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Spectroscopic and structural study of flobufen

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Abstract

Flobufen, 4-(2′,4′-difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic acid, and its 3-methyl isomer have been obtained by the Friedel–Crafts reaction of 2,4-difluorobiphenyl with itaconic or citraconic anhydride, respectively, followed by hydrogenation of the products. The structures of both compounds have been elucidated by mass spectrometry and ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. The structure of flobufen has been confirmed by a single-crystal X-ray study.

Keywords: Flobufen; Mass spectrometry; NMR spectroscopy; Crystal structure determination

1. Introduction

The substituted ω-biphenyl-ω-oxoalkanoic acids are biologically active compounds exhibiting interesting anti-inflammatory, anti-aggregation, immunomodulating and fibrinolysis activating activities. Representative examples are 4-(biphenyl-4-yl)-4-oxobutanoic acid (fenbufen) [1], 4-(biphenyl-4-yl)-4-oxo-2-methylbutanoic acid (metbufen) and 4-(2′-chlorobiphenyl-4-yl)-4-oxo-2-methylenebutanoic acid (itanoxone) [2]. In the course of our systematic study of quantitative relations between the structure and anti-inflammatory activity of various aryloxoalkanoic acids, a new fluorine-containing compound has been developed and named flobufen (**1**) (for the structure, see ion *m/z* 304, Scheme 1). The synthesis and biological activities have been described in our recent papers [3,4]. In the present paper we report its detailed spectral and structural study.

2. Results and discussion

Flobufen was synthesized by the Friedel–Crafts reaction of itaconic anhydride and 2,4-difluorobiphenyl, followed by hydrogenation of the resulting 4-(2′,4′-difluorobiphenyl-4-yl)-2-methylen-4-oxobutanoic acid. The reaction gave predominantly the required 2-methyl isomer (**1**) together with about 2% of its 3-methyl isomer (**2**). Their separation was achieved by crystallization from acetic acid. Compound **2** was also prepared by the reaction of 2,4-difluorobiphenyl with citraconic anhydride, followed by hydrogenation of 5-(2′,4′-difluorobiphenyl-4-yl)-1,5-dihydro-5-hydroxy-4-methyl-2-furanone. The general synthetic route is described elsewhere [5].

The electron impact mass spectrum of **1** showed a molecular cation-radical of moderate intensity at *m/z* 304 (composition $C_{17}H_{14}O_3F_2$). The base peak at mass 217 is attributed to a stable $[M-C_4H_7O_2]^+$ acylium ion. Finally, the elimination of carbon monoxide from *m/z* 217 gave an intense 2,4-difluorobiphenyl ion (*m/z* 189). The tricyclic cation-radical at *m/z* 188 (Scheme 1) is the difluoro analogue of *m/z* 152 that serves as a diagnostic ion for the detection of unsubstituted biphenyls, for example of 4-(biphenyl-4-yl)-4-oxo-2-methylbutanoic acid (metbufen) [2]. The overall fragmentation pattern of **1** is presented in Scheme 1. The EI mass spectrum of **2** was almost identical to that of **1**. The only difference was the absence of ions *m/z* 232 and 87 in the spectrum of **2**.

^{1}H and COSY NMR spectra of **1** revealed a partial structure $-CH(CH_3)CH_2-$, an aromatic four-spin system (AA′BB′X, where X = ^{19}F) representing a 1,4-disubstituted phenyl ring),

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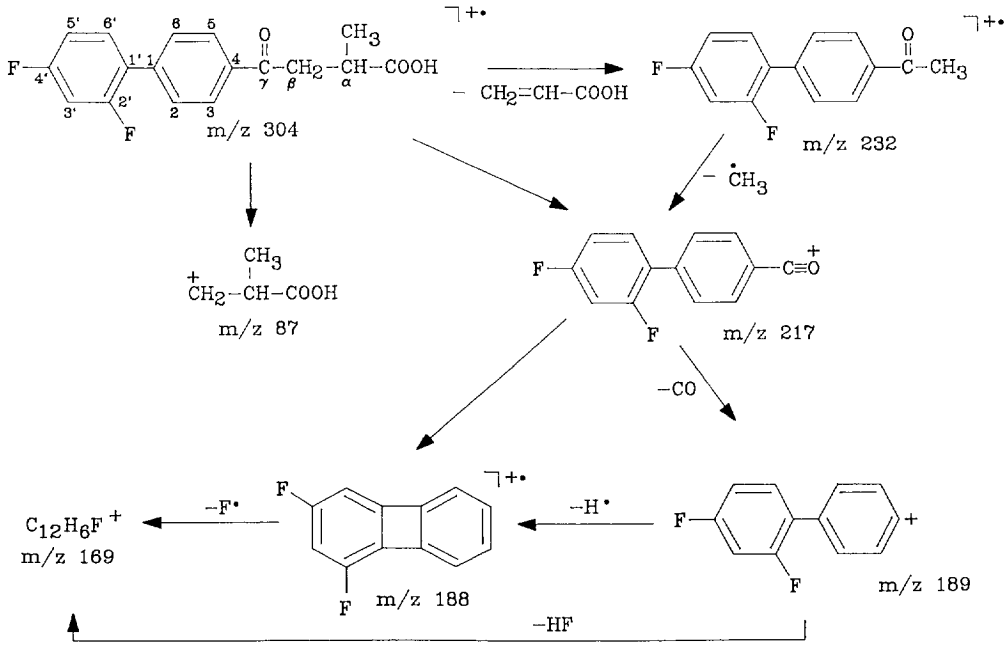

Scheme 1. Major fragmentation pathways of $M^{+\cdot}$ of flobufen (EI 70 eV).

and a three-spin system of aromatic protons showing additional couplings to fluorine (see Scheme 1 and Table 1, for correlation between numbering used here for the NMR spectra with that used to describe the solid-state structure).

The coupling of the high-field multiplet of the above-mentioned AA'BB'X system to one fluorine atom was established by means of a *J*-resolved experiment (HOM2DJ), Fig. 1(a). The potential of this method for distinguishing between homonuclear and heteronuclear scalar couplings was recognized in the early stages of the development of 2D NMR spectroscopy [6]. The coupling pattern of the ABC system protons (evident upon the removal of couplings to fluorine) in this 2D NMR spectrum indicates 1',2',4'-trisubstitution. Each of these protons is coupled to two fluorines. The observed coupling constants J_{HF} confirm the location of fluorine atoms at positions 2' and 4'. The ^{13}C NMR spectrum showed two aromatic CHs (each representing two carbons), six carbons were coupled to two fluorines and two others to

Table 1
^{1}H and ^{13}C NMR data [a] for 4-(2',4'-difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic acid (**1**)

Atom	X-ray [b]	δ_C	m_H [c]	m_F [d]	J_{CF}	δ_H	*m*	J_{HH} or J_{HF}
COOH	C1	178.85	s	–	–	–		
α	C2	35.20	d	–	–	3.090	ddq	7.4, 5.6, 7.1
β	C4	42.34	t	–	–	3.021	dd	17.4, 5.6
						3.484	dd	17.4, 7.4
γ	C5	198.72	s	–	–	–		
α-Me	C3	17.49	q	–	–	1.277 [e]	d	7.1
1	C9	140.21	s	d	1.6	–		
2,6	C8, C10	129.42 [f]	d	d	3.0	7.568 [g]	AA'BB'X	Σ(*J*) = 8.5, **1.7**
3,5	C7, C11	128.59 [f]	d	–	–	8.000 [g]	AA'BB'	Σ(*J*) = 8.5
4	C6	135.99	s	–	–	–		
1'	C12	124.44	s	dd	13.4, 3.9	–		
2'	C17	160.13	s	dd	251.5, 12.0	–		
3'	C16	104.87	d	dd	25.9, 25.9	6.903	ddd	2.6, **10.6, 8.8**
4'	C15	163.14	s	dd	250.3, 12.0	–		
5'	C14	112.17	d	dd	21.3, 3.7	6.953	dddd	8.6, 2.6, **7.9, 1.1**
6'	C13	131.75	d	dd	9.6, 4.7	7.403	ddd	8.6, **8.8, 6.4**

[a] $CDCl_3 + CD_3OD$ 4:1 v/v, 25 °C, chemical shifts in ppm, δ-scale, coupling constants in Hz, bold numbers indicate coupling to fluorine.
[b] Correlation with the numbering used for the X-ray data.
[c] Multiplicity due to protons.
[d] Multiplicity due to fluorine.
[e] 3 H.
[f] 2 C.
[g] 2 H. ^{19}F NMR δ: −114.17 ddddt (8.8, 8.8, 1.1, **6.2**, 1.7, 2'-F); −110.55 dddd (10.6, 7.9, 6.4, **6.2**, 4'-F) ppm.

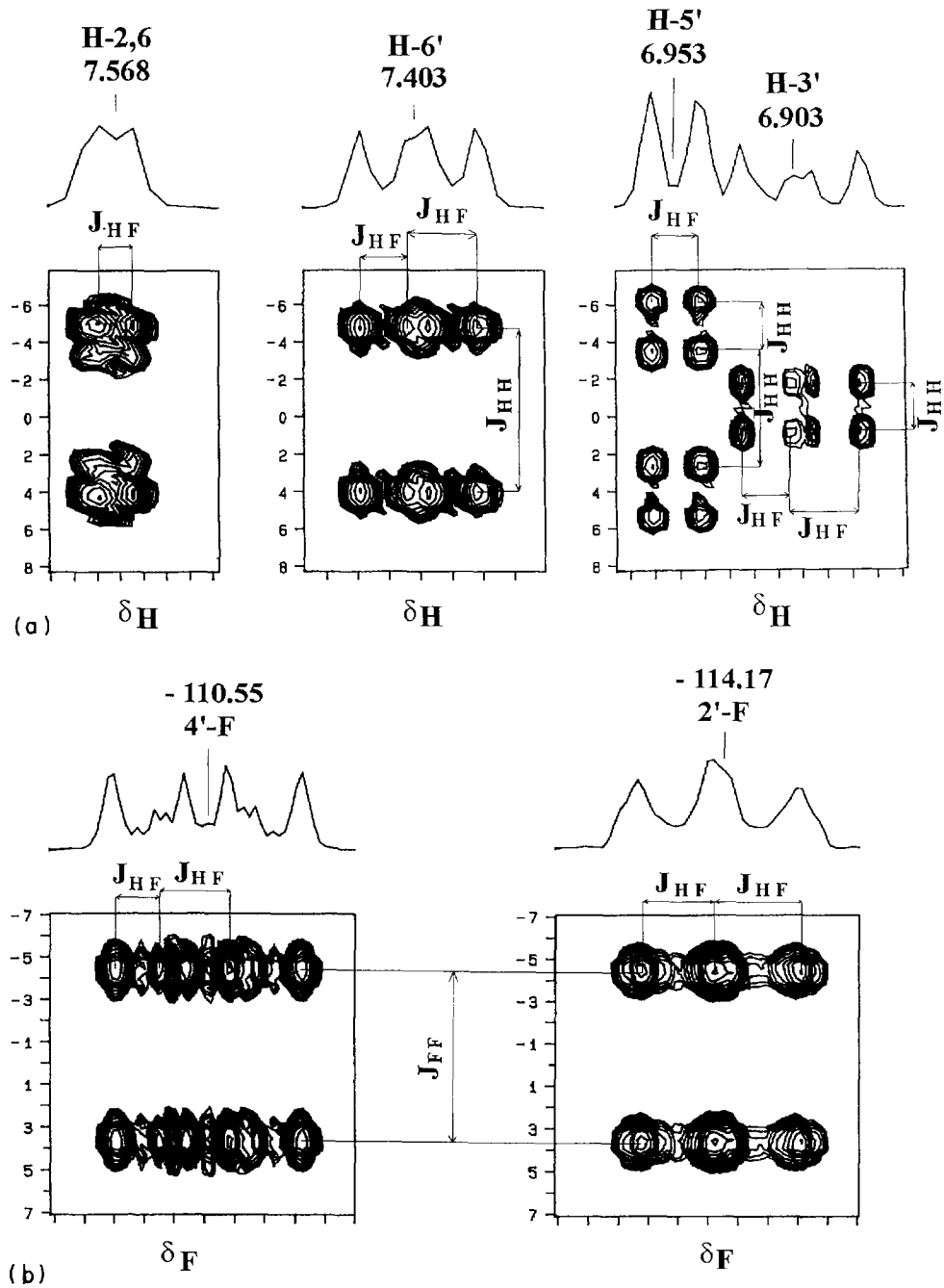

Fig. 1. (a) Proton *J*-resolved spectrum of flobufen [rotated, symmetrized, contour plot, projection on the top; F1 dimension: J_{HH} (Hz); F2 dimension; δ_H (ppm)]; proton–proton couplings are resolved in the F1 dimension, couplings to fluorine are visible in F2. (b) Fluorine *J*-resolved spectrum of flobufen [rotated, symmetrized, contour plot, projection on the top; F1 dimension: J_{FF} (Hz); F2 dimension: δ_F (ppm)]; J_{FF} is resolved in the F1 dimension, J_{HF} appears in F2.

one fluorine only. The latter signals represent C-1 (not carrying a proton) and C-2+C-6 (2 C, doublet according to APT). Since the coupling constant J_{CF} decreased with the number of intervening bonds, the carbons exhibiting one large ($^1J_{CF}$) coupling and one medium ($^2J_{CF}$) coupling, thus represent C-2′ and C-4′; they are further differentiated by the multiplet width of the signal (sum of all proton–carbon couplings) in the proton-coupled spectra. Similarly assigned were carbons C-3′ (d, two $^2J_{CF}$), C-5′ (d, $^2J_{CF}+^4J_{CF}$), C-6′ (d, two $^3J_{CF}$), and C-1′ (s, $^2J_{CF}+^4J_{CF}$).

The identical assignment of proton-bearing carbons was obtained from heteronuclear correlation (HETCOR). The previously-mentioned coupling of C-1 and C-2/C-6 to fluorine at C-2′ yields the assignment for the AA′BB′X system. Furthermore, its low-field part exhibits a cross-peak to the methylene protons of the side-chain in the delay-COSY experiment. The assignment of aliphatic protons of the side-chain was inferred from the COSY experiment. A similar procedure was adopted for **2** and both assignments are presented in Tables 1 and 2.

Table 2
^1H and ^{13}C NMR data [a] for 4-(2′,4′-difluorobiphenyl-4-yl)-3-methyl-4-oxobutanoic acid (**2**)

Atom	δ_C	m_H [b]	m_F [c]	J_{CF}	δ_H	m	J_{HH} or J_{HF}
COOH	175.28	s	–	–	–		
α	37.67	t	–	–	2.459	dd	16.9, 5.6
					2.946	dd	16.9, 8.5
β	37.75	d	–	–	3.951	ddq	8.5, 5.6, 7.1
γ	203.59	s	–	–	–		
β-Me	18.13	q	–	–	1.227 [d]	d	7.1
1	140.18	s	d	1.7	–		
2,6	129.58 [e]	d	d	3.1	7.586 [f]	AA′BB′X	$\Sigma(J)=8.6$, **1.8**
3,5	129.12 [e]	d	–	–	8.031 [f]	AA′BB′	$\Sigma(J)=8.6$
4	135.30	s	–	–	–		
1′	124.55	s	dd	13.4, 3.8	–		
2′	160.24	s	dd	251.5, 11.9	–		
3′	104.94	d	dd	26.0, 26.0	6.905	ddd	2.6, **10.7, 8.8**
4′	163.23	s	dd	250.3, 11.9	–		
5′	112.27	d	dd	21.3, 3.7	6.956	dddd	8.8, 2.6, **7.8, 1.0**
6′	131.86	d	dd	9.7, 4.7	7.403	ddd	8.8, **8.6, 6.4**

[a] $CDCl_3 + CD_3OD$ 4:1 v/v, 25 °C, chemical shifts in ppm, δ-scale, coupling constants in Hz, bold numbers indicate coupling to fluorine.
[b] Multiplicity due to protons.
[c] Multiplicity due to fluorine.
[d] 3H.
[e] 2C.
[f] 2H. ^{19}F NMR δ: −114.7 ddddt (8.8, 8.8, 1.0, **6.2**, 1.8, 2′-F); −117.07 dddd (10.7, 7.8, 6.4, **6.2**, 4′-F) ppm.

Table 3
Atomic coordinates ($\times 10^4$) for non-H atoms and their equivalent isotropic temperature factors ($Å^2 \times 10^3$) with e.s.d.s in parentheses

Atom	x	y	z	U_{eq}
O1	4193(4)	11069(4)	5851(1)	60(1)
O2	2881(4)	7832(4)	5183(1)	57(1)
O3	4054(4)	7420(4)	6895(1)	70(1)
F1	−3459(4)	876(4)	9115(1)	76(1)
F2	−2368(4)	−4625(3)	9879(1)	77(1)
C1	2791(5)	9131(5)	5711(2)	47(1)
C2	812(6)	8590(6)	6211(2)	57(2)
C3	−1293(7)	8759(7)	5814(2)	78(2)
C4	132(6)	6424(6)	6376(2)	58(2)
C5	2004(5)	6205(5)	6851(2)	49(1)
C6	1341(5)	4507(5)	7281(2)	42(1)
C7	3088(5)	4327(5)	7726(2)	47(1)
C8	2519(5)	2846(5)	8162(2)	45(1)
C9	159(5)	1508(5)	8165(2)	42(1)
C10	−1581(5)	1690(5)	7717(2)	50(1)
C11	−1013(5)	3160(5)	7280(2)	49(1)
C12	−482(6)	−106(5)	8623(2)	43(1)
C13	700(6)	−1426(5)	8620(2)	51(1)
C14	70(6)	−2958(5)	9040(2)	56(2)
C15	−1763(6)	−3156(5)	9459(2)	52(1)
C16	−2981(6)	−1888(5)	9495(2)	52(1)
C17	−2316(5)	−413(5)	9072(2)	46(1)

Two signals were observed in the ^{19}F NMR spectra of both **1** and **2** as expected. Their fine structure revealed all the J_{HF} values determined more precisely from ^1H NMR. Fluorine at C-2′ was assigned the more complex signal also recognized through its triplet splitting due to coupling with isochronous (having the same chemical shift) H-2 and H-6. Homonuclear coupling $J_{FF}=6.2$ Hz [apparent in Fig. 1(b)] was obtained as the difference between the multiplet width and the sum of all the $J_{HF'}$ values. The observation of the AA′BB′X pattern for the protons of the 1,4-substituted phenyl ring shows no signs of hindered rotation around the 1,1′-biphenyl bond at ambient temperature. This indicates that the conformation is flexible in solution and the rotation barrier should be smaller than ca. 7 kcal mol^{-1} [7].

The structure of **1** was also verified by a single-crystal X-ray study. The atomic and the important geometrical parameters are summarized in Tables 3 and 4. In the crystallographic numbering scheme of **1** (Fig. 2), all individual C,

Table 4
Selected bond distances (Å), angles (°) and torsion angles (°) with e.s.d.s in parentheses

Bond distances		*Bond torsion angles*	
O1–C1	1.283(4)	O2–C1–C2–C3	−82.5(4)
O2–C1	1.230(4)	O1–C1–C2–C3	91.8(3)
O3–C5	1.213(3)	O2–C1–C2–C4	39.5(5)
F1–C17	1.348(5)	O1–C1–C2–C4	−146.3(3)
F2–C15	1.356(4)	C1–C2–C4–C5	67.9(4)
C1–C2	1.524(5)	C3–C2–C4–C5	−172.6(2)
C2–C3	1.521(6)	C2–C4–C5–O3	−21.1(5)
C2–C4	1.523(6)	C2–C4–C5–C6	158.0(3)
C4–C5	1.495(6)	C4–C5–C6–C7	−179.4(3)
C5–C6	1.496(5)	O3–C5–C6–C7	−0.4(5)
C9–C12	1.485(5)	C4–C5–C6–C11	−3.0(5)
C16–C17	1.363(5)	O3–C5–C6–C11	176.1(3)
		C9–C12–C17–F1	−3.3(5)
Bond angles		C13–C12–C17–F1	177.6(3)
F2–C15–C14	118.9(3)	C13–C14–C15–F2	−179.0(3)
F2–C15–C16	118.1(3)	F2–C15–C16–C17	179.4(3)
F1–C17–C16	117.4(3)	C15–C16–C17–F1	−178.5(3)
F1–C17–C12	118.2(3)		

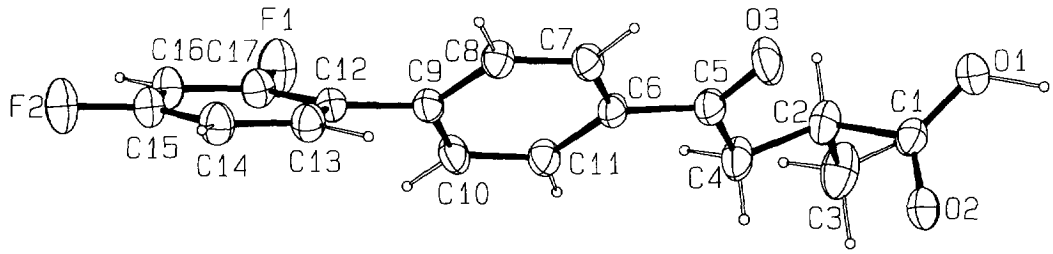

Fig. 2. ORTEP drawing of the flobufen molecule showing the numbering scheme.

O, F atoms are denoted by consecutive numerals. Since the NMR spectra provided only an estimation of the rotation barrier data obtained from the crystal structure determination enabled calculation of this barrier more precisely as well as the determination of the energetically favoured dihedral angle between the planes of the phenyl rings. PCILO conformation calculations carried out on an unsubstituted biphenyl gave an absolute conformation energy minimum of 1.9 kcal mol^{-1} at an angle of 40° for the energy barrier for a coplanar arrangement [8]. In structures related to **1**, the following dihedral angles were found: 2,2′-dibromobiphenyl (80.1°) [9], 2,3,5,6-tetrafluorobiphenyl (57.9°) [10], 2,3,4,5,6-pentafluorobiphenyl (52.9°) [11], 4-ethyl-2′-fluoro-4′-(4″-pentylcyclohexyl)biphenyl (41.9°) [12], 4′-n-butyl-2,3,5,6-tetrafluorobiphenyl-4-carbonitrile (40.8°) [13], 4′-n-butylbiphenyl-4-carbonitrile (40.5°) [14] and 4-ethyl-4′-(4″-pentylcyclohexyl)biphenyl (3.9°) [12].

The semi-empirical quantum mechanical calculation (MOPAC6, AM1 parametrization [15]) for **1** provided four energetical favoured at minima −141°, −48°, 39° and 132° for the C8–C9–C12–C17 torsion angle, Fig. 3 (corresponding to atoms C2–C1–C1′–C2′ in Scheme 1). The minima for the second enantiomer are the same with opposite signs. It corresponds to 3.9 kcal mol^{-1} for the higher rotation barrier (a 2.1 kcal mol^{-1} value recalculated for biphenyl using the same method). This energy barrier appears to be too high to be associated with packing effects and, consequently, the torsion angle found in the crystal structure of **1** [−48.2(1)°] is not random but fully consistent with the energetical rules.

Due to the presence of two fluorine atoms, the aromatic C–C bonds are on average slightly shorter in the difluorophenyl ring [1.379(5) Å] than in the phenyl ring [1.389(5) Å]. As in other biphenyls, the longest ring bonds are those adjacent to the central C9–C12 (i.e. 1,1′, Scheme 1) [9–14,16]. The neighbouring difluorophenyl group C atoms (C12, C13, C14, C15, C16, C17) are coplanar to within 0.007(4) Å and the attached fluorine atoms lie within 0.043(2) Å of this plane. The C–F bond lengths (Table 4) are similar to those in related structures [10–13,16].

The pattern of the molecular packing in the crystalline state is shown in Fig. 4. The basic structural motif is created by pairs of individual 2-(*RS*)-enantiomers of **1** lying with their long axes nearly parallel in a head-to-head arrangement. The carboxy groups of pair molecules are connected by a typical centrosymmetric double hydrogen bridge [O1–H1···O2′ ($-x+1$, $-y+2$, $-z+1$), H1···O2′ = 1.88(1) Å,

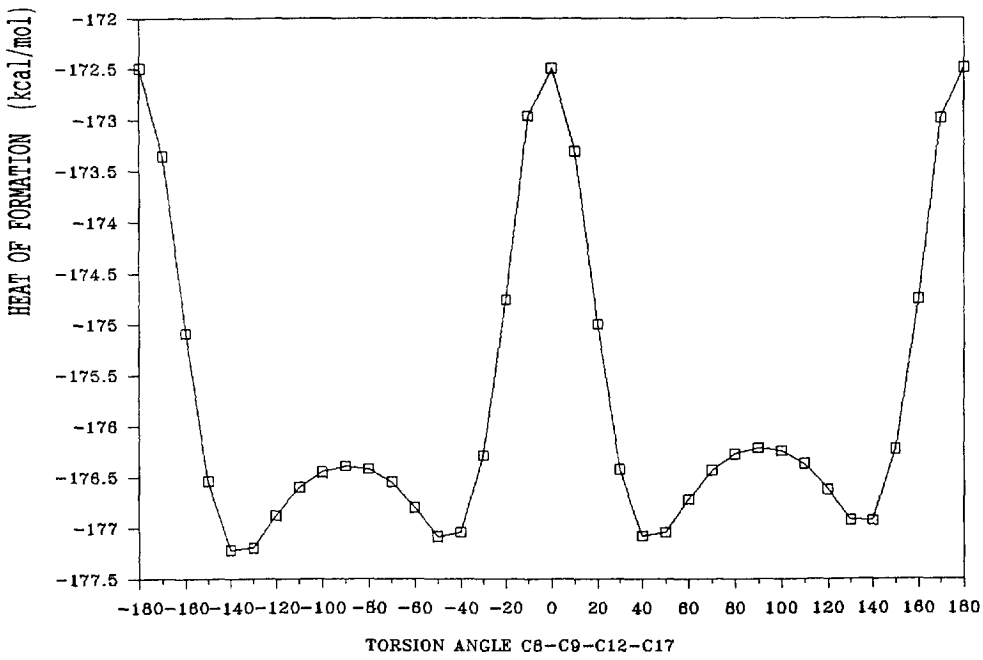

Fig. 3. Rotation barrier of flobufen calculated by the MOPAC6 program.

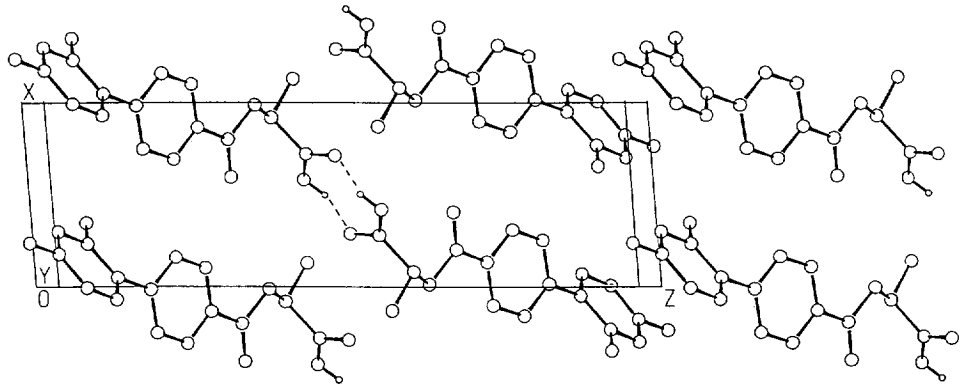

Fig. 4. Packing scheme for flobufen. Dotted lines indicate H-bonds.

O1···O2′ = 2.68(1) Å, O1–H1···O2′ = 174.8(2)°]. The neighbouring flobufen molecules ($-x, -y, -z+2$) are connected by $\pi\cdots\pi$ interactions of their difluorophenyl groups with the carbon atoms at an average distance of 3.48(1) Å, thus forming an infinite stack. Hence the structure can best be described as consisting of ribbons of oriented domains alternately connected by hydrogen and $\pi\cdots\pi$ bonds. The $\pi\cdots\pi$ interaction in the solid state seems likely to contribute to the crystallization of one of four possible energetically equivalent rotamers.

3. Experimental details

^{1}H, ^{13}C and ^{19}F NMR, APT, proton-coupled ^{13}C NMR, delay-COSY, HOM2DJ, HETCOR and long-range HETCOR experiments were performed on a Varian VXR-400 instrument. ^{1}H and ^{13}C NMR spectra ($CDCl_3 + CD_3OD$ 4:1 v/v, 25 °C) were recorded at 399.95 and 100.58 MHz, respectively, while ^{19}F NMR spectra [$CDCl_3$, 25 °C, internal C_6F_6 standard ($\delta_F - 163.0$)] were recorded at 376.29 MHz.

Positive-ion electron-impact mass spectra were recorded on a double-sector instrument (Finnigan MAT 90) of BE geometry (ionizing energy 70 eV, source temperature 250 °C, emission current 1 mA, accelerating voltage 5 kV; direct inlet, DIP temperature 120 °C, samples dosed in microgram amounts for evaporation). The products of collisionally activated decompositions in the first field-free region of the instrument were analyzed via the following linked scans: daughter ions (B/E constant), parent ions (B^2/E constant), neutral losses ($B^2/E^2[E_0 - E]$ constant) using the manufacturers software. The reproducibility of spectral patterns was confirmed. The collision gas (He) pressure was adjusted for 50% attenuation of the primary ion beam, with the collision cell voltage maintained at the ground potential. High-resolution measurements were carried out via the peak-matching method using Ultramark 1600F (PCR Inc., FL, USA) as a standard. The instrument was tuned to a resolution of 10 000 (10% valley definition).

Flobufen (**1**): m.p. 160–161 °C. UV (5×10^{-5} M methanol) (nm): 272 [$\epsilon_M = 2.04\times10^4$, α-transition ($^1B_{2u}$)]. IR (Nujol) ν_{max} (cm^{-1}): 1713 (stretch, C=O); 1678 (asym. stretch, COOH). EI-MS m/z (rel. int.): 305 (3%); 304.0913 ($M^{+\bullet}$, $C_{17}H_{14}F_2O_3$, calc. 304.0911, 15%); 232.0699 ($C_{14}H_{10}F_2O$, calc. 232.0700, 6%); 218 (14%); 217.0470 ($C_{13}H_7F_2O$, calc. 217.0465, 100%); 190 (7%), 189.0530 ($C_{12}H_7F_2$, calc. 189.0516, 24%); 188.0455 ($C_{12}H_6F_2$, calc. 188.0438, 39%); 187 (3%); 170 (3%); 169.0453 ($C_{12}H_6F$, calc. 169.0454, 6%); 168 (3%); 162 (1%); 138 (1%); 94 (1%); 87.0447 ($C_4H_7O_2$, calc. 87.0446, 1%); 45 (2%); 43 (1%); 42 (1%); 41 (2%); 39 (1%); 27 (1%). NMR data are summarized in Table 1.

Isoflobufen (**2**): m.p. 151–153 °C. UV (5×10^{-5} M methanol) (nm): 272 [$\epsilon_M = 2.06\times10^4$, α-transition ($^1B_{2u}$)]. IR (Nujol) ν_{max} (cm^{-1}): 1713 (stretch, C=O); 1681 (asym. stretch, COOH). EI-MS m/z, (rel int.): 305 (1%); 304 (5%); 219 (1%); 218 (13%); 217 (100%); 190 (4%); 189 (56%); 188 (14%); 187 (1%); 170 (1%); 169 (4%); 168 (1%); 138 (1%); 94 (3%); 45 (2%); 43 (4%); 42 (1%); 41 (3%); 39 (1%); 29 (1%). ^{1}H and ^{13}C NMR data are summarized in Table 2.

3.1. Crystal data

$C_{17}H_{14}F_2O_3$: M = 304.29, triclinic; space group $P\bar{1}$ (No. 2), $a = 6.159(1)$ Å, $b = 7.106(1)$ Å, $c = 18.372(2)$ Å, $\alpha = 100.51(1)°$, $\beta = 91.98(1)°$, $\gamma = 112.70(1)°$, $V = 724.4(2)$ Å^3, $Z = 2$, $D_c = 1.395$ g cm^{-3}, $\lambda = 0.71073$ Å, $F(000) = 316$, μ(Mo Kα) = 0.105 mm^{-1}; colourless prisms, crystal dimensions $0.21\times0.49\times0.70$ mm. Enraf-Nonius CAD4 diffractometer, ω–2θ scan mode, temperature 293 K. Total of 2515 reflections were measured with $0 < h < 7$, $-8 < k < 8$, $-21 < l < 21$ with 2152 considered as unique and observed [$I \geqslant 1.96\sigma(I)$] and included in the structure analysis. The structure was solved by direct methods and anisotropically refined by block-diagonal least-squares methods in three blocks. The position of O-bonded hydrogen atoms was found from difference synthesis and others from the expected geometry. All H-positional parameters were held constant during refinement and thermal factors were taken from their bond partners. Absorption was neglected. The function minimized was $\Sigma(|F_o| - |F_c|)^2$, 199 parameters were refined, ratio of

max. least-squares shift to e.s.d. was less than 1×10^{-3}. The refinement converged to $R = 0.065$, $R_w = 0.065$, $S = 0.627$ for 2152 reflections. The largest residual electron-density peaks were at -0.24 and 0.19 e $Å^{-3}$. Programs used were SDP, SHELX76, SHELXS86 and PARST [17–20].

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