than 3°. The main deviations are limited to rotations around the N–C–C–N bridge [171·8 (3) instead of 180°] and around the N(2)–C(2) bond. The conformation around this bond [C(26)–N(2)–C(2)–C(1) 79·5 (2), C(22)–N(2)–C(2)–C(1) −160·3 (2)°] differs by *ca* 13° from that at the N(1)–C(1) bond, this flexibility evidently being due to the lack of an O substituent at the N(2) atom. Comparison of corresponding torsion angles indicates that the independent 'halves' of $PEtP(NO)_2$ and $PEtP(NO)_2H^+$ and the 'N(1) half' of PEtP(NO) have nearly the same conformation. In conclusion, one can say that the PEtP(NO) molecule adopted a *transoidal* form similar to the *transoidal* conformation characteristic of the $PEtP(NO)_2$ skeleton.

In contrast to $PEtP(NO)_2.4H_2O$, PEtP(NO) crystallizes as the trihydrate. All water molecules are involved in H bonding as double donors (Fig. 3). Water 1 is a donor in H bonds with two *N*-oxide acceptors. Water 3 uses one of its H atoms in an H bond with water 1 and the other one is donated to N(2). Water 2 is a donor in two H bonds with the other two H_2O molecules. The three water molecules show quite different acceptor properties. Water 1 accepts two H bonds, water 3 one H bond and water 2 does not show any acceptor activity. The remaining acceptor centers are located on the PEtP(NO) molecule: N(2) is a single acceptor and O(1) accepts two H bonds. It is interesting to note that the *N*-oxide O atom is much more active as an acceptor (it accepts two relatively strong H bonds) than the N(2) amino atom (which accepts only one, relatively weak, H bond). Geometrical parameters for the H bonds are reported in Table 2.

Table 2. *Geometry of the* H *bonds*

	D–H (Å)	H···*A* (Å)	*D*···*A* (Å)	∠*D*–H···*A* (°)
O(*W*1)–H(*W*11)···O(1^{i})	0·92	1·84	2·755 (2)	176
O(*W*1)–H(*W*12)···O(1)	0·96	1·81	2·760 (2)	171
O(*W*3)–H(*W*31)···N(2^{ii})	0·98	2·11	3·080 (3)	172
O(*W*3)–H(*W*32)···O(*W*1)	1·12	1·78	2·854 (3)	160
O(*W*2)–H(*W*21)···O(*W*3^{iii})	1·05	1·87	2·866 (3)	159
O(*W*2)–H(*W*22)···O(*W*1^{iv})	1·09	1·85	2·933 (2)	173

Symmetry code: (i) 1·5−*x*, *y*−0·5, 0·5−*z*; (ii) 1·5−*x*, 0·5+*y*, 0·5−*z*; (iii) *x*−1, *y*, *z*; (iv) 1−*x*, 1−*y*, 1−*z*.

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Structure of Remoxipride, a New Antipsychotic Agent. Comparison of Base and Hydrochloride Forms

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Abstract. (−)-(*S*)-3-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide, remoxipride base form, $C_{16}H_{23}BrN_2O_3$, $M_r = 371{\cdot}27$, monoclinic, $P2_1$, $a = 13{\cdot}605$ (1), $b = 14{\cdot}302$ (1), $c = 9{\cdot}794$ (2) Å, $\beta = 103{\cdot}67$ (1)°, $V = 1851{\cdot}7$ (4) Å^3, $Z = 4$, $D_x = 1{\cdot}332$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 31{\cdot}44$ cm^{-1}, $F(000) = 768$, room temperature, $R = 0{\cdot}066$ for 2499 reflections. The absolute-configuration analysis, from

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Bijvoet ratios, confirmed the (*S*)-enantiomeric form. In the asymmetric unit there are two molecules *A* and *B*, in which the benzamide parts are related by a pseudo-centre of symmetry. Two intermolecular amide NH···O hydrogen bonds [N···O distances 2·83 (1) and 2·88 (1) Å] link the *A* and *B* molecules into infinite chains along the *c* axis. As observed for remoxipride hydrochloride monohydrate, the amide group is almost perpendicular to the benzene ring plane for both base conformers. However, the overall molecular conformations of the salt and the two base forms are different. The biological effects are discussed in terms of solid-state conformations.

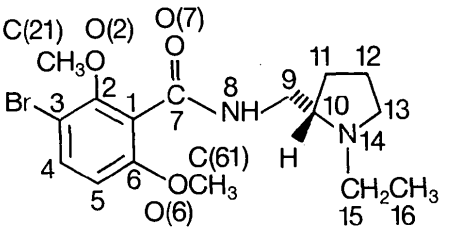
Introduction. Remoxipride is a recently developed atypical antipsychotic compound, belonging to the class of substituted benzamides, which preferentially block the dopamine D_2 receptors (Florvall & Ögren, 1982). Remoxipride is a considerably more active inhibitor of dopamine-mediated responses in rats under *in vivo* conditions than its *in vitro* affinity for the dopamine D_2 receptor, *i.e.* the [^{3}H] spiperone binding site, would indicate (Ögren, Hall, Köhler, Magnusson, Lindbom, Ängeby & Florvall, 1984). Investigations in the rat suggested that one explanation of this discrepancy in activity may be the formation of an active metabolite, *e.g.* (−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl]-6-methoxysalicylamide, FLA 797, through demethylation of one of the methoxy groups (M. Widman, private communication).

X-ray crystallographic studies of the remoxipride hydrochloride salt, (−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide hydrochloride monohydrate, and of the FLA 797 base form, show that the solid-state conformations of these two compounds are quite different (Högberg, Rämsby, de Paulis, Stensland, Csöregh & Wägner, 1986). The major structural difference lies in the orientation of the amide moiety. In remoxipride hydrochloride the amide group is almost perpendicular to the benzene ring plane. In FLA 797 the amide is coplanar with the benzene ring, which allows the closure of two virtual six-membered rings by intramolecular hydrogen bonds; one between the amide H atom and the methoxy group and the other between the phenol H atom and the carbonyl group. The former pseudoring is frequently found in mono *ortho*-methoxy substituted benzamides (Collin, Durant & Evrard, 1986; Dapporto & Sega, 1986; Furuya, Fujita, Iwanami, Takenaka & Sasada 1986; Furuya, Iwanami, Takenaka & Sasada, 1986*a*; Foresti, Riva Di Sanseverino & Sabatino, 1986; Wägner, Stensland, Csöregh & de Paulis, 1985; Houttemane, Boivin, Thomas, Berthelot & Debaert, 1983; Blaton, Peeters, De Ranter, Denisoff & Molle, 1982; Ma, Camerman & Camerman, 1982; Cesario, Pascard, El Moukhtari & Jung, 1981; and referenced methoxybenzamides within these papers) and has been suggested to be an essential structural feature for this type of dopamine antagonist (Testa, van de Waterbeemd & Carrupt 1986; Högberg *et al.*, 1986; Högberg, Norinder, Rämsby & Stensland, 1987).

The X-ray studies cited above show that the side chains can adopt folded as well as extended conformations. Theoretical calculations also show that substituted benzamides with a 1-ethyl-2-pyrrolidinylmethyl side chain are flexible molecules with small energy differences between various extended and folded conformations (Högberg *et al.*, 1987; van de Waterbeemd & Testa, 1981, 1983).

The modest *in vitro* activity of remoxipride was suggested to be due to the prevented formation of the essential coplanar hydrogen-bonded pseudoring (Högberg *et al.*, 1986). Thus, in the crystal structure of remoxipride hydrochloride monohydrate, the twisted amide group is framed in infinite chains through hydrogen bonding to the crystal water. This particular conformation, with the amide group out of planarity with the benzene ring, would prevent an efficient π–π stacking interaction at the receptor. It cannot be ruled out, however, that this conformation is induced by the intermolecular hydrogen bonding to the crystal water. Such interactions have been documented by ^{1}H NMR studies (Anker, Lauterwein, van de Waterbeemd & Testa, 1984).

In order to investigate the influence of the crystal water on the molecular conformation in the solid state, the base-form structure of anhydrous remoxipride was subjected to X-ray diffraction analysis.



Experimental. Remoxipride was synthesized according to Florvall & Ögren (1982). Suitable prismatic crystals for the X-ray diffraction study were obtained after recrystallization of the free base from diisopropyl ether (m.p. 371·6–372·6 K). Accurate unit-cell parameters were determined by a least-squares fit to 20 centred high-angle reflections. Data were collected on a Stoe automated four-circle diffractometer, with graphite-monochromated Cu $K\alpha$ radiation. The crystal selected was 0·16 × 0·46 × 0·50 mm in size, and intensities were recorded with the ω–2θ scan technique; 35 steps, $\Delta\omega = 0{\cdot}03°$, $\Delta\theta = 0{\cdot}03°$ and 5 steps for background before and after each scan. Min. and max. time per step: 0·5 and 1·5 s for prescanned min. and max. $I/\sigma(I)$ ratios of 3 and 25. 2θ range covered: 2–140° with max. *hkl* index 16,17,±11.

Intensities of 3 reference reflections, monitored every 120 min of exposure time, showed 25–30% deterioration at the end of the data collection. Corrections for gradual crystal decay were applied through rescaling against the standard reflections. 3199 unique reflections were recorded and corrected for Lorentz, polarization and absorption effects. The absorption correction was based on the crystal shape (transmission-factor range: 0·30–0·66).

The main part of the structure was solved by direct methods, using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Systematic extinctions and intensity statistics at first indicated the centrosymmetric space group $P2_1/c$, but the noncentrosymmetric space group $P2_1$ was confirmed by the identification of some weak reflections from precession photographs.

A varied two-block full-matrix least-squares procedure with *SHELX*76 (Sheldrick, 1976) was used to refine 227 and 228 variables of molecules *A* and *B*, respectively (one *y* parameter fixed), exploiting 2499 reflections with $F \geq 6\sigma(F)$. The minimization of the function $\sum w(\Delta F)^2$, $w^{-1} = \sigma^2(F) + 0{\cdot}0002F^2$, was performed with anisotropic thermal factors for all non-H atoms. The H atoms were positioned geometrically with methyl groups in rigid positions. Individual isotropic thermal factors were assigned to all H atoms, except for methyl H atoms which were given group factors. In the final refinement cycle max. $\Delta/\sigma = 1{\cdot}0$; $\Delta\rho_{max} = 0{\cdot}7$ and $\Delta\rho_{min} = -0{\cdot}7$ e Å^{-3}. $\Delta\rho_{max}$ close to the Br atom in molecule *A*. Final $R = 0{\cdot}066$ and $wR = 0{\cdot}081$.

The absolute configurations of the two independent molecules in the asymmetric unit were determined from diffraction intensity measurements of Bijvoet pairs (Bijvoet, Peerdeman & van Bommel, 1951). The 20 reflection pairs most sensitive to the anomalous-dispersion effects were selected, which all confirmed the (*S*)-enantiomeric form previously assigned on the basis of synthetic evidence. A list of the Bijvoet ratios is included in the supplementary material.* The correction terms (f', f'') for the anomalous dispersion of non-H atoms were taken from Cromer & Liberman (1970). Atomic scattering factors from *SHELX*76.

Discussion. Final atomic coordinates and equivalent isotropic thermal factors are given in Table 1. Selected bond lengths, bond angles and torsion angles are listed in Table 2, with the corresponding data for remoxipride hydrochloride monohydrate included for comparison.

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and Bijvoet differences have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44273 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates, for the (S)-enantiomeric molecular conformers of remoxipride in base form, with e.s.d.'s in parentheses and with equivalent isotropic thermal parameters, B_{eq} (Å^2), for non-H atoms*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i\mathbf{a}_j.$$

	x	*y*	*z*	B_{eq}
Molecule *A*				
C(1)	0·5385 (7)	0·6686 (6)	0·6286 (9)	4·8 (2)
C(2)	0·6398 (9)	0·6476 (7)	0·6773 (11)	6·2 (3)
O(2)	0·6707 (5)	0·5551 (4)	0·7073 (6)	5·1 (2)
C(21)	0·6922 (9)	0·5281 (7)	0·8463 (8)	5·9 (3)
C(3)	0·7146 (9)	0·7224 (9)	0·6932 (10)	7·3 (4)
Br(3)	0·8532 (1)	0·6872 (1)	0·7644 (2)	10·13 (6)
C(4)	0·6792 (8)	0·8098 (7)	0·6620 (11)	6·0 (3)
C(5)	0·5837 (8)	0·8268 (6)	0·6113 (11)	6·1 (3)
C(6)	0·5089 (8)	0·7636 (5)	0·5932 (11)	5·7 (3)
O(6)	0·4123 (5)	0·7743 (4)	0·5365 (6)	5·4 (2)
C(61)	0·3694 (9)	0·8668 (7)	0·4988 (10)	6·5 (3)
C(7)	0·4691 (5)	0·5952 (5)	0·5904 (6)	3·3 (2)
O(7)	0·4437 (4)	0·5546 (4)	0·4758 (5)	4·6 (2)
N(8)	0·4234 (5)	0·5700 (4)	0·6879 (6)	3·9 (2)
C(9)	0·3388 (5)	0·5011 (6)	0·6718 (9)	4·7 (2)
C(10)	0·2309 (8)	0·5500 (11)	0·6219 (19)	10·2 (6)
C(11)	0·2176 (8)	0·6353 (8)	0·6918 (12)	6·6 (3)
C(12)	0·1095 (12)	0·6379 (13)	0·6839 (22)	12·1 (7)
C(13)	0·0617 (9)	0·5471 (13)	0·6176 (17)	10·7 (6)
N(14)	0·1505 (5)	0·4856 (6)	0·6343 (9)	6·5 (3)
C(15)	0·1347 (11)	0·4086 (10)	0·5374 (15)	9·3 (5)
C(16)	0·0747 (17)	0·3308 (20)	0·5805 (24)	18·5 (13)
Molecule *B*				
C(1′)	0·5423 (5)	0·5214 (4)	0·1205 (6)	3·0 (2)
C(2′)	0·6438 (5)	0·5441 (5)	0·1796 (6)	3·0 (2)
O(2′)	0·6658 (5)	0·6368 (5)	0·2024 (5)	5·6 (2)
C(21′)	0·6747 (8)	0·6631 (11)	0·3554 (11)	7·9 (4)
C(3′)	0·7176 (6)	0·4765 (6)	0·2063 (9)	4·5 (2)
Br(3′)	0·8544 (1)	0·5033	0·2659 (2)	9·40 (6)
C(4′)	0·6975 (7)	0·3835 (8)	0·1702 (9)	5·9 (3)
C(5′)	0·5924 (8)	0·3569 (6)	0·1185 (8)	5·5 (3)
C(6′)	0·5164 (5)	0·4311 (5)	0·0879 (6)	3·4 (2)
O(6′)	0·4149 (4)	0·4140 (4)	0·0367 (7)	5·6 (2)
C(61′)	0·3888 (7)	0·3233 (6)	−0·0121 (11)	6·1 (3)
C(7′)	0·4583 (6)	0·6002 (5)	0·0888 (8)	4·1 (2)
O(7′)	0·4449 (5)	0·6332 (3)	−0·0326 (5)	4·9 (2)
N(8′)	0·4174 (5)	0·6260 (5)	0·1947 (6)	4·1 (2)
C(9′)	0·3354 (8)	0·6897 (7)	0·1718 (11)	6·0 (3)
C(10′)	0·2458 (7)	0·6523 (8)	0·1769 (17)	9·3 (5)
C(11′)	0·2178 (9)	0·5478 (9)	0·1349 (17)	9·1 (5)
C(12′)	0·1089 (12)	0·5474 (13)	0·1107 (24)	13·1 (8)
C(13′)	0·0742 (9)	0·6452 (14)	0·1449 (18)	11·8 (6)
N(14′)	0·1569 (7)	0·7060 (8)	0·1314 (9)	7·5 (3)
C(15′)	0·1497 (11)	0·7930 (14)	0·1792 (27)	15·6 (10)
C(16′)	0·0605 (11)	0·8537 (11)	0·0935 (22)	14·7 (9)

In agreement with the solid-state conformation of the hydrochloride, the amide group is nearly perpendicular to the benzene ring plane in the two molecules *A* and *B* of the free base, as shown by the torsion angle τ_1 [C(6)C(1)C(7)N(8)]. As mentioned above, this conformation contrasts with that of other *ortho*-methoxy-substituted benzamides, which do not have a sterically demanding methoxy group in the remaining *ortho* position. Owing to the large standard deviations observed in the calculated bond lengths, partly explained by the crystal decay during the data collection, the distance values agree moderately well between molecules *A* and *B*. The mean bond lengths are all within the 3σ limit, compared with the hydrochloride salt form.

The structures of the two non-equivalent conformers *A* and *B* of the base with the adopted atom numbering are shown in Fig. 1. Here the pseudocentric relation-

ship between the benzamide parts of *A* and *B* are clearly observed in the orientations of the methyl parts of the 2-methoxy groups as well as in the opposite directions of the amide moieties. Both molecules have a rather flattened spatial arrangement as deduced from the dihedral angles formed by the calculated least-squares planes through the benzene and pyrrolidine rings, which are 26·4 (5) and 16·0 (6)° in molecules *A* and *B*, respectively. The conformation of the five-membered pyrrolidine rings is best described as near envelope, taking the phase angles $\varphi = -30$ (3) (*A*) and $\varphi = -41$ (3)° (*B*), with the twofold axis through the N(14) atom in both rings. For an envelope conformation $\varphi = 0 \pm 36°$, while for a half-chair $\varphi = 18 \pm 36°$ (Cremer & Pople, 1975).

Table 2. *Bond lengths* (Å), *bond angles* (°) *and torsion angles* (°) *of remoxipride free base*

The remoxipride hydrochloride form has been included for comparison.

	Remoxipride (base)		
	Molecule *A*	Molecule *B*	Remoxipride (HCl)
C(1)–C(2)	1·38 (1)	1·40 (1)	1·39 (1)
C(1)–C(6)	1·44 (1)	1·36 (1)	1·40 (1)
C(1)–C(7)	1·40 (1)	1·58 (1)	1·52 (1)
C(2)–O(2)	1·39 (1)	1·37 (1)	1·37 (1)
C(2)–C(3)	1·46 (2)	1·37 (1)	1·39 (1)
O(2)–C(21)	1·41 (1)	1·52 (1)	1·44 (1)
C(3)–Br(3)	1·92 (1)	1·85 (1)	1·92 (1)
C(3)–C(4)	1·35 (2)	1·39 (1)	1·37 (1)
C(4)–C(5)	1·30 (1)	1·45 (1)	1·39 (1)
C(5)–C(6)	1·34 (1)	1·46 (1)	1·37 (1)
C(6)–O(6)	1·31 (1)	1·38 (1)	
O(6)–C(61)	1·46 (1)	1·40 (1)	1·44 (1)
C(7)–O(7)	1·24 (1)	1·25 (1)	1·24 (1)
C(7)–N(8)	1·31 (1)	1·34 (1)	1·30 (1)
N(8)–C(9)	1·50 (1)	1·42 (1)	1·46 (1)
C(9)–C(10)	1·60 (1)	1·34 (2)	1·51 (1)
C(10)–C(11)	1·43 (2)	1·57 (2)	1·52 (1)
C(10)–N(14)	1·46 (2)	1·41 (1)	1·48 (1)
C(11)–C(12)	1·46 (2)	1·44 (2)	1·49 (1)
C(12)–C(13)	1·53 (3)	1·54 (3)	1·51 (1)
C(13)–N(14)	1·47 (2)	1·45 (2)	1·51 (1)
N(14)–C(15)	1·44 (2)	1·34 (2)	1·49 (1)
C(15)–C(16)	1·50 (3)	1·56 (2)	1·52 (1)
C(6)–C(1)–C(7)	120·7 (8)	119·8 (6)	122·4 (8)
C(2)–C(1)–C(7)	118·9 (8)	120·7 (6)	118·4 (8)
C(2)–C(1)–C(6)	119·4 (8)	119·5 (7)	119·1 (8)
C(1)–C(2)–C(3)	119·4 (10)	121·3 (6)	118·4 (9)
C(1)–C(2)–O(2)	120·3 (9)	116·6 (6)	119·3 (8)
O(2)–C(2)–C(3)	120·2 (9)	121·9 (6)	122·1 (8)
C(2)–O(2)–C(21)	115·2 (7)	111·4 (7)	113·0 (8)
C(2)–C(3)–C(4)	116·9 (11)	122·4 (8)	122·1 (8)
C(2)–C(3)–Br(3)	116·6 (8)	123·3 (6)	119·5 (7)
Br(3)–C(3)–C(4)	126·4 (9)	113·7 (6)	118·3 (7)
C(3)–C(4)–C(5)	122·1 (10)	117·4 (9)	119·7 (9)
C(4)–C(5)–C(6)	125·6 (9)	118·2 (8)	118·9 (9)
C(1)–C(6)–C(5)	116·4 (9)	120·8 (7)	121·6 (8)
C(5)–C(6)–O(6)	129·1 (8)	123·0 (7)	125·2 (8)
C(1)–C(6)–O(6)	114·2 (7)	115·9 (6)	113·1 (8)
C(6)–O(6)–C(61)	121·1 (7)	116·2 (6)	117·3 (7)
C(1)–C(7)–N(8)	114·7 (6)	117·2 (6)	114·6 (9)
C(1)–C(7)–O(7)	128·2 (7)	113·1 (6)	119·2 (9)
O(7)–C(7)–N(8)	117·0 (6)	129·6 (7)	126·2 (9)
C(7)–N(8)–C(9)	126·3 (6)	120·7 (6)	123·4 (8)
N(8)–C(9)–C(10)	111·9 (8)	115·3 (9)	110·6 (7)
C(9)–C(10)–N(14)	110·6 (10)	110·3 (10)	112·0 (7)
C(9)–C(10)–C(11)	116·0 (10)	122·3 (10)	115·9 (8)
C(11)–C(10)–N(14)	108·5 (11)	107·3 (10)	103·5 (7)
C(10)–C(11)–C(12)	103·7 (11)	102·8 (11)	104·1 (7)
C(11)–C(12)–C(13)	109·0 (13)	108·4 (14)	109·3 (8)
C(12)–C(13)–N(14)	101·8 (12)	103·9 (12)	102·9 (7)
C(10)–N(14)–C(13)	103·0 (10)	105·6 (11)	106·1 (6)
C(13)–N(14)–C(15)	113·2 (10)	113·6 (12)	113·3 (7)
C(10)–N(14)–C(15)	115·3 (10)	121·5 (12)	116·0 (7)
N(14)–C(15)–C(16)	113·0 (13)	116·0 (17)	113·9 (8)
τ_1C(6)C(1)C(7)N(8)	−95·1 (10)	96·4 (8)	−72·8 (12)
τ_2C(1)C(7)N(8)C(9)	173·3 (7)	−174·1 (7)	−175·5 (8)
τ_3C(7)N(8)C(9)C(10)	−89·7 (10)	108·6 (11)	116·4 (10)
τ_4N(8)C(9)C(10)N(14)	−168·6 (8)	−169·0 (10)	−177·8 (7)
τ_5C(9)C(10)N(14)C(15)	−69·1 (13)	−50·9 (19)	−69·2 (9)
τ_6C(10)N(14)C(15)C(16)	163·0 (14)	164·6 (14)	178·1 (7)

From comparison of the torsion angles (*cf.*Table 2) it can be concluded that all three observed molecular conformers of remoxipride found in the base and the hydrochloride salt forms are different with respect to τ_1 and τ_3. However, the torsion angles τ_2, τ_4, τ_5 and τ_6 are all of the same sign and magnitude.

An overlay of the structures *A* and *B*, by superimposing the aromatic moieties, more clearly reveals the conformational differences (Fig. 2*a*). Thus, the carbonyl group can be oriented either upwards or downwards with respect to the aromatic ring plane. The closest resemblance of the side chains is found between molecule *B* and remoxipride hydrochloride, showing the same sign of torsion angle τ_3. However, the different signs of τ_1 lead to non-equivalence of the positions of the bromo substituents (Fig. 2*b*).

Attempts to correlate the structural features and the activity of potential antipsychotic agents are often based on parameters describing the relations between the benzene ring and the tertiary N atom (Cesario,

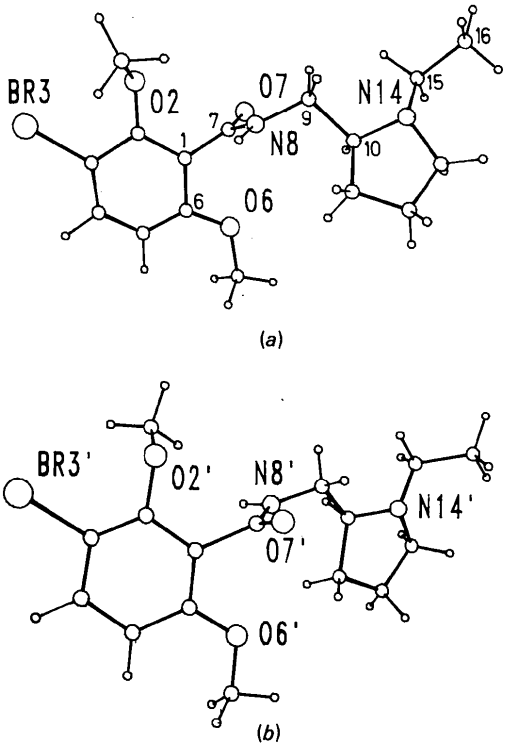


Fig. 1. The two independent molecular conformers (*a*) *A* and (*b*) *B* of remoxipride free base, with numbering for selected atoms. Primed labels refer to atoms in molecule *B*.

Pascard, El Moukhtari & Jung, 1981). The distances between the centre of the benzene ring and the N(14) atom are 7·23 (1) and 7·06 (1) Å, and the out-of-plane deviations are 1·35 (1) and 1·70 (1) Å, for molecules *A* and *B*, respectively.

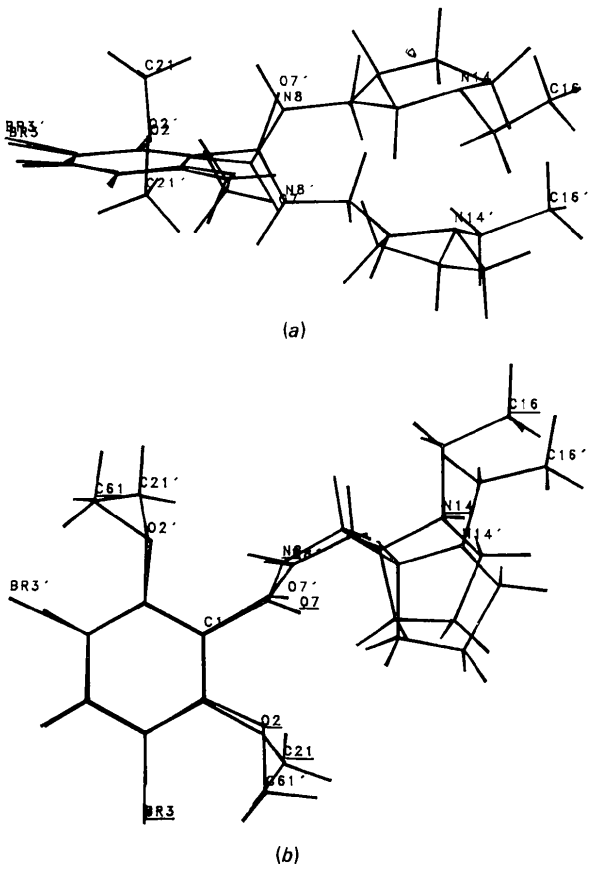


Fig. 2. (*a*) The conformational differences between molecules *A* and *B* of remoxipride free base, visualized through the fitting of C(1)C(1′), C(3)C(3′) and C(5)C(5′). Primed numbers refer to molecule *B*. (*b*) Superposition of remoxipride hydrochloride and molecule *B* fitted through C(1)C(1′), C(3)C(5′) and C(5)C(3′). Underlined labels refer to the remoxipride hydrochloride salt conformer.

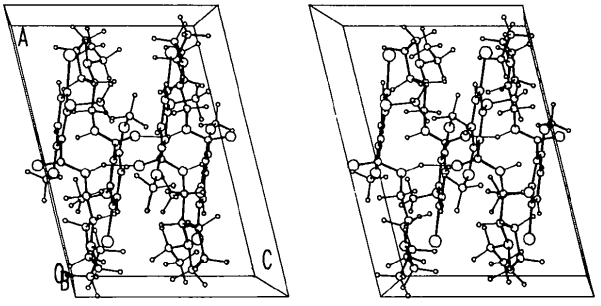


Fig. 3. Molecular packing of remoxipride base, viewed along the *b* axis. Notable is the intermolecular NH···O bonds linking the molecules *A* and *B* parallel to the *c* axis.

A stereoview of the molecular packing scheme is given in Fig. 3, showing the alternate linking of the *A* and *B* conformers along the *c* axis. Two intermolecular hydrogen bonds join the amide H atom and the carbonyl O atom of the two molecules, N(8)H···O(7′) = 2·832 (8) (*x*,*y*,*z*+1) and N(8′)H···O(7) = 2·878 (9) Å (*x*,*y*,*z*), both N—H···O angles 156°. In the remoxipride hydrochloride salt form, the intermolecular amide hydrogen bond is bridged by the crystal water.

Apparently, the present investigation gives no conclusive information about the influence of the water of crystallization on the solid-state conformation of remoxipride hydrochloride (see below), since the external hydrogen bond of the amide group to the water is substituted by an external hydrogen bond to a neighbouring benzamide. However, there are numerous examples of anhydrous and hydrated mono *ortho*-methoxy benzamides with intermolecular hydrogen bonds which involve the carboxamide moiety without affecting the coplanar benzamide orientation (Houttemane, Boivin, Thomas, Berthelot & Debaert, 1983; Ma, Camerman & Camerman, 1982; Blaton, Peeters, De Ranter, Denisoff & Molle, 1981; Cesario, Pascard, El Moukhtari & Jung, 1981; Houttemane, Boivin, Nowogrocki, Thomas & Bonte, 1981; Peeters, Blaton, De Ranter, Denisoff & Molle, 1980; Furuya, Iwanami, Takenaka & Sasada, 1986*b*; Blaton, Peeters, De Ranter, Denisoff & Molle, 1980). Therefore, it seems likely that the steric crowding of the 2,6-dimethoxy substituents evokes this effect, despite the intermolecular amide hydrogen bonding. Consequently, the X-ray study supports the view that the modest *in vitro* activity of remoxipride stems from the unfavourable nonplanar conformation of the benzamide moiety.

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Structure of 13-Ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one (3-Ketodesogestrel)

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Abstract. $C_{22}H_{28}O_2$, $M_r = 324{\cdot}46$, monoclinic, $P2_1$, $a = 6{\cdot}653$ (1), $b = 18{\cdot}413$ (1), $c = 7{\cdot}9653$ (8) Å, $\beta = 107{\cdot}49$ (1)°, $V = 930{\cdot}6$ (2) Å^3, $Z = 2$, $D_x = 1{\cdot}158$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, μ (Mo $K\alpha$) = 0·7 cm^{-1}, $F(000) = 352$, room temperature, $R = 0{\cdot}053$ for 1910 unique reflections with $I \geq 2{\cdot}5\sigma(I)$. The ethyl group is in the usual *trans* conformation relative to the *C/D* ring junction. The *A* ring is statistically disordered (1:1) and shows a normal 1α,2β-half-chair as well as an inverted 1β,2α-half-chair conformation. Molecular mechanics gives a steric energy difference of 4 kJ mol^{-1} between the minimized normal and inverted half-chair structures in favour of the normal 1α,2β-half-chair conformation. The steroid molecules are hydrogen-bonded head to tail.

Introduction. The title compound is the biologically active metabolite of the orally active progestogen desogestrel (13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17β-ol). The carbonyl function at the 3-position is introduced by metabolic oxidation in the liver. The 4-en-3-one *A* ring is essential for proper binding to the progestogen receptor and for steroids without any further unsaturation this ring shows the greatest conformational flexibility of the steroid backbone. Usually the conformation of the *A* ring is somewhere between a 1α,2β-half-chair and a 1α-sofa, but in a small number of crystal structures an inverted 1β,2α-half-chair has been observed (Duax, Fronckowiak, Griffin & Rohrer, 1982). Most cases of inverted *A*-ring conformations include 2β-substituted steroids where steric effects favour this conformation in the crystal as well as in solution. Medroxyprogesterone acetate (17α-acetoxy-6α-methylprogesterone) was found to have a normal *A*-ring conformation in solution (Barrett, Farrant, Kirk, Mersh, Sanders & Duax, 1982) but an inverted conformation in the crystal (Duax, Cody, Griffin, Hazel & Weeks, 1978). Barrett *et al.* (1982) suggested that the energy difference between the two conformations is small and that packing forces in the crystal which stabilize the inverted conformation may mimic those at the binding site for progestational activity. The energy difference between the different conformers is thought to be in the range of 0 to 10

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