ON THE QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTIAGGREGATION ACTIVITY OF ω-ARYL-ω--OXOALKANIC ACIDS

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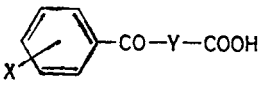
A series of ω-aryl-ω-oxoalkanoic acids, *I*—*IV*, has been prepared and investigated for dissociation constants in 80% methylcellosolve, retention characteristics in thin-layer partition chromatography and partition coefficients *P* in the system octanol–water. Also evaluated were their anti--inflammatory efficacy and inhibitory effect on the platelet aggregation induced by collagen. Analysing the relations between structure and antiagregation effect, we obtained a non-linear, quadratic dependence of this effect on lipophilicity, the optimum being at log $P = 3$. The antiaggregation effect increased with shortening the chain between the carbonyl and the carboxyl, and with increasing acidity. It was also diminished by the presence of a methyl group on the interlinking chain. To assess the role of lipophilicity we used the R_M values of partition chromatography. The relation between anti-inflammatory efficacy and structure was assessed only qualitatively. In this aspect, too, the nature of the chain between the carbonyl and carboxyl proved to have a marked influence. The anti-inflammatory activity proved considerably enhanced by the presence of another aromatic ring in ω-oxoalkanoic acids derived from biphenyl.

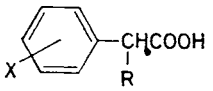
The high anti-inflammatory efficacy of 4-biphenylyl-4-oxobutanoic acid[1,2] (Cinopal) spurred us to synthetize its derivatives. We have prepared a series of ω-aryloxoalkanoic acids, *I*—*IV*, with substituents not only on the aromatic ring, but also on the chain interlinking the carboxyl and the carbonyl groups. We have determined their anti-inflammatory action in two experimental models of inflammation and discuss how structural alterations affect this action. Since a number of anti-inflammatory drugs had been shown[3–5] to inhibit collagen-induced aggregation of thrombocytes, we also tested the acids prepared for the antiaggregation activity. Employing regression analysis we searched for relations between this activity and structure. We had previously correlated[6,7] the antiaggregation activity with the physico--chemical properties of a group of arylalkanoic acids *V* (wherein R was a hydrogen atom or a lower alkyl group). We had arrived at the equation:

$$\log (1/C^{A}) = 7{\cdot}687 \log P - 0{\cdot}947 (\log P)^2 + 0{\cdot}590 I_{11} + 0{\cdot}835 E_S - 12{\cdot}524 ,$$
$$n = 19, r = 0{\cdot}949, s = 0{\cdot}272, \mathrm{F} = 31{\cdot}5 , \qquad (I)$$

wherein I_H denotes the indicator variable, corresponding to the number of hydrogen atoms on C_α of the alkyl R, and E_S the Taft steric constant of this alkyl.



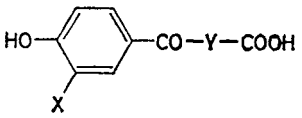
I, Y = CH_2CH_2
II, Y = $CH_2CH(CH_3)$



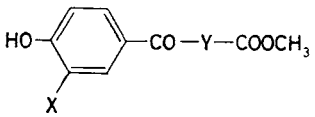
III, Y = $CH_2CH_2CH_2$
IV, Y = $CH_2CH(CH_3)CH_2$

V

VI



VII



VIII

The acids *I*—*IV* were obtained by the Friedel–Crafts reaction of anhydrides of dicarboxylic acids *VI* with suitable derivatives of benzene[8,9]. Isopropoxy derivatives *Id*, *Ie*, *IIb*, and *IVb* were prepared by O-alkylation, with isopropyl bromide in dimethyl sulphoxide, of methyl esters of the corresponding hydroxy acids *VIII*, followed by hydrolysis.

EXPERIMENTAL

Methods

^{1}H NMR spectra of acids *I*—*IV* and esters of hydroxy acids *VIII* were measured in 6% solutions in deuterochloroform, with tetramethylsilane as internal standard, employing a spectrometer BS 487 s — 80 MHz (Tesla, Czechoslovakia). With all the compounds the spectra were consistent with the structures assumed. Purity of anhydrides *VI* and esters *VIII* was tested by gas chromatography in an apparatus Fractometer F-7 (Perkin–Elmer), using a stainless-steel column (i.d. 3 mm, length 2 m) packed with Gas Chrom Q, mesh 100/120, moistened with 15% OV-17 or, in the case of esters *VIII*, with 3% OV-17.

The partition coefficients of selected acids *I*—*IV* were determined by a "shake-flask" technique[10] in the system octanol–aqueous acetate buffer (pH 3·5). Concentrations of the acids were measured spectrophotometrically in either phase with a spectrophotometer Unicam SP 8000; the partition coefficients were calculated as ratios of concentrations in the octanol and the aqueous phases: $P = C_0/C_w$. The experimental data are in good agreement with the values of log P calculated by the fragment method[11]. Chromatographic properties of the acids *I*—*IV* were determined using a thin layer of silanized silica gel (Kieselgel 60, F_{254} silanisiert, Merck, F.R.G.), impregnated with a silicone oil (Lukoil 100, VCHZ Kolín, Czechoslovakia). The mobile phase was a mixture of acetone and a citrate buffer, pH 3·4, in a ratio of 1 : 1 (ref.[12]). Logarithms of partition coefficients of the acids *I*—*IV*, whose partition coefficients were not determined experimentally, were calculted from the equation $\log P = \log P_H + \Sigma\pi$, wherein P_H denotes the partition coefficient of the corresponding non-substituted acid and $\Sigma\pi$ the sum of lipophilicity

parameters π of the substituents on the aromatic ring, calculated for benzoic acids. These values of log *P* accord with the lipophilicity determined chromatographically[12,13], as is apparent from the relation between *P* and R_M expressed by equation (2). This equation does not cover the 4-phenyl derivatives *Ig*, *IIc*, *IIId*, *IVc*, whose log *P*'s are significantly higher than would correspond to the values of R_M.

	n	*r*	*s*	F	
$\log P = 2{\cdot}715R_M + 2{\cdot}127$	22	0·994	0·105	1678·6	(2)

The p*K*'s of selected acids were determined in 80% methylcellosolve at 25°C, employing a potentiometer Titrigraph Radiometer SBR-2c (Copenhagen, Denmark); they are:

Ib	*If*	*Ig*	*Ik*	*IIc*	*IIIc*	*IIId*	*IVc*
6·32	6·33	6·33	6·27	6·60	6·48	6·46	6·76

As can be seen from these data, acidity of these acids is just slightly affected by substituents on the aromatic ring, but modification of the interlinking chain Y has a marked effect on p*K*. In the regression analysis we used the following values of Δp*K*: zero for acids *I*, 0·27 for *II*, 0·13 for *III* and 0·43 for *IV*, derived from the corresponding 4-phenyl derivatives *Ig*, *IIc*, *IIId*, *IVc*,

The regression coefficients in the correlation equations were calculated from experimental data by repeated regression analysis. Statistical significance of the equations was evaluated by the correlation coefficient *r*, root-mean-square deviation *s*, and the Fischer–Snedecor criterion F. The individual parameters in the multi-parameter equations were evaluated by the Student *t*-test on a statistical significance level of $\alpha \leqq 0{\cdot}005$.

Inhibition of aggregation of thrombocytes was followed by Born's method[14], as modified by Čepelák[15]. The efficacy was expressed by concentration C^A, causing 50% inhibition of the collagen-induced aggregation (maximum slope). To compare the individual acids, we used a reference inhibitor (2-(4-isobutylphenyl)propionic acid, ibuprofen), to the inhibitory concentration of which the efficacy of the other compounds is referred.

The anti-inflammatory efficacy was tested on two experimental models of inflammation. Inhibition of the oedema induced by the Freund adjuvans was assessed according to Pearson and Wood[16], inhibition of the kaolin-induced oedema according to Hillebrecht[17]; the experimental techniques are described elsewhere[18,19]. The efficacy of a compound was expressed as % of inhibition of an inflammation related to a group of untreated rats as controls, and the activity indices I^F and I^K were calculated as efficacy ratios of the compound tested and the standard, viz. 2-(4'-isobutylphenyl)propionic acid (ibuprofen).

Anhydrides *VI*

Glutaric anhydride was obtained adhering to a described procedure[20], in a yield of 89%; b.p. 130–131°C/0·4 kPa (reported[20] b.p. 150°C/1·3 kPa). Methylsuccinic anhydride was prepared analogously[20], yield 86%, b.p. 100–102°C/0·4 kPa. For $C_8H_8O_3$ 128·1 calculated: 52·63% C, 5·30% H; found: 52·68% C, 5·17% H. Methylsuccinic acid was prepared according to ref.[21], yield 50%. 3-Methylglutaric anhydride was prepared[22] in a yield of 57%, b.p. 109–11°C/0·13 kPa (ref.[22] b.p. 118–122°C/0·5 kPa).

ω-Aryl-ω-oxoalkanoic Acids *I–IV*

Procedure A: anhydride *VI* (0·188 mol) and aluminium chloride (33·2 g, 0·25 mol) were dissolved in a suitable solvent (200 ml, Table II). A solution of a substituted benzene was added

under stirring and cooling, keeping the temperature to $\leqq 20°C$. After stirring for 3 more h at 20°C and 1 h at 45°C the mixture was poured into ice (500 g) and conc. hydrochloric acid (250 ml). The precipitate was collected on a filter. The organic phase of the filtrate was washed with 5% sodium hydroxide (3 × 100 ml). The precipitate that had been filtered off was dissolved in the combined alkaline extracts and the turbid solution was filtered with activated carbon. The filtrate was acidified with 50% sulphuric acid and the crude product was crystallized from a suitable solvent.

Procedure B: a mixture of 4-methoxy- or 3-chloro-4-methoxyphenyloxoalkanoic acid (0·2 mol) and 50% hydrobromic acid (140 ml) was boiled 16 h, 20 ml portions of 50% hydrobromic acid being added after 4, 8, and 12 h. The mixture was then chilled to −5°C. The precipitate of the crude acid *VII* was collected on a filter and heated 5 h in boiling methanol (150 ml) containing *p*-toluenesulphonic acid (2·0 g). The methanol was distilled off and the residue was extracted with ether. The extract was washed with water and dried with magnesium sulphate. The ether was removed and the crude product was purified by crystallization or by column chromatography on silica gel (Table II) and identified by ^{1}H NMR spectra.

To a solution of sodium (1·0 g) in methanol (40 ml) a solution of ester *VIII* (0·035 mol) in methanol (50 ml) was added and after stirring for 10 min., the mixture was taken to dryness. The residue was dissolved in dimethyl sulphoxide (50 ml), an alkyl bromide (0·0525 mol) was added and the mixture was heated to 100°C for 8 h. After cooling the turbid solution was poured into water (250 ml) and the separated oil was taken into ether. The solution was washed with 5% sodium hydroxide (50 ml) and water (50 ml), and dried with magnesium sulphate. The ether was removed and the crude ester was boiled for 6 h in a solution of potassium hydroxide (10 g), water (10 ml), and methanol (70 ml). The methanol was removed, the residue was dissolved in water (100 ml) and filtered with activated carbon. The filtrate was brought to pH 1 with 50% sulphuric acid and the product was purified by crystallization (Table I).

RESULTS AND DISCUSSION

Evaluation of the antiaggregation activity of acids *I*–*IV* is summed up in Table III. Multiple regression analysis afforded the following two, statistically equivalent equations:

$$\log(1/C^A) = 0{\cdot}869\,(\pm 0{\cdot}372)\log P - 0{\cdot}144\,(\pm 0{\cdot}057)(\log P)^2 + 0{\cdot}330\,(\pm 0{\cdot}101)\,I_L + 0{\cdot}145\,(\pm 0{\cdot}081)\,E_S + 0{\cdot}652\,(\pm 0{\cdot}465), \quad (3)$$

$$n = 22,\ r = 0{\cdot}973,\ s = 0{\cdot}064,\ F = 75{\cdot}3,\ \log P_{opt} = 3{\cdot}02,$$

$$\log(1/C^A) = 0{\cdot}863\,(\pm 0{\cdot}341)\log P - 0{\cdot}143\,(\pm 0{\cdot}057)(\log P)^2 + 0{\cdot}420\,(\pm 0{\cdot}118)\,I_L - 0{\cdot}632\,(\pm 0{\cdot}351)\,\Delta pK + 0{\cdot}656\,(\pm 0{\cdot}511), \quad (4)$$

$$n = 22,\ r = 0{\cdot}972,\ s = 0{\cdot}065,\ F = 73{\cdot}1,\ \log P_{opt} = 3{\cdot}02.$$

The non-linear dependence of antiaggregation efficacy on lipophilicity, approximated by a parabola, is in agreement with an analogous relation for a series of alkyl-substituted arylaliphatic acids (Eq. (*1*)). An obvious difference is in the optimum value of lipophilicity, since in the group of arylaliphatic acids the optimum is shifted to

TABLE I

Characterization of ω-aryl-ω-oxoalkanoic acids *I*–*IV*

Compound X	Procedure/ Solvent[a] Yield, %	M.p., °C (Solvent[b])	Formula (M.w.)	Calculated/found	
				% C	% H
Ia	I/DC	113[c]	$C_{10}H_{10}O_3$	67·60	5·70
H	79	(M–W 2 : 1)	(178·2)	67·40	5·66
Ib	I/NB	144–145[d]	$C_{11}H_{12}O_4$	63·61	5·68
4-CH_3O	59	(M)	(208·2)	63·45	5·81
Ic	I/NB	186–188	$C_{11}H_{11}ClO_4$	54·55	4·58[e]
3-Cl-4-CH_3O	79	(M)	(242·7)	54·44	4·57
Id	II	112	$C_{13}H_{16}O_4$	66·51	6·84
4-i-C_3H_7O	78	(H–B 2 : 1)	(236·3)	66·08	6·83
Ie	II	116–118	$C_{13}H_{15}ClO_4$	57·54	5·57[f]
3-Cl-4-i-C_3H_7O	48	(M–W 2 : 1)	(270·7)	57·67	5·59
If	I/DS	99–101	$C_{14}H_{18}O_3$	72·06	7·60
4-i-C_4H_9	60	(M–W 2 : 1)	(234·2)	71·76	7·74
Ig	I/DC	183–184[g]	$C_{16}H_{14}O_3$	75·25	5·55
4-C_6H_5	46	(E)	(254·2)	75·57	5·77
Ih	I/DC	134–136[h]	$C_{16}H_{20}O_3$	74·11	7·76
4-c-C_6H_{11}	65	(M–W 2 : 1)	(260·3)	73·82	7·74
Ii	III[i]	155–156[k]	$C_{16}H_{19}ClO_4$	65·44	6·55[l]
3-Cl-4-c-C_6H_{11}	52	(A)	(294·8)	65·19	6·50
IIa	I/B	136–138	$C_{11}H_{12}O_3$	68·82	6·63
H	68	(A)	(192·2)	68·73	6·29
IIb	II	106–108	$C_{14}H_{18}O_4$	67·45	7·32
4-i-C_3H_7O	44	(H–B 3 : 1)	(250·3)	67·18	7·25
IIc	I/DC	213–214	$C_{17}H_{16}O_3$	76·32	6·00
4-C_6H_5	83	(A)	(268·3)	76·10	6·01
IId	I/DC	130–131	$C_{17}H_{22}O_3$	74·39	7·97
4-c-C_6H_{11}	71	(M–W 3 : 1)	(274·3)	74·40	8·00
IIIa	I/NB	160–162	$C_{12}H_{13}ClO_4$	56·15	5·11[m]
3-Cl-4-CH_3O	43	(M)	(256·7)	56·32	5·07
IIIb	I/DC	79–81	$C_{14}H_{18}O_3$	71·77	7·74
4-i-C_3H_7	33	(H–B 3 : 1)	(234·3)	71·64	7·86
IIIc	I/DC	106–108	$C_{15}H_{20}O_3$	72·55	8·12
4-i-C_4H_9	32	(H–B 5 : 1)	(248·3)	72·52	8·35
IIId	I/DC	157–158	$C_{17}H_{16}O_3$	76·10	6·01
4-C_6H_5	38	(E)	(268·3)	76·36	6·07

TABLE I
(*Continued*)

Compound X	Procedure/ Solvent[a] Yield, %	M.p., °C (Solvent[b])	Formula (M.w.)	Calculated/found	
				% C	% H
IIIe	I/DC	158—160	$C_{17}H_{22}O_3$	74·42	8·08
4-c-C_6H_{11}	43	(A)	(274·3)	74·64	8·21
IVa	I/NB	129—132	$C_{13}H_{15}ClO_4$	57·67	5·58[n]
3-Cl-4-CH_3O	52	(A)	(270·1)	57·96	5·57
IVb	II	78—79	$C_{15}H_{19}ClO_4$	60·30	6·41[o]
3-Cl-4-i-C_3H_7O	50	(M–W 2 : 1)	(298·8)	60·02	6·53
IVc	I/DC	122—124	$C_{18}H_{18}O_3$	76·57	6·43
4-C_6H_5	61	(E)	(282·3)	76·56	6·34
IVd	I/DC	111—112	$C_{18}H_{24}O_3$	74·97	8·39
4-c-C_6H_{11}	46	(A)	(288·4)	74·84	8·57

[a] In procedure *A* the reaction medium was nitrobenzene (NB), 1,2-dichloroethane (DC) or benzene (B); [b] crystallized from: M methanol, W water, H n-hexane, B benzene, E ethanol, A acetic acid; [c] reported[23] m.p. 114—115°C; [d] rep.[24] m.p. 145 . 146°C; [e] for Cl calculated 14·76%, found 14·61; [f] for Cl calculated 13·59%, found 13·10%; [g] rep.[6] m.p. 185—187°C; [h] rep.[25] m.p. 160—161°C; [i] the acid *Ii* was prepared by chlorination of acid *Ih* (ref.[25]); [k] rep.[25] m.p. 160—161°C; [l] for Cl calculated 11·75%, found 12·03%; [m] for Cl calculated 13·81%, found 13·80%; [n] for Cl calculated 13·10%, found 13·09%; [o] for Cl calculated and found 11·87.

TABLE II
Isolation of esters *VIII*

Compound	X	Y	Isolation	M.p., °C	Yield[a], %
VIIIa	H	CH_2CH_2	M–W 2 : 1[b]	114—117	30
VIIIb	Cl	CH_2CH_2	M–W 2 : 1[b]	44—47	34
VIIIc	H	$CH_2CH(CH_3)$	B–E 3 : 1[c]	140—143	27
VIIId	Cl	$CH_2CH(CH_3)CH_2$	B–E 10 : 1[c]	oil	49

[a] Purity of the esters, judged by gas chromatography (Experimental), was 97—99%. The yields refer to the starting methoxyaryloxoalkanoic acid; [b] isolated by crystallization from: M methanol, W water; [c] isolated by column chromatography: B benzene, E ether.

TABLE III

Biological activity of aryloxoalkanoic acids *I*—*IV*

Compound	Log P^a	$R_M{}^b$	C^A_{exp} mol l^{-1} . 10^3	Log $(1/C^A)_{exp}$	Log $(1/C^A)_{calc}{}^c$	Anti-inflammatory efficacy[d]	
						I^F	I^K
Ia	1·30+	−0·28	4·21	2·376	2·379	N	0·40
Ib	1·38+	−0·28	2·88	2·541	2·418	N	N
Ic	1·98	−0·055	2·50	2·602	2·649	NE	0·33
Id	2·18	0·02	2·29	2·640	2·704	0·54	0·69
Ie	2·78	0·24	1·64	2·785	2·797	0·65	0·51
If	3·20	0·35	1·46	2·836	2·801	0·64	0·34
Ig	3·20+	0·21	1·66	2·780	2·801	1·18	1·02
Ih	3·76	0·585	1·68	2·775	2·728	0·79	0·65
Ii	4·36	0·79	3·16	2·500	2·549	1·20	0·80
IIa	1·62+	−0·155	5·75	2·240	2·343	N	0·43
IIb	2·50	0·19	2·00	2·699	2·587	NE	NE
IIc	3·40+	0·37	2·30	2·638	2·606	1·39	0·98
IId	4·08	0·72	3·83	2·417	2·466	1·06	0·52
IIIa	2·17+	0·03	0·98	3·009	3·031	N	N
IIIb	2·89	0·28	0·68	3·167	3·134	0·70	N
IIIc	3·39	0·515	0·85	3·071	3·117	0·35	0·34
IIId	3·35+	0·31	0·65	3·185	3·121	0·98	0·60
IIIe	3·95	0·685	1·06	2·975	3·013	0·76	N
IVa	2·60+	0·15	1·27	2·896	2·931	0·23	0·23
IVb	3·40	0·50	1·16	2·936	2·936	0·60	0·61
IVc	3·82	0·48	1·45	2·839	2·865	0·43	NE
IVd	4·38	0·76	1·73	2·762	2·692	0·60	N

[a] The asterisk+ denotes experimental values; [b] in deriving Eq. (*2*) we also employed the values of log *P* and R_M of the derivatives of acids *I*: 4-Br, 2·28, −0·03; 4-i-C_3H_7, 2·70, 0·18; 4-n-$C_6H_{13}O$, 3·88, 0·70 and acids *II*: 3-Cl-4-i-C_4H_9O, 3·60, 0·58; [c] values obtained from Eq. (*3*); [d] N designates inefficient compounds, NE compounds that were not tested.

$\log P_{opt} = 4{\cdot}05$. The corresponding maximum efficacy, calculated from Eq. (*1*), is $\log (1/C^A)_{max} = 4{\cdot}9$. The indicator variable I_L gives the length of the interlinking chain between the carbonyl and the carboxyl; it equals 2 for the acids *I* and *II*, and 3 for *III* and *IV*. Elongation of the chain enhances the antiaggregation efficacy, whereas the opposite is true of the arylaliphatic acids[8,9].

The virtually equal statistical significance of the two equations makes it impossible to decide whether the antiaggregation activity of acids *I*–*IV* is affected by bulkiness of the alkyls on the interlinking chain or by p*K* changes between the individual groups of the acids *I*–*IV*. The cause is a high colinearity of the two parameters with the correlation coefficient $r = 0{\cdot}904$. However, the two equations reveal that the presence of a methyl group on the interlinking chain diminishes the activity. From the optimum of lipophilicity and the other parameters the maximum activity can be calculated as $\log (1/C^A)_{max} = 3{\cdot}15$, which is nearly two orders of magnitude lower than for the arylaliphatic acids. Consequently, the carbonyl group in the interlinking chain between the carboxyl and the aromatic ring has a strongly negative effect on antiaggregation efficacy.

In Eqs (*5*) and (*6*) the lipophilicity is expressed by means of R_M values from thin-layer chromatography.

$$\log (1/C^A) = 0{\cdot}739\,(\pm 0{\cdot}303)\,R_M - 1{\cdot}152\,(\pm 0{\cdot}469)\,R_M^2 + 0{\cdot}160\,(\pm 0{\cdot}081)\,E_S + 0{\cdot}328\,(\pm 0{\cdot}105)\,I_L + 1{\cdot}839\,(\pm 0{\cdot}263)\,, \quad (5)$$

$$n = 22,\ r = 0{\cdot}972,\ s = 0{\cdot}065,\ F = 72{\cdot}0\,,$$

$$\log (1/C^A) = 0{\cdot}736\,(\pm 0{\cdot}303)\,R_M - 1{\cdot}145\,(\pm 0{\cdot}469)\,R_M^2 - 0{\cdot}697\,(\pm 0{\cdot}354)\,\Delta pK + 0{\cdot}427\,(\pm 0{\cdot}118)\,I_L + 1{\cdot}836\,(\pm 0{\cdot}263)\,, \quad (6)$$

$$n = 22,\ r = 0{\cdot}972,\ s = 0{\cdot}066,\ F = 72{\cdot}2\,.$$

The anti-inflammatory efficacy was tested on two models of experimental inflammation (Table III). The results suggest that this effect depends on a number of physico-chemical and structural factors. Extension of the interlinking chain Y from 2 to 3 atoms of carbon had a negative effect, whereas attachment of a methyl group to the interlinking chain, mainly in the acids *II*, raised the anti-inflammatory efficacy. An extraordinary enhancement of anti-inflammatory efficacy was brought about by the cyclic substituents on the aromatic ring in the 4-cyclohexylphenyl and 4-biphenylyl derivatives.

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