

- BROT, C. & DARMON, I. (1966). *J. Chim. Phys.* **63**, 100–107.
- BROT, C., DARMON, I. & DAT-XUONG, N. (1967). *J. Chim. Phys.* **64**, 1061–1063.
- CHAPLOT, S. L., MCINTYRE, G. J., MIERZEJEWSKI, A. & PAWLEY, G. S. (1981). *Acta Cryst.* **B37**, 1896–1900.
- CHARBONNEAU, G. P. & TROTTER, J. (1967). *J. Chem. Soc. A*, pp. 2032–2035.
- CHARBONNEAU, G. P., SANQUER, M. & MEINNEL, J. J. (1967). *J. Chim. Phys.* **64**, 273–275.
- DAVID, W. I. F., GLAZER, A. M., IBBERSON, R. M. & INABA, A. (1992). ISIS Annual Report, A4 (HRPD).
- DEWAR, M. J. S. & THIEL, W. (1977). *J. Am. Chem. Soc.* **99**, 4899–4906.
- DEWAR, M. J. S., ZOEBSCH, E. G., HEALY, E. F. & STEWART, J. J. P. (1985). *J. Am. Chem. Soc.* **107**, 3902–3909.
- DOMENICANO, A. & MURRAY-RUST, P. (1979). *Tetrahedron Lett.* **24**, 2283–2286.
- DOMENICANO, A., VACIAGO, A. & COULSON, C. A. (1975). *Acta Cryst.* **B31**, 221–234.
- EVENO, M. & MEINNEL, J. J. (1966). *J. Chim. Phys.* **63**, 108–113.
- FOURME, R., RENAUD, M. & ANDRÉ, D. (1972). *Mol. Cryst. Liq. Cryst.* **17**, 209–221.
- FUJIWARA, T., A TAKE, T. & CHIHARA, H. (1990). *Bull. Chem. Soc. Jpn.* **63**, 657–665.
- GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368–376.
- GROKE, G. (1992). Doktor Ingenieur Dissertation, Univ. of Darmstadt.
- GYOTEN, H., YOSHIMOTO, Y., A TAKE, T. & CHIHARA, H. (1982). *J. Chim. Phys.* **77**, 5097–5107.
- HAMDELLOU, L. (1989). Magister diploma, Univ. of Constantine.
- HAMILTON, W. C., EDMONDS, J. W., TIPPE, A. & RUSH, J. J. (1969). *Discuss. Faraday Soc.* **48**, 192–204.
- KHOTSYANOVA, T. L. (1966). *Zh. Strukt. Khim.* **7**, 472–473.
- KHOTSYANOVA, T. L., BABUSHKINA, T. A. & KUZNETSOV, S. I. (1969). *Zh. Strukt. Khim.* **10**, 525–529.
- KHOTSYANOVA, T. L., BABUSHKINA, T. A., KUZNETSOV, S. I. & SEMIN, G. K. (1972). *Kristallografiya*, **17**, 552–556.
- KHOTSYANOVA, T. L., ROBAS, V. I. & SEMIN, G. K. (1964). *Zh. Strukt. Khim.* **5**, 644–646.
- KITAIGORODSKY, A. I. (1973). *Molecular Crystals and Molecules*. New York: Academic Press.
- KRIGBAUM, W. R. & WILDMAN, G. C. (1971). *Acta Cryst.* **B27**, 2353–2358.
- LAGARRIGUE, M. (1972). *Mol. Cryst. Liq. Cryst.* **17**, 237–249.
- LAGARRIGUE, M. (1973). Thesis. Orsay, France.
- MEINNEL, J., HUSLER, W., MANI, M., TAZI, M., NUSIMOVICI, M., SANQUER, M., WYNCKE, B., HEIDEMANN, A., CARLILE, C., TOMKINSON, J. & HENNION, B. (1992). *Physica B*, 180–181, 711–713.
- MEINNEL, J., MANI, M., TONNARD, F., NUSIMOVICI, M. & SANQUER, M. (1993). *C. R. Acad. Sci. Paris Ser. II*, **17**, 885–890.
- MESSAGER, J. C. & BLOT, J. (1971). *C. R. Acad. Sci. Paris*, **272**, 684–686.
- MESSAGER, J. C., CALLEAU, H. & YELON, W. B. (1978). *Acta Cryst.* **A34**, 384–388.
- MIRSKY, K. & COHEN, M. D. (1978). *Chem. Phys.* **28**, 193–204.
- NUSIMOVICI, M., MEINNEL, J., TAZI, M., WYNCKE, B., SANQUER, M., HEIDEMANN, A. & HENNION, B. (1995). *Z. Physik*. To be published.
- PAWLEY, G. S., MACKENZIE, G. A. & DIETRICH, O. W. (1977). *Acta Cryst.* **A33**, 142–145.
- PERTSIN, A. J. & KITAIGORODSKY, A. I. (1987). *The Atom-Atom Potential Method*. Berlin: Springer-Verlag.
- STEWART, J. J. P. (1989). *Quantum Chem. Program Exch. Bull.* **9**, 10.
- STREL'TSOVA, I. N. & STRUCHKOV, YU. T. (1961). *J. Struct. Chem.* **2**, 296–308.
- TAKEDA, S., FUJIWARA, T. & CHIHARA, H. (1989). *J. Chem. Phys. Jpn.* **58**, 1793–1800.
- TAZI, M. (1990). Doctorate Thesis. Univ. of Rennes.
- TULINSKY, A. & WHITE, J. G. (1958). *Acta Cryst.* **11**, 7–14.
- WHITE, A. H., BIGGS, B. S. & MORGAN, S. O. (1940). *J. Am. Chem. Soc.* **62**, 16–25.
- WILLIAMS, D. E. (1967). *J. Chem. Phys.* **47**, 4680–4684.
- WILLIAMS, D. E. (1972). *Acta Cryst.* **A28**, 84–88.

Acta Cryst. (1995). **B51**, 847–856

Conformation of the Two Potential Antipsychotic Agents (–)-(S)-3-Bromo-5,6-dimethoxy-N-[(1-ethyl-2-pyrrolidiny)methyl]benzamide, FLB 457, and its 2-Hydroxy Analogue, FLB 463

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(Received 2 December 1994; accepted 6 February 1995)

Abstract

The crystal structures and absolute configurations of two potent dopamine-D₂ receptor antagonists, FLB 457, ‡ (–)-(S)-3-bromo-5,6-dimethoxy-N-[(1-ethyl-2-pyrrolidi-

nyl)methyl]benzamide, and FLB 463, (–)-(S)-3-bromo-5,6-dimethoxy-N-[(1-ethyl-2-pyrrolidiny)methyl]salicylamide, have been determined by X-ray diffraction methods. The crystal structure of FLB 457 was derived from its salt with hydrobromide, C₁₆H₂₄BrN₂O₃⁺Br[–], crystallizing in the orthorhombic space group *P*2₁2₁2₁, *a* = 28.900 (18), *b* = 8.747 (3), *c* = 7.585 (1) Å, *Z* = 4, and FLB 463 from its methylsulfonate salt, C₁₆H₂₄BrN₂O₄⁺CH₃SO₃[–], crystallizing in the monoclinic space group *P*2₁, *a* = 15.264 (5), *b* = 8.087 (4),

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‡ FLB 457 was previously known as 5-bromo-2,3-dimethoxy-N-[(1-ethyl-2-pyrrolidiny)methyl]benzamide.

$c = 8.541(3) \text{ \AA}$, $\beta = 93.44(5)^\circ$, $Z = 2$. FLB 457 and FLB 463 are two potential antipsychotic agents with extremely high and stereospecific blocking affinity for the dopamine D_2 -receptors both *in vitro* and *in vivo*. The biological activities are confined to the *S*-enantiomeric forms. The molecular conformations of the two examined compounds are almost identical, despite differences in their anionic environments. The benzamide moieties are essentially planar, stabilized by an intramolecular hydrogen bond between the amide group and the 6-methoxy (*ortho*) O atom, reinforced by a second intramolecular hydrogen bond between the other *ortho*-substituent (2-hydroxyl group) and the carbonyl O atom in FLB 463. In both structures, the 5-methoxy group is coplanar with the benzene ring plane, while the methyl part of the 6-methoxy group is directed away from the aromatic plane. The conformation of the amide side chain, which is associated with the area of greatest conformational flexibility, adopts a folded (+)-perpendicular-*gauche* trend. In both crystals, the molecular packing schemes are mainly achieved through salt bridging. A weak hydrogen bond joins the bromide anion to the protonated pyrrolidine nitrogen of FLB 457, whereas the methylsulfonate anion is more closely connected to the FLB 463 cationic nucleus *via* a complex hydrogen-bonding scheme, involving the pyrrolidine nitrogen as well as the amide nitrogen. Except for the salt interactions, the intermolecular forces are mainly of normal or weak van der Waals character.

Introduction

During the recent decade a number of potential antipsychotic agents of the *ortho*-methoxybenzamide type with remarkable selectivity for dopamine- D_2 receptors have been developed. Benzamides with *N*-(ethyl-2-pyrrolidinyl)methyl sidechains display high and stereoselective affinity for dopamine- D_2 receptors, with the activity confined to the *S*-enantiomers (Högberg, Råmsby, Ögren & Norinder, 1987, and references therein; Högberg, 1991, and references therein). In a series of 5,6-dimethoxy-substituted benzamides and salicylamides, the compounds FLB 457 (Högberg, Ström, Hall & Ögren, 1990; Högberg, de Paulis *et al.*, 1990) and FLB 463 (Högberg, Bengtsson *et al.*, 1990) have proved to be extremely potent both *in vitro* and *in vivo*. Their high and selective affinity for the dopamine- D_2 receptors makes these two compounds suitable as ^{11}C and ^{76}Br radioligands for visualization and characterization of dopaminergic processes also in living humans, using positron emission tomography [PET (Hallin *et al.*, 1993; Loc'h *et al.*, 1994; Högberg, Mohell & Ström, 1992)]. The corresponding ^{123}I ligands have been developed for the complementary technique single photon emission computed tomography [SPECT (Högberg, 1993; Högberg, Ström *et al.*, 1990; Hall *et al.*, 1991)].

The most common structural feature among benzamides and salicylamides is the hydrogen bond between the amide group and the 6-methoxy (*ortho*) O atom. This hydrogen bond, which favours the coplanarity of the aromatic ring and the carboxamide moiety, seems to be necessary for high antagonistic dopamine- D_2 activity (Högberg, 1991, and references therein). Comparative structure-activity studies of 5,6-dimethoxy compounds have clearly emphasized the favourable properties provided by the two adjacent methoxy groups (Högberg, de Paulis *et al.*, 1990; Högberg, Bengtsson *et al.*, 1990). The two analogues FLB 457 and FLB 463 exhibit almost the same dopamine- D_2 activity, suggesting that the additional hydrogen bond provided by the 2-hydroxyl group in FLB 463 has a minor influence. Experimental studies suggest that the phenolic group of salicylamides must be neutral upon binding to the receptor (Tsai *et al.*, 1993). Thus, the electronic properties of the benzamides and the corresponding salicylamides are similar. Quantitative structure-activity relationship (QSAR) studies on *N*-[(ethyl-2-pyrrolidinyl)methyl]benzamides and -salicylamides also indicate that they bind to the same binding site in the dopamine- D_2 receptor (Norinder & Högberg, 1992).

However, the influence of the 5-substituent on the strength of the intramolecular 6-methoxy hydrogen bond has been discussed (Högberg, de Paulis *et al.*, 1990; Högberg, Bengtsson *et al.*, 1990; Collin *et al.*, 1989). Arguments for both coplanar and perpendicular 6-methoxy conformations enforcing the methoxy-amide hydrogen bond have been raised (Högberg, Råmsby, Ögren & Norinder, 1987, and references therein; Högberg, 1991, and references therein; Högberg, de Paulis *et al.*, 1990; Högberg, Bengtsson *et al.*, 1990; Collin *et al.*, 1989; Norinder & Högberg, 1989). In order to gain more insight into these conformational aspects and the relations between benzamides and salicylamides, the crystal structures of the hydrobromide of FLB 457 and the methylsulfonate of FLB 463 have been determined. The X-ray analyses have been supplemented by simple molecular-mechanics MM2(87) calculations to reveal the possible and energetically most favourable 6-methoxy conformations.

Experimental

X-ray data collection

Colourless elongated and well shaped crystals of FLB 457 were grown from acetone-ether (1:1) by slow evaporation at room temperature. Preliminary X-ray diffraction experiments revealed that the crystals were commonly twinned along the *b* axis. Well shaped colourless prismatic crystals of FLB 463 were grown from acetone by ordinary evaporation techniques. Accurate unit-cell dimensions of FLB 457 and FLB 463 were obtained by least-squares refinement using the

Table 1. *Experimental data and selected details of the refinement calculations*

	FLB 457	FLB 463
Molecular formula	C ₁₆ H ₂₃ BrN ₂ O ₃ (HBr)	C ₁₆ H ₂₃ BrN ₂ O ₄ (HSO ₃ CH ₃)
Molecular weight	452.2	483.4
D _x (Mg m ⁻³)	1.563	1.525
Intensity data collection		
Crystal size (mm)	0.08 × 0.02 × 0.48	0.04 × 0.15 × 0.15
θ range (°)	2–67	1–67
h	0–32	0–19
k	0–9	0–10
l	0–8	–11–11
Scan speed (° s ⁻¹)	0.04	0.04
Scan width (°)	1.5	1.6
Absorption correction		
Linear absorption coefficient (mm ⁻¹)	5.535	3.941
Number of sampling points	6 × 2 × 36	4 × 10 × 10
Transmission factor range	0.58–0.90	0.39–0.74
Structure refinement		
Minimization procedure	Σw(ΔF) ²	Σw(ΔF) ²
Weighting scheme (w ⁻¹)	σ ² (F) + 0.0012(F) ²	σ ² (F) + 0.0146(F) ²
Number of independent reflections	1652	2111
Criterion of significance	F ≥ 3σ(F)	F ≥ 6σ(F)
Number of observed reflections	1299	1821
Number of refined parameters	220	268
Goodness-of-fit parameter, S	0.75	1.00
Final R value (%)	7.49	3.71
wR value	7.28	4.37
Max., average shift e.s.d.: Δ/σ	0.15, 0.04	0.16, 0.04
Max., min. electron density: Δρ (e Å ⁻³)	0.75, 0.53	0.30, 0.23

positions of powder diffraction lines recorded at 298 K in a Guinier–Hägg focusing camera with strictly monochromatized CuK α radiation, $\lambda = 1.5406 \text{ \AA}$, and Si ($a = 5.4309 \text{ \AA}$) as internal standard (Malmros & Werner, 1973; Johansson, Palm & Werner, 1980). In Table 1 some relevant crystal data and experimental details of the single-crystal analyses are summarized. The reflection intensities of FLB 457 and FLB 463 were collected on a Philips PW1100 computer-controlled four-circle diffractometer with graphite monochromatized CuK α radiation, $\lambda = 1.5418 \text{ \AA}$, at room temperature, exploiting the ω - 2θ scan mode. During the data collection three standard reflections were monitored periodically every second hour. No significant deviations from the average intensities could be observed. The net intensities of the reflections were corrected for Lorentz, polarization and absorption effects. In order to correct for the twin character of the reflection profiles of FLB 457, the weaker but separated peak was partly eliminated by applying the unaffected background value on both sides of the reflection scan.

Structure determinations and refinements

The initial structural models were derived by combining Patterson and direct methods. In FLB 457 and FLB 463, the Br-atom positions were transferred to the MULTAN80 (Main *et al.*, 1980) program system, which

revealed 23 and 24 non-H atoms, respectively. Completion and full-matrix least-squares refinement of the structures were carried out, using the *SHELX76* program package (Sheldrick, 1976), with all non-H atoms treated anisotropically. The H-atom positions, except H(2) and H(14) in FLB 463, were calculated after each cycle assuming ideal geometries (C—H = 1.08 Å) and group vibrational parameters. The H atoms in the methyl groups were refined as rigid groups, each with a common displacement factor. In FLB 463 the positions of the H(2) and H(14) atoms were located from a late difference electron-density map; these positions were held fixed in subsequent calculations, and only their vibrational parameters were refined. Final agreement factors, together with crystal data and selected details of the data reduction and refinement calculations are collected in Table 1. The atomic scattering factors were taken from *SHELX76* (Sheldrick, 1976). The correction terms for the anomalous dispersion of non-H atoms were taken from Cromer & Liberman (1970). Geometrical calculations were carried out with the program *PARST* (Nardelli, 1983).

Determination of absolute configurations

The absolute stereochemistry of FLB 457 was determined by careful intensity measurements of 28 Friedel pairs of reflections, with θ less than 36°, exhibiting the greatest influence of anomalous scattering effects. From calculated Bijvoet ratios (Bijvoet, Peerdeman & van Bommel, 1951), defined as $2(I_{hkl} - I_{-h-k-l}) / (I_{hkl} + I_{-h-k-l})$, Friedel pairs were selected and measured under equal conditions with CuK α radiation. Comparison between observed and calculated intensities uniquely established the *S*-enantiomeric configuration. A list of calculated and observed Bijvoet ratios is included in the supplementary material.* The absolute configuration of FLB 463 was determined differently. The final refinement calculation of FLB 463 was carried out twice, supposing either *R* or *S* configurations. The resulting final agreement factors are $R = 0.0384$ and 0.0371 , and $wR = 0.0454$ and 0.0437 for the *R* and *S* enantiomers, respectively. Statistical tests (Hamilton, 1965; Rogers, 1981) of the wR_S/wR_R ratios confirmed at a significance level of 0.001 that the studied compound has the *S*-configuration, as expected.

Molecular illustrations were drawn using *ORTEPII*, (Johnson, 1976), *PLUTO* (Motherwell & Clegg, 1978) and *CHEM-X* (developed and distributed by Chemical Design Ltd, Oxford, 1989).

* Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry, least-squares planes data, deviations of atoms from the planes and dihedral angles between the planes, and powder diffraction data have been deposited with the IUCr (Reference: AB0336). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Results and discussion

FLB 457 and FLB 463, which belong to the classes of 5,6-dimethoxy-substituted benzamides and salicylamides, respectively, have for convenience been labelled with the same scheme in the crystallographic approach as in other studies (Högberg, Ström, Hall & Ögren, 1990; Högberg, de Paulis *et al.*, 1990). Perspective views of the solid-state structures with adopted labelling are shown in Fig. 1, where also a specification of the anionic contacts is given. Refined fractional coordinates of non-H atoms and equivalent isotropic temperature factors are listed in Table 2. Relevant intramolecular bond lengths, bond angles and some selected torsion angles are found in Table 3.

Despite the lower quality of the X-ray structure determination of FLB 457, probably caused by crystal twinning, it is clear that the conformations of FLB 457 and FLB 463 are very similar. Most of the equivalent bond distances and angles do not differ significantly from each other and are likewise in good agreement with previously reported values of other *N*-[(ethyl- and -benzyl-2-pyrrolidinyl)methyl]benzamides (Houttemane, Boivin, Nowogrocki, Thomas & Bonte, 1981; Blaton, Peeters, De Ranter, Denisoff & Molle, 1981; Ma, Camerman & Camerman, 1982; Houttemane, Boivin, Thomas, Berthelot & Debaert, 1983; Stensland, Högberg & Rämby,

Table 2. Fractional atomic coordinates of the *S*-configurational forms of FLB 457 and FLB 463 (with *e.s.d.*'s in parentheses)

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

	x	y	z	U_{eq}
FLB 457(HBr)				
C(1)	0.1030 (5)	-0.1878 (17)	-0.0358 (22)	0.042 (5)
C(2)	0.0827 (5)	-0.2838 (17)	-0.1533 (23)	0.046 (5)
C(3)	0.0382 (6)	-0.3320 (18)	-0.1288 (25)	0.056 (6)
Br(3)	0.01098 (8)	-0.4645 (3)	-0.3021 (3)	0.0894 (9)
C(4)	0.0124 (6)	-0.2919 (20)	0.0170 (21)	0.057 (6)
C(5)	0.0322 (6)	-0.1956 (19)	0.1360 (21)	0.050 (6)
O(5)	0.0087 (4)	-0.1383 (15)	0.2787 (16)	0.071 (5)
C(51)	-0.0389 (7)	-0.1732 (29)	0.2906 (35)	0.098 (10)
C(6)	0.0780 (6)	-0.1449 (20)	0.1181 (21)	0.050 (6)
O(6)	0.0956 (4)	-0.0448 (15)	0.2390 (13)	0.056 (4)
C(61)	0.1020 (7)	-0.1060 (25)	0.4106 (22)	0.074 (8)
C(7)	0.1518 (5)	-0.1347 (22)	-0.0729 (23)	0.049 (6)
O(7)	0.1704 (4)	-0.1896 (16)	-0.2036 (18)	0.077 (5)
N(8)	0.1712 (4)	-0.0241 (14)	0.0258 (15)	0.044 (4)
C(9)	0.2174 (5)	0.0363 (20)	-0.0157 (22)	0.046 (5)
C(10)	0.2164 (4)	0.1645 (15)	-0.1475 (21)	0.034 (4)
C(11)	0.2650 (5)	0.2280 (21)	-0.1783 (22)	0.062 (6)
C(12)	0.2710 (6)	0.3505 (23)	-0.0367 (29)	0.072 (8)
C(13)	0.2244 (8)	0.4281 (21)	-0.0442 (25)	0.074 (8)
N(14)	0.1907 (5)	0.2994 (15)	-0.0700 (18)	0.053 (5)
C(15)	0.1489 (6)	0.3537 (22)	-0.1783 (29)	0.076 (8)
C(16)	0.1107 (6)	0.2343 (24)	-0.1903 (28)	0.080 (8)
Br	0.17184 (7)	0.2602 (3)	0.3470 (2)	0.0728 (7)
FLB 463(HSO₃CH₃)				
C(1)	-0.1974 (3)	-0.7645 (5)	-0.2436 (5)	0.036 (1)
C(2)	-0.1502 (3)	-0.8599 (6)	-0.1292 (5)	0.039 (1)
O(2)	-0.1815 (3)	-0.8942 (6)	0.0119 (4)	0.054 (1)
C(3)	-0.0686 (3)	-0.9225 (6)	-0.1621 (6)	0.043 (1)
Br(3)	-0.00513 (4)	-1.05600†	-0.01246 (8)	0.0639 (2)
C(4)	-0.0331 (3)	-0.8938 (7)	-0.3048 (7)	0.048 (2)
C(5)	-0.0773 (3)	-0.7980 (7)	-0.4164 (6)	0.044 (1)
O(5)	-0.0428 (4)	-0.7522 (6)	-0.5551 (6)	0.060 (1)
C(51)	0.0176 (5)	-0.8574 (12)	-0.6184 (8)	0.076 (3)
C(6)	-0.1596 (3)	-0.7337 (6)	-0.3882 (5)	0.036 (1)
O(6)	-0.2024 (2)	-0.6356 (5)	-0.4973 (4)	0.042 (1)
C(61)	-0.2256 (5)	-0.7069 (10)	-0.6469 (7)	0.061 (2)
C(7)	-0.2867 (3)	-0.7044 (6)	-0.2045 (5)	0.039 (1)
O(7)	-0.3159 (3)	-0.7412 (6)	-0.0771 (5)	0.060 (1)
N(8)	-0.3347 (2)	-0.6144 (6)	-0.3080 (5)	0.039 (1)
C(9)	-0.4217 (3)	-0.5535 (8)	-0.2737 (6)	0.042 (1)
C(10)	-0.4206 (3)	-0.4000 (7)	-0.1698 (5)	0.039 (1)
C(11)	-0.5129 (3)	-0.3427 (9)	-0.1346 (7)	0.056 (2)
C(12)	-0.5330 (5)	-0.2106 (14)	-0.2573 (13)	0.092 (4)
C(13)	-0.4495 (5)	-0.1206 (10)	-0.2741 (10)	0.071 (2)
N(14)	-0.3805 (3)	-0.2524 (6)	-0.2526 (5)	0.043 (1)
C(15)	-0.2993 (4)	-0.1817 (8)	-0.1711 (3)	0.056 (2)
C(16)	-0.2234 (4)	-0.2994 (11)	-0.1589 (10)	0.072 (2)
S	-0.6702 (1)	0.2757 (2)	-0.3367 (1)	0.0489 (4)
O(1S)	-0.6494 (4)	0.4360 (9)	-0.4042 (7)	0.084 (2)
O(2S)	-0.6582 (4)	0.1432 (6)	-0.4488 (5)	0.065 (2)
O(3S)	-0.6249 (4)	0.2458 (10)	-0.1897 (5)	0.088 (2)
C(1S)	-0.7840 (5)	0.2825 (16)	-0.3048 (11)	0.091 (3)

† Fixed to define the origin.

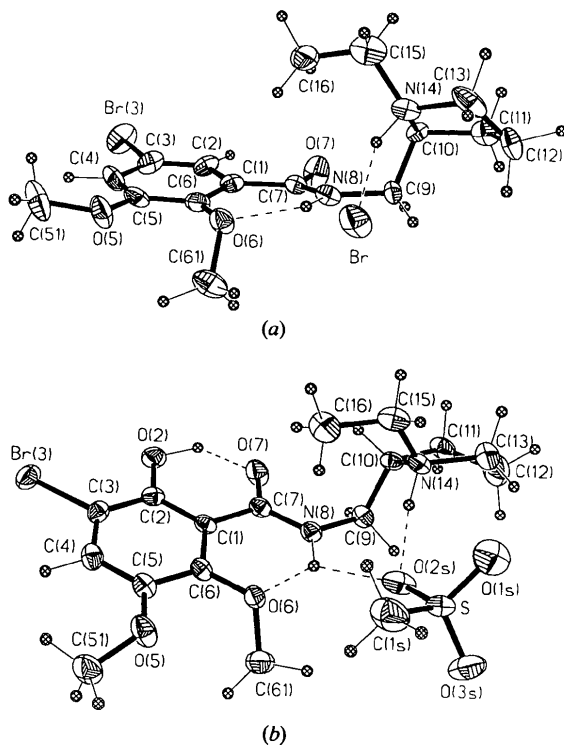


Fig. 1. Perspective drawings of the molecular structures and atomic numbering of (a) FLB 457 hydrobromide and (b) FLB 463 methylsulfonate. Intramolecular hydrogen bonds and anionic contacts are indicated by broken lines. The displacement ellipsoids are drawn for 30% probabilities using ORTEPII (Johnson, 1976).

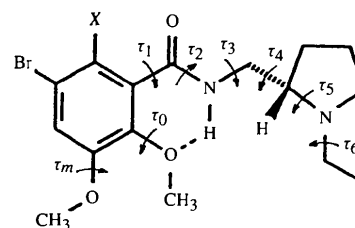
1987; De Winter, Blaton, Peeters & De Ranter, 1990; De Winter, Verlinde, Blaton, Peeters & De Ranter, 1990; Csöregy & Högberg, 1992) and -salicylamides (Wagner, Stensland, Csöregy & de Paulis, 1985; Högberg *et al.*, 1986; Högberg, Norinder, Rämby & Stensland, 1987; Högberg, Ström *et al.*, 1991). The minor conformational differences between the two analogues are best illustrated by a molecular overlay, *cf.* Fig. 2. In this figure the two methoxy C(51) atoms are separated by 0.8 Å and positioned 0.29(3) Å above and 0.399(9) Å below the

Table 3. Intramolecular bond lengths (Å), angles (°) and selected torsion angles (°) of the non-H atoms of the *S*-enantiomeric forms of FLB 457 and FLB 463 (with *e.s.d.*'s in parentheses)

	FLB 457	FLB 463
Br(3)—C(3)	1.92 (2)	1.895 (5)
C(1)—C(2)	1.36 (2)	1.409 (6)
C(1)—C(6)	1.42 (2)	1.417 (7)
C(1)—C(7)	1.51 (2)	1.503 (7)
C(2)—O(2)		1.352 (6)
C(2)—C(3)	1.36 (2)	1.388 (7)
C(3)—C(4)	1.38 (2)	1.382 (8)
C(4)—C(5)	1.36 (2)	1.374 (8)
C(5)—O(5)	1.37 (2)	1.376 (7)
C(5)—C(6)	1.40 (2)	1.394 (7)
O(5)—C(51)	1.41 (2)	1.388 (10)
C(6)—O(6)	1.36 (2)	1.361 (6)
O(6)—C(61)	1.42 (2)	1.427 (7)
C(7)—O(7)	1.23 (2)	1.237 (7)
C(7)—N(8)	1.35 (2)	1.331 (6)
N(8)—C(9)	1.47 (2)	1.462 (6)
C(9)—C(10)	1.50 (2)	1.526 (8)
C(10)—C(11)	1.53 (2)	1.531 (7)
C(10)—N(14)	1.51 (2)	1.533 (7)
C(11)—C(12)	1.53 (3)	1.515 (13)
C(12)—C(13)	1.51 (3)	1.482 (12)
C(13)—N(14)	1.50 (2)	1.501 (9)
N(14)—C(15)	1.54 (2)	1.498 (7)
C(15)—C(16)	1.52 (3)	1.499 (10)
S—O(1S)		1.462 (7)
S—O(2S)		1.456 (5)
S—O(3S)		1.417 (5)
S—C(1S)		1.774 (7)
C(6)—C(1)—C(7)	123 (1)	124.0 (4)
C(2)—C(1)—C(7)	118 (1)	117.4 (4)
C(2)—C(1)—C(6)	119 (1)	118.8 (4)
C(1)—C(2)—C(3)	121 (2)	119.1 (4)
C(1)—C(2)—O(2)		122.4 (5)
O(2)—C(2)—C(3)		118.4 (4)
Br(3)—C(3)—C(2)	119 (1)	120.0 (4)
C(2)—C(3)—C(4)	123 (2)	121.5 (5)
Br(3)—C(3)—C(4)	119 (1)	118.6 (4)
C(3)—C(4)—C(5)	117 (2)	120.2 (5)
C(4)—C(5)—C(6)	122 (2)	120.0 (5)
C(4)—C(5)—O(5)	123 (2)	123.5 (5)
O(5)—C(5)—C(6)	115 (1)	116.4 (5)
C(5)—O(5)—C(51)	117 (1)	117.9 (6)
C(1)—C(6)—C(5)	118 (1)	120.3 (4)
C(5)—C(6)—O(6)	119 (1)	120.0 (4)
C(1)—C(6)—O(6)	122 (1)	119.7 (4)
C(6)—O(6)—C(61)	115 (1)	117.5 (5)
C(1)—C(7)—N(8)	120 (1)	120.0 (4)
C(1)—C(7)—O(7)	116 (1)	119.8 (5)
O(7)—C(7)—N(8)	123 (2)	120.5 (5)
C(7)—N(8)—C(9)	121 (1)	121.5 (4)
N(8)—C(9)—C(10)	113 (1)	114.3 (4)
C(9)—C(10)—N(14)	109 (1)	110.8 (4)
C(9)—C(10)—C(11)	111 (1)	112.5 (4)
C(11)—C(10)—N(14)	103 (1)	104.6 (4)
C(10)—C(11)—C(12)	105 (1)	103.2 (2)
C(11)—C(12)—C(13)	101 (2)	105.9 (7)
C(12)—C(13)—N(14)	104 (2)	103.9 (7)
C(10)—N(14)—C(13)	109 (1)	108.2 (4)
C(13)—N(14)—C(15)	110 (1)	109.9 (5)
C(10)—N(14)—C(15)	115 (1)	115.1 (4)
N(14)—C(15)—C(16)	113 (2)	113.9 (6)
O(3S)—S—C(1S)		107.4 (4)
O(2S)—S—C(1S)		106.7 (4)
O(2S)—S—C(3S)		112.5 (4)
O(1S)—S—C(3S)		113.2 (4)
O(1S)—S—C(2S)		110.8 (3)
τ_1 [C(6)—C(1)—C(7)—N(8)]	-11 (2)	-1.0 (7)
τ_2 [C(1)—C(7)—N(8)—C(9)]	-176 (1)	-179.8 (4)
τ_3 [C(7)—N(8)—C(9)—C(10)]	87 (2)	79.4 (6)

Table 3 (cont.)

τ_4 [N(8)—C(9)—C(10)—N(14)]	64 (2)	64.4 (5)
τ_5 [C(9)—C(10)—N(14)—C(15)]	-123 (1)	-119.0 (5)
τ_6 [C(10)—N(14)—C(15)—C(16)]	64 (2)	63.4 (7)
τ_m [C(6)—C(5)—O(5)—C(51)]	173 (2)	-154.5 (6)
τ_o [C(5)—C(6)—O(6)—C(61)]	68 (2)	62.2 (7)



FLB 457: X = H
FLB 463: X = OH
(I)

aromatic plane of FLB 457 and FLB 463, respectively. All remaining discrepancies between equivalent atomic positions are less than 0.3 Å. Notable from this figure is also the out-of-plane locations of the 6-methoxy groups, displacing the C(61) atoms 1.09 (2) and 1.023 (8) Å from the pertinent benzene planes.

X-ray molecular descriptions

The benzamide moieties in FLB 457 and FLB 463 are essentially planar, stabilized by an intramolecular N(8)H...O(6) hydrogen bond between the amide group and the 6-methoxy O atom. This planar conformation, giving rise to a six-membered pseudo-ring, is observed in most *ortho*-methoxy benzamides in the solid state. Exceptions have so far only been reported for 2,6-dimethoxy-substituted benzamides, having the two methoxy groups in *ortho*-positions with respect to the sidechain (Stensland, Högborg & Råmsby, 1987; Högborg *et al.*, 1986; Durant, Renard, Evrard & Michel, 1985; Blanpain, Melebeck & Durant, 1977) and within the related class of tropamide-benzamides, having the nortropane group in an axial (*endo*)- position (Durant, De

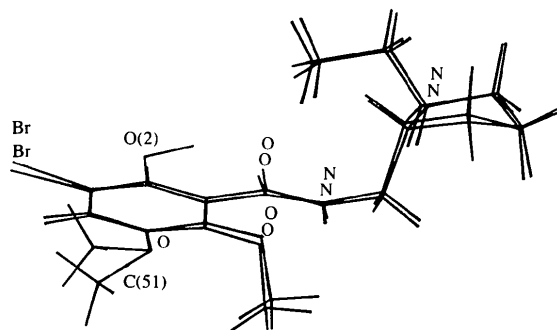


Fig. 2. Molecular superposition illustrating the conformational differences between FLB 457 and FLB 463. The O(2) and C(51) atoms of FLB 463 are labelled. The overlay comparison was made by making a least-squares fit through the atoms C(3), C(5) and N(8) using CHEM-X (Chemical Design Ltd, Oxford, 1989).

Table 4. *The geometry of possible intramolecular hydrogen bonds, salt interactions and intermolecular distances less than 3.5 Å in the crystal structures of FLB 457(HBr) and FLB 463(HSO₃CH₃) (with e.s.d.'s in parentheses)*

D—H...A	D...A (Å)	D—H* (Å)	H...A (Å)	<D—H...A (°)
FLB 457(HBr)				
N(8)—H(8)...O(6)	2.72 (2)	1.08	1.91	130
N(14)—H(14)...Br	3.23 (1)	1.08	2.23	153
N(8)—H(8)...Br	3.48 (1)	1.08	2.69	130
FLB 463(HSO₃CH₃)				
O(2)—H(2)...O(7)	2.476 (6)	1.08†	1.530	142.2
N(8)—H(8)...O(6)	2.668 (6)	1.08	1.837	130.5
N(14)—H(14)...O(2S ⁱ)	2.783 (6)	1.00†	1.793	172.1
N(8)—H(8)...O(2S ⁱ)	2.939 (6)	1.08	2.207	123.0

Short intra- and intermolecular contacts

FLB 457(HBr)		FLB 463(HSO₃CH₃)	
Br(3)...C(4 ⁱⁱ)	3.36 (2)	O(6)...O(2S ⁱ)	3.116 (6)
Br(3)...C(5 ⁱⁱ)	3.47 (2)	C(9)...O(2S ⁱ)	3.159 (7)
O(5)...C(4 ⁱⁱⁱ)	3.46 (2)	C(61)...O(2S ⁱ)	3.465 (9)
O(7)...C(12 ^{iv})	3.35 (2)	C(13)...O(1S ⁱ)	3.246 (11)
N(8)...C(11 ^v)	3.41 (2)	N(14)...O(1S ⁱ)	3.359 (8)
C(9)...C(11 ^v)	3.48 (2)	C(10)...O(3S ^{vi})	3.323 (7)
		C(11)...O(3S ^{vi})	3.452 (8)
		C(15)...O(3S ^{vi})	3.406 (8)
		C(2)...C(15 ^{vii})	3.462 (8)
		O(2)...C(15 ^{vii})	3.278 (8)
		O(2)...C(61 ^{viii})	3.387 (8)
		O(5)...C(4 ^{ix})	3.367 (8)

Symmetry codes: (i) $-x-1, y-\frac{1}{2}, -z-1$; (ii) $-x, y-\frac{1}{2}, -z-\frac{1}{2}$; (iii) $-x, y+\frac{1}{2}, \frac{1}{2}-z$; (iv) $\frac{1}{2}-x, -y, z-\frac{1}{2}$; (v) $\frac{1}{2}-x, -y, z+\frac{1}{2}$; (vi) $-x-1, y-\frac{1}{2}, -z$; (vii) $x, y-1, z$; (viii) $x, y, z+1$; (ix) $-x, y+\frac{1}{2}, -z-1$.

*Unmarked H atoms are geometrically positioned 1.08 Å from pivotal non-H atoms.

† H-atom positions are located in a late electron-density map but not refined (*cf.* text).

Beys, Collin & Evrard, 1986). In FLB 463 a second intramolecular O(2)H...O(7) hydrogen bond between the 2-hydroxyl group and the carbonyl oxygen further stabilizes the benzamide. The strengthening of the hydrogen bonding in FLB 463 is shown by the smaller torsion angle τ_1 [C(6)—C(1)—C(7)—N(8)]: $-1(1)^\circ$ compared with $-11(2)^\circ$ for FLB 457. Detailed values of the intramolecular hydrogen-bonding schemes are listed in Table 4.

One of the most important conformational features within the substituted benzamides concerns the orientation of the methoxy groups. The 6-methoxy group can be in a coplanar or out-of-plane orientation with respect to the benzene ring plane. In the solid state the planar orientation seems to be normal if the 5-position is unsubstituted, while the 6-methoxy group is forced out of the aromatic plane if the 5-substituent is a non-H atom. In full agreement with other classes of 5,6-dimethoxybenzamides investigated by X-ray methods, the out-of-plane displacement of the 6-methoxy C atom from the benzene ring is most probably a consequence of steric hindrance by the neighbouring 5-substituent (Wagner, Stensland, Csöregy & de Paulis, 1985; Högberg, Norinder, Råmsby & Stensland, 1987; Durant, De Beys, Collin & Evrard,

1986; Durant, Renard & Evrard, 1984; Collin, Durant & Evrard, 1986; Collin, Evrard & Durant, 1986; Collin, Norberg, Evrard & Durant, 1986; Collin, Patiny, Evrard & Durant, 1987; Collin, Evrard & Durant, 1987) forcing the lone pair of the 6-methoxy oxygen into a more coplanar orientation with the amide group (Collin *et al.*, 1989). An out-of-plane orientation has been calculated to be accompanied by a higher electron density on the oxygen (Jardon *et al.*, 1984), facilitating the hydrogen bonding (Högberg, Bengtsson *et al.*, 1990).

The amide sidechains of FLB 457 and FLB 463 both show a near (+)perpendicular-*gauche* trend as indicated by the torsion angles τ_3 [C(7)—N(8)—C(9)—C(10)]: $87(2), 79.4(6)^\circ$ and τ_4 [N(8)—C(9)—C(10)—N(14)]: $64(2), 64.4(5)^\circ$, respectively (*cf.* Table 3). The conformations of the pyrrolidinyl rings are near-envelope, with the mirror symmetry planes passing through the out-of-plane C(12) atom and bisecting the C(10)—N(14) bond. The phase angles are $-114(2)$ and $-114.3(8)^\circ$ for FLB 457 and FLB 463, and the corresponding total puckering amplitudes are $0.42(2)$ and $0.362(9)$ Å, respectively (Cremer & Pople, 1975).

Intermolecular hydrogen bonding and crystal packing

The solid-state conformations of the two analogues are remarkably similar, despite the variety in their anions and crystal packing, thus indicating that the protonated molecular conformation is well defined. In FLB 457 the bromide anion participates in two weak interactions: $3.23(1)$ Å to the protonated N(14) atom and $3.48(1)$ Å to the amide N(8) atom. Adopted angles between the cationic molecule and the anion are O(6)...N(8)...Br $69(2)^\circ$ and N(8)...Br...N(14) $53(2)^\circ$. A more complex and rigid hydrogen-bonding scheme is found in FLB 463. The O(2S) atom of the methylsulfonate anion participates as a proton acceptor in two hydrogen bonds: $2.783(6)$ Å to the protonated pyrrolidine N(14) atom and $2.939(6)$ Å to the protonated amide N(8) atom. As a consequence of this binding arrangement, the intramolecular 6-methoxy hydrogen-bonded N(8) atom participates in a bifurcated hydrogen-bonding scheme. The close similarity of the angles O(6)...N(8)...O(2Sⁱ) $67(1)^\circ$ and N(8)...O(2Sⁱ)...N(14) $64(1)^\circ$ [(i) $= -1-x, y-\frac{1}{2}, -1-z$] for FLB 463 compared with those of FLB 457 indicates that the bonding direction to the two different anions is highly specific. Diagrams illustrating the molecular packing arrangement of FLB 457 and FLB 463 are given in Fig. 3. In both crystals the packing of the discrete molecules is, except for salt bridging, mainly dominated by normal or weak van der Waals forces. Possible hydrogen bonds and intermolecular distances less than 3.5 Å are given in Table 4.

Molecular mechanics calculations

The results of the X-ray crystallographic analysis were complemented by molecular mechanics calculations

MM2(87) (Allinger & Yuh, 1987) in order to evaluate the possible and energetically most favourable conformations of the mobile 6-methoxy groups. Based on the X-ray coordinates, dihedral driver calculations were performed to illustrate the relative steric energies as a function of the torsion angle $\tau[\text{C}(5)–\text{C}(6)–\text{O}(6)–\text{C}(61)]$. The torsion angle was

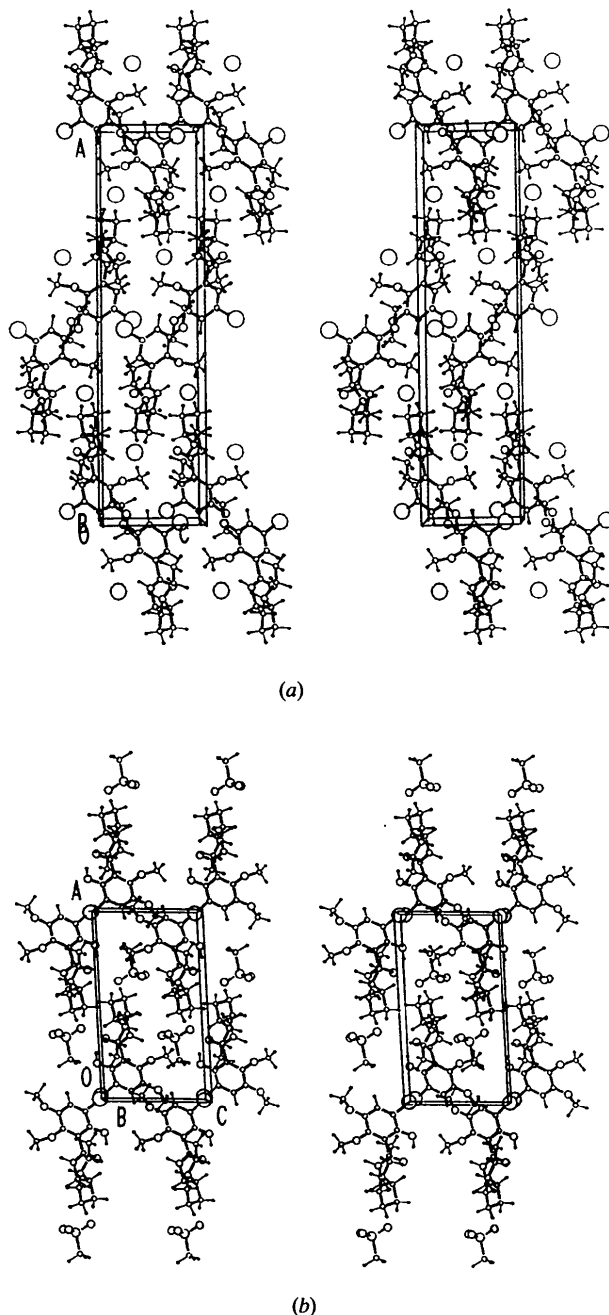


Fig. 3. Stereopacking diagrams of the crystal structures of (a) FLB 457 and (b) FLB 463. In both packings the *c* axis is horizontal, the *a* axis is vertical, the *b* axis is directed up from the plane of the paper and the origin is at the left corner [*PLUTO* (Motherwell & Clegg, 1978)].

varied in steps of 20° over the range -180 – 180° . The relative energies less than 17 kJ mol^{-1} are presented in Fig. 4. The diagram shows energy minima at approximately -90 and 90° for both analogues, indicating an almost perpendicular preference of the 6-methoxy groups. In the two structures examined the corresponding torsion angles are $68(2)$ and $62.2(7)^\circ$ for FLB 457 and FLB 463, respectively. As seen from Fig. 4, the energy cost for driving the torsion angle into the aromatic plane is *ca* 11.7 kJ mol^{-1} . The out-of-plane preference of the 6-methoxy group is also observed in NMR spectroscopy studies in solution (Högberg, de Paulis *et al.*, 1990; Högberg, Bengtsson *et al.*, 1990).

Comparative conformational analysis

In Table 5 some selected X-ray conformational parameters of published *N*-[(ethyl-2-pyrrolidinyl)methyl]- and *N*-[(benzyl-2-pyrrolidinyl)methyl]benzamides have been gathered for comparison (Cambridge Crystallographic Database, August 1994). These two classes of benzamides have reversed stereochemical requirements for the dopamine- D_2 receptors (Högberg, 1991, and references therein; Högberg, Ström *et al.*, 1991). Thus, the *N*-ethyl compounds have the activity confined to the *S*-enantiomer and the *N*-benzyl compounds to the *R*-enantiomer.

In attempts to map the pharmacophoric requirements for dopamine activity, distances describing the position of the N atom in relation to the aromatic ring plane parameters are frequently used (*cf.* Table 5). For FLB 457 and FLB 463 the pyrrolidine N(14) atom is located $2.66(1)$ and $2.225(5) \text{ \AA}$ from the benzene plane (*cf.* Fig. 2), while the distances from the N(14) atom to the centre of the aromatic ring are $6.10(2)$ and $6.21(1) \text{ \AA}$, respectively. The dihedral angle between the pyrrolidine and benzene least-squares planes is $34.0(6)^\circ$ for FLB 457 and $38.0(2)^\circ$ for FLB 463.

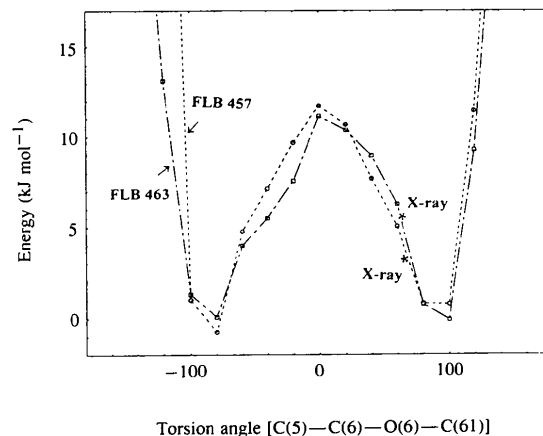


Fig. 4. Rotational barriers of the 6-methoxy group in FLB 457 and FLB 463. The relative steric energies were calculated by MM2(87) force-field, by changing the torsion angle: $\tau[\text{C}(5)–\text{C}(6)–\text{O}(6)–\text{C}(61)]$ in 20° steps. The X-ray torsional angles are indicated by stars.

Table 5. Selected topographical X-ray features of *N*-(ethyl-2-pyrrolidinyl)methyl and *N*-(benzyl-2-pyrrolidinyl)-methyl-substituted benzamides

Compound	Torsion angles (°)*				Distances (Å)†		(°)‡	Reference
	τ_1	τ_2	τ_3	τ_4	Ar—N	N-plane		
<i>S</i> -Eticlopride§ (HCl)	-5	-179	93	60	6.2	+2.62	37	(1)
(±)-Sulpiride¶ (HCl)	-5	178	84	59	6.1	+2.33	44	(2)
<i>R</i> -FLB 481§**	1	-177	-83	-66	6.3	-2.25	37/18††	(3)
<i>R</i> -NCQ 115¶** (HCl·xH ₂ O)	14	176	-90	-72	6.3	-2.85	37/23††	(4)
<i>S</i> -FLA 797§ (base)	-4	177	-160	-51	6.0	+0.47	90	(5)
(±)-Amisulpiride¶ (base)	-29	180	-160	-65	6.4	+2.24	84	(6)
(±)-Sulpiride¶ (base)	15	179	-124	171	7.4	-0.84	28	(7)
<i>S</i> -Sulpiride¶ (base) (A)‡‡	-8	-171	-111	171	8.0	-1.06	13	(8)
(B)	14	-175	114	166	7.5	+0.73	56	
<i>S</i> -Raclopride§ (tartrate)	-7	-173	-78	176	7.3	-0.81	42	(9)
<i>S</i> -Remoxipride (HCl·xH ₂ O)	-73	-176	116	-178	7.3	+2.75	27	(5)
<i>S</i> -Remoxipride (base) (A)‡‡	-95	173	-90	-169	7.2	+0.89	26	(10)
(B)	96	-174	109	-169	7.1	-1.10	17	

(1) Wagner, Stensland, Csoregh & de Paulis (1985); (2) Blaton, Peeters, De Ranter, Denisoff & Molle (1981); (3) Hogberg, Strom *et al.* (1991); (4) Csoregh & Hogberg (1992); (5) Hogberg, Ramsby *et al.* (1986); (6) De Winter, Verlinde, Blaton, Peeters & De Ranter (1990); (7) Houttemane, Boivin, Nowogrocki, Thomas & Bonte (1981); (8) Houttemane, Boivin, Thomas, Berthelot & Debaert (1983); (9) Hogberg, Norinder, Ramsby & Stensland (1987); (10) Stensland, Hogberg & Ramsby (1987).

* For definition see Table 3. Positive sign for clockwise rotation. Torsion angles of racemic structures are those of the *S*-configurational form.

† Distances of the pyrrolidinyl N to the centre of the benzene ring (Ar—N) and to the benzene plane (N-plane). Positive sign *above* and negative sign *below* benzene plane, *cf.* Fig. 2.

‡ Dihedral angle between the benzene and pyrrolidine planes.

§ Salicylamides, *i.e.* 2-hydroxy analogues.

¶ Benzamides, *i.e.* non-salicylamide analogues.

** *N*-[(Benzyl-2-pyrrolidinyl)methyl]benzamide.

†† Dihedral angle between benzene/pyrrolidine and benzene/benzyl planes.

‡‡ Two independent molecules (A) and (B) within the asymmetric unit.

The solid-state conformations of FLB 457(HBr) and FLB 463(HSO₃CH₃) are very similar and closely related to the conformations previously found in the hydrochlorides of *S*-eticlopride (Wagner, Stensland, Csoregh & de Paulis, 1985) and the *S*-isomer of racemic sulpiride (Blaton *et al.*, 1981). The conformational resemblance between the two analogues and the mirror-image related hydrochlorides of *R*-FLB 481 (Hogberg, Strom *et al.*, 1991) and *R*-NCQ 115 (Csoregh & Hogberg, 1992) is also readily observed. It is apparent that the sidechain conformations of the free bases or salts of weak acids (tartrate) are more extended than the folded and uniform conformation found in salts of strong acids (hydrochloride, hydrobromide and methylsulfonate). Although a close comparison of the sidechain conformations reveals similarities in the torsion angles between the free bases of FLA 797 (Hogberg *et al.*, 1986) and racemic amisulpiride (De Winter, Blaton, Peeters & De Ranter, 1990), a comparison of their *N*-plane distances [0.47 (1) and 2.24 (1) , respectively] illustrates how different they are. The unusually large τ_1 angle in amisulpiride is influenced by crystal-packing effects of the two 3-SO₂CH₂CH₃ and 4-NH₂ substituents.

Moreover, a comparison between the different base forms of *S*-sulpiride (Houttemane, Boivin, Thomas, Berthelot & Debaert, 1983) and racemic sulpiride (Houttemane, Boivin, Nowogrocki, Thomas & Bonte, 1981) reveals an almost identical conformation of their sidechains. The two crystallographically independent molecules of the *S*-enantiomer [$\tau_3 = 114(2)^\circ$ and

$-111(2)^\circ$] are related like the mirror-image conformers [$\tau_3 = \pm 124(1)^\circ$] of the racemic mixture. However, the conformers of the base forms and the hydrochloride salt of sulpiride differ substantially. It is also worth noting that $\tau_3 = -78(1)^\circ$ in *S*-raclopride tartrate (Hogberg, Norinder, Ramsby & Stensland, 1987) has the opposite sign of $\tau_3 = 93(1)^\circ$ in *S*-eticlopride hydrochloride.

The hydrochloride and free base forms of *S*-remoxipride (Hogberg *et al.*, 1986; Stensland, Hogberg & Ramsby, 1987) have been included in Table 5. Remoxipride, the prototype of the 2,6-dimethoxy-*N*-[(ethyl-2-pyrrolidinyl)methyl]benzamide series, has the carboxamide moiety oriented almost perpendicular (τ_1) to the benzene plane as a consequence of the two methoxy-substituents flanking the sidechain. There are two independent molecules in the asymmetric unit of the free base, with their sidechains almost perfectly mirror-image related to each other. However, none of these co-crystallized conformations are consistent with that of the hydrochloride salt. Despite a close numerical agreement of the torsion angle values, the combination of the τ_1 and τ_3 signs are different, and hence the conformations of the sidechains of the three conformers are quite different. The principal conformational difference in the τ_3 angle as observed in the hydrochloride and the free base is worth noting.

Results from the crystal structure determinations, listed in Table 5, show a small but significant difference of the benzamide planarity (τ_1) between the salicylamides and non-salicylamides. A low value of the τ_1 -

angle indicates that the benzamide part of the salicylamides is more flattened as a consequence of the extra intramolecular hydroxyl-carbonyl (OH...O) hydrogen bond.

An investigation of the intramolecular amide *ortho*-methoxy (NH...OCH₃) hydrogen-bond distances of the (2-pyrrolidinylmethyl)benzamides (included in the supplementary material) shows no significant differences between compounds having a coplanar or perpendicular methoxy-group orientation. Thus, the solid-state conformations lend no support to hydrogen-bond enforcement by out-of-plane orientations of the *ortho*-methoxy groups. Neither is any significant influence on the neighbouring *meta*-substituent reflected in the strength of the amide *ortho*-methoxy hydrogen bond in the solid-state structures. These findings are in agreement with NMR data on (2-pyrrolidinylmethyl)benzamides (Högborg, de Paulis *et al.*, 1990; Högborg, Bengtsson *et al.*, 1990), but in contrast to the studies on the closely related tropapride analogues (Collin *et al.*, 1989).

Concluding remarks

The sidechain conformations of (2-pyrrolidinylmethyl)benzamides in the solid state seem to be a direct consequence of the protonation. Generally, the conformations of salts of strong acids are folded and quite rigid, while more extended and flexible conformations are found in free bases or salts of weak acids. A comparison of the (2-pyrrolidinylmethyl)benzamides also reveals that the solid-state conformations of the amide sidechains may adopt both positive and negative τ_3 -values. The crystal structures provide useful information on the intramolecular hydrogen bonding that influences the benzamide moiety. Furthermore, no differences in the NH...OCH₃ hydrogen-bond distances are observed among benzamides with widely different *meta*-substituents (H, Cl, OCH₃).

References

- ALLINGER, N. L. & YUH, Y. H. (1987). *MM2(87)*, QCPE No. 400.
- BIJVOET, J. M., PEERDEMAN, A. F. & VAN BOMMEL, A. J. (1951). *Nature (London)*, **168**, 271–272.
- BLANPAIN, P., MELEBECK, M. & DURANT, F. (1977). *Acta Cryst.* **B33**, 580–582.
- BLATON, N. M., PEETERS, O. M., DE RANter, C. J., DENISOFF, O. & MOLLE, L. (1981). *Cryst. Struct. Commun.* **10**, 833–838.
- COLLIN, S., DURANT, F. & EVRARD, G. (1986). *Acta Cryst.* **C42**, 199–201.
- COLLIN, S., EL TAYAR, N., VAN DE WATERBEEMD, H., MOUREAU, F., VERCAUTEREN, D. P., DURANT, F., LANGLOIS, M. & TESTA, B. (1989). *Eur. J. Med. Chem.* **24**, 163–169.
- COLLIN, S., EVRARD, G. & DURANT, F. (1986). *J. Cryst. Spectrosc. Res.* **16**, 255–269.
- COLLIN, S., EVRARD, G. & DURANT, F. (1987). *Acta Cryst.* **C43**, 697–699.
- COLLIN, S., NORBERG, B., EVRARD, G. & DURANT, F. (1986). *Bull. Soc. Chim. Belg.* **95**, 213–214.
- COLLIN, S., PATINY, A., EVRARD, G. & DURANT, F. (1987). *Bull. Soc. Chim. Belg.* **96**, 337–339.
- CREMER, D. & POPLÉ, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1367.
- CROMER, D. T. & LIBERMAN, D. (1970). *J. Chem. Phys.* **53**, 1891–1898.
- CSÖREGH, I. & HÖGBERG, T. (1992). *Acta Pharm. Nord.* **4(1)**, 1–4.
- DE WINTER, H. L., BLATON, N. M., PEETERS, O. M. & DE RANter, C. J. (1990). *Acta Cryst.* **C46**, 667–669.
- DE WINTER, H. L., VERLINDE, C. L., BLATON, N. M., PETERS, O. M. & DE RANter, C. J. (1990). *Acta Cryst.* **C46**, 313–317.
- DURANT, F., DE BEYS, V., COLLIN, S. & EVRARD, G. (1986). *Bull. Soc. Chim. Fr.* **4**, 497–503.
- DURANT, F., RENARD, P. & EVRARD, G. (1984). *Bull. Soc. Chim. Belg.* **93**, 419–420.
- DURANT, F., RENARD, P., EVRARD, G. & MICHEL, A. (1985). *Acta Cryst.* **C41**, 1361–1362.
- HALL, H., HÖGBERG, T., HALLDIN, C., KÖHLER, C., STRÖM, P., ROSS, S. B., LARSSON, S. A. & FARDE, L. (1991). *Psychopharmacology*, **103**, 6–18.
- HALLDIN, C., HÖGBERG, T., HALL, H., KARLSSON, P., HAGBERG, C.-E., STRÖM, P. & FARDE, L. (1993). *J. Label. Compd. Radiopharmacol.* **32**, 282–283.
- HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.
- HÖGBERG, T. (1991). *Drugs Future*, **16**, 333–357.
- HÖGBERG, T. (1993). *Drug Des. Discov.* **9**, 333–350.
- HÖGBERG, T., BENGTSSON, S., DE PAULIS, T., JOHANSSON, L., STRÖM, P., HALL, H. & ÖGREN, S.-O. (1990). *J. Med. Chem.* **33**, 1155–1166.
- HÖGBERG, T., MOHELL, N. & STRÖM, P. (1992). *Acta Pharm. Nord.* **4**, 297–300.
- HÖGBERG, T., NORINDER, U., RÄMSBY, S. & STENSLAND, B. (1987). *J. Pharm. Pharmacol.* **39**, 787–796.
- HÖGBERG, T., DE PAULIS, T., JOHANSSON, L., KUMAR, Y., HALL, H. & ÖGREN, S.-O. (1990). *J. Med. Chem.* **33**, 2305–2309.
- HÖGBERG, T., RÄMSBY, S., ÖGREN, S.-O. & NORINDER, U. (1987). *Acta Pharm. Suec.* **24**, 289–328.
- HÖGBERG, T., RÄMSBY, S., DE PAULIS, T., STENSLAND, B., CSÖREGH, I. & WÄGNER, A. (1986). *Mol. Pharmacol.* **30**, 345–351.
- HÖGBERG, T., STRÖM, P., HALL, H., KÖHLER, C., HALLDIN, C. & FARDE, L. (1990). *Acta Pharm. Nord.* **2**, 53–60.
- HÖGBERG, T., STRÖM, P., HALL, H. & ÖGREN, S.-O. (1990). *Helv. Chim. Acta*, **73**, 417–425.
- HÖGBERG, T., STRÖM, P., DE PAULIS, T., STENSLAND, B., CSÖREGH, I., LUNDIN, K., HALL, H. & ÖGREN, S.-O. (1991). *J. Med. Chem.* **34**, 948–955.
- HOUTTEMANE, C., BOIVIN, J. C., NOWOGROCKI, G., THOMAS, D. J. & BONTE, J. P. (1981). *Acta Cryst.* **B37**, 981–984.
- HOUTTEMANE, C., BOIVIN, J. C., THOMAS, D. J., BERTHELOT, P. & DEBAERT, M. (1983). *Acta Cryst.* **C39**, 1285–1287.
- JARDON, P. W., VICKERY, E. H., PAHLER, L. F., POURAHMADY, N., MAINS, G. J. & EISENBRAUN, E. J. (1984). *J. Org. Chem.* **49**, 2130–2135.
- JOHANSSON, K.-E., PALM, T. & WERNER, P.-E. (1980). *J. Phys. E. Sci. Instrum.* **13**, 1289–1291.
- JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- LOC'H, C., HALLDIN, C., BOTTLAENDER, M., SWAHN, C. G., MORESCO, R. M., MAZIERE, M., FARDE, L. & MAZIERE, B. (1994). *J. Label. Compd. Radiopharmacol.* **35**, 437–438.
- MA, Y. Y., CAMERMAN, N. & CAMERMAN, A. (1982). *Acta Cryst.* **B38**, 2861–2865.
- MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERQ, J.-P. & WOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.
- MALMROS, G. & WERNER, P.-E. (1973). *Acta Chem. Scand.* **27**, 493–502.
- MOTHERWELL, W. D. S. & CLEGG, W. (1978). *PLUTO. Program for Plotting Molecular and Crystal Structures*. Univ. of Cambridge, England.
- NARDELLI, M. (1983). *Comput. Chem.* **7**, 95–98.
- NORINDER, U. & HÖGBERG, T. (1989). *Acta Pharm. Nord.* **2**, 75–88.
- NORINDER, U. & HÖGBERG, T. (1992). *Acta Pharm. Nord.* **4**, 73–78.
- ROGERS, D. (1981). *Acta Cryst.* **A37**, 734–741.

SHELDRIK, G. M. (1976). *SHELX76. Program for Crystal Structure Determination*. Univ. of Cambridge, England.
 STENSLAND, B., HÖGBERG, T. & RÄMSBY, S. (1987). *Acta Cryst.* C43, 2393–2398.

TSAI, R.-S., CARRUPT, P.-A., TESTA, B., GAILLARD, P., EL TAYAR, N. & HÖGBERG, T. (1993). *J. Med. Chem.* 36, 196–204.
 WÄGNER, A., STENSLAND, B., CSÖREGH, I. & DE PAULIS, T. (1985). *Acta Pharm. Suec.* 22(2), 101–110.

Acta Cryst. (1995). B51, 856–863

Structure, Solid-State Photochemistry and Reactivity in Asymmetric Synthesis of 3,4-Bis(diphenylmethylene)-*N*-methylsuccinimide

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(Received 1 August 1994; accepted 13 December 1994)

Abstract

The synthesis and structural features of 3,4-dihydro-3,4-bis(diphenylmethylene)-*N*-methylsuccinimide [3,4-bis(diphenylmethylene)-1-methyl-2,5-pyrrolidinedione (*6b*), C₃₁H₂₃NO₂, *M_r* = 441.53] are described. (*6b*) crystallizes at room temperature in three polymorphic forms: (A) monoclinic, *P*2₁, *a* = 11.640 (3), *b* = 9.257 (2), *c* = 12.103 (4) Å, β = 114.83 (1)°, *V* = 1183.6 (6) Å³, *Z* = 2, *F*(000) = 464, *D_x* = 1.239 g cm⁻³, μ = 0.72 cm⁻¹, *R_F* = 0.077 for 1560 observations [*I* > 3σ(*I*)]; (B) orthorhombic, *Pbcn*, *a* = 9.964 (1), *b* = 20.181 (3), *c* = 11.622 (3) Å, *V* = 2337.0 (7) Å³, *Z* = 4, *F*(000) = 928, *D_x* = 1.255 g cm⁻³, μ = 0.73 cm⁻¹, *R_F* = 0.044 for 1466 observations [*I* > 3σ(*I*)]; (C) monoclinic, *P*2₁/*n*, *a* = 9.485 (3), *b* = 11.014 (2), *c* = 22.945 (3) Å, β = 98.62 (2)°, *V* = 2369.9 (9) Å³, *Z* = 4, *F*(000) = 928, *D_x* = 1.238 g cm⁻³, μ = 0.72 cm⁻¹, *R_F* = 0.060 for 2200 observations [*I* > 3σ(*I*)]. The (*6b*) molecule adopts a helical (prochiral) configuration with approximate *C*₂ symmetry in order to accommodate the steric hindrance between the aryl substituents; the conformation is very similar in the three polymorphs. Transformations between the different polymorphs can be induced easily, and it is possible to vary the amount of chiral polymorph in the crystallization mixture by seeding techniques and the use of acidic additives. Crystalline (*6b*) undergoes a photocyclization reaction to yield *N*-methyl-1,1,4-triphenyl-1,2-dihydronaphthalene-2,3-dicarboximide (*8b*). In the observed conformation of (*6b*), the intramolecular distances between the unsaturated carbon sites which join during the photochemical reaction are within 3.27–3.38 Å. The solid-state photoreaction of the chiral

polymorph *A* gives an optically active molecular product (*8b*) of 64% enantiomeric excess (e.e.), and represents a chiral enrichment process assisted by the crystal medium. The corresponding photochemical reactions with the racemic polymorphs *B* and *C* yield racemic (*8b*).

Introduction

Several successful examples of the so-called 'absolute' asymmetric synthesis (Green, Lahav & Rabinovich, 1979; Vaida, Popovitz-Biro, Leiserowitz & Lahav, 1990) by solid-state photoirradiation, applied to chiral crystals of achiral compounds, have accumulated in recent years (e.g. Sakamoto *et al.*, 1993; Roughton, Muneer & Demuth, 1993; Sekine, Hori, Ohashi, Yagi & Toda, 1989; Kaupp & Haak, 1993, and references therein). Molecules, which in solution equilibrate rapidly between inverted configurations, adopt in a chiral crystalline environment (even in the absence of external chiral inducing agents) a chiral arrangement, and this chirality can be subsequently frozen by photoreaction to give a molecularly chiral product. A suitable example is provided by the *N,N*-dialkylarylglyoxamide system (1). Crystalline solids of selected derivatives of (1) yield, upon irradiation, the corresponding derivatives of optically active β-lactams (2) of very high optical purity in almost quantitative yields (Scheme 1; Toda & Miyamoto, 1993; Toda, Soda & Yagi, 1987). The photoreaction and ring closure involves the two carbonyl groups of (1). The formation of chiral crystals of (1) was found to be very sensitive to the nature of the substituent, and could be obtained only for the glyoxamide which is substituted with an isopropyl group on the N atom, and for selected substitutions on the aryl ring (the *meta*-substituted compounds revealed a higher propensity to

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