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Structure of the Opioid κ-Agonist (−)-(1*R*,5*R*,9*R*,2″*S*)-2′-Hydroxy-2-(2-methoxypropyl)-5,9-dimethyl-6,7-benzomorphan Hydrobromide (I) and its Inactive (−)-(1*R*,5*R*,9*R*,2″*R*) Diastereomer (II)*†

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Abstract. (I) $C_{18}H_{28}NO_2^+.Br^-$, $M_r = 370{\cdot}33$, monoclinic, $P2_1$, $a = 8{\cdot}446\,(1)$, $b = 13{\cdot}137\,(3)$, $c = 8{\cdot}6953\,(4)$ Å, $\beta = 113{\cdot}73\,(1)°$, $V = 883{\cdot}2\,(2)$ Å^3, $Z = 2$, $D_m = 1{\cdot}37\,(2)$, $D_x = 1{\cdot}390$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 2{\cdot}31$ mm^{-1}, $F(000) = 388$, room temperature, final $R = 0{\cdot}041$ for 1523 observed reflections. (II) $C_{18}H_{28}NO_2^+.Br^-$, $M_r = 370{\cdot}33$, monoclinic, $P2_1$, $a = 8{\cdot}623\,(2)$, $b = 13{\cdot}570\,(3)$, $c = 8{\cdot}005\,(2)$ Å, $\beta = 107{\cdot}71\,(2)°$, $V = 892{\cdot}3\,(4)$ Å^3, $Z = 2$, $D_m = 1{\cdot}36\,(2)$, $D_x = 1{\cdot}378$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 2{\cdot}29$ mm^{-1}, $F(000) = 388$, room temperature, final $R = 0{\cdot}046$ for 2885 observed reflections. The NCCO conformations in the two molecules are each other's mirror image: (+)-synclinal for (I) and (−)-synclinal for (II). Also, in (I) an intramolecular hydrogen bond is present between H(1) and the O of the *N*-side chain. These observations fit nicely the hypothesis of the κ-opioid pharmacophore.

Introduction. The title compound (I) emerged from a series of *N*-[(tetrahydrofuryl)alkyl] and *N*-(alkoxyalkyl) derivatives of the 6,7-benzomorphan (−)-normetazocine as the most potent opioid compound of the series (at least more than 100 times more active than morphine) and the least toxic one (therapeutic ratio is 27 times that of morphine); furthermore, the action profile was that of a κ-opioid (Merz & Stockhaus, 1979). In the same study the title compound (II), which is a diastereomer of (I), was found to be completely inactive. Subsequently the κ-opioid properties of these compounds were reassessed *in vitro*: (I) was identified as a full agonist, (II) was inactive (Verlinde & De Ranter, 1988). This pronounced stereoselectivity with regard to the configuration at C2″ was also observed with the *N*-tetrahydrofurfuryl compounds in the series (Merz & Stockhaus, 1979) and has already been evaluated through crystal-structure analysis (Peeters, De Ranter & Blaton, 1982). The crystal structures of (I) and (II) are an essential part of the further analysis of the phenomenon.

Experimental. (I) Crystals obtained at room temperature from a methanol/diethyl ether solution. Density measured by flotation in *n*-heptane/CCl_4, crystal dimensions ~0·6 × 0·4 × 0·4 mm, Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Cu $K\alpha$ radiation, $\omega/2\theta$-scan technique ($2\theta_{max} = 130°$, $0 \le h \le 9$, $0 \le k \le 15$, $-10 \le l \le 10$), cell dimensions by least-squares refinement of the θ values of 15 reflections with $38 < 2\theta < 43°$, space group $P2_1$ from systematic absences $0k0$ for k odd (optically active compound). One standard reflection ($49\bar{3}$) monitored every 30 reflections did not reveal a significant change in intensity. 1572 independent reflections measured, 1523 observed reflections [$I > 2{\cdot}5\sigma(I)$], Lorentz–polarization corrections, absorption ignored, scattering factors from Cromer & Mann (1968), and Stewart, Davidson & Simpson (1965) (for H), anomalous-dispersion correction for Br

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* *Chemical Abstracts* names: (2*R*,6*R*,11*R*,2″*S*)- and (2*R*,6*R*,11*R*,2″*R*)-1,2,3,4,5,6-hexahydro-3-(2-methoxypropyl)-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol.

† Structural Studies of Substituted 6,7-Benzomorphan Compounds. XVI. Part XV: Verlinde, Blaton, Peeters & De Ranter (1989).

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0108-2701/90/040663-04$03.00

(*International Tables for X-ray Crystallography*, 1974).

The structure was obtained from a Patterson synthesis followed by the calculation of a minimum function map, resulting from superpositions of the Patterson map with the origin placed in turn in the symmetry-related positions of the Br atom (*SCHUIF*; Bode, 1976). Refinement with *XRAY76* (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) by block-diagonal least squares on F, first with isotropic temperature factors and then anisotropically. H atoms (from a difference synthesis) were included in the refinement with fixed positions and an overall temperature factor. Final $R = 0{\cdot}041$, $wR = 0{\cdot}052$ and $S = 0{\cdot}23$, $w = (8{\cdot}0 + |F_o| + 0{\cdot}05|F_o|^2)^{-1}$; $(\Delta/\sigma)_{\rm av} = 0{\cdot}14$, $(\Delta/\sigma)_{\rm max} = 0{\cdot}58$, $-0{\cdot}65 \le$ final $\Delta\rho \le 1{\cdot}03$ e Å^{-3} (minimum and maximum near Br).

(II) Crystals obtained at room temperature from an equimolar ethyl acetate–methanol solution. Density measured by flotation in n-heptane/CCl_4, crystal dimensions $\sim 0{\cdot}5 \times 1{\cdot}4 \times 0{\cdot}5$ mm, Syntex $P2_1$ computer-controlled four-circle diffractometer, graphite-monochromated Mo $K\alpha$ radiation, ω-scan technique ($2\theta_{\rm max} = 50°$, two quadrants measured, $0 \le h \le 10$, $0 \le k \le 17$, $-10 \le l \le 10$ and $-10 \le h \le 0$, $-17 \le k \le 0$, $-10 \le l \le 10$), cell dimensions by least-squares refinement of the setting angles of 24 reflections with $25 < 2\theta < 30°$, space group $P2_1$ from systematic absences $0k0$ for k odd (optically active compound). A set of three standard reflections (060, $\bar{1}1\bar{2}$, $30\bar{2}$) monitored every 50 reflections fluctuated between 98·6% and 104·3% of their initial intensity. For each measured set a scale factor relative to the first set was calculated. These scale factors were smoothed using the two preceding and the two following ones. Each reflection intensity was corrected by a scale factor derived by interpolation from the smoothed scale-factor table. Symmetry-related reflections were averaged to give 3148 unique reflections (Friedel opposites were not averaged) of which 2885 were considered observed [$I > 2\sigma(I)$], Lorentz–polarization corrections, absorption corrections by the method of North, Phillips & Mathews (1968), scattering factors from Cromer & Mann (1968), and Stewart *et al.* (1965) (for H), anomalous-dispersion correction for Br (*International Tables for X-ray Crystallography*, 1974).

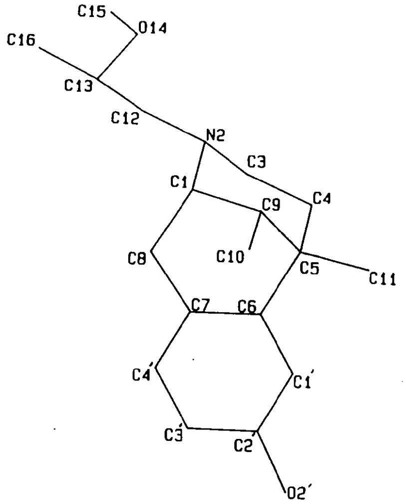


Fig. 1. Atomic numbering scheme.

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$$B_{\rm eq} = (4/3)\textstyle\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$(Å^2)
(I)				
Br	6004 (1)	71*	5575 (1)	4·09 (1)
C(1′)	11800 (6)	−2116 (4)	2820 (5)	2·7 (1)
C(2′)	12279 (6)	−2439 (3)	1533 (6)	2·7 (1)
O(2′)	13537 (5)	−3140 (2)	1794 (5)	3·6 (1)
C(3′)	11483 (7)	−2020 (4)	−49 (6)	3·1 (1)
C(4′)	10244 (6)	−1273 (4)	−344 (6)	3·0 (1)
C(1)	8070 (5)	316 (3)	1979 (6)	2·8 (1)
N(2)	6475 (5)	−226 (2)	1984 (5)	2·7 (1)
C(3)	6769 (6)	−1355 (4)	2177 (6)	3·1 (1)
C(4)	8362 (6)	−1585 (4)	3745 (6)	3·1 (2)
C(5)	10016 (6)	−1005 (3)	3919 (5)	2·7 (1)
C(6)	10558 (5)	−1355 (3)	2529 (5)	2·5 (1)
C(7)	9790 (5)	−917 (3)	936 (5)	2·5 (1)
C(8)	8549 (6)	−38 (4)	546 (5)	3·0 (1)
C(9)	9549 (5)	147 (5)	3698 (5)	2·8 (1)
C(10)	11071 (7)	833 (4)	3879 (7)	3·8 (2)
C(11)	11404 (7)	−1192 (5)	5672 (5)	3·7 (2)
C(12)	4852 (5)	54 (6)	474 (5)	3·4 (1)
C(13)	3801 (6)	851 (4)	893 (6)	3·3 (1)
O(14)	4896 (4)	1703 (3)	1583 (5)	3·9 (1)
C(15)	4252 (8)	2373 (5)	2506 (9)	4·7 (2)
C(16)	2241 (7)	1143 (5)	−698 (8)	4·3 (2)
(II)				
Br	6176 (1)	4*	5874 (1)	3·74 (1)
C(1′)	2624 (6)	2240 (3)	11518 (6)	2·3 (1)
C(2′)	1258 (6)	2547 (3)	11941 (6)	2·4 (1)
O(2′)	1306 (5)	3241 (3)	13188 (5)	3·5 (1)
C(3′)	−234 (6)	2115 (3)	11135 (7)	2·8 (1)
C(4′)	−333 (6)	1365 (4)	9931 (7)	2·8 (1)
C(1)	2347 (5)	−128 (3)	7835 (5)	2·3 (1)
N(2)	2472 (5)	414 (3)	6228 (5)	2·4 (1)
C(3)	2685 (7)	1510 (3)	6544 (7)	3·0 (1)
C(4)	4076 (7)	1725 (3)	8157 (7)	2·7 (1)
C(5)	4025 (5)	1165 (3)	9825 (6)	2·3 (1)
C(6)	2525 (5)	1489 (3)	10311 (6)	2·2 (1)
C(7)	1033 (5)	1035 (3)	9531 (6)	2·3 (1)
C(8)	829 (6)	167 (3)	8321 (6)	2·6 (1)
C(9)	3902 (5)	63 (6)	9348 (5)	2·4 (1)
C(10)	3945 (8)	−617 (4)	10882 (7)	3·3 (2)
C(11)	5603 (6)	1361 (4)	11261 (8)	3·0 (2)
C(12)	1102 (8)	228 (4)	4580 (7)	3·4 (2)
C(13)	758 (7)	−845 (4)	4160 (7)	3·0 (2)
O(14)	2258 (5)	−1247 (3)	4153 (6)	4·2 (1)
C(15)	2358 (15)	−2276 (6)	4274 (13)	6·5 (3)
C(16)	−563 (10)	−962 (6)	2448 (9)	4·8 (2)

* Parameter kept fixed for origin definition.

The position of the Br atom obtained from a sharpened Patterson synthesis served as input for *DIRDIF* (Beurskens, Bosman, Doesburg, Gould, van den Hark, Prick, Noordik, Beurskens & Parthasara-

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

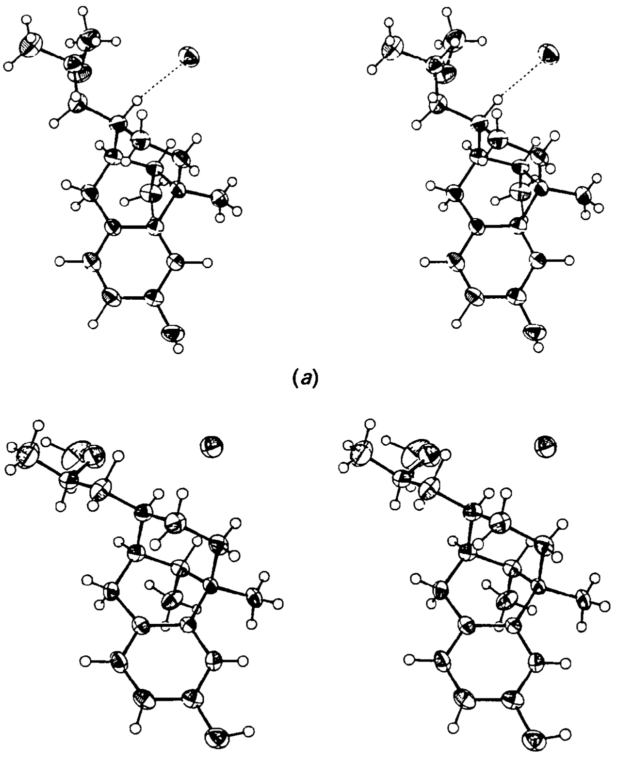
	(I)	(II)		(I)	(II)
C(1′)—C(2′)	1·400 (8)	1·385 (8)	C(4)—C(5)	1·544 (8)	1·548 (8)
C(1′)—C(6)	1·395 (7)	1·389 (7)	C(5)—C(6)	1·526 (8)	1·524 (7)
C(2′)—O(2′)	1·355 (6)	1·365 (6)	C(5)—C(9)	1·558 (8)	1·539 (9)
C(2′)—C(3′)	1·380 (6)	1·383 (6)	C(5)—C(11)	1·523 (5)	1·514 (6)
C(3′)—C(4′)	1·381 (8)	1·387 (8)	C(6)—C(7)	1·386 (6)	1·391 (6)
C(4′)—C(7)	1·396 (8)	1·386 (8)	C(7)—C(8)	1·504 (7)	1·501 (7)
C(1)—N(2)	1·526 (6)	1·515 (6)	C(9)—C(10)	1·525 (8)	1·528 (8)
C(1)—C(8)	1·529 (8)	1·528 (8)	C(12)—C(13)	1·509 (9)	1·505 (8)
C(1)—C(9)	1·530 (5)	1·531 (5)	C(13)—O(14)	1·421 (6)	1·406 (8)
N(2)—C(3)	1·502 (6)	1·511 (6)	C(13)—C(16)	1·527 (7)	1·501 (8)
N(2)—C(12)	1·514 (5)	1·500 (6)	O(14)—C(15)	1·437 (9)	1·400 (9)
C(3)—C(4)	1·511 (6)	1·499 (7)			
C(2′)—C(1′)—C(6)	120·6 (4)	120·9 (4)	C(6)—C(5)—C(11)	112·9 (4)	113·1 (4)
C(1′)—C(2′)—O(2′)	122·1 (4)	123·2 (4)	C(9)—C(5)—C(11)	109·6 (4)	109·7 (3)
C(1′)—C(2′)—C(3′)	119·6 (4)	119·9 (4)	C(1′)—C(6)—C(5)	121·0 (4)	120·8 (4)
O(2′)—C(2′)—C(3′)	118·2 (5)	116·8 (5)	C(1′)—C(6)—C(7)	119·4 (5)	119·3 (4)
C(2′)—C(3′)—C(4′)	119·8 (5)	119·2 (5)	C(5)—C(6)—C(7)	119·6 (4)	119·9 (4)
C(3′)—C(4′)—C(7)	121·4 (4)	121·4 (4)	C(4′)—C(7)—C(6)	119·1 (4)	119·2 (4)
N(2)—C(1)—C(8)	112·6 (3)	112·1 (3)	C(4′)—C(7)—C(8)	117·9 (4)	117·5 (4)
N(2)—C(1)—C(9)	107·7 (4)	108·5 (4)	C(6)—C(7)—C(8)	123·0 (4)	123·2 (4)
C(8)—C(1)—C(9)	111·8 (4)	111·4 (4)	C(1)—C(8)—C(7)	116·1 (4)	115·4 (4)
C(1)—N(2)—C(3)	110·8 (3)	111·9 (4)	C(1)—C(9)—C(5)	109·1 (4)	109·8 (4)
C(1)—N(2)—C(12)	112·1 (4)	115·1 (4)	C(1)—C(9)—C(10)	109·8 (4)	109·5 (4)
C(3)—N(2)—C(12)	112·9 (4)	109·6 (3)	C(5)—C(9)—C(10)	113·6 (4)	113·9 (4)
N(2)—C(3)—C(4)	110·2 (3)	111·1 (4)	N(2)—C(12)—C(13)	112·0 (4)	114·1 (4)
C(3)—C(4)—C(5)	115·6 (4)	115·0 (4)	C(12)—C(13)—O(14)	107·6 (4)	105·0 (4)
C(4)—C(5)—C(6)	108·8 (3)	109·2 (3)	C(12)—C(13)—C(16)	109·4 (4)	110·5 (5)
C(4)—C(5)—C(9)	107·1 (3)	106·3 (4)	O(14)—C(13)—C(16)	111·3 (4)	113·5 (5)
C(4)—C(5)—C(11)	108·6 (4)	108·3 (4)	C(13)—O(14)—C(15)	113·0 (5)	115·1 (7)
C(6)—C(5)—C(9)	109·7 (4)	110·1 (4)			

	(I)	(II)
C(1)—N(2)—C(12)—C(13)	−99·5 (5)	−51·5 (6)
C(3)—N(2)—C(12)—C(13)	134·6 (5)	−178·7 (5)
N(2)—C(12)—C(13)—O(14)	55·8 (6)	−54·2 (6)
N(2)—C(12)—C(13)—C(16)	176·9 (5)	−177·0 (5)
C(12)—C(13)—O(14)—C(15)	−161·7 (5)	163·1 (6)

thi, 1981). The resulting *E* map showed all non-H atoms but C(15). Refinement with *XRAY76* (Stewart *et al.*, 1976) by block-diagonal least squares on *F*, first with isotropic temperature factors and then anisotropically; full-matrix least squares in the final cycles. H atoms (from a difference synthesis) were included in the refinement with fixed isotropic temperature factors (1·1 times those of their parent atoms). Final $R = 0{\cdot}046$, $wR = 0{\cdot}060$ and $S = 0{\cdot}21$, $w = (5{\cdot}0 + |F_o| + 0{\cdot}005|F_o|^2)^{-1}$; $(\Delta/\sigma)_{\rm av} = 0{\cdot}14$, $(\Delta/\sigma)_{\rm max} = 1{\cdot}59$ [*y* parameter of H(13)], $-0{\cdot}66 \le$ final $\Delta\rho \le 1{\cdot}05$ e Å^{-3} (minimum and maximum near Br). Molecular parameters derived from the crystal structure were calculated with the program *PARST* (Nardelli, 1983).

Discussion. The atomic numbering scheme is given in Fig. 1 and atomic parameters are listed in Table 1.* Bond lengths, bond angles and selected torsion angles are given in Table 2. *ORTEP* stereopairs (Johnson, 1965) are shown in Fig. 2. The bond distances and angles display a close correspondence between equivalents in the two molecules, *e.g.* the angle C(1′)—C(2′)—O(2′) is substantially larger than 120° with a synperiplanar arrangement of C(1′)—C(2′)—O(2′)—H(2′). The largest difference in bond length between (I) and (II), namely 0·037 Å for O(14)—C(15), should not be considered as significant as the temperature factor of C(15) in (II) is large and quite anisotropic (ratio between largest and the smallest principal axis = 3·7). The libration of the methoxy group in (I) is much less pronounced, probably due to the presence of the weak C(1)—H(1)···O(14) hydrogen bond [H(1)···O(14) 2·524 (5) Å, C(1)—H(1)···O(14) 115·5 (3)°]. The characteristics of this hydrogen bond are in agreement with the description of Taylor & Kennard (1982): a 'nearest neighbour contact' [difference between the sum of the van der Waals radii and the (C—)H···O interatomic distance] of 0·18 Å and a decreased electron density of the donor (C—)H group resulting from the inductive effect of a neighbouring electronegative group [here the protonated N(2)].

In both molecules the piperidine ring exhibits a distorted chair conformation [flattened at C(3) and C(4)], and the ring connecting the phenol and


(*a*)

(*b*)

Fig. 2. Stereoscopic view with 50% probability ellipsoids for the non-H atoms of (*a*) (I) and (*b*) (II).

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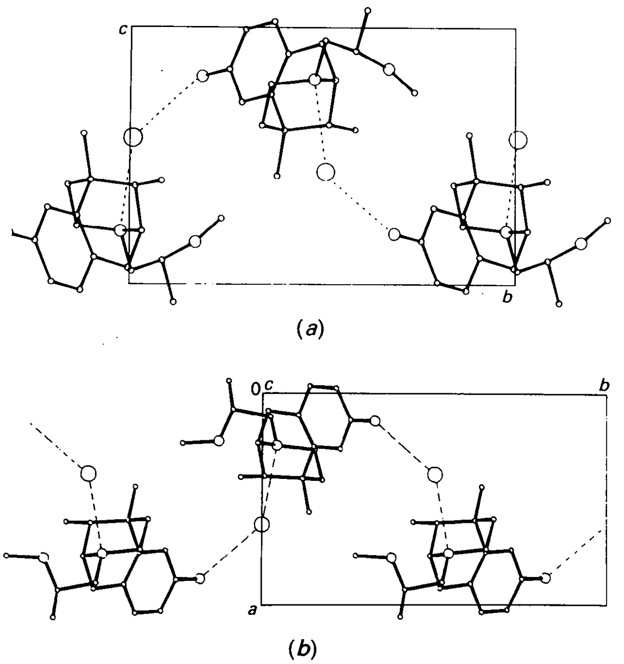
* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, distances and angles involving H atoms, least-squares-planes details and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52483 (38 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

piperidine moieties adopts a half-boat conformation. Also, in both molecules the synclinal N(2)—C(12)—C(13)—O(14) arrangement, a consequence of the so-called '*gauche* effect' (Juaristi, 1979), is combined with an antiperiplanar N(2)—C(12)—C(13)—C(16) arrangement, which is the preferred conformation for propylamine (Profeta, 1978). All known crystal structures of benzomorphans exhibit these NCCO and NCCC conformational preferences (Verlinde, 1988). The deviation from antiperiplanarity for C(12)—C(13)—O(14)—C(15) is identical for (I) and (II).

On the other hand the C(1)—N(2)—C(12)—C(13) conformation is less straightforward to interpret. In (II) the usual (−)-synclinal arrangement is adopted [only (−)-synclinal and antiperiplanar are observed for benzomorphans (Verlinde, 1988)], but in (I) the arrangement is (−)-anticlinal. The most likely explanation for this exceptional conformation is that it allows the formation of the forementioned (C—)H···O hydrogen bond. Calculations show that the H(1)···O(14) distance is the minimum for the observed torsion angle.

Recently, the O atom in the *N*-side chain has been shown to be an essential part of the *κ*-pharmacophore: it forms a hydrogen bond with a protonated residue of the receptor when the torsion angle C(1)—N(2)—C(12)—C(13) is 240° and N(2)—C(12)—C(13)—O(14) is somewhere between 70 and 90° (Verlinde, 1988). The conformation of the *N*-side chain in (I) is fairly close to this active conformation, which explains its great potency. On the other hand, the combined effect of antiperiplanarity for NCCC and *gauche* for NCCO in (II) leads to a (—)-synclinal value for NCCO as a result of the opposite configuration at C(13). This makes (II) inactive.



(*a*)

(*b*)

Fig. 3. Crystal packing of (*a*) (I) and (*b*) (II). Hydrogen bonds are indicated by dashed lines.

In both crystals the packing (Fig. 3) is mainly achieved by hydrogen bonds between the piperidinium N and the bromide ion, and between the bromide ion and the phenol group [(I): N(2)···Br 3·325 (5), H(2)···Br 2·297 (1) Å, ∠N(2)—H(2)···Br 164·6 (2)°, O(2′)···Br^{i} 3·192 (4), H(2′)···Br^{i} 2·220 (1) Å, ∠O(2′)—H(2′)···Br^{i} 177·1 (2)°; (II): N(2)···Br 3·337 (5), H(2)···Br 2·52 (7) Å, ∠N(2)—H(2)···Br 172 (5)°, O(2′)···Br^{ii} 3·162 (4), H(2′)···Br^{ii} 2·30 (7) Å, ∠O(2′)—H(2′)···Br^{ii} 157 (7)°; (i) $-x+2, y-\frac{1}{2}, -z+1$, (ii) $-x+1, y+\frac{1}{2}, -z+2$].

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