BENZYLOXYARYLALIPHATIC ACIDS: SYNTHESIS AND QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTIINFLAMMATORY ACTIVITY

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The paper describes synthesis of substituted benzyloxyarylaliphatic acids, *I*—*V*, and their efficacy in stabilization the erythrocyte membrane against hypotonic haemolysis and their antiinflammatory effect in inhibition of the kaolin oedema. The quantitative relations between these efficacies and the physico-chemical and structural parameters of the acids have been analysed. The two activities depend on the overall lipophilicity and acidity of the acids. In the investigated range of lipophilicity the dependence of the antiinflammatory effect on lipophilicity had a parabolic course, whereas in stabilization of the erythrocyte membrane this dependence was linear. In either case the efficacy was suppressed by extending the connecting chain between the carboxyl and the aromatic ring. Regression analysis suggests that in the group of benzyloxyarylaliphatic acids it is not possible to prepare compounds more effective than 3-chloro-4-benzyloxyphenylacetic acid (benzofenac, *Ia*) and its 2-methyl analogue *IIa*.

To optimize the structure of antiinflammatory arylaliphatic acids[1-3], by means of regression analysis[4,5] of quantitative relations between structure and biological activity, we synthetized[6,7] a series of substituted benzyloxyarylacetic acids, *I*. The results thus far obtained have shown that inhibition of the kaolin oedema is dependent quadratically on lipophilicity of the variable substituents, and is linearly proportional to electronegativity of the substituents at *meta*-position to the residue of acetic acid. One of the compounds of this series, *viz.* 3-chloro-4-benzyloxyphenylacetic acid (benzofenac VÚFB), has proved so promising pharmacologically[8] that it was taken for clinical studies. Judging by the almost identical results obtained with a series of the acids *I*, extended to include further alkoxy derivatives[9], the antiinflammatory effect is not influenced by other properties of the benzyloxy group than lipophilicity and electronegativity. We arrived at a similar conclusion previously[9] by analysing the relation of stabilization of the erythrocyte membrane to the physico-chemical properties in the same series of acids. As in the series of 3-aryl-n-butyric acids[3], the difference between the two activities manifested itself only in the region of higher lipophilicity, where the dependence of inhibition of the kaolin oedema on lipo-

philicity took a parabolic course, whereas the dependence of the stabilization effect was linear.

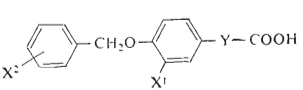
In the regression analyses of the antiinflammatory and stabilization effects of series of arylacetic acids we characterized[9] the lipophilicity of the benzyloxy derivatives in terms of the π or $\sum\pi$ values obtained from partition chromatography[10]. These values were lower than the tabulated ones, probably because of a hydrophobic interaction between the two aromatic rings. The partition chromatography of a series of the acids *I* showed[9] that further substitution on the benzyl residue influences the overall lipophilicity in the additive way.

To assess the effect of the chain connecting the carboxyl and the aromatic ring on the antiinflammatory and stabilization efficacy we also prepared, in addition to the substituted benzyloxyarylacetic acids *I*, analogous derivatives of arylaliphatic acids, *II* – *V*. Regression analyses of dependences of these efficacies on the physico-chemical properties have been performed and the obtained regression relations have been compared with the results[6,7,9] of QSAR in a series of arylacetic acids. The compounds *II* – *V* were prepared by benzylation of methyl esters of the corresponding 4-hydroxyarylaliphatic acids *VI*, which method proved good in synthesis of the acids *I*. The acids *II* – *V* were identified by elemental analyses and ^{1}H NMR spectra which were consistent with the structures proposed in all cases. Most of the esters *VI* were described in the syntheses of the analogous alkoxy derivatives[6,11,12].

I, Y = CH_2 *III*, Y = $CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}H$

II, Y = $\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}H$ *IV*, Y = CH_2-CH_2

V, Y = $\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}H-CH_2$



I – *V*

EXPERIMENTAL

Methods

The ^{1}H NMR spectra of acids *II* – *V* were obtained employing a spectrometer BS 487c-80 Hz (Tesla, Czechoslovakia) and 6% solutions in deuteriochloroform, with tetramethylsilane as internal standard. The p*K* values of the acids *Ia* (6·78), *IIa* (6·81), *IIIa* (6·96), *IVa* (7·02), *IVe* (6·89) and *Va* (7·21 were determined at 25°C in 80% methylcellosolve, using a potentiometer Titrigraph Radiometer SBR-2c (Copenhangen, Denmark). The partition coefficients of the acids, given in Table I, were obtained by the standard technique[13] in a system n-octanol–water, with either phase being pre-saturated with the other. To eliminate the effect of dissociation, the aqueous phase employed was an acetate buffer pH 3·5. Concentrations of the acids in the two phases were determined spectrophotometrically with a spectrometer Unicam SP 8000, and the distribution coefficients were calculated as the ratio of concentrations in the n-octanol and the aqueous phases, $P = C_0/C_w$.

The lipophilicities of 4-benzyloxy and 3-chloro-4-benzyloxy substituents are expressed by π values, 1·31 and 1·81 respectively, obtained[10] from partition chromatography on a thin layer of silica gel impregnated with silicone oil, 50% acetone being employed as the mobile phase. Parameters π calculated[14] for substituted benzyl alcohols were used for substituents X[2] on the benzyl residue. To calculate the parameters π of the higher alkyls and alkoxy groups, the following increments[13] were used: $\Delta\pi(CH_2$ aliphatic$) = 0{\cdot}50$, $\Delta\pi$ (branching) $= -0{\cdot}20$. With the 3,4-disubstituted derivatives we took into account the decrease in lipophilicity associated with intramolecular interactions of the two substituents at the *ortho*-position. The sum of the parameters π was reduced by 0·23, in accordance with the results of partition chromatography of 3,4-disubstituted derivatives of arylaliphatic acids[9,10,15,16]. The lipophilicity of the connecting chain between the carboxyl and the aromatic ring was characterized by values $\Delta\pi$ (Table I), which were calculated as the difference between the lipophilicities of the corresponding phenylaliphatic acid and phenylacetic acid:

$$\Delta\pi = \log P(C_6H_5\text{—Y—COOH}) - \log P(C_6H_5CH_2COOH)$$

The polar effects on acidity of the acids *I* and *V* are expressed by differences of pK values in 80% methylcellosolve from the pK of the strongest acid of the series, *Ia*. Since substitution on the benzyl residue practically does not affect the acidity[17,18], a common value of ΔpK was used for each group of the acids *I*—*V*. These quantities were calculated from the experimental values of the pK of the corresponding non-substituted benzyloxy derivatives, *IIa*, *IIIa*, *IVa*, *IVf* and *Va*, by subtracting the pK value of the acid *IIa* (see note *c* under Table III).

The regression coefficients in the equations were calculated from experimental data by multiple regression analysis on a computer Hewlett-Packard 9820. The statistical significance of the equations was evaluated by means of the correlation coefficient r, standard deviation s and the Fischer–Snedecor criterion F. The individual parameters in the multiparameter equations were statistically evalued by the Student t-test on a statistical significance level of $\alpha \leq 0{\cdot}005$ (the corresponding limits of reliability are given in parentheses after the regression coefficients).

Assessment of Biological Activities

The stabilization of erythrocyte membranes was determined according to Kalbhen[19], using a modification of the method[1]. The efficacy, expressed by molar concentration C^{s1}, producing

TABLE I

Values of $\Delta\pi$ characterizing lipophilicity of the connecting chain

Acid	Y	log $P(C_6H_5$—Y—COOH)	$\Delta\pi$
Phenylacetic	—CH_2—	1·45[a]	0
2 Phenylpropionic	—$CH(CH_3)$—	1·80	0·35
2-Methyl-3-phenylpropionic	—$CH(CH_3)CH_2$—	2·20[b]	0·75
3-Phenylpropionic	—CH_2CH_2—	1·91[c]	0·46
3-Phenyl-n-butyric	—$CH_2CH(CH_3)$—	2·18[b]	0·73

[a] The same value is given in the literature[14]; [b] reported[17] log P of the isomeric 4-phenylbutyric acid is 2·42; [c] reported[17] log $P = 1{\cdot}84$.

a 50% stabilization was referred to that of the standard compound, *viz.* the acid *Ia*. Inhibition of the kaolin oedema was assessed by the Hillebrecht method[20], which was described previously[6,9]. The effect of a compound was expressed in % of inhibition of an inflammation in comparison with the untreated groups, and the activity index I^K was calculated as ratio of the effects of a tested compound and the standard, which was 2-(4′-isobutylphenyl)propionic acid.

Methyl Esters of 4-Hydroxyarylaliphatic Acids (*VI*)

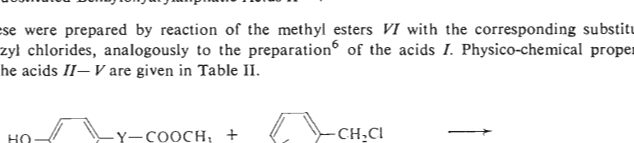
Preparation of ester *VIa* (Y = CH_2, X^1 = Cl) is described in ref.[6], esters *VIb* (Y = $CH(CH_3)$, X^1 = Cl) and *VIc,d* (Y = CH_2CH_2, X^1 = H, Cl) in ref.[12], and ester *VIe* (Y = $CH_2CH(CH_3)$, X^1 = Cl) in ref.[11].

Methyl Ester of 3-(4′-Hydroxyphenyl)-n-butyric Acid (*VIf*)

A mixture of 3-(4-methoxyphenyl)-n-butyric acid (50 g) and 52% hydrobromic acid (400 ml) was stirred and refluxed for 15 h. After cooling down the mixture was extracted with ether. The ethereal extract was washed with water and dried with magnesium sulphate. After evaporation of the ether there was obtained 45 g of 3-(4-hydroxyphenyl)-n-butyric acid, m.p. 133—135°C (reported[21], m.p. 136—138°C). The crude acid was esterificed by boiling in 5% methanolic hydrogen chloride, analogously to a described procedure[21]. Distillation gave the product *VIf* as a liquid boiling at 118—120°C/13 Pa (reported[21] b.p. 165—170°C/1·07—1·2 kPa). For $C_{11}H_{14}O_3$ (194·2) calculated: 68·02% C, 7·26% H; found: 68·21% C, 7·18% H.

Substituted Benzyloxyarylaliphatic Acids *II—V*

These were prepared by reaction of the methyl esters *VI* with the corresponding substituted benzyl chlorides, analogously to the preparation[6] of the acids *I*. Physico-chemical properties of the acids *II—V* are given in Table II.



SCHEME 1

RESULTS AND DISCUSSION

Using regression analysis of the experimental results, stabilization of red-blood-cell membrane in the series of acids *I – V* (Table III) can be described by the equation:

$$\log(1/C^{St}) = 0{\cdot}271(\pm 0{\cdot}094)(\sum\pi + \Delta\pi) - 1{\cdot}283(\pm 0{\cdot}402)\,\Delta pK + 3{\cdot}265(\pm 0{\cdot}284)$$
$$n = 27\,,\quad r = 0{\cdot}946\,,\quad s = 0{\cdot}089\,,\quad F = 102{\cdot}4 \qquad (1)$$

The quantity $\sum\pi$ denotes the sum of parameters π of substituents X^1 and X^2, including the benzyloxy group, $\Delta\pi$ characterizes the lipophilicity of the chain connecting the carboxyl and the aromatic ring. As an electron parameter we used the quantity ΔpK, whose values are given in note *c* under Table III. The statistical significance of equation (*1*) was not increased by introducing squares of the lipophilicity parameters into it, but a marked improvement was achieved by introduction of an indicator

TABLE II

Physico-chemical data of acids *II*–*V*

Number	X^1 X^2	Yield[a] %	M.p., °C solvent[b]	Calculated/Found		
				% C	% H	% Cl
		2-Arylpropionic				
IIa	Cl	68·8	109–110	66·05	5·20	12·19
	H		M/W 2 : 1	65·90	5·01	12·35
IIb	Cl	70·4	125·5–127	57·50	4·55	19·98
	3-Cl-4-CH_3O		M/W 2 : 1	57·08	4·73	19·72
IIc	Cl	52·0	95·5–97·5	65·42	6·07	10·16
	4-i-C_3H_7O		M/W 2 : 1	65·81	6·22	9·81
IId	Cl	70·8	103·5–105	59·05	4·35	21·82
	4-Cl		M/W 2 : 1	59·07	4·32	21·66
IIe	Cl	60·2	101·5–103	68·56	6·36	10·65
	4-i-C_3H_7		M/W 3 : 1	68·27	6·74	10·40
IIf	Cl	56·0	84–86	59·50	5·25	18·50
	3-Cl-4-i-C_3H_7O		M/W 2 : 1	59·36	5·29	18·53
		2-Methyl-3-arylpropionic				
IIIa	Cl	64·5	84–85	67·02	5·62	11·64
	H		M/W 2 : 1	66·96	5·75	11·93
IIIb	Cl	76·2	116–117	58·52	4·92	19·21
	3-Cl-4-CH_3O		M/W 3 : 1	58·12	4·94	19·37
IIIc	Cl	75·0	69–71	66·20	6·39	9·77
	4-i-C_3H_7O		M/W 3 : 1	66·11	6·46	9·92
IIId	Cl	71·6	98–100	60·19	4·75	20·91
	4-Cl		M/W 4 : 1	59·73	5·04	21·06
IIIe	Cl	50·0	72·5–74	69·25	6·68	10·22
	4-i-C_3H_7		M/W 4 : 1	68·97	6·90	10·42

TABLE II
(*Continued*)

Number	X^1 X^2	Yield[a] %	M.p., °C solvent[b]	Calculated/Found		
				% C	% H	% Cl
		3-Arylpropionic				
IVa	H	64·7	120—121	74·98	6·29	—
	H		B/H 1 : 1	74·86	6·46	—
IVb	H	45·0	128—130	63·65	5·34	11·05
	3-Cl-4-CH_3O		H/B 3 : 2	63·82	5·31	11·13
IVc	H	40·0	149—151	72·58	7·05	—
	4-i-C_3H_7O		H/B 1 : 1	72·38	7·22	—
IVd	H	50·0	134—137	76·48	7·43	—
	4-i-C_3H_7		H/B 1 : 1	76·78	7·63	—
IVe	Cl	50·0	118—119	66·09	5·20	12·20
	H		H/B 1 : 1	66·21	5·33	11·98
IVf	Cl	49·0	109—112	53·65	5·34	11·05
	4-CH_3O		H/B 1 : 1	63·80	5·32	11·39
IVg	Cl	32·5	82—84	65·42	6·07	10·17
	4-i-C_3H_7O		H/B 5 : 3	65·66	6·22	10·31
IVh	Cl	53·0	93—95	68·56	6·36	10·65
	4-i-C_3H_7		H/B 5 : 3	68·77	6·22	10·48
		3-Aryl-n-butyric				
Va	H	60·0	96·5—97·5	75·53	6·71	—
	H		M/W 2 : 1	75·67	6·72	—
Vb	H	75·0	104—106	73·14	7·36	—
	4-i-C_3H_7O		M/W 2 : 1	73·33	7·42	—
Vc	H	55·0	129—130	66·99	5·62	11·63
	4-Cl		M/W 2 : 1	67·28	5·57	11·49

[a] The yield corresponds to reaction of ester of 4-hydroxyarylaliphatic acid with a substituted benzyl chloride, followed by hydrolysis; [b] symbols for solvents: M methanol, W water, H n-hexane, B benzene.

variable I_L, governed by the length of the connecting chain between the carboxyl and the aromatic ring (see equation (*8*)). For the acids *I* and *III* $I_L = 0$, *III*—*V* $I_L = 1$.

TABLE III

Physico-chemical and biological properties of benzyloxyarylaliphatic acids

Number	X^1 X^2	$\sum\pi + \Delta\pi$	C^{St} mol l^{-1}	$\log (1/C^{St})_{exp}$ $\log (1/C^{St})_{calc}$ [a]	I^K	$\log (I^K)_{exp}$ $\log (I^K)_{calc}$ [b]
Ia	Cl [c]	1·81	2·023	3·694	1·18	0·072
	H			3·787		−0·062
Ib	Cl	2·61	0·929	4·032	0·76	−0·119
	4-i-C_3H_7O			3·995		−0·133
Ic	Cl	2·42	0·966	4·015	0·76	−0·119
	3-Cl-4-CH_3O			3·945		−0·086
Id	Cl	3·22	0·566	4·247	0·25	−0·602
	3-Cl-4-i-C_3H_7O			4·153		−0·417
Ie	Cl	3·21	0·533	4·273	0·15 [d]	—
	4-i-C_3H_7			4·151		—
IIa	Cl	2·16	1·687	3·773	1·08	0·036
	H			3·856		−0·062
IIb	Cl	2·77	1·000	4·000	0·43	−0·367
	3-Cl-4-CH_3O			4·015		−0·197
IIc	Cl	2·96	0·733	4·135	0·37	−0·432
	4-i-C_3H_7O			4·064		−0·310
IId	Cl	3·02	0·880	4·056	0·37	−0·432
	4-Cl			4·080		−0·310
IIe	Cl	3·56	0·656	4·183	0·15 [d]	—
	4-i-C_3H_7			4·220		—
IIf	Cl	3·57	0·568	4·246	0·22	−0·658
	3-Cl-4-i-C_3H_7O			4·223		−0·681
IIIa	Cl	2·51	1·972	3·705	0·48	−0·318
	H			3·661		−0·313
IIIb	Cl	3·12	1·567	3·805	0·33	−0·482
	3-Cl-4-CH_3O			3·891		−0·564
IIIc	Cl	3·31	1·202	3·920	0·26	−0·585
	4-i-C_3H_7O			3·869		−0·684
IIId	Cl	3·37	1·127	3·948		−0·721
	4-Cl			3·884	0·19	−0·725
IIIe	Cl	3·91	1·216	3·915	0·15 [d]	—
	4-i-C_3H_7			4·025		—
IVa	H	1·77	3·507	3·455	0·66	−0·180
	H			3·425		−0·298

TABLE III
(*Continued*)

Number	X^1 X^2	$\sum\pi + \Delta\pi$	C^{St} mol l^{-1} .	$\log(1/C^{St})_{exp}$ $\log(1/C^{St})_{calc}$ [a]	I^K	$\log(I^K)_{exp}$ $\log(I^K)_{calc}$ [b]
IVb	H	2·38	3·027	3·519	0·39	−0·409
	3-Cl-4-CH_3O			3·584		−0·303
IVc	H	2·57	2·085	3·681	0·27	−0·549
	4-i-C_3H_7O			3·636		−0·369
IVd	H	3·17	1·486	3·828	0·22	−0·658
	4-i-C_3H_7			3·789		−0·611
IVe	Cl	2·27	2·754	3·560	0·56	−0·252
	H			3·648		−0·250
IVf	Cl	2·27	2·404	3·619	0·63	−0·201
	4-CH_3O			3·648		−0·250
IVg	Cl	3·07	1·420	3·848	0·29	−0·538
	4-i-C_3H_7O			3·857		−0·615
IVh	Cl	3·67	0·802	4·096	0·15[d]	—
	4-i-C_3H_7			4·013		—
Va	H	2·01	4·121	3·385	0·61	−0·215
	H			3·351		−0·331
Vb	H	2·81	2·992	3·524	0·25	−0·602
	4-i-C_3H_7O			3·560		−0·483
Vc	H	2·87	2·904	3·537	0·25	−0·602
	4-Cl			3·575		−0·509

[a] Values calculated from equation (*3*); [b] values calculated from Eq. (*4*); [c] from the experimental values of pK of acids *Ia*, *IIa*, *IIIa*, *IVa*, *IVe* and *Va* the following ΔpK were calculated: 0 for acids *I*, 0·03 for acids *II*, 0·18 for acids *III*, 0·24 for acids *IVa—d*, 0·11 for acids *IVe—h*, and 0·43 for acids *V*; [d] the antiinflammatory activity was not significant and is not included in the regression analysis.

$$\log(1/C^{St}) = 0{\cdot}285(\pm 0{\cdot}068)\,(\sum\pi + \Delta\pi) - 0{\cdot}731(\pm 0{\cdot}462)\,\Delta pK - \\ - 0{\cdot}190(\pm 0{\cdot}124)\,I_L + 3{\cdot}260(\pm 0{\cdot}208)$$

$$n = 27\,, \quad r = 0{\cdot}973\,, \quad s = 0{\cdot}064, \quad F = 138{\cdot}3 \qquad (2)$$

In the series of the acids employed, the significance of the indicator variable is somewhat affected by its colinearity with the quantity ΔpK ($r = 0{\cdot}771$). For this reason we performed a common regression analysis of the series of acids *I—V*, supplemented

by the original[9] 15 substituted benzyloxyarylacetic acids. This led to equation (*3*), which is practically identical with equation (*2*). The interrelations of the parameters used are apparent from the correlation matrix (Table IV).

$$\log (1/C^{St}) = 0{\cdot}260(\pm 0{\cdot}048)\,(\sum\pi + \Delta\pi) - 0{\cdot}717(\pm 0{\cdot}256)\,\Delta pK - \\ - 0{\cdot}179(\pm 0{\cdot}068)\,I_L + 3{\cdot}316(\pm 0{\cdot}137)$$

$$n = 42\,, \quad r = 0{\cdot}969\,, \quad s = 0{\cdot}062\,, \quad F = 192{\cdot}7 \qquad (3)$$

Equation (*3*) shows that in the series of the arylaliphatic acids the stabilization effect depends not only on lipophilicity and acidity, but also on the length of the chain connecting the carboxyl and the aromatic ring. The lipophilicity and acidity being constant, extension of the connecting one-carbon-atom link by another carbon atom reduced the stabilization effect by 0·179 in a logarithmic scale.

Our earlier results[2,3,9] of regression analysis of the stabilization of erythrocyte membrane and of the antiinflammatory efficacy (assessed by inhibition of the kaolin oedema) showed that in the series of the arylaliphatic acids the two effects were

TABLE IV
Correlation matrix of the parameters in equation (*3*)

	$\sum\pi + \Delta\pi$	ΔpK	I_L	$\log (1/C^{St})$
$\sum\pi + \Delta\pi$	1	−0·196	0·158	0·731
ΔpK		1	0·430	−0·684
I_L			1	−0·420

TABLE V
Correlation matrix of the parameters in equation (*4*)

	$\sum\pi + \Delta\pi$	$(\sum\pi + \Delta\pi)^2$	ΔpK	I_L	$\log I^K$
$\sum\pi + \Delta\pi$	1	0·989	−0·191	0·181	−0·641
$(\sum\pi + \Delta\pi)^2$		1	−0·202	0·176	−0·708
ΔpK			1	0·321	−0·104
I_L				1	−0·470

influenced by the same physico-chemical quantities. Differences appeared only in the relations of the two activities to lipophilicity. In the inhibition of the kaolin oedema, assessed *in vivo*, the optimum of lipophilicity was attained sooner. Consequently within the same range of lipophilicity the dependence of inhibition of the kaolin oedema on lipophilicity took a parabolic course[3,9]. These conclusions are corroborated even by regression analysis of the kaolin oedema inhibition in a series of 23 acids $I-V$ (Table III) supplemented by the original 27 substituted benzyloxyarylacetic acids[6,9]; the result of the analysis is the equation:

$$\log I^{K} = 1{\cdot}125(\pm 0{\cdot}479)\,(\textstyle\sum\pi + \Delta\pi) - 0{\cdot}273(\pm 0{\cdot}095)\,(\textstyle\sum\pi + \Delta\pi)^2 - \\ - 0{\cdot}388(\pm 0{\cdot}349)\,\Delta pK - 0{\cdot}155\,(\pm 0{\cdot}097)\,I_L - 1{\cdot}210(\pm 0{\cdot}591)$$

$$n = 50\,, \quad r = 0{\cdot}909\,, \quad s = 0{\cdot}099\,, \quad F = 53{\cdot}7 \qquad (4)$$

The correlation matrix of the parameters is given in Table V. The value of optimum lipophilicity calculated from equation (*4*), *i.e.* $\sum\pi + \Delta\pi_{opt} = 2{\cdot}06$, is in agreement with that calculated earlier[9] for a series of arylacetic acids (2·09). It corresponds to the overall lipophilicity, expressed by logarithm of the partition coefficient, log . $P \sim 3{\cdot}5$. As can be seen from its dependence on the indicator variable, I_L, even the antiinflammatory activity was markedly suppressed by extension of the connecting chain from one to two carbon atoms. This fact demonstrates again the existence of a relation between the erythrocyte-membrane stabilization and the antiinflammatory efficacy, evaluated by inhibition of the kaolin oedema. Equation (*4*) shows that the groups of substituted benzyloxyarylaliphatic acids could hardly be enriched by derivatives that would prove more effective than the acids *Ia* and *IIa*.

The negative dependence of the indicator variable I_L is in accordance with the well-known fact[22] that any of the known antiinflammatory agents classifiable as an arylaliphatic acid is either an arylacetic acid or a 2-arylpropionic acid.

The elemental analyses were performed at the Microanalytical Department of the Institute (head: Dr J. Körbl), the ^{1}H NMR *spectra were measured by Dr J. Holubek, and the gas chromatography was performed by Mr S. Vaněček (head of the department: Dr V. Rábek).*

REFERENCES

1. Kuchař M., Grimová J., Roubal Z., Němeček O., Kakáč B.: Česk. Farm. *22*, 388 (1973).
2. Kuchař M., Brůnová B., Rejholec V., Roubal Z., Němeček O.: This Journal *40*, 3545 (1975).
3. Kuchař M., Brůnová B., Rejholec V., Grimová J.: Eur. J. Med. Chem. *13*, 363 (1978).
4. Hansch C. in the book: *Drug Design*, Vol. I (E. J. Ariens, Ed.), p. 271. Academic Press, London 1971.
5. Hansch C.: Accounts Chem. Res. *2*, 232 (1969).
6. Kuchař M., Brůnová B., Rejholec V., Grimová J., Němeček O.: This Journal *42*, 1723 (1977).
7. Kuchař M., Grimová J., Němeček O.: Pharmazie *34*, 371 (1979).
8. Grimová J., Kuchař M., Pavlíková L., Němeček O.: Česk. Farm. *29*, 305 (1980).

9. Kuchař M., Brůnová B., Grimová J., Rejholec V., Čepelák V., Němeček O.: Česk. Farm. *29*, 276 (1980).
10. Kuchař M., Rejholec V., Jelínková M., Rábek V., Němeček O.: J. Chromatogr. *162*, 197 (1979).
11. Kuchař M., Rejholec V., Roubal Z., Němeček O.: This Journal *44*, 183 (1979).
12. Kuchař M., Brůnová B., Rejholec V., Roubal Z., Němeček O.: This Journal *46*, 1173 (1981).
13. Leo A., Hansch C., Elkins D.: Chem. Rev. *71*, 525 (1971).
14. Fujita T., Iwasa J., Hansch C.: J. Amer. Chem. Soc. *86*, 5175 (1964).
15. Kuchař M., Brůnová B., Roubal Z., Schlanger J., Němeček O.: This Journal *45*, 1401 (1980).
16. Kuchař M., Rejholec V., Brůnová B., Jelínková M.: J. Chromatogr. *195*, 329 (1980).
17. Iwasa J., Fujita T., Hansch C.: J. Med. Chem. *8*, 150 (1965).
18. Kuchař M., Rejholec V., Kraus E.: Česk. Farm. *29*, 281 (1980).
19. Kalbhen D. A., Gelderblom P., Domenjoz R.: Pharmacology *3*, 353 (1970).
20. Hillebrecht J.: Arzneim.-Forsch. *9*, 625 (1959).
21. Levshina K. V., Ivanushkina T. A., Sergievskaya S. J.: Zh. Org. Khim. *2*, 213 (1966).
22. Kuchař M., Němeček O.: Česk. Farm. *29*, 309 (1980).

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