Structure of (R)-(3-Hydroxy-2,3-dimethylbutyl)triphenylphosphonium Iodide n.Hydrate (n ≃ 1·3)

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Abstract. $C_{24}H_{28}OP^+ . I^- . nH_2O$ ($n \simeq 1·3$), $M_r = 513·78$, monoclinic, $P2_1$, $a = 9·044$ (1), $b = 14·173$ (1), $c = 10·441$ (1) Å, $\beta = 115·23$ (1)°, $V = 1210·7$ (2) Å^3, $Z = 2$, $D_x = 1·409$ g cm^{-3}, $\lambda(\text{Mo } K\alpha) = 0·71073$ Å, $\mu = 13·9$ cm^{-1}, $F(000) = 522$, $T = 295$ K, $R = 0·018$ for 2854 unique observed diffractometer data [$I \geq 2·5\sigma(I)$]. The absolute configuration at the chiral centre is retained during the four-step synthesis of the title compound from (S)-methyl 3-hydroxy-2-methylpropanoate. The structure contains an infinite hydrogen-bond chain in the a direction involving I, H_2O and the hydroxyl group.

Introduction. The chiral title compound was synthesized in four steps starting from commercially available (S)-(+)-methyl 3-hydroxy-2-methylpropanoate. The phosphonium salt is a valuable intermediate in the total synthesis of a class of steroids (Van den Heuvel, Boer Rookhuizen, Bosch, Brandsma & Hanekamp, 1990). A crystal structure determination of this intermediate was carried out to establish the absolute configuration at the chiral centre.

Experimental. The title compound was recrystallized by evaporation from water/ethanol. Data were collected on a CAD4-F diffractometer for a transparent, yellowish crystal ($0·9 \times 0·7 \times 0·4$ mm), mounted on a glass fibre. The cell parameters were calculated by a least-squares fit of the setting angles of 25 reflections with $13·9 \leq \theta \leq 18·1°$. 6340 reflections were scanned, 2898 unique ($R_{int} = 0·016$) [$h - 11:11$, $k - 18:0, l - 13:13$; $\theta \leq 27·5°$; $\omega/2\theta$-scan mode; $\Delta\omega = (0·70 + 0·35\tan\theta)°$; Zr-filtered Mo $K\alpha$ radiation]. Three reference reflections ($3\bar{4}0$, 304, $0\bar{4}4$) showed fluctuations of 2% and a small decay of less than 2% during the 77 h of X-ray exposure time. The data were corrected for Lp, for decay and for absorption [*ABSORB* (Spek, 1983); absorption factors $1·66$–$2·31$], resulting in the unique set of 2854 reflections [$I > 2·5\sigma(I)$] used in the structure refinement. $\sigma^2(I) = \sigma^2_{cs}(I) + (pI)^2$ (McCandlish, Stout &

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Andrews, 1975) with $p = 0·03$. The iodine ion was found by Patterson interpretation (*SHELXS*86; Sheldrick, 1986). All other non-H atoms were located from difference Fourier syntheses. The structure was refined on F by full-matrix least-squares procedures using anisotropic thermal parameters for all non-H atoms (*SHELX*76; Sheldrick, 1976). The hydrogens of the water molecule and of the hydroxyl were located from a difference Fourier map. The water H atoms were refined with distance restraints. All other H atoms were introduced at calculated positions (C—H = 0·98 Å) and refined in the riding mode on their carrier atoms with individual isotropic thermal parameters ($U = 0·06$–$0·15$ Å^2). A subsequent difference Fourier map revealed an additional partially occupied [$p = 0·30$ (1)] water-molecule site and related positional disorder in the other water molecule. No H atoms could be located for this water molecule. Final convergence was reached at $R = 0·018$ [$wR = 0·023$, $w = 1·0/\sigma^2(F)$; $S = 0·31$; $(\Delta/\sigma)_{max} = 0·76$; 310 parameters]. No residual density outside the range $-0·30$–$0·37$ e Å^{-3}. Scattering factors from Cromer & Mann (1968), anomalous-dispersion corrections from Cromer & Liberman (1970). The opposite absolute configuration was rejected based on significantly higher R values at convergence ($R = 0·021$, $wR = 0·027$). The final atomic coordinates and equivalent isotropic temperature factors are listed in Table 1.† The program package *EUCLID* (Spek, 1982) was used for geometrical calculations and illustrations. All calculations were carried out on a microVAX II.

Discussion. Bond lengths and angles are collected in Table 2. A perspective view of the molecule showing part of the hydrogen-bond chain and adopted atomic labeling is depicted in Fig. 1.

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† Lists of anisotropic thermal parameters, H-atom positions, bond angles and distances, torsion angles, water parameters, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53156 (24 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final coordinates and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{eq}(Å^2)$
I	0·81606 (2)	0	0·03587 (1)	0·0547 (1)
P	0·42729 (6)	0·10030 (4)	0·55433 (6)	0·0339 (2)
O(1)	0·4063 (3)	0·0785 (2)	0·9497 (3)	0·0629 (8)
C(1)	0·4830 (3)	0·1525 (2)	0·7257 (3)	0·0419 (7)
C(2)	0·3388 (3)	0·1893 (2)	0·7550 (3)	0·0472 (7)
C(3)	0·2986 (5)	0·2925 (3)	0·7045 (4)	0·071 (1)
C(4)	0·3740 (3)	0·1769 (2)	0·9133 (3)	0·0547 (9)
C(5)	0·5186 (6)	0·2353 (4)	1·0127 (5)	0·074 (1)
C(6)	0·2208 (5)	0·1995 (3)	0·9349 (5)	0·080 (2)
C(11)	0·3247 (2)	−0·0102 (3)	0·5400 (2)	0·0399 (7)
C(12)	0·3147 (3)	−0·0517 (2)	0·6570 (3)	0·0507 (8)
C(13)	0·2390 (4)	−0·1384 (3)	0·6416 (5)	0·069 (1)
C(14)	0·1745 (4)	−0·1844 (2)	0·5149 (5)	0·071 (1)
C(15)	0·1839 (4)	−0·1442 (3)	0·3987 (5)	0·068 (1)
C(16)	0·2596 (3)	−0·0576 (2)	0·4104 (3)	0·0526 (8)
C(21)	0·6092 (3)	0·0774 (2)	0·5300 (3)	0·0371 (6)
C(22)	0·5963 (3)	0·0661 (2)	0·3935 (3)	0·0521 (8)
C(23)	0·7321 (4)	0·0384 (2)	0·3737 (4)	0·0592 (9)
C(24)	0·8775 (3)	0·0219 (2)	0·4878 (4)	0·056 (1)
C(25)	0·8918 (3)	0·0335 (2)	0·6222 (3)	0·0564 (9)
C(26)	0·7574 (3)	0·0621 (2)	0·6458 (3)	0·0453 (7)
C(31)	0·3013 (3)	0·1781 (2)	0·4160 (2)	0·0376 (6)
C(32)	0·3734 (3)	0·2567 (2)	0·3854 (3)	0·0501 (8)
C(33)	0·2789 (4)	0·3202 (2)	0·2832 (4)	0·060 (1)
C(34)	0·1144 (4)	0·3059 (2)	0·2110 (3)	0·0574 (9)
C(35)	0·0414 (3)	0·2289 (2)	0·2396 (3)	0·0555 (8)
C(36)	0·1345 (3)	0·1635 (2)	0·3415 (3)	0·0458 (8)
O(2)†	0·761 (1)	0·4609 (9)	0·918 (1)	0·132 (5)

† Population parameter: 0·70 (1).

The absolute configuration at C(2) is *R*. The stereochemical and mechanistic implications of this configuration will be reported elsewhere (Van den Heuvel, Boer, Rookhuizen, Bosch, Brandsma & Hanekamp, 1990).

The triphenylphosphonium moiety shows no unexpected features. The common (*e.g.* Goldstein, Seff & Trueblood, 1968; Domenicano, Vaciago & Coulson, 1975) observation that the C—C bonds distant from the P atom are shorter than the C—C bonds near the P atom is clearly displayed by this fairly accurate structure determination: 1·3578 (2), 1·3872 (2) and 1·3913 (2) Å (averaged over six bonds).

No unusual bond distances or angles are found in the C(1)–C(6) side chain. This chain does not have an extended conformation as displayed by the deviations from ±180° of the torsion angles P—C(1)—C(2)—C(4) [146·2 (2)°] and C(1)—C(2)—C(4)—C(6) [−171·4 (3)°]. This conformation is probably dominated by the hydrogen-bond interactions within the crystal.

An infinite hydrogen-bond chain I< ···H—O(2)—H··· >O(1)—H··· >I runs in the **a** direction (Fig. 1). Details of the hydrogen-bond geometry are collected in Table 2. The O(1)—I and O(2)—I distances [3·597 (3) and 3·68 (1) Å, respectively] lie within the normal range. In diethylmethyl(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl)ammonium iodide hydrate (Laugier, Grand & Rey, 1981), the O—I

Table 2. *Bond distances (Å), bond angles (°) and hydrogen-bond geometry (Å, °)*

P—C(1)	1·798 (3)	C(14)—C(15)	1·375 (6)
P—C(11)	1·794 (4)	C(15)—C(16)	1·385 (5)
P—C(21)	1·798 (3)	C(21)—C(22)	1·390 (4)
P—C(31)	1·788 (2)	C(21)—C(26)	1·387 (4)
O(1)—C(4)	1·442 (4)	C(22)—C(23)	1·386 (5)
C(1)—C(2)	1·551 (4)	C(23)—C(24)	1·367 (5)
C(2)—C(3)	1·545 (5)	C(24)—C(25)	1·363 (5)
C(2)—C(4)	1·554 (4)	C(25)—C(26)	1·399 (4)
C(4)—C(5)	1·522 (6)	C(31)—C(32)	1·395 (4)
C(4)—C(6)	1·530 (6)	C(31)—C(36)	1·387 (4)
C(11)—C(12)	1·393 (4)	C(32)—C(33)	1·379 (4)
C(11)—C(16)	1·396 (4)	C(33)—C(34)	1·366 (5)
C(12)—C(13)	1·382 (5)	C(34)—C(35)	1·373 (4)
C(13)—C(14)	1·363 (6)	C(35)—C(36)	1·392 (4)

C(1)—P—C(11)	110·9 (1)	C(12)—C(13)—C(14)	121·6 (4)
C(1)—P—C(21)	109·2 (1)	C(13)—C(14)—C(15)	119·8 (3)
C(1)—P—C(31)	111·2 (1)	C(14)—C(15)—C(16)	120·2 (4)
C(11)—P—C(21)	107·6 (1)	C(11)—C(16)—C(15)	120·0 (3)
C(11)—P—C(31)	110·0 (1)	P—C(21)—C(22)	119·0 (2)
C(21)—P—C(31)	107·7 (1)	P—C(21)—C(26)	120·5 (2)
P—C(1)—C(2)	115·6 (2)	C(22)—C(21)—C(26)	120·3 (3)
C(1)—C(2)—C(3)	110·3 (3)	C(21)—C(22)—C(23)	119·5 (3)
C(1)—C(2)—C(4)	111·3 (2)	C(22)—C(23)—C(24)	120·2 (3)
C(3)—C(2)—C(4)	112·4 (3)	C(23)—C(24)—C(25)	120·7 (3)
O(1)—C(4)—C(2)	108·4 (2)	C(24)—C(25)—C(26)	120·5 (3)
O(1)—C(4)—C(5)	109·1 (3)	C(21)—C(26)—C(25)	118·8 (3)
O(1)—C(4)—C(6)	105·0 (3)	P—C(31)—C(32)	118·6 (2)
C(2)—C(4)—C(5)	113·0 (3)	P—C(31)—C(36)	121·9 (2)
C(2)—C(4)—C(6)	110·2 (3)	C(32)—C(31)—C(36)	119·5 (2)
C(5)—C(4)—C(6)	110·8 (3)	C(31)—C(32)—C(33)	120·2 (3)
P—C(11)—C(12)	121·3 (2)	C(32)—C(33)—C(34)	120·0 (3)
P—C(11)—C(16)	119·4 (2)	C(33)—C(34)—C(35)	120·6 (3)
C(12)—C(11)—C(16)	119·2 (3)	C(34)—C(35)—C(36)	120·4 (3)
C(11)—C(12)—C(13)	119·2 (3)	C(31)—C(36)—C(35)	119·3 (3)

D—H···A	D—A	D—H	H···A	D—H···A
O(1)—H(10)···I^i	3·597 (3)	0·80 (7)	2·88 (8)	151 (6)
O(2)—H(998)···I^{ii}	3·684 (13)	0·98 (9)	2·78 (8)	154 (8)
O(2)—H(999)···O(1^{iii})	2·963 (13)	0·99 (8)	2·02 (9)	160 (7)

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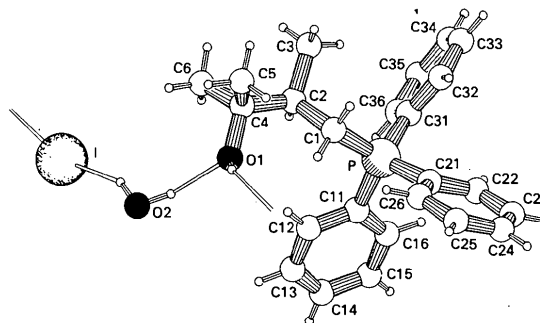

Fig. 1. *PLUTON* drawing of the molecular structure with adopted labeling and hydrogen-bond scheme.

distance is 3·680 Å. In morphine methyl iodide monohydrate (Wongweichintana, Holt & Purdie, 1984) the O—I distance is 3·549 Å. In this case, however, the iodine ion is not considered part of the hydrogen-bond network, despite the fair hydrogen-bond geometry (O—I = 3·549, O—H = 0·98, H···I = 2·634 Å, O—H···I = 155°).

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†

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Abstract. (S)-Timolol hemihydrate, $2C_{13}H_{24}N_4O_3S$. H_2O, $M_r = 650·9$, monoclinic, $C2$, $a = 23·435$ (3), $b = 6·384$ (1), $c = 11·591$ (1) Å, $\beta = 103·08$ (1)°, $V = 1687$ (3) Å^3, $Z = 2$, $D_x = 1·28$ Mg m^{-3}, $\lambda(Mo~K\alpha) = 0·71073$ Å, $\mu = 0·20$ mm^{-1}, $F(000) = 700$, $T = 296$ K, final $R = 0·035$ 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, $C_{21}H_{32}N_4O_{10}S$, $M_r = 532·6$, monoclinic, $P2_1$, $a = 9·670$ (4), $b = 8·853$ (2), $c = 31·053$ (7) Å, $\beta = 93·49$ (2)°, $V = 2651$ (2) Å^3, $Z = 4$, $D_x = 1·33$ Mg m^{-3}, $\lambda(Mo~K\alpha) = 0·71073$ Å, $\mu = 0·17$ mm^{-1}, $F(000) = 1128$, $T = 296$ K, final $R = 0·050$ 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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