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1-(2-Fluoro-2-phenylethyl)piperidine Hydrochloride, $C_{13}H_{18}FN.HCl$: Enantiomer and Racemic Solid-Solution Structures

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Abstract. $M_r = 243{\cdot}59$, enantiomer: orthorhombic, $P2_12_12_1$, $a = 7{\cdot}171$ (6), $b = 8{\cdot}020$ (6), $c = 22{\cdot}73$ (1) Å, $V = 1307{\cdot}23$ Å^3, $Z = 4$, $D_x = 1{\cdot}238$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54184$ Å, $\mu = 24{\cdot}9$ cm^{-1}, $F(000) = 524$, room temperature, $R = 0{\cdot}055$ for 716 reflexions; solid solution: orthorhombic, *Pnma*, $a = 7{\cdot}190$ (6), $b = 8{\cdot}022$ (6), $c = 22{\cdot}81$ (1) Å, $V = 1315{\cdot}6$ Å^3, $Z = 4$, $D_x = 1{\cdot}231$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54184$ Å, $\mu = 24{\cdot}9$ cm^{-1}, $F(000) = 524$, room temperature, $R = 0{\cdot}092$ for 1116 reflexions (block molecular refinement). The title compound is an optically active compound which crystallizes as a racemic solid solution. Asymmetric synthesis has been realized from chiral mandelic acid using Yarovenko's fluorinating reagent. The molecular model, obtained from the enantiomer crystal structure, is similar to those of (phenylethyl)amines already known.

Introduction. This compound (Guedj, Nabet & Wade, 1972, 1973) is one of a series of fluorinated molecules analogous to (phenylethyl)amine, which have a pharmaceutical interest as neuroleptics, anaesthetics and anti-inflammatory agents.

We started working on crystals from a racemic-mixture crystallization. Extinctions led to two possible space groups: $Pna2_1$, molecules in general position: racemate structure; *Pnma*, molecule in special position (*m* or $\bar{1}$): solid solution. The first case is the most frequent so we started with this hypothesis. Statistical methods worked but the first refinements did not give a good molecular model. This could have been because the crystal or data quality was not good enough. Actually, it is not a racemate but a solid solution (statistics confirmed the centrosymmetry): on a given site there is a probability 1/2 for a left molecule, 1/2 for a right one (Chion, Lajzérowicz, Collet & Jacques, 1976; Chion, Lajzérowicz, Bordeaux, Collet & Jacques, 1978). In order to solve a solid-solution structure it is necessary to have a molecular model so we had to synthetize the enantiomer to solve its structure and obtain the model.

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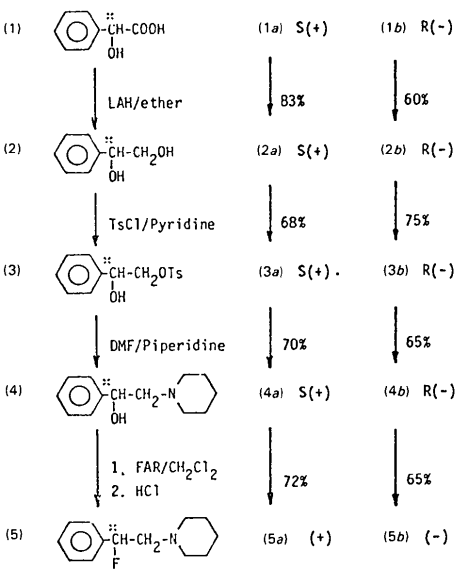
Experimental. Asymmetric synthesis of the title compound has been realized from chiral mandelic acid, using Yarovenko's fluorinating amine reagent (FAR) according to the method preconized by Cavalleri & Bellasio (1970).



(LAH = lithium aluminium hydride, DMF = *N*,*N*-dimethylformamide.) Although the FAR mechanism has not yet been elucidated, it seems that the formation of (5*a*) and (5*b*) takes place with stereospecificity (S_N2 or S_N1). Moreover, FAR is known to react generally with retention of configuration (Cavalleri & Bellasio, 1970; Knox, Velarde, Berger, Cuadriello & Cross, 1964; Ayer, 1962; Mousseron-Canet & Borgna, 1969).

DTA: Melting points: enantiomer 478 K; solid solution 480 K. The diagram is Roozeboom type II (Jacques, Collet & Wilen, 1981). Purity was confirmed by micropolarimetry and ^{19}F NMR.

Micropolarimetry: white crystals (5*a*) $[\alpha]_D^{20°C} = +33{\cdot}70°$ ($c = 7{\cdot}53$ g dm^{-3}, H_2O); (5*b*) $[\alpha]_D^{20°C} = -34{\cdot}6°$ ($c = 6{\cdot}73$ g dm^{-3}, H_2O).

NMR: We formed diastereoisomeric salts of (5) base with a chiral acid. The salt is observed in ^{19}F NMR in $CDCl_3$: by heteronuclear irradiation of protons we obtain a flourine signal [reduced to a singlet (Fig. 1)]. (*a*) base (5*a*) + (5*b*) racemic/acid (1*a*) (Fig. 1*a*): 2 singlets corresponding to the two salts in equal percentage with chemical displacement of $\delta/C_6F_6 = -13{\cdot}65$ and $-14{\cdot}2$ p.p.m.; (*b*) base (5*b*) (−)/acid (1*a*): one signal (Fig. 1*b*) $\delta/C_6F_6 = -13{\cdot}63$ p.p.m.; (*c*) check: if we assume that (5*b*) (−) enantiomeric purity is 100%, an equal mixture of (5*b*) (−)/(1*a*) and (5*a*) + (5*b*) racemate/(1*a*) leads to a proportion 75/25 between the two diastereoisomers (Fig. 1*c*).

X-ray measurements made on the Siemens four-circle diffractometer of the Institut Laue–Langevin, ω–2θ scan, crystals cubes of 0·2 mm side, no extinction correction, scattering factors from *International Tables for X-ray Crystallography* (1974) (Cl^- used), *F* magnitudes in least-squares refinement; enantiomer: $\sin\theta/\lambda < 0{\cdot}59$ Å^{-1} ($h < 7$, $k < 8$, $l < 23$), 14 reflexions used for lattice-parameter calculation, 3 standard reflexions, 3% intensity variation, 1010 reflexions measured, $R_w = 0{\cdot}058$ (unit weights) for 716 reflexions [$I > 2\sigma(I)$]; solid solution: $\sin\theta/\lambda < 0{\cdot}61$ Å^{-1} ($h < 9$, $k < 10$, $l < 28$), 10 reflexions used for lattice-parameter calculation, 3 standard reflexions, 4% intensity variation, 1574 reflexions measured, $R_w = 0{\cdot}095$ (unit weights) for 1116 reflexions [$I > 2\sigma(I)$]. Enantiomer structure solved by direct methods, *MULTAN* (Germain, Main & Woolfson, 1971), refined with *ORXFLS* (Busing, Martin & Levy, 1971), anisotropic temperature factors, hydrogen atoms theoretically positioned and not refined; max. $\Delta/\sigma = 1{\cdot}2$. For solid solution, refinement was made with molecular blocks and **TLS** using *ORION* (André, Fourme & Renaud, 1971); Cl atom remained independent (on the mirror) with anisotropic temperature factors, max. $\Delta/\sigma = 0{\cdot}8$; it is interesting to emphasize that cell dimensions (very similar) and space groups ($P2_12_12_1$ is a subgroup of *Pnma*) confirm the solid-solution nature of the racemate.*

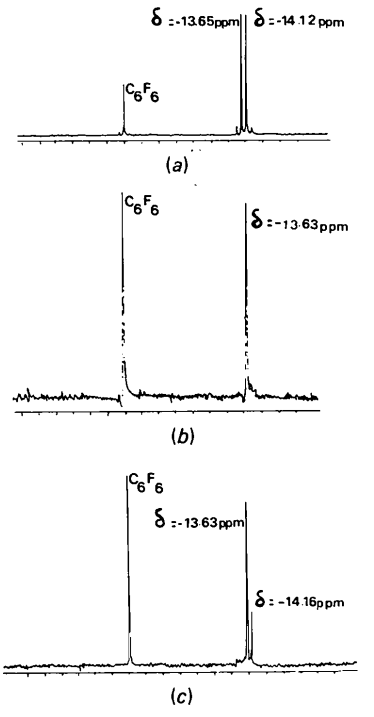


Fig. 1. NMR diagrams.

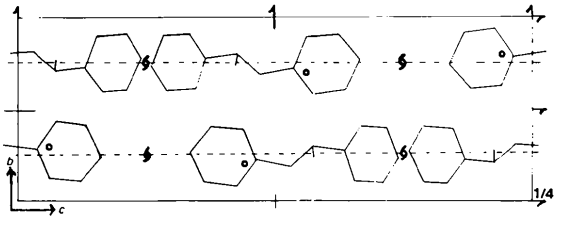


Fig. 2. Projection of the enantiomer structure on (**b**, **c**). The origin is the origin of the *Pnma* group. The solid-solution mirror is on the dashed line. o: Cl atom.

Discussion. *Enantiomer*. The crystallographic coordinates are given in Table 1. The origin has been taken at the origin of the *Pnma* group. Fig. 2 is a projection of the structure on the plane (**b**, **c**). Distances and angles are in Fig. 3, which is a projection of the molecule on the plane C(7)C(8)C(9). The molecule has a pseudo mirror plane which can be defined as a mean plane through atoms C(1), N, C(7), F, C(8), C(9), C(12) and

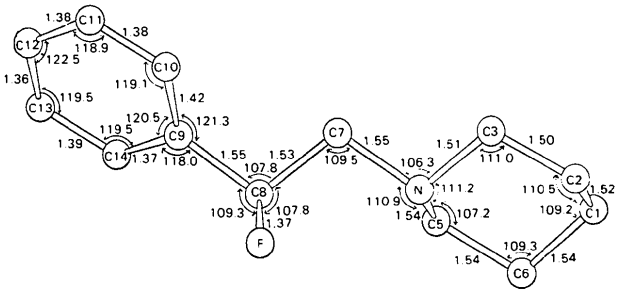


Fig. 3. Projection of the molecule on the plane C(9)C(8)C(7) showing angles (°), distances (Å) and numbering of atoms ($\sigma \sim 0{\cdot}01$ Å, $\sim 0{\cdot}08°$).

* Lists of structure factors, anisotropic thermal parameters, **TLS** tensors, H-atom coordinates, dihedral angles and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39097 (40 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Enantiomer: crystallographic coordinates (xyz) and coordinates* (Å) *in a system related to the model molecule (X Y Z) with origin* C(8); *X axis* C(8)–F; *Y axis parallel to* C(9)–C(7)

$B_{eq} = (U_1 U_2 U_3)^{1/3}$.

	x	y	z	X	Y	Z	B_{eq}(Å^2)
N	0·2117 (9)	0·2761 (9)	0·5349 (3)	−0·07	2·52	−0·03	2·53
F	0·0126 (6)	0·2624 (9)	0·4242 (2)	1·37	0·0	0·0	3·63
C(9)	0·2887 (13)	0·2254 (13)	0·3678 (3)	−0·51	−1·24	0·76	2·52
C(2)	0·1975 (21)	0·4046 (13)	0·6347 (4)	0·25	4·96	0·30	3·49
C(6)	0·2053 (23)	0·0959 (11)	0·6242 (4)	−0·61	4·09	−1·87	3·34
C(3)	0·2691 (19)	0·4225 (9)	0·5724 (4)	−0·10	3·66	0·96	2·65
C(5)	0·2807 (20)	0·1136 (12)	0·5614 (4)	−1·04	2·77	−1·20	3·22
C(14)	0·3316 (19)	0·0880 (14)	0·3354 (5)	−1·16	−2·22	0·04	3·39
C(10)	0·3209 (20)	0·3856 (12)	0·3449 (4)	−0·26	−1·42	2·15	3·18
C(7)	0·2956 (13)	0·3067 (11)	0·4738 (3)	−0·47	1·25	0·76	2·78
C(13)	0·4061 (19)	0·1038 (15)	0·2803 (5)	−1·54	−3·40	0·68	3·12
C(11)	0·3973 (20)	0·3976 (16)	0·2880 (5)	−0·65	−2·59	2·76	4·07
C(8)	0·1946 (13)	0·2045 (11)	0·4275 (3)	0·0	0·0	0·0	2·88
C(12)	0·4363 (12)	0·2567 (26)	0·2562 (4)	−1·26	−3·56	2·00	3·71
C(1)	0·2674 (14)	0·2418 (15)	0·6617 (3)	−0·70	5·24	−0·85	3·81
Cl	0·7238 (2)	0·7436 (3)	0·0494 (1)				2·88

Table 2. *Positions and orientations of the molecules (a rotation of θ_1 around* **a**, *θ_2 around* **b** *and θ_3 around* **c** *makes the molecule system coincide with the crystallographic system; u_i are the coordinates of the origin of the group)*

	θ_1	θ_2	θ_3	u_1	u_2	u_3
Enantiomer	104·7	3·35	159·75	0·1917	0·2025	0·4277
Solid solution	103·96 (12)	3·44 (6)	159·21 (29)	0·1923 (4)	0·1978 (6)	0·4281 (1)
	76·04	3·44	−159·21	0·1923	0·3022	0·4281

the middle of C(2)–C(6), C(3)–C(5), C(14)–C(10) and C(13)–C(11). The Cl atom is close to this plane and situated between the two nitrogenous rings related by the translation **a** (see Fig. 2).

Solid solution. Coordinates of the atoms in a system related to the molecule are given in Table 1. Table 2 gives the orientations and positions of the molecules in the unit cell for the enantiomer and the solid solution. The orientation of the enantiomer molecule is very close to one of the two possible orientations in the solid solution. The 'mean mirror plane' defined above makes an angle of 3 (0·7)° with the crystallographic mirror plane of *Pnma*. When a chiral molecule has pseudo mirror symmetry or a pseudo centrosymmetry it crystallizes often as a solid solution (Chion, Lajzérowicz, Bordeaux, Collet & Jacques, 1978). The resolution of the structure with only one possible molecule on each site leads to a result which is not completely unlikely but does not correspond to reality. It is then necessary to have a molecular model and to refine with a molecular block in order to prevent the correlations between atomic coordinates.

The molecular model obtained from the enantiomer structure has an extended form in which the aromatic and nitrogenous rings are antiperiplanar and the nitrogen and fluorine atoms in the *trans* position. The structure is very close to structures of (phenylethyl)-amines already described (Carlström & Bergin, 1967; Carlström, 1973; Hearn, Freeman & Bugg, 1973). The important similarity is seen in the conformational angles σ_1 F–C(8)–C(9)–C(10) = 65·5 (9)°, σ_2 F–C(8)–C(7)–N = 65·1 (9)° and the distances: phenyl–F = 3·71 (2) Å, phenyl–N = 5·20 (2) Å, F–N = 2·90 (0·015) Å which are very close to those obtained in other (phenylethyl)amines and which seem to play an important role in the activity of this type of molecule (Gadret, Léger, Carpy & Berthod, 1978; Barrans, Cotrait & Dangoumau, 1973; Ammon, Balsamo, Macchia, Macchia, Howe & Keefe, 1975; Ammon, Howe, Erhardt, Balsamo, Macchia, Macchia & Keefe, 1977).

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SHORT COMMUNICATIONS

Contributions intended for publication under this heading should be expressly so marked; they should not exceed about 1000 *words; they should be forwarded in the usual way to the appropriate Co-editor; they will be published as speedily as possible.*

Acta Cryst. (1984). C**40**, 712

Structure of 8,5′-anhydro-8-hydroxy-9-β-D-ribofuranosyladenine (8,5′-*O*-cyclo-A) monohydrate: corrigendum.

By RICHARD E. MARSH, *Arthur Amos Noyes Laboratory of Chemical Physics,* California Institute of Technology, Pasadena, California* 91125, *USA*

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Abstract

The crystal structure of $C_{10}H_{11}N_5O_4.H_2O$ should be described as orthorhombic, space group $P2_12_12_1$, with $a = 8{\cdot}485$ (1), $b = 28{\cdot}005$ (5), $c = 4{\cdot}975$ (1) Å rather than monoclinic, $P2_1$, as originally reported [Sugio, Mizuno, Kitamura, Hamada, Ikehara & Tomita (1983). *Acta Cryst.* C**39**, 745–747].

Sugio, Mizuno, Kitamura, Hamada, Ikehara & Tomita (1983) have described the structure of this compound as monoclinic, space group $P2_1$, with $a = 32{\cdot}747$ (6), $b = 4{\cdot}975$ (1), $c = 8{\cdot}485$ (1) Å, $\beta = 121{\cdot}22$ (1)°, $Z = 4$. Choosing [102] as the a axis leads to an effectively orthorhombic unit cell [$\beta' = 90{\cdot}01$ (1)°] and the two independent molecules in the $P2_1$ description are related, almost within the coordinate e.s.d.'s, by the additional 2_1 axes of space group $P2_12_12_1$. The necessary coordinate transformations are $x' = x$, $y' = y - 0{\cdot}1009$, $z' = z - 2x + 0{\cdot}25$. A permutation of axes $a'b'c' = cab$ then gives the standard setting. Successful refinement in $P2_12_12_1$ is documented in the following paper (Sugio *et al.*, 1984).

Contrary to the final sentence by Sugio *et al.* (1983), the water molecule apparently *does* participate as a hydrogen-bond donor – to N(3), at 2·923 (7) Å, and possibly to a second N(3) at x, y, $z + 1$, 3·219 (7) Å. [These numbers become 2·924 (4) and 3·215 (4) Å after the $P2_12_12_1$ refinement of Sugio *et al.* (1984).]

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Acta Cryst. (1984). C**40**, 712–713

Structure of 8,5′-anhydro-8-hydroxy-9-β-D-ribofuranosyladenine (8,5′-*O*-cyclo-A) monohydrate, $C_{10}H_{11}N_5O_4.H_2O$: errata.

By SHIGETOSHI SUGIO, HIROSHI MIZUNO, KUNIHIRO KITAMURA, KENSAKU HAMADA, MORIO IKEHARA and KEN-ICHI TOMITA, *Faculty of Pharmaceutical Sciences, Osaka University, Yamadaoka* 1–6, *Suita, Osaka* 565, *Japan*

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Abstract

The space group of the title compound [Sugio, Mizuno, Kitamura, Hamada, Ikehara & Tomita (1983). *Acta Cryst.* C**39**, 745–747] is not $P2_1$ but $P2_12_12_1$. The new cell parameters refined using the 2θ values of 25 reflections are $a = 8{\cdot}485$ (1), $b = 28{\cdot}002$ (4), $c = 4{\cdot}975$ (4) Å, $Z = 4$. Refinement based on the correct space group gave $R = 0{\cdot}042$ for 1127 reflections.

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