4-(2′,4′-DIFLUOROBIPHENYL-4-YL)-2-METHYL-4-OXOBUTANOIC ACID AND ITS DERIVATIVES

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Friedel–Crafts reaction of itaconic anhydride (*III*) with 2,4-difluorobiphenyl (*II*) afforded unsaturated acid *IV* which was hydrogenated to give 4-(2′,4′-difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic acid (*I*). A series of functional derivatives and salts of the acid *I* has been prepared. The antiinflammatory effect of these compounds was compared with that of acid *I* using selected experimental inflammation models. The analgesic activity in the intraperitoneal irritation test was also evaluated. In the case of (*R*)-(+)-1-phenylethylamide *Vf* the ratio of the diastereoisomers was determined by HPLC.

In the second half of the eighties we have developed[1] a new antiinflammatory compound, 4-(2′,4′-difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic acid (flobufen, *I*). Its discovery is the result of our investigation of antiinflammatory activity of aryloxoalkanoic acids[2] in which the structure of the studied compounds was optimized using the regression analysis of structure–activity relationships[3,4]. In accord with the proposed biotransformation pathway of compounds of this type, the antiinflammatory activity of the acid *I* was markedly protracted[4]. During the preclinical evaluation it has been found[5] that the inhibition of prostaglandin biosynthesis is not decisive for the mechanism of the antiinflammatory effect of this compound. The IC_{50} value toward cyclooxygenase from rat PMN cells for the antiinflammatory drugs based on arylalkanoic acids is up to 1 000 times lower than for flobufen. A significant immunomodulatory effect of compound *I* has been found[6] which probably plays an important role in the mechanism of its antiinflammatory activity, particularly in a model of adjuvant arthritis, by decreasing lymphocyte proliferation induced by PPD (purified protein) or ConA (concanavalin A). In the mechanism of the antiinflammatory action of acid *I* the inhibition of biosynthesis of leukotriene B_4 plays a non-negligible role because this acid inhibits more 5-lipoxygenase than cyclooxygenase[5]. Flobufen *I* now undergoes the II. – III. phase of clinical trials.

EXPERIMENTAL

Melting points were determined on a Kofler block Boetius M. ^{1}H NMR spectra were measured in deuteriochloroform (6% solution) with tetramethylsilane as internal standard on a BS 487s-80 MHz Tesla spectrometer. The presence of the 3-methyl isomer in compound *I* was evaluated by gas liquid chromatography on a Fractovap 2450 chromatograph (Carlo Erba) on a fused silica capillary column (25 m, i.d. 0.22 μm) coated with SE-54 (thickness 0.2 μm). Prior to the measurements, compound *I* was converted into its methyl ester by treatment with diazomethane. The presence of the 3-methylene isomer in compound *IV* was determined by HPLC on a 3.9 × 300 mm μ-Bondapak C_{18} column (Waters) in an acetonitrile–phosphate buffer pH 3.5 (50 : 50 v/v), using a liquid chromatograph consisting of an LC-6A (Shimadzu) pump, a Rheodyne 7125 injector and an SPD-6AV (Shimadzu) detector. The content of diastereoisomers of (*R*)-(+)-1-phenylethylamide *VIf* was determined on the same liquid chromatograph on a 3.9 × 300 mm μ-Bondapak-CN column (Waters) in heptane–dichloromethane (80 : 20 v/v, 1 ml of acetic acid was added to 1 000 ml of the mixture). Similar results were obtained with a β-Cyclodextrin–Daltosil column (4 μm, 4.5 × 250 mm, Serva) with methanol–water (50 : 50 v/v) as the mobile phase.

Itaconic Anhydride (*III*)

A mixture of itaconic acid (131.4 g, 0.1 mol) and acetic anhydride (280 ml) was heated at 80 °C for 4 h. After removal of acetic acid and acetic anhydride by distillation at diminished pressure (0.4 kPa), the distillation residue was mixed with dichloromethane (360 ml) and hexane (100 ml) and the deposited itaconic acid was filtered off. The filtrate was concentrated and the residue diluted with hexane (50 ml) at 50 – 60 °C. The crystalline material was collected; yield 103.7 g (92%) of the anhydride *III*, 98.5% purity (HPLC), m.p. 64 – 67 °C (reported[7] m.p. 66 – 68 °C).

4-(2′,4′-Difluorobiphenyl-4-yl)-2-methylene-4-oxobutanoic Acid (*IV*)

A solution of 2,4-difluorobiphenyl[8] (76.7 g, 0.4 mol) and anhydride *III* (45.1 g, 0.4 mol) in dichloromethane (260 ml) was added dropwise at 0 °C to a suspension of aluminium chloride (106.7 g, 0.8 mol) in dichloromethane (60 ml). The mixture was stirred at 10 °C for 4 h and at 20 °C for 2 h and then poured into a mixture of ice (800 g) and concentrated hydrochloric acid (260 ml). The precipitate was filtered, washed with dichloromethane and suspended in 80% methanol (620 ml). After brief boiling and subsequent cooling to 20 °C, the solid was filtered and washed with 80% methanol. This procedure reduced the content of the 3-methylene isomer from 2% to 0.5%. Yield 75.6 g (63%) of *IV*, m.p. 172 – 174 °C, purity 99.2% (HPLC).

4-(2′,4′-Difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic Acid (*I*)

Compound *IV* (15.1 g, 0.05 mol) was hydrogenated over a Pd/C catalyst (1.0 g, Hereaus K.0224, 3% of Pd in dry material) in dioxane (100 ml) at 20 °C and 0.5 MPa in an autoclave. After the hydrogenation had ended, the catalyst was filtered off and the filtrate was concentrated under diminished pressure (0.4 kPa). The residue was dissolved in acetic acid (45 ml) at 90 °C, cooled and the crude product was collected by filtration. Further crystallization from 90% acetic acid afforded 11.3 g (74%) of compound *I*, m.p. 160 – 161 °C. For $C_{17}H_{14}F_2O_3$ (304.3) calculated: 67.10% C, 4.64% H, 12.49% F; found: 67.15% C, 4.82% H, 12.41% F.

General Method for Preparation of Amides *Va – Vf*

1-Ethylpiperidine (2.7 g, 24 mmol) and ethyl chloroformate (2.6 g, 24 mmol) were added at –15 °C to a solution of acid *I* (5.0 g, 16 mmol) in a mixture of *N*,*N*-dimethylformamide (35 ml) and dichloromethane (150 ml). After stirring for 30 min, the mixture was cooled to –30 °C and a solution of the corresponding amine (16 mmol) in dichloromethane (10 ml) was added. The mixture was stirred at 20 °C for 2 h and then washed with 5% $NaHCO_3$ (3 × 100 ml), water (100 ml) and 1 M HCl (3 × 100 ml). The organic phase was separated, the solvent evaporated and the residue crystallized from an appropriate solvent (for melting points, solvents and analyses see Table I). The amides were obtained in the following yields: *Va* 67%, *Vb* 73%, *Vc* 72%, *Vd* 66%, *Ve* 38%, and *Vf* 40%.

R-(+)-1-Phenylethylamide of 4-(2′,4′-Difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic Acid (*Vf*, sample 19d)

Amide *Vf* (4.5 g, sample 17, Table I), prepared from racemic acid *I* and (*R*)-(+)-1-phenylethylamine as described in the preceding experiment, was dissolved in boiling mixture of methanol and water (4 : 1, 150 ml). After cooling to 20 °C, the crystalline portion (sample 19a) was collected and recrystallized from a minimum amount of methanol–water (4 : 1). Two more crystallizations afforded a product (sample 19d) which was homogeneous according to HPLC (for analytical details see the first part of Experimental, for results Table II).

General Method for Preparation of Esters *Vg* and *Vh*

Thionyl chloride (1.8 ml, 27 mmol) was added to ethanol (37.5 ml, 0.64 mol) at –15 °C. After 30 min, acid *I* (6.1 g, 20 mmol) was added, the mixture was stirred for further 30 min at –15 °C and then heated at 40 – 45 °C for 2 h. The mixture was cooled, concentrated in vacuo and the residue was coevaporated with benzene (2 × 30 ml). Crystallization from acetone afforded 4.6 g (69%) of ethyl ester *Vg*.

Isobutyl ester *Vh* was prepared in 91% yield by the same procedure from butanol, thionyl chloride and acid *I*.

For melting points and analytical data see Table I.

Potassium 4-(2′,4′-Difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoate (*VIa*)

A solution of potassium hydroxide (1.0 g, 18 mmol) in methanol (50 ml) was added to a solution of acid *I* (6.1 g, 20 mmol) in methanol (60 ml). The mixture was concentrated in vacuo and the viscous residue was stirred with ether (50 ml). The crystalline portion was collected on filter and again mixed with ether (50 ml) to give 4.72 g (65%) of monohydrate of salt *VIa*.

Calcium 4-(2′,4′-Difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoate (*VIb*)

A solution of calcium chloride (1.1 g, 10 mmol) in water (20 ml) was added at 70 °C to a solution of sodium salt of *I* (prepared by dissolving acid *I* (3.05 g, 10 mmol) in 5 M NaOH (55 ml)). The precipitate that deposited after cooling was collected; yield 2.7 g (84%) of calcium salt *VIb*; content of acid *I*: 99.4% of theoretical amount (determined potentiometrically).

General Method for Preparation of Salts *VIc*, *VIe* and *VIf*

A solution of the corresponding amine (10 mmol) in acetone–ether (2 : 1, 20 ml) was added to a solution of acid *I* (3.05 g, 10 mmol) in acetone–ether (2 : 1, 25 ml). After standing for 1 h, the

TABLE I
Physicochemical characteristics of compounds *Va – Vh* and *VIa –VIf*

Compound	X (B^+)	M.p., °C Solvent[a]	Formula (M.w.)	Calculated/Found			
				% C	% H	% F	% N
Va	$NHCH_2COOC_2H_5$	95 – 96	$C_{21}H_{21}F_2NO_4$	64.77	5.44	9.76	3.60
		A	(389.4)	64.84	5.35	9.66	3.34
Vb	NHC_2H_5	128	$C_{19}H_{19}F_2NO_2$	68.87	5.78	11.47	4.23
		A	(331.4)	68.49	5.88	11.26	4.14
Vc	$NH(CH_2)_3CH_3$	114 – 115	$C_{21}H_{23}F_2NO_2$	70.18	6.45	10.57	3.90
		A	(359.4)	70.40	6.60	10.44	3.89
Vd	$N(CH_2CH_2)_2O$	95 – 97	$C_{21}H_{21}F_2NO_3$	67.55	5.67	10.18	3.75
		A/H 4 : 1	(373.4)	67.36	5.81	10.29	3.66
Ve	$NHCH_2C_6H_5$	123 – 125	$C_{24}H_{21}F_2NO_2$	73.27	5.38	9.66	3.56
		M/W 4 : 1	(393.4)	72.99	5.44	9.68	3.36
Vf	$NHCH(CH_3)C_6H_5$	115 – 130	$C_{25}H_{23}F_2NO_2$	73.69	5.69	9.33	3.44
		M/W 4 : 1	(407.5)	73.22	5.86	8.99	3.34
Vg	OC_2H_5	67 – 68	$C_{19}H_{18}F_2O_3$	68.67	5.46	11.43	–
		A	(332.4)	68.41	5.41	11.37	
Vh	$OCH_2CH(CH_3)_2$	50 – 52	$C_{21}H_{22}F_2O_3$	69.99	6.15	10.54	–
		A	(360.4)	69.78	6.16	10.28	
VIa[b]	K^+	173 – 174	$C_{17}H_{13}F_2KO_3$ . . H_2O	56.66	4.20	10.54	–
				56.71	4.04	10.28	
		–	(360.4)				
VIb[c]	Ca^{2+}	155 – 157	$C_{34}H_{26}CaF_4O_6$	63.15	4.05	11.75	–
		–	(646.7)	*d*	*d*	*d*	
VIc	c-$C_6H_{11}NH_3^+$	139 – 140	$C_{23}H_{27}F_2NO_3$	68.47	6.75	9.42	3.47
		–	(403.5)	68.18	6.74	9.25	3.42
VId	*S*-(+)-	165 – 167	$C_{23}H_{28}F_2N_2O_5$	61.32	6.26	8.43	6.22
	$HOOCCH(NH_2)(CH_2)_4NH_3^+$	–	(450.5)	61.13	6.43	8.34	6.01
VIe	$C_6H_5CH_2NH_3^+$	123 – 125	$C_{24}H_{23}F_2NO_3$	70.06	5.63	9.23	3.40
		–	(411.5)	69.75	5.75	9.14	3.36
VIf	*R*-(+)-$C_6H_5CH(CH_3)NH_3^+$	115 – 125	$C_{25}H_{25}F_2NO_3$	70.57	5.92	8.93	3.29
		–	(425.5)	70.65	6.02	8.73	3.70

[a] Solvents: A acetone, H hexane, M methanol, W water. [b] Monohydrate. [c] Calculated: 6.20% Ca; found: 6.42% Ca. [d] Not determined.

deposited salt was filtered and washed with acetone (2 × 10 ml). The respective yields of the salt *VIc* and *VIe* were 86% and 72%.

The (*R*)-(+)-1-phenylethylammonium salt *VIf*, $[\alpha]_D^{20}$ +0.72° (*c* 0.2, 50% methanol), was prepared in 97% yield by a similar procedure using only ether as solvent. The acid *I*, liberated from a sample of this salt, had m.p. 158 – 160 °C and $[\alpha]_D^{20}$ 0° (*c* 0.4, 50% methanol).

(*S*)-(+)-Lysine Salt of 4-(2′,4′-Difluorobiphenyl-4-yl)-2-methyl-4-oxobutanoic Acid (*VId*)

An aqueous solution (57%) of (*S*)-(+)-lysine (15.2 g, 0.104 mol) was added to a stirred solution of acid *I* (35.0 g, 0.115 mol) in dimethyl sulfoxide (150 ml). After dilution with acetone (1 050 ml), the deposited product was filtered, yield 44.5 g (95%) of the salt *VId*, $[\alpha]_D^{20}$ +3.21° (*c* 0.2, 50% methanol). The acid *I*, liberated from a sample of this salt, had m.p. 158 – 160 °C and $[\alpha]_D^{20}$ −0.94° (corresponds to 97% content of racemate).

Biological Assays

Inhibition of carrageenan-induced rat paw edema was evaluated by the method of Winter[9]; the experimental conditions are described elsewhere[10]. Inhibition of rat paw adjuvant edema was assayed using the method of Pearson[11] described in ref.[12]. In both cases, the effect was expressed in per cent of edema inhibition compared with an untreated control.

Inhibition of experimental pleuritis was evaluated by the method of Hidaka[13] in a group of Wistar Han female rats pre-treated with 0.5% carrageenan in saline (intrapleural injection). The tested compounds, in suspension with gum arabic, were applied orally in a single dose 1 h before the carrageenan injection. The volume of the exudate in the pleural cavity was compared with that of untreated animals; the total cell number and cellularity (determined by Sysmex cell counter) were also compared.

Adjuvant arthritis was studied with male rats by the method of Pearson[11]. The effect on the development of arthritis was assayed by body weight growth, swelling of hind footpads, mobility and grip strength, and bone and joint damages as compared with both arthritic and naive controls.

Analgetic effect was evaluated in male mice using the test[14] based on intraperitoneal irritation with 0.7% acetic acid. The tested compounds were applied orally 30 min before the application of acetic acid. The lysine salt *VId* was applied also parenterally in saline. The pain inhibition was expressed in per cent as compared with the untreated group.

TABLE II
Optical resolution of *R*-(+)-1-phenylethylamide *Vf* diastereoisomers

Sample	1st peak[a]	2nd peak[a]	$[\alpha]_D^{20}$, °	M.p., °C
17	51.3	48.7	+78.84	115 – 130
19a	60.1	39.9	+76.03	115 – 130
19b	75.7	24.3	+69.63	135 – 145
19c	84.7	15.3	+66.10	135 – 150
19d	100.0	0	+57.74	154 – 157

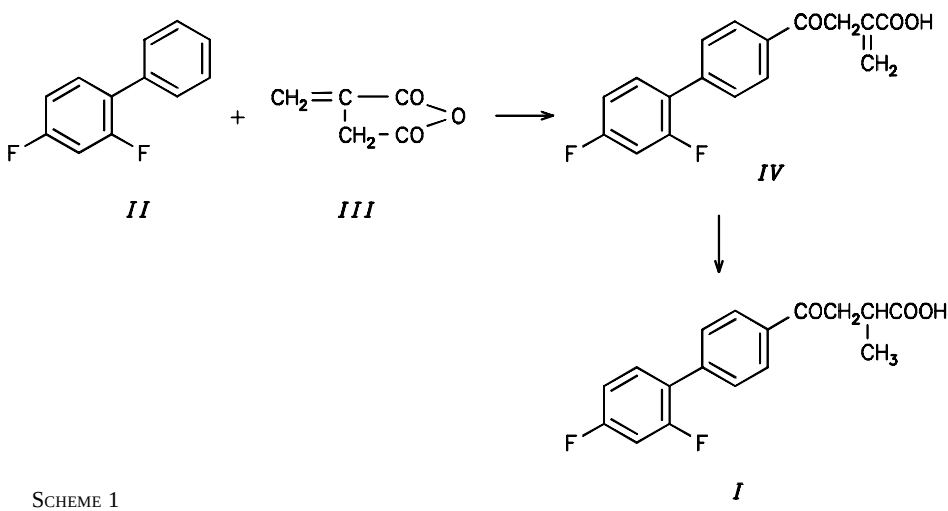
[a] HPLC was performed on μ-Bondapak CN (cf. Experimental).

Immunosuppressive activity was evaluated by the GVHR method (graft versus host reaction[15]) in which local GVHR was evoked by transfer of spleen cells into the left hind foot of A/PHaxC57BL10 hybrid mice. The GVHR was expressed as the weight difference between the left and right popliteal lymph nodes (L – R). After GVHR, the compound was elicitation of administered once daily for five days.

RESULTS AND DISCUSSION

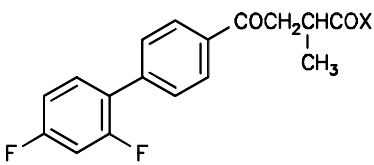
Originally, 2-methyl-4-oxobutanoic acids were synthesized[3,4] by reaction of methylsuccinic anhydride with the corresponding aromatic compounds. With 2,4-difluorobiphenyl (*II*), however, this reaction gives more than 10% of the undesired isomeric 3-methyl derivative. We therefore studied other, potentially more regioselective, approaches to the acid *I*. The method of choice is based on the reaction of itaconic anhydride (*III*) with 2,4-difluorobiphenyl (*II*). The obtained 4-(2′,4′-difluorobiphenyl-4-yl)-2-methylene-4-oxobutanoic acid (*IV*) was hydrogenated over Pd/C to give the desired product[16] (Scheme 1) containing usually less than 0.3% of the 3-methyl isomer. In the crude product *IV*, the content of the 3-methylene isomer, determined by TLC densitometry, did not exceed 2%. This finding agrees with the results described[17,18] for the preparation of Itanoxon, i.e. 4-(2′-chlorobiphenyl-4-yl)-2-methylene-4-oxobutanoic acid.

Because of the hitherto promising results obtained with flobufen *I*, we prepared a series of its functional derivatives *Va – Vh* and salts *VIa – VIf* (ref.[19]) whose physico-

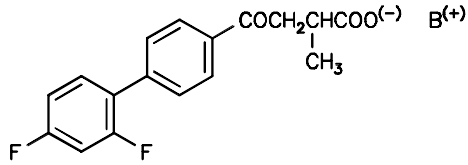


II *III* *IV* *I*

SCHEME 1



Va – Vh



VIa – VIf

For X and $B^{(+)}$ in formulae *V* and *VI* see Table I

TABLE III
Biological properties of compounds *Va – Vh* and *VIa – VIf* [a]

Compound	Mortality [b] %	Inhibition CE [c] %	Inhibition FA [d] %	Pleuritis [e], %			Analgesic activity %
				A	*B*	*C*	
Va	0	40	51	27	62	50	41
Vb	0	42	50	[f]	[f]	[f]	30
Vc	0	33	44	[f]	[f]	[f]	33
Vd	[f]	38	[f]	20	35	47	[f]
Ve	20	42	[f]	12	60	53	[f]
Vf	0	35	[f]	7	32	28	[f]
Vg	0	49	55	[f]	[f]	[f]	38
Vh	10	45	48	28	40	27	42
VIa	20	39	50	30	56	40	47
VIb	30	44	51	35	62	43	35
VIc	0	47	53	[f]	[f]	[f]	58
VId	0	46[g]	58	57	73	39	77[h]
VIe	20	68	[f]	16	33	37	[f]
VIf	20	74	[f]	34	63	45	[f]
Flobufen	50	46	65	46	61	42	79

[a] The antiinflammatory and analgesic activities were compared with those of flobufen (in equimolar doses); doses of flobufen 20 mg/kg in antiinflammatory assays and 100 mg/kg in analgesic activity tests. [b] Acute oral toxicity in female mice after single 500 mg/kg doses; % of mortality 7 days after application. [c] Carrageenan edema. [d] Freund's adjuvans-induced edema. [e] *A* volume of the edema, *B* total cell number, *C* cellularity in volume unit. [f] Not evaluated. [g] 40% CE inhibition after parenteral dose of 10 mg/kg. [h] 48% inhibition of pain after parenteral dose of 80 mg/kg.

chemical characteristics are summarized in Table I. In the preparation of (*R*)-(+)-1-phenylethylamide of flobufen (*Vf*) we obtained a mixture of two diastereoisomers, the ratio of which was determined by HPLC on μ-Bondapak, Separon SGX and β-Cyclodextrin–Daltosil (see Experimental). The isomers were very well separated on all these stationary phases; the obtained results correspond to the measured optical rotations (Table II). For the biological assays we used a sample (No. 17, Table II) that contained the diastereoisomers in the ratio 51 : 49 (i.e. amide of the (*R*)-(+)-amine with racemic acid *I*). A practically pure diastereoisomer derived from (–)-flobufen was obtained by crystallization from 80% methanol.

The synthesized derivatives *Va – Vh* and salts *VIa – VIf* have shown an analogous antiinflammatory activity as flobufen: none of the compounds was significantly more active than the starting acid *I*. The results of the assays, including the analgesic activities, are summarized in Table III. Some of the compounds exhibit an enhanced solubility in water which extends potentialities of their therapeutical utilization. For this reason, we paid particular attention to the (*S*)-(+)-lysine salt of flobufen (*VId*) whose antiarthritic and immunomodulatory activity was compared with the parent flobufen *I*. The results, summarized in Table IV, confirm that the acid *I* and its lysine salt *VId* have analogous pharmacodynamic profiles. The solubility of the salt *VId* in water enabled its parenteral application in aqueous solution. Also this salt is a mixture of two diastereoisomers which can be separated by crystallization. We prepared this salt under conditions (see Experimental) leading to the (*S*)-(+)-lysine salt of racemic flobufen; with this substance we also performed the biological assays.

TABLE IV
Antiarthritic and immunosuppressive activity of compound *VId* (for details see Experimental)

Conditions	Adjuvant arthritis[a]				GVHR	
	A	*B*	*C*	*D*	L – R, mg	%[b]
Application of *VId*	8.13	0.08	0.75	43.0	1.89	65.4
Naive control	23.13	0	0	60.0	–	–
Arthritic control	–6.88	1.37	2.75	16.1	2.89	100.0

[a] *A* body weight growth, *B* size of edema, *C* mobility and grip strength, *D* bone and joint damage. [b] Compared with untreated control.

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