THE EFFECTS OF LIPOPHILICITY ON THE INHIBITION OF DENATURATION OF SERUM ALBUMIN AND ON THE ACTIVATION OF FIBRINOLYSIS OBSERVED WITH A SERIES OF BENZYLOXYARYLALIPHATIC ACIDS

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Activation of fibrinolysis and inhibition of denaturation of serum albumin by a series of substituted benzyloxyarylaliphatic acids have been measured and analysed in relation to the physico-chemical parameters of these acids. The lipophilicity of the benzyloxy derivatives was characterised both by the tabulated parameters π and by experimental data obtained by TLC. Regression analysis has revealed that the derivatives manifest higher lipophilicities in both the activation of fibrinolysis and the inhibition of denaturation, and that these lipophilicities are better described by the tabulated data than by experimental values. Taking into account the earlier results of regression analysis of erythrocyte membrane stabilization and antiinflammatory activity it can be judged that the role of lipophilicities of these substances is influenced by the nature of their interaction with the biological system.

Regression analysis has shown[1-5] that the activation of fibrinolysis (AF) by arylaliphatic acids, differing in the chain between the carboxyl and the aromatic ring, is linearly proportional to the overall lipophilicity of the acids and is not affected by their other physico-chemical properties. This linear dependence on lipophilicity is described[4] by the equation

	n	r	s	F	
$\log(1/C^F) = 0{\cdot}620 \log P - 0{\cdot}324$,	95	0·960	0·131	1 082	(*1*)

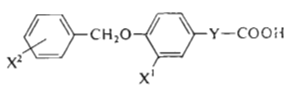
When the optimum lipophilicity has been attained, a steep decrease of fibrinolytic capacity follows in a narrow lipophilicity range near to $\log P \approx 4{\cdot}6$, irrespective of the character of the linking chain.

A similar dependence on lipophilicity was obtained[4] with the same series of acids by regression analysis of their effects on inhibition of denaturation of serum albumin (IDA), which can be regarded as a good criterion of the interaction of substances with this protein[6,7]. The linear relation expressed by equation (*2*) is valid throughout the lipophilicity range of the acids studied (*i.e.* up to $\log P \sim 5{\cdot}00$), but most substances of high lipophilicity ($\log P > 4{\cdot}3$) are not so effective as would correspond to equation (*2*).

	n	r	s	F	
$\log (1/C^1) = 0{\cdot}532 \log P + 1{\cdot}991$	95	0·983	0·071	2 706	(2)

Equations (*1*) and (*2*) show that the interactions of arylaliphatic acids with fibrin on the site of the fibrinolytic activation and with serum albumin are very hydrophobic. From the slopes of the two activity-lipophilicity dependences it can be assumed[8,9] that the interactions occur on the surface of the biomacromolecules. This conclusion is in accordance with the hypotheses[10] of activation of fibrinolysis, postulating linkage of substances to the surface of fibrin.

In a series of arylacetic acids we determined[3] the values of AF and IDA for 4-benzyloxyphenylacetic acid (*1a*) and its 3-substituted derivatives *1j*, *1o* and *1w*. The lipophilicities of these compounds can be expressed both by the π-parameters, which were obtained[3,11] experimentally with the use of partition chromatography, or were taken as tabulated data[12]. The experimental values, which were lower than the tabulated ones, proved good for the characterization of lipophilicity in regression analyses of anti-inflammatory efficacy and stabilization of erythrocyte membrane observed with substituted benzyloxy derivatives of arylacetic acids[13] and analogous derivatives of arylaliphatic acids[14]. However, in assessing the lipophilicities of the acids *1a*, *j*, *o*, *w* in the regression analyses[3] of AF and IDA it appeared preferable to use the tabulated parameters π. In this work we have determined the two effects in a series of substituted benzyloxy derivatives of arylaliphatic acids, *I* – *V*, in order to verify the general validity of the finding that lipophilicity of benzyloxy derivatives is increased on their binding to the hydrophobic surface of a biomacromolecule. We have also determined the lipophilicities and efficacies in IDA of 3-chloro-4-phenethyloxyphenylacetic (*VI*) and 3-chloro-4-phenylpropoxyphenylacetic (*VII*) acids, where we expected an even greater decrease of the experimentally measured lipophilicity parameters as against the tabulated ones. Preparation of the acids *I* – *V* by benzylation of methyl esters of the corresponding 4-hydroxyarylaliphatic acids is described elsewhere[14,15].



I, Y = $-CH_2-$

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

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

IV, Y = $-CH_2CH_2-$

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

EXPERIMENTAL

Methods

The partition coefficients of the acids *Ia*, *Ij*, *Io*, *Iw*, *VI* and *VII* were measured by the standard technique[14,16] in a system n-octanol–buffer of pH 3·5. Inhibition of heat denaturation of serum albumin (IDA) was determined according to Mizushima[6,17]. The effectiveness was expressed by the molar concentration, C^I, causing 50% inhibition. The activation of fibrinolysis (AF) was assessed by the method of hanging clot[18], prepared from human plasma in a solution of the compound tested. The effectiveness was expressed by the minimum molar concentration, C^F, that dissolved the coagulum within 24 h incubation at 37°C.

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

The lipophilicities of substituents X^1 and phenylalkoxy groups were expressed by parameters π derived for arylacetic acids[12]; with substituents X^2 attached to the benzyl residue we used parameters π derived for substituted benzyl alcohols[12]. To calculate the parameters π of higher alkyls and alkoxy groups the following increments[16] were used: $\Delta\pi$ (CH_2 aliph.) = 0·50; $\Delta\pi$ (branching = −0·20. With the 3,4-disubstituted derivatives we considered the decrease in lipophilicity associated with intramolecular interactions of the two substituents in *ortho*-position. Where a chlorine atom or alkyl was combined with an alkoxy group the sum of the parameters π was

TABLE I

Lipophilicity parameters of acids

Acid	n	X^1	log P	$\sum\pi_{tab}$ [a]	$\sum\pi_{exp}$ [b]	$\sum\pi_{part}$ [c]
Ia	1	H	2·72	1·91	1·31	1·27
Ij	1	Cl	3·43	2·36	1·81	1·98
Io	1	CH_3	3·37	2·17	1·81	1·92
Iw	1	CH_3O	2·59	1·35	1·10	1·14
VI	2	Cl	3·53	2·86	2·12	2·08
VII	3	Cl	3·90	3·36	2·52	2·45

[a] For calculation see Experimental; [b] values obtained by inserting experimental values of R_M into the regression relation $\sum\pi - R_M$ in the series of arylacetic acids[19]; [c] values calculated as difference between logarithms of partition coefficients of a substituted acid and phenylacetic acid (log P = 1·45).

reduced by 0·23, in accordance with the results of partition chromatography of 3,4-disubstituted arylaliphatic acids[3,11,13,19]. With 3-methoxy-4-benzyloxyphenylacetic acid (*Ij*) and its derivatives *Ik* — *In* the sum of the tabulated parameters π was reduced by 0·60, which value corresponds to the decrease of lipophilicity of 3-methoxy-4-alkoxyphenylaliphatic acids[3,19,20]. In addition to the tabulated values we used the values of π or $\sum\pi$ obtained from partition TLC of arylacetic acids[19] on silica gel impregnated with silicone oil, with 50% acetone as mobile phase. The values of lipophilicity parameters of the phenylalkoxy derivatives *Ia*, *j*, *o*, *w*, *VI*, and *VII* are compiled in Table I, where the experimentally determined partition coefficients of these acids are also given for the sake of comparison. The lipophilicity of the chain connecting the carboxyl group and the aromatic ring was characterized by $\Delta\pi$ values calculated as differences between the experimentally determined logarithms of partition coefficients of a phenylaliphatic acid and phenylacetic acid[14]. These differences $\Delta\pi$ were: 0 for the acid *I*, 0·35 for *II*, 0·75 for *III*, 0·46 for *IV* and 0·73 for *V*.

3-Chloro-4-phenethyloxyphenylacetic Acid (*VI*) and 3-Chloro-4-(3′-phenyl-n-propoxy)phenylacetic Acid (*VII*)

They were prepared by reaction of methyl 3-chloro-4-hydroxyphenyl acetate with 2-phenethyl bromide or 3-phenylpropyl bromide according to a described procedure[15]. Further given are: number of the compound, m.p. (°C), solvent: *VI*, 91—92, toluene–n-hexane 1 : 4, for $C_{16}H_{15}ClO_3$ calculated: 66·09% C, 5·20% H, 12·20% Cl, found: 66·37% C, 5·39% H, 12·21% Cl. *VII*, 75—76, toluene–n-hexane 1 : 3, for $C_{17}H_{17}ClO_3$ calculated: 66·99% C, 5·62% H, 11·63% Cl, found: 66·89% C, 5·78% H, 11·38% Cl.

RESULTS AND DISCUSSION

As stated in the introduction, inhibition of denaturation of serum albumin by high-lipophilicity arylaliphatic acid usually deviates from the regression equation (*1*). In this region of lipophilicity the linear dependence evidently changes into a quadratic one. The statistical significance of the quadratic term is lower than that of the linear one, which may be due to disproportion in the numbers of low-lipophilicity and high-lipophilicity compounds. For this reason we increased the number of highly lipophilic compounds by extending the series of the 22 arylacetic acids[3] by 12 arylaliphatic acids having $(\sum\pi + \Delta\pi) > 2{\cdot}8$, *i.e.* $\log P > 4{\cdot}3$ (Table II). Thus we obtained equation (*3*) where the quadratic dependence on lipophilicity is significant.

$$\log(1/C^{1}) = 0{\cdot}994(\pm 0{\cdot}157)(\textstyle\sum\pi + \Delta\pi) - 0{\cdot}131(\pm 0{\cdot}039)(\textstyle\sum\pi + \Delta\pi)^2 + 2{\cdot}425(\pm 0{\cdot}142) \qquad (3)$$

$$n = 34,\ r = 0{\cdot}991,\ s = 0{\cdot}067,\ F = 835$$

In this equation, as in other regression equations, $\sum\pi$ designates the sum of π parameters of substituents on the aromatic ring and $\Delta\pi$ characterizes the lipophilicity change of the connecting chain, Y.

To verify the suitability of experimental or tabulated parameters π for charac-

terizing the lipophilicity of the benzyloxy derivatives we performed regression analysis of IDA with the original series of acids, but supplemented by the benzyloxy derivatives *I* – *V*. Using tabulated data $\sum\pi_{tab}$, equations (*4*) and (*5*) were derived

$$\log(1/C^1) = 1{\cdot}250(\pm 0{\cdot}285)\left(\sum\pi_{tab} + \Delta\pi\right) - 0{\cdot}193(\pm 0{\cdot}052)\left(\sum\pi_{tob} + \Delta\pi\right)^2 + \\ + 2{\cdot}149(\pm 0{\cdot}375) \qquad (4)$$

$n = 70$, $r = 0{\cdot}918$, $s = 0{\cdot}070$, $F = 178$

TABLE II

Inhibition of denaturation of serum albumin by arylaliphatic acids of higher lipophilicities

Type of acid	$\sum\pi + \Delta\pi$	C^1 mol . l^{-1} . 10^5	$\log(1/C^1)_{exp}$	$\log(1/C^1)_{calc}$ [a]
		2-Arylpropanoic[b]		
4-c-C_6H_{11}	2·81	5·5	4·187	4·182
3-Cl-4-c-$C_6H_{11}CH_2O$	3·27	4·8	4·319	4·272
		3-Arylpropanoic[b]		
4-n-$C_6H_{13}O$	2·97	6·5	4·187	4·220
		3-Arylbutanoic[c]		
3-Br-4-i-C_4H_9	2·90	5·6	4·252	4·204
4-$C_6H_5CH_2$	3·04	5·5	4·260	4·234
4-i-C_5H_{11}	3·10	5·3	4·276	4·245
4-c-C_6H_{11}	3·16	5·0	4·301	4·256
4-c-$C_6H_{11}CH_2O$	3·17	5·75	4·240	4·257
4-n-C_5H_{11}	3·35	5·3	4·276	4·282
3-Br-4-n-C_5H_{11}	3·65	6·3	4·201	4·307
		Cinnamic[b,d]		
3-CH_3O-4-n-$C_6H_{13}O$	2·94	5·3	4·276	4·213
		2-n-Propylcinnamic[b,d]		
4-Cl	2·85	6·3	4·201	4·192
4-Br	2·96	5·2	4·284	4·217

[a] Values calculated from equation (*3*); [b] experimental values of inhibitory concentrations taken from ref.[4]; [c] experimental values of inhibitory concentrations of 3-arylbutanoic acids were measured along with the series of acids *I* – *V*; [d] values of $\Delta\pi$ for cinnamic and 2-n-propylcinnamic acids are 0·68 and 1·98 respectively (calculated from log *P* of cinnamic acid[16] 2·13).

TABLE III

Physico-chemical and biological properties of benzyloxyarylacetic acids *I*

Number	X^1 / X^2	$\sum\pi_{tab}$ [a] / $\sum\pi_{exp}$ [b]	C^I mol . l^{-1} . 10^5	$\log(1/C^I)_{exp}$ / $\log(1/C^I)_{calc}$ [c]	C^F mol . l^{-1} . 10^5	$\log(1/C^F)_{exp}$ / $\log(1/C^F)_{calc}$ [d]
Ia	H	1·91	17·0	3·770	9·5	2·022
	H	1·31		3·777		1·876
Ib	H	1·91	15·1	3·821	15·0	1·824
	4-CH_3O	1·31		3·777		1·876
Ic	H	2·61	8·5	4·071	7·0	2·155
	4-CH_2=$CHCH_2O$	2·01		4·052		2·306
Id	H	2·71	9·0	4·046	6·0	2·222
	4-i-C_3H_7O	2·11		4·076		2·368
Ie	H	3·31	6·5	4·187	3·0	2·523
	4-i-C_3H_7	2·71		4·139		2·736
If	H	2·16	9·8	4·009	7·0	2·155
	3-CH_3-4-CH_3O	1·56		3·906		2·030
Ig	H	3·38	6·7	4·174	— [e]	—
	3,4-Cl_2	2·78		4·138		—
Ih	H	2·89	— [e]	—	4·0	2·301
	4-C_2H_5	2·29		—		2·480
Ii	H	3·32	7·4	4·131	— [e]	—
	3-Cl-4-i-C_3H_7O	2·72		4·139		—
Ij	CH_3O	1·35	36·4	3·439	30·0	1·523
	H	1·10		3·421		1·538
Ik	CH_3O	2·15	12·0	3·921	7·0	2·155
	4-i-C_3H_7O	1·90		3·893		2·030

Il	CH_3O	2·33	8·4	4·076	6·0	2·222
	4-C_2H_5	2·08		3·965		2·140
Im	CH_3O	2·75	7·7	4·113	4·0	2·398
	4-i-C_3H_7	2·50		4·085		2·398
In	CH_3O	2·66	—[e]	—	4·0	2·398
	3-Cl-4-CH_2=$CHCH_2O$	2·41		—		2·337
Io	CH_3	2·17	11·1	3·955	6·0	2·222
	H	1·81		3·901		2·036
Ip	CH_3	2·87	8·5	4·071	>100	<1·000
	4-CH_2=$CHCH_2O$	2·51		4·106		—
Ir	CH_3	3·47	7·2	4·140	>100	<1·000
	4-i-C_4H_9O	3·11		4·133		—
Is	CH_3	2·65	8·4	4·076	>100	<1·000
	3-CH_3-4-CH_3O	2·29		4·003		—
It	CH_3	2·78	8·6	4·066	>10[f]	<2·000
	3-Cl-4-CH_3O	2·42		4·091		—
Iu	CH_3	2·58	7·3	4·137	>100	<1·000
	3-Cl-4-i-C_3H_7O	3·22		4·123		—
Iv	CH_3	3·15	7·8	4·108	>100	<1·000
	4-C_2H_5	2·79		4·136		—
Iw	Cl	2·36	9·6	4·018	5·0	2·301
	H	1·81		3·976		2·153
	Cl	2·36	9·9	4·002	6·0	2·222
	4-CH_3O	1·81		3·976		2·153
Ix	Cl	3·06	8·0	4·097	>10[f]	<2·000
	4-CH_2=$CHCH_2O$	2·51		4·130		—
Iz	Cl	3·16	7·1	4·149	>100	<1·000
	4-i-C_3H_7O	2·61		4·137		—

TABLE III
(*Continued*)

Number	X^1 X^2	$\sum\pi_{lab}$ [a] $\sum\pi_{exp}$ [b]	C^I mol . l^{-1} . 10^5	$\log(1/C^I)_{exp}$ [c] $\log(1/C^I)_{calc}$	C^F mol . l^{-1} . 10^5	$\log(1/C^F)_{exp}$ [d] $\log(1/C^F)_{calc}$
Ia'	Cl	3·34	7·1	4·149	>10 [f]	$<2{\cdot}000$
	4-C_2H_5	2·79		4·136		—
Ib'	Cl	3·22	8·0	4·097	>100	$<1{\cdot}000$
	4-Cl	2·57		4·123		—
VI	Cl	2·86	6·9	4·161 [g]	— [e]	—
	H	2·08		4·105 (3·843) [h]		—
VII	Cl	3·36	6·5	4·187 [g]	— [e]	—
	H	2·45		4·138 (4·027) [h]		—

[a] $\sum\pi$ was calculated from tabulated values of π; [b] $\sum\pi$ was calculated from π values obtained by partition chromatography; [c] values calculated from equation (*5*); [d] values calculated from equation (*8*); [e] the compound was insoluble in the medium of the test; [f] the solubility is rather poor; [g] the compound was not included in the regression analysis; [h] the values in parentheses were calculated from equation (*5*) using $\sum\pi_{exp}$.

$$\log(1/C^{I}) = 1{\cdot}261(\pm 0{\cdot}204)\,(\sum\pi_{tab} + \Delta\pi) - 0{\cdot}192(\pm 0{\cdot}038)\,(\sum\pi_{tab} + \Delta\pi)^2 + \\ + 0{\cdot}106(\pm 0{\cdot}038)\,D_B + 2{\cdot}069(\pm 0{\cdot}271) \qquad (5)$$

$n = 70$, $r = 0{\cdot}959$, $s = 0{\cdot}050$, $F = 254$

The indicator variable D_B has been introduced to distinguish the benzyloxy groups from the other substituents; its value is 0 for the benzyloxy derivatives and 1 for the others. If the lipophilicities of the benzyloxy derivatives are expressed by experimental values of the lipophilicity parameters, $\sum\pi_{exp}$, the quadratic dependence on lipophilicity is described by equation (*6*); equation (*7*) shows that the introduction of the indicator variable is statistically insignificant in this case.

$$\log(1/C^{I}) = 0{\cdot}911(\pm 0{\cdot}237)\,(\sum\pi_{exp} + \Delta\pi) - 0{\cdot}141(\pm 0{\cdot}048)\,(\sum\pi_{exp} + \Delta\pi)^2 + \\ + 2{\cdot}717(\pm 0{\cdot}425) \qquad (6)$$

$n = 70$, $r = 0{\cdot}870$, $s = 0{\cdot}087$, $F = 105$

$$\log(1/C^{I}) = 0{\cdot}914(\pm 0{\cdot}241)\,(\sum\pi_{exp} + \Delta\pi) - 0{\cdot}142(\pm 0{\cdot}050)\,(\sum\pi_{exp} + \Delta\pi)^2 + \\ + 0{\cdot}004(\pm 0{\cdot}042)\,D_B + 2{\cdot}713(\pm 0{\cdot}284) \qquad (7)$$

$n = 70$, $r = 0{\cdot}870$, $s = 0{\cdot}088$, $F = 69$

These regression equations reveal that the lipophilicity of a benzyloxy derivative in the inhibition of denaturation of serum albumin is better characterized by the tabulated values than by the experimental ones. The same conclusion is valid for the acids *VI* and *VII*, as can be seen from comparison of the inhibitory activities calculated from equation (*5*) by inserting the experimental and the tabulated values of $\sum\pi$ (Table III). The indicator variable D_B cannot be eliminated from the regression equation by using the experimental lipophilicity values for the benzyloxy derivatives. Consequently, equation (*5*) proves that the inhibitory effect of any of the acids studied is quadratically dependent on lipophilicity, but the parabola for the benzyloxy derivatives is under the parabola corresponding to the other derivatives. It can be concluded that the presence of a benzyloxy group has a negative effect on the binding to serum albumin, since with the benzyloxy derivatives the inhibition of denaturation was lower by 0·106 in the logarithmic scale.

Also in the regression analysis of activation of fibrinolysis the tabulated values $\sum\pi_{tab}$ were better for characterization of lipophilicity of the benzyloxy derivatives. This fact is demonstrated by equations (*8*) and (*9*), which we obtained by a common analysis of 20 arylacetic acids[3] and their benzyloxy derivatives *I* (Table III).

$$\log(1/C^{F}) = 0{\cdot}615(\pm 0{\cdot}094)\sum\pi_{tab} + 0{\cdot}702(\pm 0{\cdot}200) \qquad (8)$$

$n = 35$, $r = 0{\cdot}962$, $s = 0{\cdot}117$, $F = 397$

TABLE IV

Physico-chemical and biological properties of benzyloxyarylaliphatic acids *II*—*V*

Number	X^1 X^2	$(\sum\pi_{tab} + \Delta\pi)^a$ $(\sum\pi_{exp} + \Delta\pi)^b$	C^1 mol . l^{-1} . 10^5	$\log(1/C^1)_{exp}$ $\log(1/C^1)_{calc}{}^c$
IIa	Cl	2·71	8·3	4·081
	H	2·61		4·076
IIb	Cl	3·32	8·6	4·066
	3-Cl-4-CH_3O	2·77		4·139
IIc	Cl	3·51	7·8	4·108
	4-i-C_3H_7O	2·96		4·130
IId	Cl	3·57	8·2	4·086
	4-Cl	3·02		4·123
IIIa	Cl	3·06	7·4	4·131
	H	2·51		4·130
IIIb	Cl	3·67	8·0	4·097
	3-Cl-4-CH_3O	3·12		4·111
IIIc	Cl	3·86	8·6	4·066
	4-i-C_3H_7O	3·21		4·076
IIId	Cl	3·92	9·0	4·046
	4-Cl	3·37		4·062
IVa	H[d]	2·37	11·8	3·928
	H	1·77		3·979
IVb	H	2·37	10·5	3·979
	4-CH_3O	1·77		3·979
IVc	H	2·98	8·5	4·071
	3-Cl-4-CH_3O	2·38		4·121
IVd	Cl[e]	2·82	8·2	4·086
	H	2·27		4·098
IVe	Cl	2·82	9·4	4·027
	4-CH_3O	2·27		4·098
IVf	Cl	3·62	9·0	4·046
	4-i-C_3H_7O	3·07		4·118
Va	H	2·61	10·7	3·971
	H	2·01		4·052
Vb	H	3·22	7·6	4·119
	3-Cl-4-CH_3O	2·62		4·136
Vc	H	3·41	7·6	4·119
	4-i-C_3H_7O	2·81		4·139
Vd	H	4·02	8·0	4·097
	3-Cl-4-i-C_3H_7O	3·42		4·036

[a] $\sum\pi$ was calculated from tabulated values of π; [b] $\sum\pi$ was calculated from experimental values of π obtained by partition chromatography; [c] values calculated from equation (*5*); [d] experimental value of activation of fibrinolysis $\log(1/C^F) = 2{\cdot}022$, the value calculated from equation (*8*) was 2·154; [e] experimental value of $\log(1/C^F = 2{\cdot}398$, the value calculated from equation (*8*) was 2·436.

$$\log(1/C^F) = 0{\cdot}608(\pm 0{\cdot}173)\sum\pi_{exp} + 0{\cdot}828(\pm 0{\cdot}339) \qquad (9)$$

$n = 35$, $r = 0{\cdot}883$, $s = 0{\cdot}201$, $F = 113$

Equation (*8*) is nearly identical with (*1*), derived[4] for a series of arylaliphatic acids. However, from a more detailed analysis it is clear that this equation cannot always be applied to benzyloxy derivatives of arylacetic acids with substituents on the benzene ring of the fundamental skeleton. Thus acids *Ip*, *s*, *t*, *v*, *y*, *b'* have no effect, although their lipophilicities are lower than the previously determined[3,4] maximum value of $\log P_{max} = 4{\cdot}6$ (*i.e.* $\sum\pi = 3{\cdot}2$). The course of the dependence of activation of fibrinolysis on lipophilicity suggests[4] that the binding capacity of hydrophobic region in the target site is limited. The presence of a substituent at *meta*-position of phenylacetic acid probably negatively affects the binding of the benzyloxy group to the surface of a biomacromolecule. The maximum of lipophilicity was therefore lower in these cases than with the non-substituted derivatives *Ia*–*Ii*. A similar negative effect was caused by the presence of a methyl group on the connecting chain of the benzyloxy-derivatives of acids *II*, *III* and *V*. Of all the derivatives given in Table IV and soluble under the conditions of the test, only the acids *IVa* and *IVd* of the series of 3-aryl-propionic acid were fibrinolytically active and their activities were consistent with equation (*8*). The other ones were ineffectual, though a number of them are in the region below the maximum of lipophilicity (acids *IIa*, *IIb*, *IIIa*, *Va*, *Vb*).

Consequently, the regression analyses of IDA and AF in the group of benzyloxy-arylaliphatic acids demonstrate that the lipophilicity of a benzyloxy group is characterized by tabulated values, which are higher than experimental ones. These differences between the experimental and tabulated lipophilicities were more marked on lengthening the chain connecting the two aromatic rings in the acids *VI* and *VII*. The increase in lipophilicity of the arylalkoxy derivatives in the two activities can then be explained by restriction of intramolecular hydrophobic interactions by coplanar conformation of the two aromatic rings in the binding to the surface of a biomacromolecule. By contrast, the experimental values of lipophilicity proved better[13,14] in the regression analysis of stabilization of erythrocyte membrane and anti-inflammatory efficacy. To conclude it can be said that the role of lipophilicity of this type of compounds is influenced by the character of their interaction with the biological system.

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