Related literature. The preparation of the title compound is an extension of the syntheses and X-ray structure analyses of annelated 2-thiohydantoin derivatives (Kieć-Kononowicz, Zejc, Mikołajczyk, Zatorski, Karolak-Wojciechowska & Wieczorek, 1980, 1981; Kieć-Kononowicz, Karolak-Wojciechowska & Kwiatkowski, 1988; Kieć-Kononowicz, Zatorski & Karolak-Wojciechowska, 1989; Karolak-Wojciechowska, Mikołajczyk, Zatorski, Kieć-Kononowicz & Zejc, 1985; Karolak-Wojciechowska & Kieć-Kononowicz, 1987). All synthesized compounds have been the subject of preliminary pharmacological screening. The aim of the work is further examination of structure–activity relationships.

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Crystal Structure and Absolute Configuration of (+)-Methadone Hydrobromide

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Abstract. $C_{21}H_{28}NO^+.Br^-$, $M_r = 390·37$, triclinic, $P1$, $a = 9·577\ (1)$, $b = 9·591\ (2)$, $c = 13·482\ (2)$ Å, $\alpha = 70·52\ (1)$, $\beta = 93·09\ (1)$, $\gamma = 119·32\ (1)^\circ$, $V = 1008·9\ (3)$ Å^3, $Z = 2$, $D_x = 1·285$ g cm^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1·54178$ Å, $\mu = 28·2$ cm^{-1}, $F(000) = 408$, $T = 298$ K, $R = 0·0346$ for 2905 reflections with $I \geq 1·5\sigma(I)$. There are two independent molecules in the asymmetric unit as predicted by solid-state NMR spectroscopy. The molecular conformations of the two molecules are similar to each other and also to the conformation previously observed in the monoclinic form.

Experimental. (+)-Methadone hydrobromide, $CH_3CH_2COC(Ph)_2CH_2CH(CH_3)N(CH_3)_2.HBr$, was crystallized as thick colorless plates from a concentrated solution of the salt in a 1:15 (v/v) mixture of methanol and ether at room temperature. In view of the polymorphous nature of methadone salts (Hanson & Ahmed, 1958) a powdered sample was checked by solid-state NMR which revealed the presence of a single crystalline form (Sumner, Moreland, Carroll, Brine & Boldt, 1989). An almost cubic fragment of approximate dimensions (0·50 × 0·50 × 0·40) mm was cut from a larger piece and used for all X-ray data collection using Cu $K\alpha$ radiation on a Nicolet $R3m/\mu$ four-circle automatic diffractometer equipped with a highly oriented graphite monochromator. Cell dimensions* were obtained by a least-squares refinement of the setting angles of 25 reflections with $50 \leq 2\theta \leq 65^\circ$. Intensity data were collected by the $\omega/2\theta$-scan method up to 115° in 2θ at variable scan speeds between 3·9 and 29·3° min^{-1} depending on intensity; range in hkl: $0 < h < 10$, $-10 < k < 9$, $-14 < l < 14$. Stationary backgrounds were measured for 1/2 of scan time on each side of a peak. Two reflections (021, 211) were measured as standards after every 48 reflections to monitor the instrument and crystal stability. A maximum variation of only ±1·0% in the intensity of either standard was observed. 2956 reflections were measured which yielded 2905 unique reflections with intensities $I \geq 1·5\sigma(I)$; $R_{\mathrm{int}} = 0·0041$. The intensities were corrected for background, Lorentz and polarization effects and absorption, the latter by empirical ψ scan ($\mu =$

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* The cell given in the *Abstract* can be transformed to the standard cell with all angles acute by the transformation (100/0$\bar{1}$0/00$\bar{1}$).

Table 1. *Atomic coordinates* (× 10^4) *and equivalent isotropic thermal parameters* (Å^2 × 10^3)

	x	*y*	*z*	*U**
Br(1)	0	0	0	88 (1)
Br(2)	3975 (1)	4383 (1)	4706 (1)	92 (1)
C(1*A*)	8182 (8)	12994 (12)	4673 (7)	139 (5)
C(2*A*)	6643 (7)	12114 (8)	4235 (5)	86 (3)
C(3*A*)	6628 (5)	10954 (6)	3698 (3)	53 (2)
O(1*A*)	7552 (4)	10473 (6)	3857 (4)	85 (2)
C(4*A*)	5264 (4)	10328 (5)	3000 (3)	40 (2)
C(5*A*)	5363 (5)	8971 (5)	2665 (3)	40 (2)
C(6*A*)	6766 (4)	9685 (5)	1797 (3)	40 (2)
C(7*A*)	6343 (6)	10102 (6)	673 (3)	53 (2)
N(1*A*)	7342 (5)	8412 (5)	1945 (3)	57 (2)
C(8*A*)	8225 (9)	8239 (10)	2888 (5)	92 (4)
C(9*A*)	6088 (8)	6745 (7)	1921 (5)	78 (3)
C(10*A*)	5491 (5)	11800 (5)	2003 (3)	45 (2)
C(11*A*)	6972 (6)	13265 (5)	1603 (4)	60 (2)
C(12*A*)	7200 (7)	14484 (6)	600 (5)	75 (3)
C(13*A*)	5906 (10)	14215 (8)	22 (5)	90 (4)
C(14*A*)	4410 (8)	12764 (9)	429 (4)	78 (3)
C(15*A*)	4222 (6)	11598 (6)	1395 (4)	58 (2)
C(16*A*)	3637 (5)	9515 (5)	3679 (3)	44 (2)
C(17*A*)	3005 (6)	10523 (7)	3759 (4)	61 (2)
C(18*A*)	1579 (6)	9777 (8)	4414 (4)	71 (3)
C(19*A*)	744 (6)	8088 (8)	4963 (4)	74 (3)
C(20*A*)	1338 (6)	7084 (7)	4877 (4)	66 (2)
C(21*A*)	2768 (5)	7784 (5)	4242 (3)	52 (2)
C(1*B*)	− 1202 (9)	− 6265 (8)	7941 (6)	97 (3)
C(2*B*)	66 (6)	− 5508 (5)	8602 (4)	62 (2)
C(3*B*)	733 (5)	− 3652 (5)	8345 (3)	45 (2)
O(1*B*)	− 13 (4)	− 2974 (4)	7905 (3)	71 (2)
C(4*B*)	2365 (4)	− 2610 (4)	8713 (3)	38 (2)
C(5*B*)	2732 (4)	− 743 (4)	8443 (3)	39 (2)
C(6*B*)	3251 (5)	401 (5)	7270 (3)	42 (2)
C(7*B*)	5040 (5)	1383 (6)	6936 (4)	57 (2)
N(1*B*)	2654 (4)	1672 (4)	6998 (3)	51 (2)
C(8*B*)	892 (6)	896 (7)	6980 (5)	73 (3)
C(9*B*)	3239 (8)	2795 (7)	7641 (5)	77 (3)
C(10*B*)	3738 (4)	− 2562 (4)	8143 (3)	40 (2)
C(11*B*)	3636 (5)	− 2792 (5)	7173 (3)	48 (2)
C(12*B*)	4920 (7)	− 2584 (6)	6633 (4)	65 (2)
C(13*B*)	6370 (6)	− 2154 (7)	7055 (5)	70 (3)
C(14*B*)	6503 (5)	− 1906 (7)	8000 (4)	63 (2)
C(15*B*)	5207 (5)	− 2113 (6)	8547 (4)	52 (2)
C(16*B*)	2131 (4)	− 3526 (5)	9935 (3)	41 (2)
C(17*B*)	2337 (6)	− 4920 (6)	10356 (4)	58 (2)
C(18*B*)	2047 (7)	− 5796 (8)	11443 (4)	78 (3)
C(19*B*)	1575 (7)	− 5256 (8)	12107 (4)	75 (3)
C(20*B*)	1380 (5)	− 3886 (7)	11711 (4)	62 (2)
C(21*B*)	1656 (5)	− 2976 (5)	10611 (3)	48 (2)

* Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor.

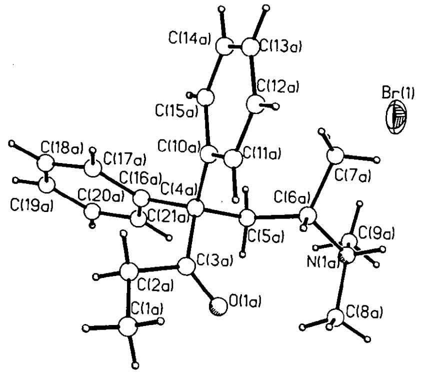

Fig. 1. A plot of molecule *A* and Br(1) showing the numbering scheme. The numbering for molecule *B* follows the same pattern.

28·2 cm^{-1}, maximum and minimum transmission factors are 0·51 and 0·21, respectively).

The structure was determined by a combination of the heavy-atom and tangent-refinement methods.

Table 2. *Bond lengths* (Å) *and bond angles* (°)

C(2*A*)—C(1*A*)	1·501 (10)	C(2*A*)—C(3*A*)	1·511 (11)
C(3*A*)—O(1*A*)	1·165 (8)	C(3*A*)—C(4*A*)	1·558 (6)
C(4*A*)—C(5*A*)	1·556 (8)	C(4*A*)—C(10*A*)	1·520 (5)
C(4*A*)—C(16*A*)	1·537 (6)	C(5*A*)—C(6*A*)	1·542 (6)
C(6*A*)—C(7*A*)	1·520 (6)	C(6*A*)—N(1*A*)	1·523 (8)
C(10*A*)—C(11*A*)	1·379 (5)	C(10*A*)—C(15*A*)	1·398 (7)
C(11*A*)—C(12*A*)	1·404 (7)	C(12*A*)—C(13*A*)	1·388 (10)
C(13*A*)—C(14*A*)	1·383 (8)	C(14*A*)—C(15*A*)	1·354 (7)
C(16*A*)—C(17*A*)	1·402 (10)	C(16*A*)—C(21*A*)	1·378 (5)
C(17*A*)—C(18*A*)	1·381 (8)	C(18*A*)—C(19*A*)	1·344 (8)
C19*A*)—C(20*A*)	1·371 (11)	C(20*A*)—C(21*A*)	1·379 (7)
C(2*B*)—C(1*B*)	1·499 (10)	C(2*B*)—C(3*B*)	1·481 (7)
C(3*B*)—O(1*B*)	1·199 (7)	C(3*B*)—C(4*B*)	1·551 (5)
C(4*B*)—C(5*B*)	1·557 (6)	C(4*B*)—C(10*B*)	1·533 (7)
C(4*B*)—C(16*B*)	1·555 (5)	C(5*B*)—C(6*B*)	1·531 (5)
C(6*B*)—C(7*B*)	1·498 (6)	C(6*B*)—N(1*B*)	1·520 (7)
C(10*B*)—C(11*B*)	1·388 (7)	C(10*B*)—C(15*B*)	1·394 (6)
C(11*B*)—C(12*B*)	1·357 (9)	C(12*B*)—C(13*B*)	1·390 (8)
C(13*B*)—C(14*B*)	1·360 (9)	C(14*B*)—C(15*B*)	1·372 (8)
C(16*B*)—C(17*B*)	1·374 (8)	C(16*B*)—C(21*B*)	1·384 (8)
C(17*B*)—C(18*B*)	1·387 (7)	C(18*B*)—C(19*B*)	1·363 (12)
C(19*B*)—C(20*B*)	1·345 (11)	C(20*B*)—C(21*B*)	1·409 (6)

C(1*A*)—C(2*A*)—C(3*A*)	114·6 (8)	C(2*A*)—C(3*A*)—O(1*A*)	120·4 (5)
C(2*A*)—C(3*A*)—C(4*A*)	117·7 (5)	O(1*A*)—C(3*A*)—C(4*A*)	121·7 (6)
C(3*A*)—C(4*A*)—C(5*A*)	108·0 (4)	C(3*A*)—C(4*A*)—C(10*A*)	110·8 (3)
C(5*A*)—C(4*A*)—C(10*A*)	108·6 (4)	C(3*A*)—C(4*A*)—C(16*A*)	107·8 (3)
C(5*A*)—C(4*A*)—C(16*A*)	110·2 (3)	C(10*A*)—C(4*A*)—C(16*A*)	111·4 (4)
C(4*A*)—C(5*A*)—C(6*A*)	115·5 (3)	C(5*A*)—C(6*A*)—C(7*A*)	114·2 (4)
C(5*A*)—C(6*A*)—N(1*A*)	110·8 (3)	C(7*A*)—C(6*A*)—N(1*A*)	106·8 (4)
C(6*A*)—N(1*A*)—C(8*A*)	113·1 (6)	C(6*A*)—N(1*A*)—C(9*A*)	114·3 (5)
C(4*A*)—C(10*A*)—C(11*A*)	122·1 (4)	C(4*A*)—C(10*A*)—C(15*A*)	119·5 (3)
C(11*A*)—C(10*A*)—C(15*A*)	118·0 (4)	C(10*A*)—C(11*A*)—C(12*A*)	120·6 (5)
C(11*A*)—C(12*A*)—C(13*A*)	119·2 (4)	C(12*A*)—C(13*A*)—C(14*A*)	120·4 (5)
C(13*A*)—C(14*A*)—C(15*A*)	119·4 (6)	C(10*A*)—C(15*A*)—C(14*A*)	122·4 (4)
C(4*A*)—C(16*A*)—C(17*A*)	120·8 (3)	C(4*A*)—C(16*A*)—C(21*A*)	121·4 (5)
C(17*A*)—C(16*A*)—C(21*A*)	117·9 (4)	C(16*A*)—C(17*A*)—C(18*A*)	119·8 (5)
C(17*A*)—C(18*A*)—C(19*A*)	121·9 (8)	C(18*A*)—C(19*A*)—C(20*A*)	118·9 (5)
C(19*A*)—C(20*A*)—C(21*A*)	121·0 (4)	C(16*A*)—C(21*A*)—C(20*A*)	120·6 (6)
C(1*B*)—C(2*B*)—C(3*B*)	114·2 (5)	C(2*B*)—C(3*B*)—O(1*B*)	120·7 (4)
C(2*B*)—C(3*B*)—C(4*B*)	119·2 (4)	O(1*B*)—C(3*B*)—C(4*B*)	120·0 (4)
C(3*B*)—C(4*B*)—C(5*B*)	109·7 (4)	C(3*B*)—C(4*B*)—C(10*B*)	110·2 (4)
C(5*B*)—C(4*B*)—C(10*B*)	108·6 (3)	C(3*B*)—C(4*B*)—C(16*B*)	105·5 (2)
C(5*B*)—C(4*B*)—C(16*B*)	110·5 (4)	C(10*B*)—C(4*B*)—C(16*B*)	112·4 (4)
C(4*B*)—C(5*B*)—C(6*B*)	116·2 (4)	C(5*B*)—C(6*B*)—C(7*B*)	114·3 (4)
C(5*B*)—C(6*B*)—N(1*B*)	110·9 (4)	C(7*B*)—C(6*B*)—N(1*B*)	108·0 (3)
C(6*B*)—N(1*B*)—C(8*B*)	114·0 (4)	C(6*B*)—N(1*B*)—C(9*B*)	113·5 (4)
C(4*B*)—C(10*B*)—C(11*B*)	122·3 (4)	C(4*B*)—C(10*B*)—C(15*B*)	119·7 (4)
C(11*B*)—C(10*B*)—C(15*B*)	117·7 (5)	C(10*B*)—C(11*B*)—C(12*B*)	121·3 (4)
C(11*B*)—C(12*B*)—C(13*B*)	120·1 (6)	C(12*B*)—C(13*B*)—C(14*B*)	119·6 (6)
C(13*B*)—C(14*B*)—C(15*B*)	120·5 (5)	C(10*B*)—C(15*B*)—C(14*B*)	120·8 (5)
C(4*B*)—C(16*B*)—C(17*B*)	.8 (5)	C(4*B*)—C(16*B*)—C(21*B*)	120·0 (4)
C(17*B*)—C(16*B*)—C(21*B*)	119·2 (4)	C(16*B*)—C?17*B*)—C(18*B*)	121·0 (6)
C(17*B*)—C(18*B*)—C(19*B*)	119·7 (7)	C(18*B*)—C(19*B*)—C(20*B*)	120·2 (5)
C(19*B*)—C(20*B*)—C(21*B*)	121·3 (6)	C(16*B*)—C21*B*)—C(20*B*)	118·5 (5)

The H atoms attached to C atoms were placed in expected positions with fixed isotropic temperature factors, which were 1·2 times greater than those of the attached C, and were varied in the riding mode. The methyl H atoms were assumed to be staggered with respect to the non-H atom to which the methyl C was attached. The NH hydrogens were located from a difference Fourier map and were not refined. The non-H atoms were refined with anisotropic thermal parameters. All calculations were performed on a Data General Microeclipse desktop computer with the crystallographic program package *SHELXTL* (Sheldrick, 1985) which has a blocked-cascade least-squares algorithm for structure refinement (Sparks, 1961). The quantity minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/[\sigma^2(F_o) + gF_o^2]$ and $g = 0{\cdot}0011$ is a factor used to downweight the strong reflections, and to compensate for instrument instability. An isotropic secondary-extinction correction was also applied, the

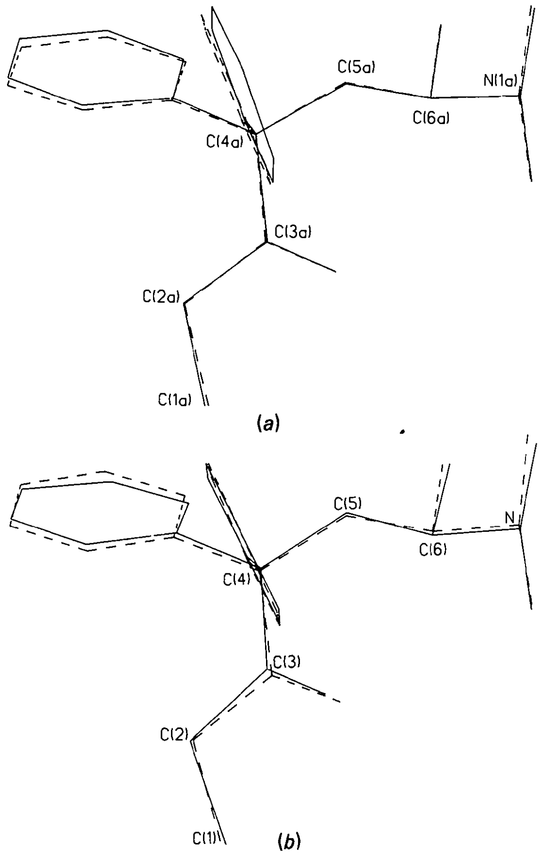

Fig. 2. (*a*) A comparative overlay drawing of molecule *A* (solid line) and molecule *B*. The labelled atoms of the two molecules were used for the least-squares fitting. (*b*) Overlay drawing of the molecule in the monoclinic form (Hanson & Ahmed, 1958) and molecule *B*.

refined value of the coefficient being $2\cdot0\,(2)\times10^{-5}$, which indicates a significant correction. The final $R = 0\cdot0346$, $wR = 0\cdot0549$, goodness-of-fit parameter $S = 1\cdot7$. Maximum $\Delta/\sigma = 0\cdot4$ in the final cycle, and the maximum and minimum peaks in the final ΔF map were $\pm0\cdot5\,\text{e}\,\text{Å}^{-3}$. The absolute configuration was determined by the methods of Rogers (1981), the refined value of the variable multiplying $\Delta f''$ being $+0\cdot99\,(4)$. Atomic scattering factors used were those provided in *SHELXTL* (Sheldrick, 1985). Atomic fractional coordinates for non-H atoms are given in Table 1 and bond lengths and angles in Table 2.* A plot of molecule *A* and Br(1) is shown in Fig. 1. A comparative overlay drawing of the two independent molecules is shown in Fig. 2(*a*) and a similar drawing of one of the molecules and the molecule in the monoclinic form (Hanson & Ahmed, 1958) is shown in Fig. 2(*b*). A crystal packing diagram is shown in Fig. 3.

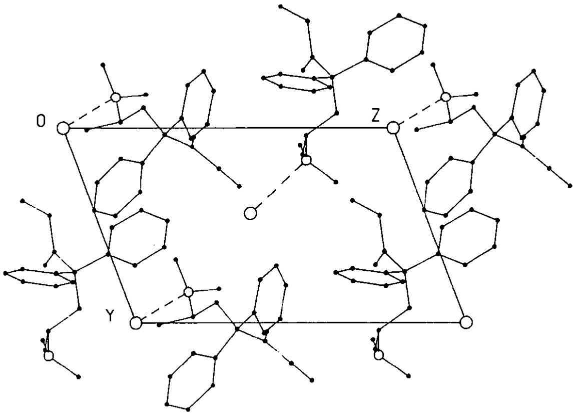

Fig. 3. A crystal packing diagram projected down the *a* axis. The large open circles represent Br atoms and the small open circles N atoms. H atoms are not shown. Dashed lines represent N—H···Br hydrogen bonds.

Related literature. D- and L-methadone hydrobromide crystallize from aqueous solution at room temperature in the triclinic or the monoclinic crystalline form. The crystal structure and absolute configuration of the D isomer of the monoclinic form has been determined using film methods (Hanson & Ahmed, 1958). The present structure determination of the triclinic form was undertaken to assist in the interpretation of the solid-state NMR (Sumner *et al.*, 1989) which indicated the presence of two independent molecules in the asymmetric unit. This is confirmed by the present structure analysis. Crystal structures of some related analgesics: L-methadone (Bye, 1974), hydrochlorides of α-acetyl methadol, α-methadol and (−)-isomethadone (Shefter, 1974), and (+)-*N*-[2-benzylmethylamino)propyl]propionanilide hydrobromide (Singh & Ahmed, 1969).

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* Tables of anisotropic thermal parameters, H-atom coordinates and structure-factor amplitudes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51912 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.