Structural study of flobufen
II. An unexpected role of packing effects on the dihedral angle of phenyl rings in crystal structures of 2,4-difluorobiphenyls

Alexandr Jegorov [a,*], Michal Hušák [b], Jan Ondráček [b], Bohumil Kratochvíl [b], Miroslav Kuchař [c], Petr Bulej [d], Martin Gilar [e], Eva Tesařová [f]

[a] Galena Co., Research Unit, Branišovská 31, 370 05 České Budějovice, Czech Republic
[b] Department of Solid State Chemistry, Prague University of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic
[c] Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3, Czech Republic
[d] Galena Co., R&D, 747 70 Opava-Komárov, Czech Republic
[e] Department of Clinical Pharmacology, 1st Department of Medicine, U nemocnice 2, 128 08 Prague 2, Czech Republic
[f] Department of Analytical Chemistry, Prague University of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic

Abstract

The absolute structure of the (R)-$(+)$-1-phenylethylammonium salt of (R)-$(+)$-flobufen (4-(2',4'-difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic acid) was determined by a single-crystal X-ray study. Comparison of the structure of this flobufen salt with those of flobufen and dehydroflobufen (4-(2',4'-difluorobiphenyl-4-yl)-2-methylen-4-oxobutanoic acid) revealed an unexpected coplanar arrangement of the 2,4-difluorobiphenyl group in the flobufen salt. This effect was attributed to the predominant role of the three-dimensional hydrogen-bond network of the molecular packing. © 1997 Elsevier Science S.A.

1. Introduction

Flobufen (4-(2',4'-difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic acid (**1**), Fig. 1) is a fluorine-substituted ω-biphenyl-ω-oxoalkanoic acid exhibiting an interesting anti-inflammatory activity. Racemic 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 (dehydroflobufen (**2**), Fig. 1). The synthesis, structure and biological activities have been described recently [1–3]. In this paper, we report the resolution of flobufen enantiomers, the determination of their absolute chirality and a comparison of the solid state structures of various 2,4-difluorobiphenyls.

2. Results and discussion

The individual $(+)$ and $(-)$ enantiomers of flobufen (**1**) were separated by crystallization of the 1-phenylethylam-
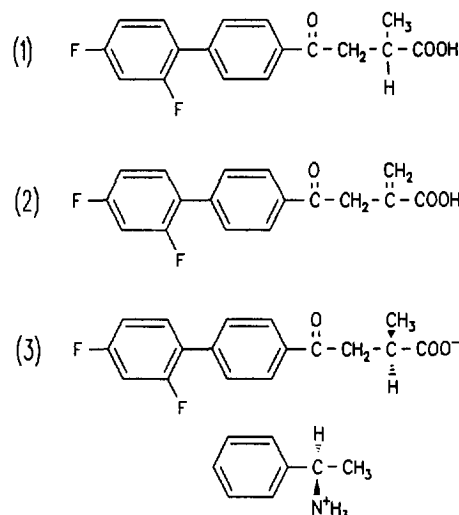

Fig. 1. Formulae of compounds whose X-ray structures have been determined: **1**, (R,S)-flobufen; **2**, dehydroflobufen; **3**, (R)-$(+)$-1-phenylethylammonium salt of (R)-$(+)$-flobufen.

* Corresponding author.

monium salt [4]. In order to test the purity of the enantiomers, a high performance liquid chromatography (HPLC) method was developed using β-cyclodextrin as the chiral selector in
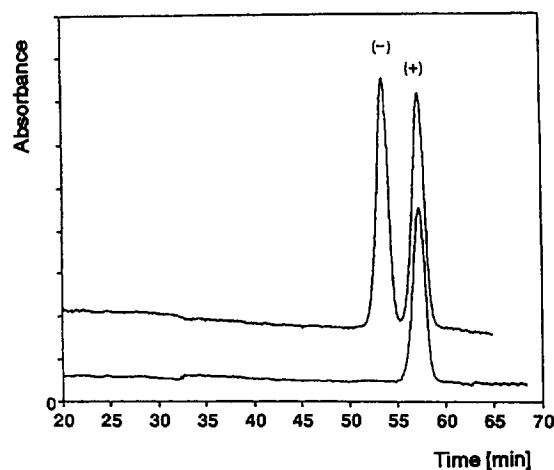

Fig. 2. Resolution of flobufen enantiomers (upper trace) on a reversed phase column with the mobile phase containing β-cyclodextrin as the chiral selector (see Section 3), $R_s = 1.58$, $\alpha = 1.07$. Bottom trace represents (R)-$(+)$-flobufen used for the X-ray study.

the mobile phase. The performance of this method is shown in Fig. 2. Using this column, the elution order of individual $(+)$ and $(-)$ enantiomers is opposite to that observed for profenes [5,6] (2-aryl-propionic acid derivatives also exhibiting anti-inflammatory activity). It was therefore concluded that the determination of the absolute chirality is needed to explain this effect.

Flobufen itself crystallizes in a form of $(2RS)$ racemate [3]. The lack of a heavy atom in both isolated enantiomers does not enable direct X-ray determination of their absolute configurations to be made based on the effect of anomalous dispersion. The crystallization of flobufen salts with various chiral amines was therefore tested. Crystals of satisfactory quality were obtained by the crystallization of the $(+)$-1-phenylethylammonium salt of $(+)$-flobufen (3) from aqueous methanol, and these were used for X-ray studies. The atomic and important geometrical parameters of 3 are summarized in Table 1 and Table 2. The crystallographic num-

Table 1
Atomic coordinates ($\times 10^4$) for the non-hydrogen atoms of the $(+)$-1-phenylethylammonium salt of $(+)$-flobufen (3) and their equivalent isotropic temperature factors ($\text{Å}^2 \times 10^3$) with the estimated standard deviations in parentheses

Atom	x/a	y/b	z/c	U_{eq}
F1	5495(11)	9868(5)	7330(2)	85(3)
F2	9193(9)	7609(6)	6363(2)	82(2)
O1	−2294(9)	7327(5)	9169(2)	38(2)
O2	−5199(9)	7844(5)	9552(1)	39(2)
O3	−3751(11)	9200(5)	8511(2)	64(3)
N1	−9678(11)	8398(6)	9721(2)	37(2)
C1	−4346(15)	7504(7)	9223(2)	39(3)
C2	−5924(13)	7250(7)	8867(2)	37(3)
C3	−7287(14)	6103(7)	8955(2)	52(4)
C4	−4620(14)	7116(7)	8474(2)	42(3)
C5	−3348(15)	8220(8)	8375(2)	43(3)
C6	−1394(15)	8090(8)	8075(2)	45(4)
C7	−1065(15)	7106(8)	7828(2)	52(4)
C8	662(16)	7063(8)	7546(2)	55(4)
C9	2160(15)	8023(8)	7503(2)	43(3)
C10	1844(16)	8997(8)	7759(2)	54(4)
C11	135(17)	9038(8)	8037(2)	56(4)
C12	4021(14)	7927(8)	7194(2)	43(3)
C13	4303(17)	6912(8)	6954(2)	55(4)
C14	5969(17)	6771(9)	6673(3)	64(4)
C15	7462(18)	7708(10)	6633(3)	61(4)
C16	7303(17)	8740(9)	6843(3)	59(4)
C17	5601(18)	8814(8)	7123(3)	56(4)
C18	−9653(14)	10392(8)	10047(2)	40(3)
C19	−10970(15)	11303(9)	10192(3)	54(4)
C20	−10404(18)	11978(9)	10521(3)	61(4)
C21	−8397(18)	11789(9)	10720(3)	63(4)
C22	−7052(16)	10893(9)	10579(3)	54(4)
C23	−7597(16)	10204(8)	10247(3)	51(4)
C24	−10349(14)	9689(7)	9685(2)	40(3)
C25	−9563(18)	10187(8)	9285(2)	70(4)

Table 2
Comparison of selected bond distances (Å), angles ($°$) and torsion angles ($°$) in the $(+)$-1-phenylethylammonium salt of $(+)$-flobufen (3), flobufen (1) [3] and dehydroflobufen (2) with estimated standard deviations in parentheses

|	3	1	2
Bond distance (Å)			
F1–C17	1.36(1)	1.348(5)	1.365(1)
F2–C15	1.37(1)	1.356(4)	1.349(2)
O1–C1	1.25(1)	1.283(4)	1.302(2)
O2–C1	1.26(1)	1.230(4)	1.226(2)
O3–C5	1.21(1)	1.213(3)	1.215(2)
C1–C2	1.53(1)	1.524(5)	1.481(1)
C2–C3	1.55(1)	1.521(6)	1.322(2)
C2–C4	1.52(1)	1.523(6)	1.500(2)
C4–C5	1.48(1)	1.495(6)	1.509(3)
C5–C6	1.54(1)	1.496(5)	1.492(2)
C9–C12	1.51(1)	1.485(5)	1.487(2)
Bond angle ($°$)			
F2–C15–C14	119.1(8)	118.9(3)	119.5(2)
F2–C15–C16	117.1(9)	118.1(3)	117.7(2)
F1–C17–C16	115.0(8)	117.4(3)	116.6(1)
F1–C17–C12	120.1(8)	118.2(3)	119.0(1)
Torsion angle ($°$)			
O2–C1–C2–C3	−70.4(9)	−82.5(4)	−177.0(2)
O1–C1–C2–C3	107.8(8)	91.8(3)	2.1(2)
O2–C1–C2–C4	167.6(7)	39.5(5)	2.8(2)
O1–C1–C2–C4	−14(1)	−146.3(3)	−178.1(1)
C1–C2–C4–C5	−60.2(9)	67.9(4)	65.3(2)
C3–C2–C4–C5	178.3(7)	−172.6(2)	−114.9(2)
C2–C4–C5–O3	−20(1)	−21.1(5)	18.4(2)
C2–C4–C5–C6	160.4(7)	158.0(3)	−162.7(1)
C4–C5–C6–C7	15(1)	−179.4(3)	165.5(1)
O3–C5–C6–C7	−164.5(9)	−0.4(5)	−15.6(2)
C4–C5–C6–C11	−166.9(8)	−3.0(5)	−15.2(2)
O3–C5–C6–C11	14(1)	176.1(3)	163.7(2)
C9–C12–C17–F1	−2(1)	−3.3(5)	−2.2(2)
C13–C12–C17–F1	178.4(8)	177.6(3)	177.8(1)
C13–C14–C15–F2	178.7(8)	−179.0(3)	−179.5(2)
F2–C15–C16–C17	−178.0(8)	179.4(3)	−179.7(2)
C15–C16–C17–F1	179.8(8)	−178.5(3)	−178.3(2)
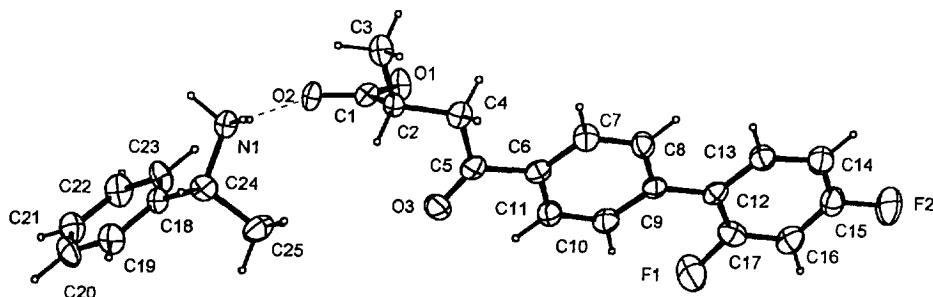
Fig. 3. An ORTEP drawing of a molecule of the (R)-$(+)$-1-phenylethylammonium salt of (R)-$(+)$-flobufen (3) showing the numbering scheme. Thermal ellipsoids are drawn at the 50% probability.

bering scheme and molecular packing are given in Fig. 3 and Fig. 5.

The most important result of the crystal structure determination of the flobufen salt involves the assignment of the absolute chirality of individual enantiomers. Since (R)-$(+)$-1-phenylethylammonium cation was used, the chiral C2 atom of $(+)$-flobufen anion has an R absolute configuration. Thus, according to the absolute configuration, the elution order of the R and S enantiomers in the HPLC system containing β-cyclodextrin is the same as observed for profenes (i.e. the S enantiomer forms a more stable inclusion complex with β-cyclodextrin), but the sign of $[\alpha]_D^{20}$ is opposite for flobufen (fenprofen and ibuprofen are $S(+)$ and $R(-)$).

However, the most surprising observation is the fact that both phenyl rings of 3 are almost coplanar (the dihedral angle is $1.6(3)°$). In previous work [3], the barrier of rotation was calculated by the semi-empirical quantum mechanical calculation for 1 (MOPAC6, AM1 parametrization). The calculation provided four energetic minima of $-141°$, $-48°$, $39°$ and $132°$ for the C8–C9–C12–C17 torsion angle (the minima for the second enantiomer are the same with the opposite sign). The torsion angle found in 3 corresponds, just, to the most disfavoured conformation with the maximum

steric hindrance of 2'-F with 2-H, which is about 3.9 kcal mol^{-1} above the optimum conformation (F...H = 2.07 Å). Since this effect was difficult to explain, we decided to determine one more crystal structure of a related compound.

The crystal structure of dehydroflobufen (4-(2',4'-difluorobiphenyl-4-yl)-2-methylen-4-oxobutanoic acid (2)) was determined as a reference compound. The atomic parameters of 2 are given in Table 3. Important geometrical parameters of structures 1, 2 and 3 are summarized in Table 2. There are no significant differences in the bond distances and angles between the three determined structures. The presence of two fluorine atoms causes certain typical well-known effects, e.g. the aromatic C–C bonds are, on average, slightly shorter in the difluorophenyl ring than in the phenyl ring, and the longest ring bonds are those adjacent to the central C9–C12 bond. The dihedral angle of the phenyl rings in 2 is $51.8(5)°$, which corresponds to the calculated minimum energy and is roughly the same as in the structure of 1 ($48.2(1)°$). An inspection of the structures reveals that, in both 2 and 3, different biphenyl rotamers occur (cf. position of F1 with respect to the C5–O3 bond in 1 vs. 2 and 3). The calculated dihedral angle can also be found in a number of related structures, e.g. 2,2'-dibromobiphenyl ($80.1°$) [7], 2,3,5,6-tetrafluorobi-
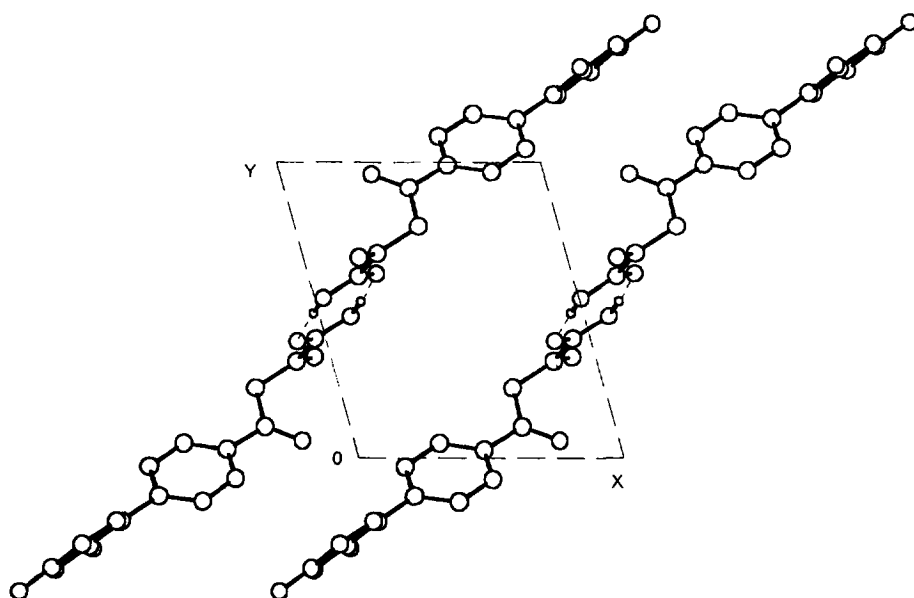

Fig. 4. Packing scheme of the (R)-$(+)$-1-phenylethylammonium salt of (R)-$(+)$-flobufen (3) along the y axis. Dotted lines indicate hydrogen bonds.

Table 3
Atomic coordinates (× 10⁴) for the non-hydrogen atoms of dehydroflobufen (2) and their equivalent isotropic temperature factors ($\text{Å}^2 \times 10^4$) with estimated standard deviations in parentheses

Atom	x/a	y/b	z/c	U_{eq}
O1	−433(1)	5301(1)	1749(1)	583(3)
O2	1975(1)	6128(1)	959(1)	499(3)
O3	2973(1)	9431(1)	2700(2)	701(4)
F1	12310(1)	12964(1)	4405(1)	627(3)
F2	15642(1)	14365(2)	1240(1)	844(4)
C1	1239(2)	6048(2)	1936(1)	395(3)
C2	2250(2)	6801(2)	3434(1)	403(3)
C3	1483(2)	6663(2)	4494(2)	590(4)
C4	4155(2)	7695(2)	3625(1)	426(3)
C5	4268(2)	8985(2)	2976(1)	414(3)
C6	6004(2)	9731(2)	2698(1)	372(3)
C7	6004(2)	10681(2)	1818(1)	419(3)
C8	7579(2)	11414(2)	1549(1)	427(3)
C9	9220(2)	11232(2)	2193(1)	385(3)
C10	9216(2)	10268(2)	3062(1)	426(3)
C11	7632(2)	9514(2)	3306(1)	414(3)
C12	10920(2)	12060(2)	1932(1)	401(3)
C13	11090(2)	12054(2)	547(2)	474(4)
C14	12676(2)	12818(2)	304(2)	554(4)
C15	14090(2)	13603(2)	1454(2)	546(4)
C16	14006(2)	13663(2)	2838(2)	523(4)
C17	12411(2)	12873(2)	3028(1)	438(3)

phenyl (57.9°) [8], 2,3,4,5,6-pentafluorobiphenyl (52.9°) [9], 4-ethyl-2′-fluoro-4′-(4″-pentylcyclohexyl)biphenyl (41.9°) [10], 4′-n-butyl-2,3,5,6-tetrafluorobiphenyl-4-carbonitrile (40.8°) [11], 4′-n-butylbiphenyl-4-carbonitrile (40.5°) [12] and 4-ethyl-4′-(4″-pentylcyclohexyl)biphenyl (3.9°) [10], i.e. according to decreasing steric repulsion of the 2,2′-substituents. Thus the unusual dihedral angle in the flobufen salt may be due to packing effects.

The molecular packing of 2 is shown in Fig. 4. As in 1, two molecules related by their centres of symmetry are connected by an O1–H_{O1}...O2 hydrogen bond creating a dimer via their carboxyl groups. The geometry of this hydrogen bond is described in Table 4. It is interesting to note that $\pi...\pi$ interaction of the phenyl rings is absent in 2. The pattern of molecular packing in the crystalline state of 3 is shown in Fig. 5. The basic structural motif is a three-dimensional hydrogen-bond network created by all three hydrogens of the 1-phenylethylammonium ($R\text{-}NH_3^+$) group and the flobufen CO_2^- oxygens (Table 4). In addition, two flobufen molecules ($x+1$, y, z) lying with their long axes nearly parallel in an extended head-to-tail arrangement are connected by $\pi...\pi$ interactions of the C6–C7–C8–C9–C10–C11 ring with the C12–C13–C14–C15–C16–C17 ring. The average distance of the atoms of the second ring from the least-
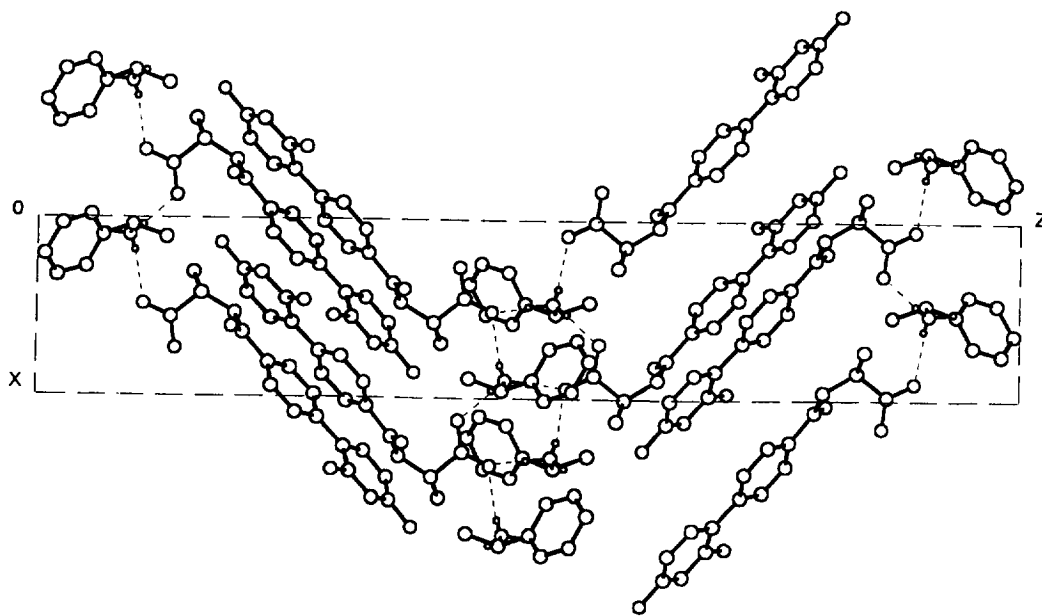

Fig. 5. Packing scheme of dehydroflobufen (2) along the z axis. Dotted lines indicate hydrogen bonds.

Table 4
Comparison of hydrogen-bond systems in 1, 2 and 3

Structure	A (donor)	B (hydrogen)	C (acceptor), symmetry operation	A–C distance (Å)	B–C distance (Å)	A–B–C angle (°)
1	O1	H_{O1}	O2 ($-x+1$, $-y+2$, $-z+1$)	2.68(1)	1.88	175
2	O1	H_{O1}	O2 ($-x$, $-y+1$, $-z$)	2.648(1)	1.72	178
3	N1	$H_{N1,1}$	O2 (x, y, z)	2.796(8)	2.16	170
3	N1	$H_{N1,2}$	O1 ($+x-1$, $+y$, $+z$)	2.979(8)	1.93	175
3	N1	$H_{N1,3}$	O2 ($+x-1/2$, $-y+1/2+1$, $-z+2$)	2.791(8)	1.79	166

squares plane through the atoms of the first ring is 3.578(9) Å. We assume that both contributions to the stabilization energy (i.e. hydrogen-bond network and $\pi \ldots \pi$ interaction) overcome the repulsion of the 2,2'-substituents, leading to a coplanar arrangement.

In contrast with profenes, where the aryl group is attached directly to the α-C atom of propionic acid (C2), the two additional atoms (C4, C5) in flobufen substantially enlarge the conformational freedom of the flobufen molecule. Moreover, the presence of a keto group (C5=O3) provides the possibility of creating additional hydrogen bonds which may contribute to the preferential formation of inclusion complexes [5] or take part in biological systems. To our knowledge, the structure of the flobufen salt is the first example of coplanar arrangement of a 2-fluoro-substituted biphenyl.

3. Experimental details

3.1. Preparation of flobufen enantiomers

Dehydroflobufen (2) (4-(2',4'-difluorobiphenyl-4-yl)-2-methylen-4-oxobutanoic acid) was prepared by the Friedel–Crafts reaction of itaconic anhydride and 2,4-difluorobiphenyl [1,2]. Racemic flobufen (1) was obtained by hydrogenation of 2. Both enantiomers, i.e. (+)- and (−)-flobufen, were prepared from the corresponding (+)- and (−)-1-phenylethylammonium salts respectively [4]. (+)-Flobufen: m.p. 128–129 °C (from acetic acid), $[\alpha]_D^{20} = + 30.42°$ ($c = 0.4$, methanol). (−)-Flobufen: m.p. 124–125.5 °C, $[\alpha]_D^{20} = − 30.52°$ ($c = 0.4$, methanol).

3.2. Chromatographic resolution of flobufen enantiomers

A Gison chromatograph (Middleton, WI, USA) with a detector set at 239 nm was used. A Nucleosil 120-5 C18 column (5 μm, 250 mm × 4.6 mm (I.D.), Macherey-Nagel, Düren, Switzerland) was used. Solvent A was 25 mM β-cyclodextrin and 7 mM triethylamine (pH 7, adjusted with acetic acid) and solvent B was acetonitrile. Isocratic elution was carried out with an A–B mixture (85 : 15, v/v) at a constant flow of 0.8 ml min^{-1}. A detailed description of the method has been given elsewhere [13].

3.3. Crystal data for the (R)-(+)-1-phenylethylammonium salt of (R)-(+)-flobufen (3)

$C_{17}H_{13}F_2O_3^- \cdot C_8H_{12}N^+$, $M_r = 425.48$, orthorhombic system, space group $P2_12_12_1$ (No. 19), $a = 5.959(2)$ Å, $b = 11.179(3)$ Å, $c = 32.992(3)$ Å, $Z = 4$, $V = 2917.6(9)$ Å^3, $D_{calc} = 1.286$ g cm^{-3}, μ(Cu Kα) = 0.76 mm^{-1}, $F(000) = 896$, colourless needles, crystal dimensions 0.06 mm × 0.09 mm × 1.47 mm. Enraf-Nonius CAD4 diffractometer, $\omega/2\theta$ scan mode, temperature 293 K, Cu Kα radiation. Absorption correction based on ψ scan. A total of 2339 reflections were measured with $-5 < h < 5$, $0 < k < 11$ and

$0 < l < 32$ with 1324 considered as independent ($I \geq 1.96\sigma(I)$) and included in the structural analysis. The structure was solved by direct methods and anisotropically refined by a full-matrix least-squares method. The coordinates chosen corresponded to the known absolute configuration of the cation. The positions of all the hydrogen atoms were found from expected geometry. All hydrogen positional parameters were held constrained during refinement and thermal factors were taken from their bond partners. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, weighting scheme $w = [\sigma^2(F_o)]^{-1}$, 280 parameters were refined, ratio of maximum least-squares shift to estimated standard deviation in the last cycle was less than 0.001. The refinement converged to $R = 0.056$, $wR = 0.058$ ($wR = [\Sigma w(|F_o| - |F_c|)^2/\Sigma |F_o|^2]^{0.5}$), $S = 2.12$. The maximum and minimum heights in the final $\Delta\rho$ map were 0.17 and -0.26 e Å^{-3}. The programs used were SIR92 [14], CRYSTALS [15], SDP [16], PARST [17] and MOLDRAW [18].

3.4. Crystal data for dehydroflobufen (2)

$C_{17}H_{12}F_2O_3$, $M_r = 302.28$, triclinic system, space group $P\bar{1}$ (No. 2), $a = 7.9311(7)$ Å, $b = 9.7345(7)$ Å, $c = 9.8792(5)$ Å, $\alpha = 101.322(5)°$, $\beta = 101.197(6)°$, $\gamma = 104.357(6)°$, $Z = 2$, $V = 700.45(5)$ Å^3, $D_{calc} = 1.433$ g cm^{-3}, μ(Cu Kα) = 0.98 mm^{-1}, $F(000) = 312$, colourless, crystal dimensions 0.4 mm × 0.4 mm × 0.7 mm. Enraf-Nonius CAD4 diffractometer, $\omega/2\theta$ scan mode, temperature 293 K, Cu Kα radiation. A total of 5119 reflections were measured with $-9 < h < 9$, $-11 < k < 11$ and $-12 < l < 12$ with 2466 considered as observed and independent ($F \geq 4\sigma(F_o)$) and included in the structural analysis. The structure was solved by direct methods and anisotropically refined by the full-matrix least-squares method. The positions of all the hydrogen atoms were found from difference synthesis. All hydrogen positional parameters and hydrogen isotropic thermal parameters were refined. Absorption was neglected. The function minimized was $\Sigma w(|F_o|^2 - |F_c|^2)^2$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0364P)^2 + 0.11P]$, $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$, 245 parameters were refined, ratio of maximum least-squares shift to estimated standard deviation in the last cycle was less than 0.001. The refinement converged to $R = 0.043$, $wR = 0.104$ ($wR = [\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|^2)^2]^{0.5}$), $S = 1.044$. Maximum and minimum heights in the final $\Delta\rho$ map were 0.19 and -0.21 e Å^{-3}. SHELXL93 [19], SHELXS86 [20] and PARST [17] programs were used.

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