QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTI-INFLAMMATORY ACTIVITY OF ARYLOXOALKANOIC ACIDS

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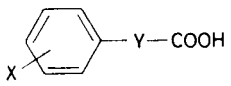
The antiinflammatory effect of a series of aryloxoalkanoic acids *II* and of their biphenyl derivatives *III* was examined by measuring the inhibition of the development of carageenan- and adjuvant-induced edemas. The quantitative relations between the antiinflammatory effect and physicochemical and structural parameters of the compounds tested were evaluated. The equations obtained by the method of regression analysis showed a significant linear dependence of both inhibitory activities on the lipophilicity of the compounds and a considerable effect of some structural changes as expressed by indicator variables. The antiinflammatory effect is especially enhanced in both tests by the presence of a cyclic substituent at the aromatic ring. The high antiinflammatory effect of biphenylyl derivatives *III* is paralleled by their prolonged action. The prolongation of the effect is most likely a result of a suitable biotransformation of acid *III* to an efficient metabolite. The structural requirements which resulted from both the regression analysis and from the hypothesis of biotransformation of acids *III* were utilized in the synthesis of suitably substituted biphenylyloxoalkanoic acids. By this approach derivatives *IIIe—i* were obtained some of which showed a high antiinflammatory and also protracted effect. 4-(2',4'-Difluorbiphenylyl)-4-oxo-2-methylbutanoic acid (VÚFB 16066, Flobufen) was chosen for further preclinical development.

As a part of our studies[1-4] on the relations between structure and biological activities of arylalkanoic acids *I* we also examined the synthesis of aryloxoalkanoic acids *II*. One of the acids which have this structure, 4-biphenyl-4-oxobutanoic acid, is a clinically tested antiphlogistic named fenbufen[5,6]. In our experiments with a series of acids *II* we examined the effect of the oxo group in the linking chain on some selected activities. We have demonstrated earlier by a comparison of the corresponding regression relations the existence of significant differences in the effect of the structural changes on fibrinolysis activation[7] and antiaggregation activity[8]. We have observed that the activation of fibrinolysis by acids *I* linearly depends on lipophilicity up to a certain optimal value[9,10] above which an abrupt decrease of the fibrinolytic capacity occurs. This lipophilicity optimum lies in the range of log *P* 4·4 to 4·9. The dependence of fibrinolytic capacity of acids *II* on lipophilicity has a quadratic character[7] with an optimum at $\log P_{opt} = 4{\cdot}4$. The range of the linear dependence on lipophilicity is slightly shifted toward higher activity values, however, in the

neighborhood of the maximum the fibrinolytic capacity does not reach those of acids *I* which have the same lipophilicity. Likewise, the antiaggregation activity as assayed by measurement of inhibition of the collagen-induced aggregation of blood platelets shows a dependence on the physico-chemical parameters which is different for the two groups of acids. We observed[9,11] in the series of 2-aryl-alkanoic acids (*I*, Y = = CH(R), R = H or alkyl), in addition to the steric and hyperconjugation effect of substituents R, a quadratic profile of the dependence on lipophilicity with an optimum at log P_{opt} = 4·05. The plot of antiaggregation activity of acids *II* and of their biphenyl derivatives *III* versus lipophilicity is also characterized[8] by a parabola yet with the optimum shifted toward a lower value of log P_{opt} = 3·02. When evaluating the antiinflammatory activity of acids *II* and *III* we also examined the dependence on the physico-chemical and structural parameters of these compounds in an effort to optimalize their structures.

Acids *II* and *III* were synthesized by the Friedel–Crafts reaction[12,13] of dicarboxylic acids anhydrides *IV* with the appropriate benzene derivatives.



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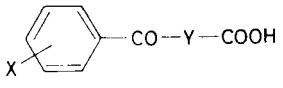

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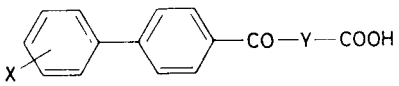

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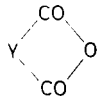


IV

EXPERIMENTAL

Methods

The ^1H NMR spectra of acids *II* and *III* were measured in 6% solution of deuteriochloroform containing tetramethylsilane as an internal standard in Model BS 487s—80 MHz Tesla(Czechoslovakia) spectrometer. The spectra of all compounds were in agreement with the structures postulated. The presence of the 3-methyl isomer in acids *IIIb,f—i* was assayed, after esterification by diazomethane, by gas chromatography in Fractovap 2 450 (Carlo Erba, Italy) using a capillary column of fused silica, 25 m long, i.d. 0·22 mm, moistened with SE-54, thickness of coating 0·2 μm.

The partition coefficients of selected acids *II* and *III* were determined by the extraction technique[14] in the system 1-octanol–aqueous acetate buffer (pH 3·5). The concentrations of the acids were measured spectrophotometrically for each phase in Unicam Model SP 8 000 spectrophotometer, the partition coefficient was calculated as a ratio of concentrations in the octanol and water phase: $P = c_o/c_w$. The logarithms of the partition coefficients of acids *II* and *III* which were

not determined experimentally were calculated from the following equation

$$\log P = \log P_H + \sum\pi ,$$

where P_H stands for the partition coefficient of the corresponding unsubstituted compound and $\sum\pi$ is the sum of lipophilicity parameters π at the aromatic ring determined[15] for benzoic acids.

The p*K values* of the selected acids were determined[8] in 80% methylcellosolve at 25°C in Model SBR-2c Titrigraph (Radiometer, Copenhagen, Denmark). The comparison of the values obtained shows that the acidity of acids *II*, *III* is practically unaffected by substituents of the aromatic ring; a more marked effect was observed after linking chain Y had been changed. The following values of ΔpK were used in the regression analysis: 0 for Y = CH_2CH_2, 0·27 for Y = $CH_2CH.(CH_3)$, 0·13 for Y = $CH_2CH_2CH_2$, and 0·43 for Y = $CH_2CH(CH_3)CH_2$, which were derived from experiments with the corresponding biphenyl derivatives *IIIa–d*.

Analysis of the quantitative relations between antiinflammatory activity and structure. For this analysis we employed indicator variables I_L, I_M and I_C. I_L characterizes the length of linking chain Y and has a value of 2 for 4-aryl-4-oxobutanoic acids and their 2-methyl derivatives, a value of 3 for 5-aryl-5-oxopentanoic acids and their 3-methyl derivatives. Variable I_M determines the presence of a methyl in linker chain Y (value of 1) whereas acids lacking the methyl have $I_M = 0$. Variable I_C has a value of 1 for acids substituted at the benzene ring by a phenyl or a cyclohexyl; for the remaining acids $I_C = 0$.

The regression coefficients in the correlation equations were computed from the experimental data by multiple regression analysis. The statistical significance of the equations was evaluated by correlation coefficient r, standard deviation s, and Fischer–Senedecor criterion F. The individual parameters were evaluated by the Student t-test at a statistical confidence level of $\alpha \leqq 0{\cdot}005$.

The antiinflammatory activity was assayed with two experimental inflammation models. The inhibition of the Freund adjuvant edema was examined according to Pearson and Wood[16], the inhibition of the carageenan edema according to Winter[17]; the experimental techniques have been described elsewhere[18]. The activity was expressed in % of edema inhibition compared to a control group of untreated rats; the activity indexes I^F and I^C were calculated as the ratio of the activity of the compound tested to that of the standard, i.e. 2-(4′-isobutylphenyl)propanoic acid (Ibuprofen).

Chemicals

Methylsuccinic anhydride IV (Y = $CH_2CH(CH_3)$) was prepared from methylsuccinic acid by treatment with acetic anhydride in analogy to procedure[19] in a yield of 86%, b.p. 100–102°C/0·4 kPa). Succinic acid was prepared according to literature[20] in a yield of 50%. The synthesis of ω-aryl-ω-oxoalkanoic acids *II* including the determination of their physico-chemical characteristics have been described elsewhere[8].

Substituted ω-biphenyl-ω-oxoalkanoic acids III. A mixture of anhydride *IV* (0·26 mol) and of the corresponding biphenyl (0·26 mol) was dissolved in 200 ml of 1,2-dichloroethane. Aluminum chloride (42·7 g; 0·32 mol) was added in parts at 8–12°C to the solution precooled at 8°C. The mixture was then stirred 4 h at 10°C, 4 h at 20°C and was poured after 12 h into a mixture of 520 g of ice and 150 ml of concentrated hydrochloric acid. The precipitate formed was filtered off by suction, was dissolved in 250 ml of 5% NaOH and the turbid solution was filtered over charcoal. Upon acidification by 50% H_2SO_4 the crude product had separated which was subsequently purified by crystallization from an aqueous solvent (cf. Table I).

TABLE I

Characterization of substituted ω-biphenylyl-ω-oxoalkanoic acids *III*

Acid yield, %	Y	X	M.p., °C solvent[a]	^{1}H NMR		Formula (mol. wt.)	Calculated/found		
				δ(2-CH_3)	δ(3-CH_3)		% C	% H	% X[b]
IIIe	CH_2CH_2	2,4-F_2	138–140	—	—	$C_{16}H_{12}F_2O_3$	66·20	4·17	13·09
23·4			AA–W 2 : 1			(390·3)	66·42	4·14	13·40
IIIf	$CH_2CH(CH_3)$	2,4-F_2	171–173	1·22	1·14	$C_{17}H_{14}F_2O_3$	67·10	4·64	12·49
40·2			T[c]			(304·3)	67·07	5·71	12·55
IIIg	$CH_2CH(CH_3)$	2,4-Cl_2	155–156·5	1·20	1·12	$C_{17}H_{14}Cl_2O_3$	60·55	4·18	21·03
10·7[d]			AA–W 2 : 1			(337·2)	60·49	4·25	21·01
IIIh	$CH_2CH(CH_3)$	4-F	170–173	1·20	1·11	$C_{17}H_{15}FO_3$	71·32	5·28	6·64
19·0			AA–W 2 : 1			(286·3)	71·21	5·42	6·62
IIIi	$CH_4CH(CH_3)$	4-Br	291	1·20	1·10	$C_{17}H_{15}BrO_3$	58·60	4·35	23·02
30·6			AA–W 3 : 1			(347·2)	58·74	4·52	22·80

[a] Solvents used: AA acetic acid, W water, T toluene; [b] i.e. a halogen; [c] the product was subjected to an additional crystallization from 1,2-dichloroethane to remove the 3-methyl isomer; [d] in addition to the 2-methyl isomer the 3-methyl isomer was also isolated in a yield of 20·2% (m.p. 136–138°C, methanol–water 3 : 1).

RESULTS AND DISCUSSION

The reaction of methylsuccinic anhydride with benzene derivatives gives rise predominantly to the required 2-methyl isomer which is accompanied by the 3-methyl isomer as minority side product. The presence of the 3-methyl isomer manifested itself by the doubling of the CH_3 signal in the ^1H NMR spectrum (cf. Table I). The quantitative determination of the content of both isomers was effected by capillary gas chromatography. The content of the 3-methyl derivative in the crude product varies between 5 and 20% according to the reaction conditions employed and most likely also according to the character of substitution of the benzene ring. The unwanted 3-methyl isomer can be separated by crystallization from an appropriate solvent.

The results of the evaluation of the antiinflammatory effect of the basic series of aryloxoalkanoic acids *IIa–p* and *IIIa–d* with two experimental edema models are summarized in Table II. The regression analysis of the inhibition of the carageenan edema yielded Eqs (*1*)–(*4*).

$$\log I^C = 0{\cdot}124 \log P - 0{\cdot}594 \qquad (1)$$
$$n = 15\,, \quad r = 0{\cdot}734\,, \quad s = 0{\cdot}106\,, \quad F = 15{\cdot}2\,.$$

$$\log I^C = 0{\cdot}107 \log P + 0{\cdot}188 I_C - 0{\cdot}579 \qquad (2)$$
$$n = 15\,, \quad r = 0{\cdot}893\,, \quad s = 0{\cdot}073\,, \quad F = 23{\cdot}7\,.$$

$$\log I^C = 0{\cdot}112 \log P + 0{\cdot}112 I_C - 0{\cdot}074 I_L - 0{\cdot}428 \qquad (3)$$
$$n = 15\,, \quad r = 0{\cdot}921\,, \quad s = 0{\cdot}068\,, \quad F = 20{\cdot}4\,.$$

$$\log I^C = 0{\cdot}111 \log P - 0{\cdot}094 I_L + 0{\cdot}194 I_C + 0{\cdot}086 I_M - 0{\cdot}412 \qquad (4)$$
$$n = 15\,, \quad r = 0{\cdot}961\,, \quad s = 0{\cdot}049\,, \quad F = 30{\cdot}0\,.$$

The correlation matrix set shown in Table III permits us to conclude that a correct interpretation of the regression equations is slightly complicated by the colinearity existing between the values of ΔpK and indicator variable I_M. The replacement of ΔpK by I_M in Eq. (*4*) leads to Eq. (*5*) which does not differ any considerably from the preceding one in its statistical significance

$$\log I^C = 0{\cdot}119 \log P + 0{\cdot}187 I_C - 0{\cdot}142 I_L + 0{\cdot}288\ \Delta pK - 0{\cdot}325 \qquad (5)$$
$$n = 15\,, \quad r = 0{\cdot}957\,, \quad F = 27{\cdot}4\,.$$

The regression equations lead us to the conclusion that the inhibition of the carageenan edema is influenced to a certain degree by the lipophilicity of the acids studied;

the dependence on lipophilicity is characterized by the low slope value. The additional structural parameters used in the regression analysis have the character of indicator variables. It is obvious from Eq. (*4*) that in addition to lipophilicity the inhibition of the carageenan edema is positively influenced by the presence of a cyclohexyl or phenyl as substituent at the aromatic ring. The dependence on variable I_L indicates the negative effect of the extension of linking chain Y on the activity. The presence of a methyl (I_M) slightly increases the inhibition of the carageenan edema, most likely due to a decrease of the acidity of the acids studied (Eq. (*5*)). We carried out the regression analysis of the inhibition of the adjuvant edema also

TABLE II

Antiinflammatory activity of aryloxoalkanoic acids *II* and *III*

Acid	X	Y	log *P*	Antiinflammatory activity[b]			
				I^C	log I^C	I^F	log I^F
IIa	H	CH_2CH_2	1·30[a]	0·40	−0·398	n	—
IIb	3-Cl-4-CH_3O	CH_2CH_2	1·98	0·36	−0·444	n	—
IIc	4-i-C_3H_7O	CH_2CH_2	2·18	0·45	−0·347	0·54	−0·268
IId	3-Cl-4-i-C_3H_7O	CH_2CH_2	2·78	0·51	−0·292	0·65	−0·187
IIe	4-i-C_4H_9	CH_2CH_2	3·20	0·54	−0·268	0·64	−0·194
IIf	4-c-C_6H_{11}	CH_2CH_2	3·76	0·78	−0·108	0·89	−0·051
IIg	3-Cl-4-c-C_6H_{11}	CH_2CH_2	4·36	0·80	−0·097	1·20	0·079
IIh	H	$CH_2CH(CH_3)$	1·62[a]	0·43	−0·366	ne	—
IIi	4-c-C_6H_{11}	$CH_2CH(CH_3)$	4·08	0·82	−0·060	1·06	0·025
IIk	4-i-C_3H_7	$CH_2CH_2CH_2$	2·89	n	—	0·44	−0·356
III	4-i-C_4H_9	$CH_2CH_2CH_2$	3·39	0·54	−0·268	0·70	−0·156
IIm	4-c-C_6H_{11}	$CH_2CH_2CH_2$	3·95	ne	—	0·76	−0·119
IIn	3-Cl-4-CH_3O	$CH_2CH(CH_3)CH_2$	2·60[a]	0·51	−0·292	0·33	−0·481
IIo	3-Cl-4-i-C_3H_7O	$CH_4CH(CH_3)CH_2$	3·40	0·61	−0·215	0·43	−0·366
IIp	4-c-C_6H_{11}	$CH_2CH(CH_3)CH_2$	4·38	ne	—	0·76	−0·222
IIIa	4-C_6H_5	CH_2CH_2	3·20[a]	1·02	0·009	1·18	0·072
IIIb	4-C_6H_5	$CH_2CH(CH_3)$	3·40[a]	1·22	0·086	1·39	0·143
IIIc	4-C_6H_5	$CH_2CH_2CH_2$	3·35[a]	0·62	−0·208	0·98	−0·009
IIId	4-C_6H_5	$CH_2CH(CH_3)CH_2$	3·82[a]	n	—	0·60	−0·222
IIIe	4-(2,4-$F_2C_6H_3$)	CH_2CH_2	3·58	0·94	−0·027	0·80	−0·097
IIIf	4-(2,4-$F_4C_6H_3$)	$CH_2CH(CH_3)$	3·78[a]	1·17	0·068	1·26	0·100
IIIg	4-(2,4-$Cl_2C_6H_3$)	$CH_2CH(CH_3)$	5·14	1·22	0·086	1·40	0·146
IIIh	4-(4-FC_6H_4)	$CH_2CH(CH_3)$	3·59	0·92	−0·036	1·05	0·021
IIIi	4-(4-BrC_6H_4)	$CH_2CH(CH_3)$	4·38	0·80	−0·065	1·32	0·120

[a] The values were determined experimentally; [b] n stands for a statistically insignificant effect, ne stands for effect not evaluated.

with a series of acids *II* and *III* and obtained the following regression equations (*6*)–(*9*).

$$\log I^F = 0{\cdot}149 \log P - 0{\cdot}196 I_L - 0{\cdot}170 \qquad (6)$$
$$n = 16\,, \quad s = 0{\cdot}780\,, \quad r = 0{\cdot}113\,, \quad F = 10{\cdot}1\,.$$

$$\log I^F = 0{\cdot}147 \log P - 0{\cdot}196 I_L + 0{\cdot}158 I_C - 0{\cdot}202 \qquad (7)$$
$$n = 16\,, \quad s = 0{\cdot}885\,, \quad r = 0{\cdot}088\,, \quad F = 14{\cdot}5\,.$$

$$\log I^F = 0{\cdot}168 \log P - 0{\cdot}170 I_L + 0{\cdot}177 I_C - 0{\cdot}115 I_M - 0{\cdot}301 \qquad (8)$$
$$n = 16\,, \quad s = 0{\cdot}940\,, \quad r = 0{\cdot}067\,, \quad F = 21{\cdot}0\,.$$

$$\log I^F = 0{\cdot}194 \log P - 0{\cdot}133 I_L + 0{\cdot}216 I_C - 0{\cdot}471\ \Delta pK - 0{\cdot}458 \qquad (9)$$
$$n = 16\,, \quad s = 0{\cdot}937\,, \quad r = 0{\cdot}082\,, \quad F = 19{\cdot}8\,.$$

Also in this case there is a considerable colinearity (Table IV) between the values of ΔpK and indicator variable I_M. As a result the statistical significance of equations (*8*) and (*9*) is similar. On the whole the results of the regression analysis have shown that the inhibition of the adjuvant edema is affected by lipophilicity, length of linking chain Y and by the presence of aromatic substituents at the aromatic ring. The presence of a methyl in position 2 manifests itself in a different manner whose interpretation is related most likely to the mechanism of action. One of the possibili-

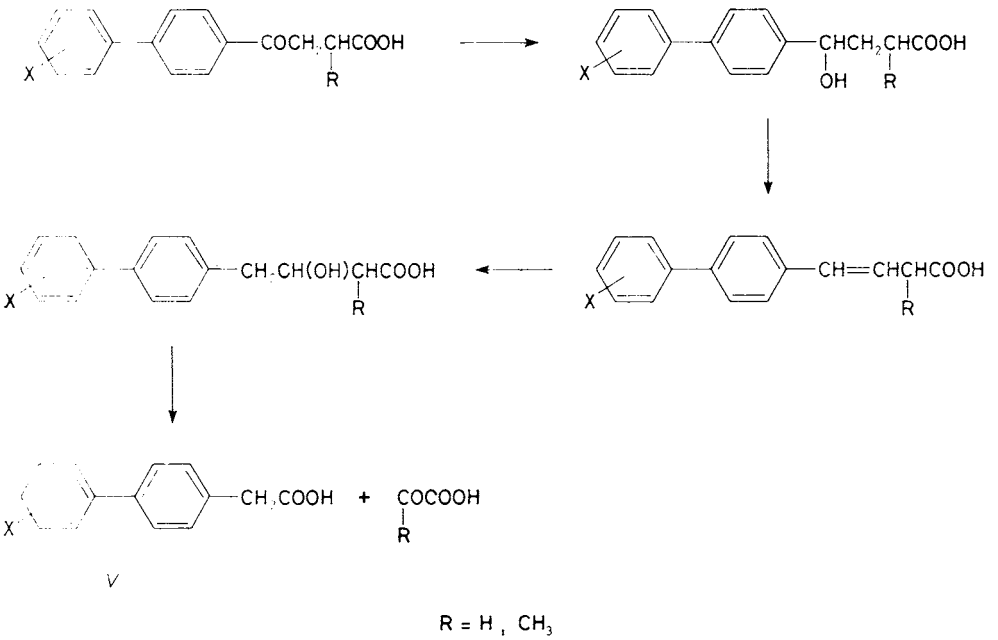
TABLE III

Correlation matrix of parameters for regression equations describing inhibition of carageenan edema (the first value holds for Eqs (*1*)–(*5*), the values in parentheses for Eq. (*10*)

Parameter	log *P*	I_L	I_M	I_C	*h*	ΔpK	log I^C
log *P*	1	0·149 (0·037)	0·039 (0·291)	0·201 (0·480)		0·096 (0·240)	0·734 (0·802)
I_L		1	0·213 (0·060)	0·075 (0·153)		0·578 (0·426)	0·087 (0·252)
I_M			1	0 (0·287)		0·920 (0·924)	0·246 (0·400)
I_C				1		0·015 (0·186)	0·647 (0·762)
ΔpK						1	0·129 (0·257)

ties is that it is due to the difference in the effect of the methyl on the acidity of these acids and on their transformation to an active metabolite.

We may conclude from the results of the regression analysis that a high antiinflammatory activity can be expected with lipophilic 4-aryl-4-oxobutanoic acids and their 2-methyl derivatives substituted by a phenyl or a cyclohexyl. The acids *IIIa* and *IIIb* belonging to the basic series conform with these requirements. They show a high antiinflammatory effect in both tests. We observed during an additional examination of the antiinflammatory activity of the biphenyl derivatives of oxoalkanoic acids *IIIa–d* that their antiinflammatory effect persists for a longer period. A high antiinflammatory effect, examined in terms of inhibition of the carageenan edema, showed acids *IIIa–c* even 24 and 48 h after their application (Table V). The prolongation of the effect of a drug is generally significantly affected by its pharmacokinetics. The controlling process in the series of oxoalkanoic acids *II* and *III* studied is probably the biotransformation which gives rise to active metabolites[21], mainly to the corresponding arylacetic acid. We may assume that the biotransformation of acids *III* to acids *V* (Scheme 1) follows a pathway similar* to that of the meta-



SCHEME 1

* The results of a metabolic study of acids *III* will be reported elsewhere.

bolism of neuroleptically active substituted 1-aminobutyrophenones[22,23]; hence, the first step in the biotransformation sequence represents the reduction of the oxo

TABLE IV

Correlation matrix of parameters for regression equations describing inhibition of adjuvant edema (the first value holds for Eqs (*6*)—(*9*), the values in parentheses for Eq. (*11*)

Parameter	log *P*	I_L	I_M	I_C	Δp*K*	log I^F
log *P*	1	0·085 (0·128)	0·247 (0·394)	0·020 (0·290)	0·230 (0·281)	0·497 (0·625)
I_L		1	0·258 (0·037)	0 (0·293)	0·620 (0·483)	0f549 (0·635)
I_M			1	0·149 (0·330)	0·917 (0·905)	0·235 (0·096)
I_C				1	0·114 (0·154)	0·447 (0·601)
Δp*K*					1	0·435 (0·216)

TABLE V

Prolongation of antiinflammatory effect of acids *III*

Number	% of inhibition of carageenan edema[a]				
	1	16	24	48	72
IIIa	46	45	38	0	—[b]
IIIb	55	33	34	12	0
IIIc	28	33	30	20	0
IIIe[c]	25	22	36	48	45
IIIf	40	45	73	58	50
IIIg	44	—[b]	66	50	35
IIIh	33	—[b]	34	25	—[b]

[a] The edema was measured 1, 16, 24, 48, and 72 h after p.o. administration of the compound (dose 100 mg/kg); [b] evaluation not performed; [c] because of its toxicity compound *IIIe* was applied in a dose of 10 mg/kg; for comparison the antiinflammatory activity of the same dose of compound *IIIf* was also evaluated and the following inhibition values were obtained (in %): 31, 35, 43, 57, and 50.

group. As a guideline for the further development of acids *III* with a prolonged antiinflammatory action we adopted a working hypothesis assuming that the acids must conform with the following requirements in order for their effect to be prolonged: (i) the biotransformation to the active metabolite must be fast, (ii) the subsequent conversion of the active metabolite must be slow to develop its sufficient pool in the blood.

Polarographic reduction may serve as a model reaction for the first step of the biotransformation sequence. We may conclude from the values of the half-wave potentials $E_{1/2}$ that the presence of a biphenyl residue decreasing the half-wave potential by c. 0·2–0·25 V makes the reduction of the carbonyl group easier. The second condition on which the prolongation of the effect is based could be probably satisfied by an appropriate substitution of the aromatic ring. Active metabolite *V* could be probably protected against elimination from the blood stream by preventing its aromatic rings from hydroxylation. The development of appropriate derivatives of oxoalkanoic acids showing a high and at the same time prolonged effect was based on the knowledge of the structural requirements which follow from the results of the regression analysis and also from the hypothesis of biotransformation of these acids. The derivatives which comply best with these requirements are the biphenyl derivatives of 4-oxobutanoic and 2-methyl-4-oxobutanoic acid with their outer aromatic rings substituted by one or more halogen atoms. The choice of the halogens as suitable substituents was dictated by an effort to prevent the hydroxylation reaction with the simultaneous stepwise increase of the lipophilicity without any large sterical consequences. We prepared therefore acids *IIIe–i*; the results of the evaluation of their antiinflammatory activity are shown in Tables II and V. It can be seen that the newly prepared derivatives possess, in accordance with our preceding assumptions, both a high and a prolonged antiinflammatory effect. The relevance of regression equations (*4*) and (*8*), derived for the basic series of oxoalkanoic acids proves a similarity of corresponding equations (*10*) and (*11*), obtained with an extended series of the acids.

$$\log I^{C} = 0{\cdot}096 \log P - 0{\cdot}070 I_{L} + 0{\cdot}146 I_{C} + 0{\cdot}040 I_{M} - 0{\cdot}399 \qquad (10)$$

$$n = 20\,, \quad r = 0{\cdot}931\,, \quad s = 0{\cdot}069\,, \quad F = 24{\cdot}4\,.$$

$$\log I^{F} = 0{\cdot}142 \log P - 0{\cdot}159 I_{L} + 0{\cdot}138 I_{C} - 0{\cdot}081 I_{M} - 0{\cdot}252 \qquad (11)$$

$$n = 21\,, \quad r = 0{\cdot}915\,, \quad s = 0{\cdot}080\,, \quad F = 20{\cdot}6\,.$$

From the above experimental results 4-(2′,4′-difluorobiphenylyl)-4-oxo-2-methylbutanoic acid (Flobufen) was chosen for further preclinical development.

The elemental analyses were carried out in the Department of Microanalysis of the Institute for Pharmacy and Biochemistry (Head Dr J. Körbl), the polarographic measurements of the

half-wave potentials were performed by Dr. E. Svátek in the Department of Physical Chemistry of the Institute for Pharmacy and Biochemistry (Head Dr V. Rejholec).

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