0 (5)	O9—C20—O10	121·4 (5)
N1′—C5′—C6′	110·2 (4)	O9—C20—C21	111·3 (5)
N1—C5—C6	108·7 (4)	O10—C20—C21	127·3 (5)
O1′—C6′—C5′	105·4 (4)	O9′—C20′—O10′	121·7 (5)
O1′—C6′—C7′	108·9 (4)	O9′—C20′—C21′	110·9 (5)
C5′—C6′—C7′	112·8 (4)	O10′—C20′—C21′	127·4 (5)
O1—C6—C5	105·9 (4)	C1′—N1′—HN1′	96·0 (3)

Fig. 1. PLUTO plot (Motherwell & Clegg, 1978) and numbering scheme for (S)-timolol hemihydrate.

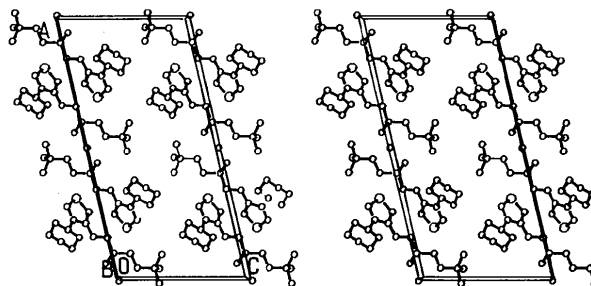Fig. 2. A stereoscopic view of the packing for (S)-timolol hemihydrate. The a axis is vertical and the c axis horizontal.

compounds is the slightly disordered morpholine ring in (2) [also, the thermal parameters are high for the ring atoms of (2)]. The molecules of (2) are packed with two different molecules in the asymmetric unit. The second molecule is designated with primed atom numbers. Bond distances and angles are similar in the two molecules. The torsion angle C8—O2— C7—C6 is 155·2° in the first and 101·5° in the second molecule while the values of C7—O2—C8—C9 are 179·0 and −158·8°, respectively. Thus the second molecule is twisted by 54° about the C7—O2 bond and by 33° about the C8—O2 bond as compared with the first molecule. The difference between the molecules (Figs. 3 and 4) is easily seen if they are viewed with the ester groups coinciding. There are intramolecular hydrogen bonds O6···N1 and O6′···N1′ with O···N = 2·793 (6) and 2·771 (6) Å,
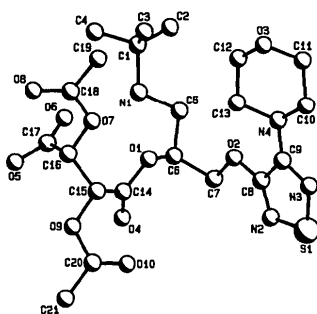
Fig. 3. *PLUTO* plot (Motherwell & Clegg, 1978) and numbering scheme for (*S*)-timolol *O,O*-diacetyl-L-tartaric acid monoester (molecule 1).
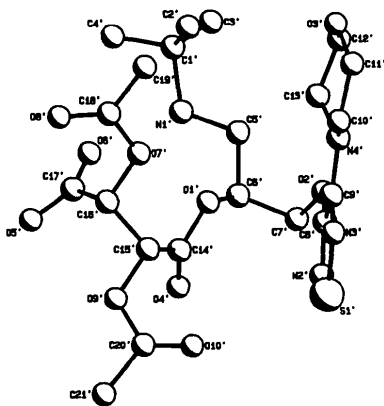

Fig. 4. *PLUTO* plot (Motherwell & Clegg, 1978) and numbering scheme for (*S*)-timolol *O,O*-diacetyl-L-tartaric acid monoester (molecule 2).
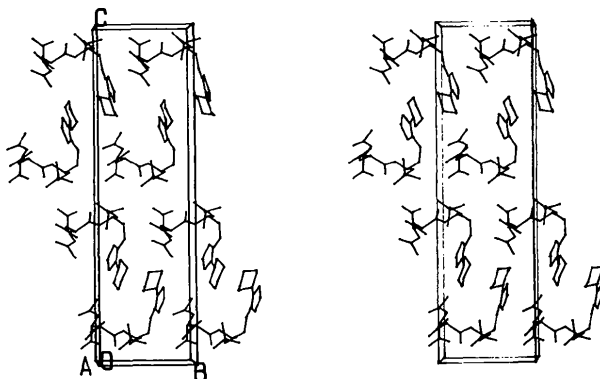

Fig. 5. A stereoscopic view of the packing for (*S*)-timolol *O,O*-diacetyl-L-tartaric acid monoester. The *c* axis is vertical and the *b* axis horizontal.

$O\cdots HN = 1.855$ (4) and 1.877 (4) Å, and $O\cdots HN\text{—}N$ = 140.4 and 136.8°, respectively. There is also an intermolecular hydrogen bond $O5\cdots N1(1 - x, y - \frac{1}{2}, 1 - z)$ in both molecules with $O\cdots N = 2.722$ (5) and 2.665 (5) Å, and $HO\cdots N = 1.722$ (4) and 1.665 (4) Å, respectively. Other distances shorter than the sum of van der Waals radii do not exist. The thiadiazole ring is planar [max. deviation 0.006 (6) for C9 and -0.007 (6) for C9'], whereas the morpholinyl ring has a chair conformation. Atoms C10, C11, C12, C13 and C10', C11', C12', C13' are in a plane. O3 is 0.712 (6) and O3' 0.425 (6) Å above the plane, while N4 is -0.609 (5) and N4' -0.421 (5) Å below the plane. The absolute configurations were not determined by X-ray diffraction since they had earlier been confirmed by the manufacturer.

The hydrophilic parts (—NH, —OH) of each pair of (*S*)-timolol molecules are arranged around one water molecule. The hydrogen bridges formed by the water molecule and the two polar groups, along with the favourable lipophilic intermolecular forces, result in optimal packing of the molecules. Similar stabilizing intermolecular hydrogen bridges (but without water molecules) are encountered between the *S* and *R* pairs of the racemic timolol base, while maleic acid has the connecting role in timolol maleate. In addition to the intermolecular forces, intramolecular hydrogen bridges also contribute in the crystal lattice of the *O,O*-diacetyl-L-tartaric acid ester of the optically pure *S* form of timolol, explaining the extraordinarily good crystallization properties of the compound.

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