SYNTHESIS OF CYCLOHEXYLALIPHATIC ACIDS AND THEIR PHARMACOLOGICAL PROPERTIES

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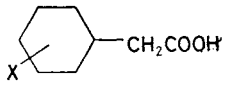
A series of substituted cyclohexylacetic acids *I* has been obtained by hydrogenation of the unsaturated analogues *II* and *III*. Esters of these analogues were prepared by the Horner–Wittig reaction of the corresponding cyclohexanones *IV* and/or 2-cyclohexenones *V* with triethyl phosphonoacetate. These esters were obtained in two isomeric forms (*Z* and *E*), differing in the double bond in the exo-position. The derivatives with a substituent in the 2-position exhibited a partial shift of the double bond to the cyclohexane ring; this shift was especially marked in the 2-phenyl derivative. With the acids *I*—*III*, activation of fibrinolysis was assessed by the hanging clot method; the anti-inflammatory effect was assessed by inhibition of two experimental model inflammations. The regression equation relating fibrinolytic capacity to lipophilicity was a quadratic one, the logarithm of optimum lipophilicity being $\log P_{opt} = 5{\cdot}55$. A qualitative assessment of the anti-inflammatory effect in relation to lipophilicity suggests that $\log P_{opt}$ is probably higher than with arylaliphatic acids. These acids seem to have an active site different from that of the acids *I*—*III*.

As a part of our study of the anti-inflammatory efficacy of arylaliphatic acids[1–4], we have synthetized a series of subtituted cyclohexylacetic acids *I* and their unsaturated analogues *II* and *III*. In these acids the aromatic ring is replaced by a cyclohexane residue, which enabled us to assess the effect of this structural alteration on the anti-inflammatory efficacy of the acids. Analysing quantitatively the relations between the anti-inflammatory activity and physico-chemical properties of a series of arylacetic acids, we previously found[1,3] this activity to increase with acidity and to depend, non-linearly, on lipophilicity, the optimum being $\log P_{opt}$ about 3·5. Apart from the anti-inflammatory effects, the acids *I*—*III* were also tested for activation of fibrinolysis, again with the view of comparison with the arylaliphatic acids. With the latter acids, regression analysis showed[5–8] the fibrinolytic activity to be governed mainly by lipophilicity. The linear dependence expressed by the equation:

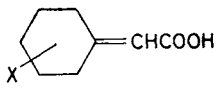
	n	*r*	*s*	F	
$\log 1/C^F = 0{\cdot}620 \log P - 0{\cdot}324$	95	0·960	0·131	1 082	(*1*)

was valid up to a certain optimum lipophilicity ($\log P_{opt}$ c. 4·7), beyond which the fibrinolytic capacity took a steeply decreasing course.

The acids *I* were obtained by hydrogenation of the acids *II* and *III*, employing palladium on activated carbon as catalyst. The unsaturated acids *II* and *III* were prepared by the Wittig–Horner reaction[9] of triethyl phosphonoacetate (*VI*) with cyclohexanones *IV* and 2-cyclohexenones *V*, respectively. The starting cyclohexanones *IV*, substituted in the position 3, were obtained by cyclization[10] of substituted benzalacetones *VII*; the arising 3-arylcyclohexane-1,3-diones *VIII* were converted into 3-methoxy derivatives *IX*, which, in turn, were hydrogenated to cyclohexanones



I



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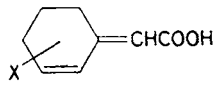

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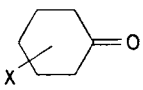
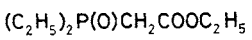


IV

V



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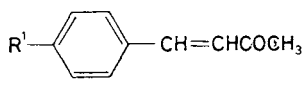

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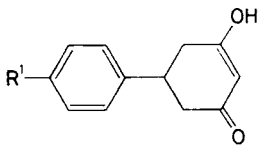
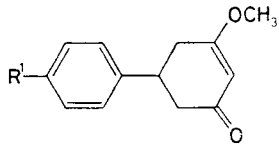
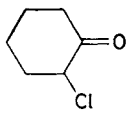


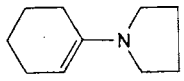
VIII



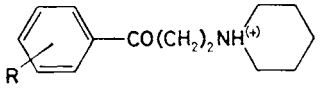
IX



X

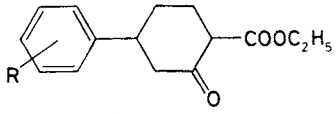


XI



Cl⁻

XII



XIII

IV. Derivatives with 2-substituents were obtained by the Grignard reaction of chlorocyclohexanone (*X*) with the corresponding alkylmagnesium bromides[11,12] and/or by reaction of 1-(1'-pyrrolidino)cyclohexene (*XI*) with alkyl bromides[13]. 2-Cyclohexenones *V* were obtained by hydrolysis and decarboxylation of keto esters *XIII*, prepared by cyclization[14] of vinyl aryl ketones, arising from piperidinium salts *XII* in alkaline media.

EXPERIMENTAL

Methods

The ^{1}H NMR spectra of the acids *I*—*III*, their cyclohexylammonium salts, cyclohexane-1,3-diones *XIII*, cyclohexanones *IV*, and 2-cyclohexenones *V* were measured in 6% solutions in deuteriochloroform, with tetramethylsilane as internal standard, employing a spectrometer BS 487 s — 80 MHz (Tesla, Czechoslovakia). Purity of the cyclohexanones *IV*, 2-cyclohexenones *V*, keto esters *XV*, esters of acids *II* and *III* with triethyl phosphonoacetate (*VI*) was tested by gas chromatography with a chromograph Fractometer F — 7 (Perkin–Elmer), using a stainless-steel column (i.d. 3 mm, lenght 2 m) packed with Gas-Chrom Q, mesh 100/120, soaked with 3% OV-17 or, in testing benzalacetones *XIII*, with 3% OV-225.

Lipophilicity is expressed by logarithm of the partition coefficient, calculated by the fragment method[15]. Log *P* of cyclohexylacetic acid (*Ia*) was calculated from the equation: log *P*(*Ia*) = log *P* (cyclohexane) + log *P*(acetic acid) — 2 *f*(H) = 3·44 — 0·24 — 0·46 = 2·74.

To calculate log *P* of the other derivatives we used the fragment constants[15] for aliphatic substituents (acids *Ib, c, e, f, IIb, c, d, f, g*), aromatic substituents (acids *Ib, i, k, l, IIi, k, l, IIa — g*), and the fragment factor for a double bond (—0·55). In the conjugation of a double bond with a carboxyl we consiered the interaction of π-electrons with the polar fragment, increasing the lipophilicity of the carboxyl ($f_{COOH} = -0{\cdot}75$); in the conjugation with an aromatic ring and carboxyl the fragment constant f_{COOH} was increased to —0·39.

Regression coefficients in the correlation equations were calculated from experimental data by multiregression analysis. The 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 were evaluated by the Student *t*-test on a statistical significance level of $\alpha \leq 0{\cdot}005$.

Activation of fibrinolysis was assessed by a method[16] in which a coagulum prepared from human plasma is suspended in a solution of the compound tested. The activation is expressed by the minimum molar concentration C^F that dissolves the coagulum within 24 h at 37°C. The anti-inflammatory efficacy was assessed in two tests on an experimental inflammation. Inhibition of the oedema induced by the Freund adjuvans was carried out as described by Pearson and Wood[17], inhibition of the kaolin-induced oedema according to Hillebrecht[18]; the experimental procedures are described in our previous papers[1,19]. The efficacy of the compounds was expressed by % of inhibition of an inflammation, related to a control group of untreated rats.

3-Arylcyclohexanones *IV*

A substituted benzaldehyde and acetone in an alkaline medium gave the corresponding benzalacetone *VII*, as described in ref.[10]. Further given are: R^1, b.p. (°C/kPa) or m.p. (°C), purity (%), yield (%): H, 129—130/1·3, 97·5, 82; CH_3O, 68—70, 93, 87; i-C_3H_7O, 120—122/0·2, 92·5, 67; i-C_3H_7, 135/0·1, 91, 62.

The subsequent condensation cyclization[10] with ethyl malonate in the presence of sodium methoxide in methanol afforded 3-arylcyclohexane-1,3-diones *VIII*. The following data denote respectively: R^1, m.p. (°C), yield (%): H, 176–178 (rep.[10] m.p. 187–189°C), 86; CH_3O, 171–173 (rep.[10] m.p. 177–178·5°C), 91; i-C_3H_7O, 172–174, 99; i-C_3H_7, 178–181, 97.

To a solution of sodium methoxide, prepared from 0·75 g of sodium and 50 ml of methanol, a suspension of *VIII* (0·035 mol) was added, which immediately dissolved. The solution was cooled down to 15°C, dimethyl sulphate (0·035 mol) was added, and the mixture was boiled under a reflux condenser for 4 h and poured into ice-cold water (400 ml). The separated oily substance was extracted into ether (2 × 150 ml). After washing with 10% sodium hydroxide (50 ml) and water (2 × 50 ml) the ethereal solution was dried with magnesium sulphate. The ether was evaporated and the product was purified by distillation (*IXa*) or crystallization from a suitable solvent (*IXb*–*IXd*). Further listed are: compound number, R^1, b.p. (°C/Pa) or m.p. (°C), solvent, purity (%), yield (%): *IXa*, H, 132/27, –, 98, 67; *IXb*, CH_3O, 54–56, benzene–n-hexane (1 : 5), 99, 91; *IXc*, i-C_3H_7O, 47–50, n-hexane, 99, 54; *IXd*, i-C_3H_7, 66–68, n-hexane, 99, 87.

3-Methoxy-2-cyclohexenone *IX* (0·03 mol) was dissolved in methanol (80 ml). To the solution activated carbon (0·5 g) and palladium dichloride (0·75 g, in the form of a 40% solution in conc. hydrochloric acid) were added. After flushing the equipment with nitrogen, the mixture was stirred and kept under hydrogen at the atmospheric pressure until no more hydrogen was absorbed. The catalyst was filtered off, the methanol was removed by distillation and the residue was extracted into ether (2 × 100 ml). The ethereal solution was washed with a saturated aqueous solution of sodium carbonate and water, then dried with magnesium sulphate and distilled. The following data give respectively compound number, R^1, b.p. (°C/kPa), purity (%), yield (%): *IVa*, H, 90–91/0·12, 92, 66; *IVb*, CH_3O, 116–118/0·07, 92, 65; *IVc*, i-C_3H_7O, 126–128/0·01, 89, 50; IVd, i-C_3H_7, 170–180/1·9, 89, 65.

2-Alkylcyclohexanones *IV*

2-Chlorocyclohexanone (*X*) was obtained by chlorination of cyclohexanone[11]. The product was isolated by distillation as a liquid boiling at 80–81°C/0·1 kPa (rep.[11] b.p. 82–83°C/0·1 kPa) in a yield of 77%. Reaction of phenylmagnesium bromide with *X*, as desdribed in ref.[12], gave 2-phenylcyclohexanone in a yield of 56·5%; the product was isolated by distillation as a fraction boiling at 90°C/0·5 kPa (rep.[12] b.p. 136–137°C/0·8 kPa) and melting at 53–56°C (rep.[12] m.p. 53–55°C); purity 93·5%.

Reaction of cyclohexanone with pyrrolidine, described in ref.[13], afforded 1-pyrrolidinocyclohexene *XI*. It was isolated, in a yield of 89%, by distillation as a liquid boiling at 103–104°C/1·3 kPa (rep.[13] b.p. 105–107°C/1·7 kPa). Reaction of *XI* with the corresponding alkyl chlorides alkyl chlorides in boiling dioxan, followed by hydrolysis in water, gave: 2-allylcyclohexane, yield 50·8%, b.p. 78°C/1·0 kPa, purity 94%; 2-benzylcyclohexane, yield 40%, b.p. 96°C/0·07 kPa (rep.[13] b.p. 165–167°C/2·4 kPa), purity 97%.

3-Arylcyclohexen-2-ones *V*

Mannich bases *XII* were prepared from the corresponding substituted acetophenones, paraformaldehyde and piperidine hydrochloride by boiling in 2-propanol, as described elsewhere[14]. The products *XIIc* and *XIIe* were worked up without having been purified, the other ones were crystallized from suitable solvents. The following data designate respectively: compound number, R, m.p. (°C), solvent, rep. m.p. (°C), yield (%): *XIIa*, H, 190–192, ethanol–ethyl acetate (2 : 1), rep.[20] 192–193, 77; *XIIb*, 4-CH_3, 174–177, ethanol, rep.[21] 177·9–177·8, 67; *XIIc*, 4-C_2H_5,

181—182, —, rep.[21] 177·9—177·8, 83·5; *XIId*, 4-i-C_3H_7, 179—181, ethanol, rep.[22] 180·1—181·5, 71; *XIIe*, 4-i-C_4H_9, 171—173, —, rep.[23] 162, 66; *XIIf*, 4-Cl, 188—190, ethanol, rep.[21] 186—187·2, 72; *XIIg*, 4-F, 166—169, ethanol, rep.[24] 190, 65.

To a solution of sodium ethoxide, prepared by dissolving 5·8 g of sodium in 150 ml of ethanol, ethyl acetoacetate (40·4 g, 0·3 mol) was added. Then, while cooling the mixture to ≦5°C, a Mannich base *XII* (0·1 mol) and dimethyl sulphate (30·2 g, 0·24 mol) were successively added. After stirring for 1 h at 5°C and 6 h at 20°C, the mixture was concentrated, mixed with water (300 ml) and extracted with ether (2 × 300 ml). The combined ethereal extracts were washed with a saturated aqueous solution of sodium carbonate (50 ml) and water (100 ml), then dried with magnesium sulphate. The ether was distilled off and the residue (crude 3-aryl-5-ethoxycarbonyl-2--cyclohexenone *XV*) was hydrolysed and decarboxylated by 20-h boiling in a mixture of ethanol (160 ml) and 10% sodium carbonate (460 ml). The ethanol was removed by distillation and the separated oil was extracted into ether (2 × 250 ml); the ethereal solution was washed with water (2 × 100 ml) and dried with magnesium sulphate. The ether was distilled off and the crude product was purified by crystallization or distillation. The following data give respectively: compound number, substituent X, m.p. (°C), solvent or b.p. (°C/kPa), yield (%), purity (%): *Va*, H, 60—61, 35% methanol, rep.[25] m.p. 64, 78, 98; *Vb*, CH_3, 42—44, n-hexane–benzene (8 : 1), rep.[26] b.p. 154/0·65, 73, 98; *Vc* C_2H_5, 130/0·5, 39, 98; *Vd*, i-C_3H_7, 148/0·9, 62, 95; *Ve*, i-C_4H_9, 135/0·3, 4·65, 96; *Vf*, Cl, 131/0·7, 68, 97; *Vg*, F, 112/0·6, 71·5, 99.

Aryl(Alkyl)cyclohexylideneacetic Acids *II* and 3-Aryl-2-cyclohexenylideneacetic Acids *III*

To a suspension of sodium hydride (0·058 mol, in the form of an 80% suspension in paraffine oil) in dimethylformamide (20 ml) was added triethyl phosphonoacetate (*VI*, 0·058 mol) in dimethylformamide (20 ml), then a solution of ketone *IV* or *V* (0·055 mol) in dimethylformamide (40 ml). The mixture was stirred at 20°C for 1 h, then at 90 to 100°C for 8 h. After pouring into 900 ml of ice-cold water, the oily phase was extracted with ether (3 × 150 ml),the ethereal extracts were washed with 5% sodium hydroxide (50 ml) and water (50 ml), then dried with magnesium sulphate. The ether was distilled off and the ethyl esters of acids *II* and *III* were purified by column chromatography on silica gel or by distillation. Their purity, determined by gas chromatography, was 92—98%. The esters were heated for 5 h in a solution of sodium hydroxide in aqueous ethanol. The ethanol was distilled off and the residue was stirred with activated carbon and filtered. Acidification of the filtrate liberated the acids *II* and *III*, respectively. The crude products were purified by distillation or crystallization (see Tables I and II); the acids *IIg—III* were isolated in the form of cyclohexylammonium salts.

Aryl(Alkyl)cyclohexylacetic Acids *I*

Ethyl esters of the acids *II* and *III* were hydrogenated as in the preparation of 3-arylcyclohexanones *IV*. To prepare acids *Ia—Ic* we hydrogenated the corresponding unsaturated acids; the products were methyl esters of *Ia—Ic*. An ester was then boiled 3 h in a solution of potassium hydroxide in 50% ethanol. The ethanol was distilled off, the residue was diluted with water and purified with activated carbon. The product was obtained by acidification of the filtrate with 50% sulphuric acid. Acids *Ib* and *Ik* were purified by crystallization, *Ia* and *Ic* were isolated directly in high purity. The other acids *I* were converted into cyclohexylammonium salts.

4-Phenylcyclohexylacetic Acid[30] (*Id*)

To a suspension of aluminium chloride (11 g, 0·08 mol) in benzene (45 ml), stirred and cooled to 15°C, a solution of *IIa* (12·6 g, 0·075 mol) in benzene (25 ml) was added, the temperature

being not allowed to exceed 30°C. After 5-h heating to 50°C the mixture was poured into a mixture of ice (200 g) and conc. hydrochloric acid (25 ml). The benzene layer was separated and the aqueous layer was washed with benzene (2 × 50 ml). The benzene solution was dried with magnesium sulphate and worked up by distillation; yield of *Id* 21% (for physico-chemical data see Table III).

Cyclohexylammonium Salts of Acids *I*—*III*

An acid (*I*—*III*, 0·02 mol) was dissolved in ether (75 ml) or its mixture with 15 ml of acetone. The solution was filtered with activated carbon, the filtrate was mixed with cyclohexylamine (0·03 mol) in ether (20 ml). After stirring for 30 min at 20°C it was cooled to 0°C, the precipitate was collected on a filter and washed with ether; yield 85—90%.

RESULTS AND DISCUSSION

The presence of a double bond in acids *II* and two double bonds in acids *III* allows of the formation of isomers differing in the arrangement of substituents on the exo double bond. After the Horner–Wittig reaction, the esters of acids *II* were found to be isomers of configurations *Z* and *E*, differing in signal of the olefinic hydrogen atom. Hydrolysis and crystallization of the acid, possibly converted into its cyclohexylammonium salt, gave in most cases a single isomer, characterized, by a singlet δ of c. 5·5 (Tables I and II). It was only with derivatives *IIk* that two isomers were obtained. The signal of a higher δ probably belonged to the *E* configuration isomer in which the hydrogen atom on the double bond is more deshielded.

With the 2-phenyl derivative *IIe*, the product of the Wittig reaction was found, by ^{1}H NMR spectra, to be a mixture of the expected ester of 2-phenylcyclohexylideneacetic acid and an ester of 2-phenylcyclohexenylacetic acid, most likely produced by a shift of the double bond to the energetically preferable conjugation with the aromatic ring. The ratio of the two isomers was about 2 : 1, in favour of the isomer with the endo double bond. The two positional isomers were separated in the form of acids by column chromatography on silica gel and crystallization from a mixture of benzene and n-hexane. With the 2-benzyl derivative *IIg* the double bond was also found to be shifted toward the ring, but to a lesser extent than in the former case. The pure acid *IIg* was isolated by column chromatography.

The acids *III* are characterized by different signals of the hydrogen atoms on the exo and endo double bonds (Table III). The greater deshielding of the endo double bond hydrogen by the *Z*-configuration carboxyl manifests itself by a shift of the corresponding signal (*b*) to higher values of δ.

Data on the anti-inflammatory efficacy and activation of fibrinolysis obtained with the acids *I*—*IIII* are compiled in Table IV. A problem in assessing the activation of fibrinolysis was insolubility of the acids or their salts under the conditions of the test. However, 12 compounds were evaluated for fibrinolytic capacity in relation to their physico-chemical properties. Like in the group of arylaliphatic acids (Eq. (*1*)),

TABLE I

Physico-chemical data of cyclohexylideneacetic acids *II* or their cyclohexylammonium salts

Number X	M.p., °C/Solvent[a] B.p., °C/kPa	Yield[b] (%)	Formula (Mol. mass)	Calculated/found % C	 % H	 % N	^{1}H NMR δ[c]
IIa	90[d]	78	$C_8H_{12}O_2$	—	—	—	5·52
H	104—106/1·46		(140·2)				
IIb	60—62[e]/M–W 1 : 1	63	$C_9H_{14}O_2$	—	—	—	5·55
4-CH_3	—		(154·2)				
IIc	95—97/M–W 3 : 2	62	$C_{12}H_{20}O_2$	73·43	10·27	—	5·60
4-t-C_4H_9	—		(196·3)	73·58	10·08	—	
IId	—	56	$C_9H_{14}O_2$	70·10	9·15	—	5·62
2-CH_3	134/1·06[f,g]		(154·2)	69·92	9·32	—	
IIe	136—140/B[h]	77[i]	$C_{14}H_{16}O_2$	77·75	7·46	—	5·13
2-C_6H_5	—		(216·3)	77·74	7·58	—	
IIf	120—123	55	$C_{17}H_{29}NO_2$	73·07	10·46	5·01	5·58
2-CH_2=$CHCH_2$[k]	—		(279·4)	72·42	10·73	4·89	
IIg	103—105[l]	60	$C_{15}H_{18}O_2$	78·23	7·88	—	5·60
2-$C_6H_5CH_2$	—		(230·3)	78·63	8·18	—	
IIh	120—123	78	$C_{20}H_{29}NO_2$	76·15	9·27	4·44	5·45
3-C_6H_5[k]	—		(315·4)	76·02	9·47	4·15	
IIi	110—112	32	$C_{21}H_{31}NO_3$	73·01	9·05	4·05	5·22
3-(4′-$CH_3OC_6H_4$)[k]	—		(345·5)	72·79	9·21	3·87	
IIk	123—125	59	$C_{23}H_{35}NO_3$	73·95	9·45	3·75	5·50,
3-(3′-i-$C_3H_7OC_6H_4$)[k]	—		(373·5)	74·12	9·53	3·30	5·82 s[m]
IIl	139—141	58	$C_{23}H_{35}NO_2$	77·26	9·87	3·92	5·49
3-(4′-i-$C_3H_7C_6H_4$)[k]	—		(357·5)	77·21	10·05	3·77	

[a] Designation of solvents: M methanol, W water, B benzene; [b] yield of the acid, based on the starting ketone; [c] signal of the double-bond hydrogen; [d] rep.[31] m.p. 90—91·5°C; [e] rep.[32] m.p. 66°C; [f] rep.[32] m.p. 68·5°C; [g] also isolated as cyclohexylammonium salt, m.p. 113—115°C, for $C_{15}H_{27}NO_2$ (255·4) calculated: 70·54% C, 11·45% C, 5·48% N; found: 70·81% C, 11·12% H, 5·39% N; [h] separated by column chromatography on silica gel (benzene–ether 9 : 1) from 2-phenylcyclohexenylacetic acid, m.p. 89—93°C; [i] overall yield of the two acids; [k] isolated as cyclohexylammonium salts (the data refer to the salts); [l] also isolated as cyclohexylammonium salt, m.p. 126—128°C, for $C_{21}H_{31}NO_2$ (389·5) calculated: 76·55% C, 9·48% H, 4·25% N; found: 76·30% C, 9·78% H, 4·01% N; [m] isolated mixture of isomers *E* and *Z*.

TABLE II

Physico-chemical data of 2-cyclohexenylideneacetic acids *III*

Number X	M.p. °C/Solvent[a] (Yield, %)[b]	Formula (Mol. mass)	Calculated/found		^{1}H-NMR, δ	
			% C	% H	Z^c	E^c
IIIa	112–113/M–W 2 : 1	$C_{14}H_{14}O_2$	78·48	6·59	5·58,	5·72,
C_6H_5	(52)	(214·2)	78·42	6·68	8·02	6·65
IIIb	170–173/M–W 2 : 1	$C_{15}H_{16}O_2$	78·92	7·07	5·52,	5·68,
4-$CH_3C_6H_4$	(59)	(228·3)	79·04	7·21	8·05	6·48
IIIc	144–147/M–W 9 : 1	$C_{16}H_{18}O_2$	79·29	7·49	5·60,	5·75,
4-$C_2H_5C_6H_4$	(64)	(242·3)	79·18	7·56	8·05	6·60
IIId	154–157/M–W 2 : 1	$C_{17}H_{20}O_2$	79·65	7·86	—	5·77,
4-i-$C_3H_7C_6H_4$	(51)	(256·3)	79·52	7·95	—	6·70
IIIe	126–129/M–W 2 : 1	$C_{18}H_{22}O_2$	79·96	8·20	5·48,	5·70,
4-i-$C_4H_9C_6H_4$	(49)	(270·6)	79·78	8·38	7·98	6·50
IIIf	138–140/B–H 1 : 2	$C_{14}H_{13}ClO_2$	67·61	5·27[d]	5·58,	5·70,
4-Cl	(47)	(248·7)	68·05	5·51	7·98	6·50
IIIg	118–120/B–H 1 : 1	$C_{14}H_{13}FO_2$	72·40	5·64[e]	5·42,	5·50,
4-F	(38)	(232·2)	72·11	5·72	7·80	6·52

[a] M methanol, W water, B benzene, H n-hexane; [b] overall yield of the Horner–Wittig reaction and hydrolysis; [c] the upper value refers to the exo double bond hydrogen, the bottom to the endo double bond hydrogen; [d] calculated: 14·26% Cl, found: 13·82% Cl; [e] calculated: 8·18% F, found: 8·24% F.

in this series, too, activation of fibrinolysis depended mostly on lipophilicity. However, replacement of the aromatic ring by a cyclohexyl residue brought about a decrease in fibrinolytic capacity and changed the character of this relation to lipophilicity. In the series of acids *I–III* the effect of lipophilicity on fibrinolytic

TABLE III

Physico-chemical data of cyclohexylacetic acids or their cyclohexylammonium salts

Number X	M.p., °C (Yield, %)	Formula (Mol. mass)	Calculated/found		
			% C	% H	% N
Ia H	26–27[a] (73)	$C_8H_{14}O_2$ (142·2)	—	—	—
Ib 4-CH_3	64–65[b] (71)	$C_9H_{16}O_2$ (156·2)	—	—	—
Ic 4-t-C_4H_9	81–83[c] (97)	$C_{12}H_{22}O_2$ (198·2)	—	—	—
Id 4-C_6H_5	128–130[d] —	$C_{14}H_{18}O_2$ 218·3	77·03 77·39	8·31 8·68	—
Ie 2-CH_3[e]	118–120 (60[f])	$C_{15}H_{29}NO_2$ (255·4)	70·54 70·32	11·45 11·72	5·48 5·24
If 2-n-C_3H_7[e]	126–128 (50[f])	$C_{17}H_{33}NO_2$ (283·4)	72·03 71·94	11·73 11·58	4·94 4·59
Ig 3-C_6H_5[e]	132–134 (64[f,g])	$C_{20}H_{31}NO_2$ (317·15)	75·66 75·88	9·84 10·14	4·41 4·16
Ih 3-(4′-$CH_3OC_6H_4$)[e]	135–137 (72[f,h])	$C_{21}H_{33}NO_3$ (347·5)	72·58 72·29	9·57 9·70	4·03 3·78
Ii 3-(4′-$CH_3C_6H_4$)[e]	116–118 (64[f])	$C_{21}H_{33}NO_2$ (331·5)	76·09 76·40	10·03 9·82	4·23 4·22
Ik 3-(4′-i-$C_3H_7C_6H_4$)	81·5–83[i,k] (68)	$C_{17}H_{24}O_2$ (260·4)	78·42 78·17	9·29 9·45	—

[a] Rep.[27] m.p. 30°C; [b] rep.[28] b.p. 105–106°C/0·4 kPa; [c] rep.[29] 94·8–95·5°C; [d] b.p. at 1·3 kPa; [e] isolated as cyclohexylammonium salts, the data refer to the salts; [f] yield of the acid; [g] m.p. of the acid 48–50°C; [h] m.p. of the acid 83–85°C (50% ethanol), for $C_{15}H_{20}O_3$ (248·3) calculated: 72·55% C, 8·12% H, found: 72·25% C, 8·26% H; [i] crystallized from n-hexane; [k] isolated as cyclohexylammonium salt, m.p. 135°C, for $C_{23}H_{37}NO_2$ (359·5) calculated: 76·83% C, 10·37% H, 3·89% N, found: 76·55% C, 10·11% H, 3·72% N.

TABLE IV

Biological properties of acids *I*—*III*

Number X	Log P^a	Activation of fibrinolysis		Anti-inflammatory efficacy[b]	
		C^F(mol l^{-1}) Log $(1/C^F)_{exp}$	Log $(1/C^F)_{calc}$[c] Log $(1/C^F)_{calc}$[f]	KE[d]	FA[e]
Ia H	2·74	0·15 0·823	1·375 0·782	na	na
Ib 4-CH_3	3·28	0·06 1·222	1·710 1·332	na	na
Ic 4-t-C_4H_9	4·73	0·006 2·222	2·609 2·246	nd	nd
Id 4-CH_3	4·41	0·01 1·222	2·410 1·332	15	nd
Ic 4-t-C_4H_9	4·73	0·006 2·222	2·609 2·246	nd	nd
Id 4-C_6H_5	4·41	0·01 2·000	2·410 2·102	15	nd
Ie 2-CH_3[h]	3·28	<0·1[g] <1·000	— 1·332	23	29
If 2-n-C_3H_7	4·48	<0·01[g] <2·000	— 2·147	15	12
Ig 3-C_6H_5[h]	4·41	ud[i] —	— —	34	18
Ih 3-(4′- -$CH_3OC_6H_4$)[h]	4·39	<0·01[g] <2·000	— 2·105	16	18
Ii 3-(4′- -$CH_3C_6H_4$)[h]	4·97	ud[i] —	— —	21	17
Ik 3-(4′-i- -$C_3H_7C_6H_4$)	5·94	0·005 2·301	0 2·377	35	18
IIa H	2·43	<0·1[g] <1·000	— 0·413	na	na
IIb 4-CH_3	2·97	<0·01[g] <2·000	— 1·030	nd	nd
IIc 4-t-C_4H_9	4·42	0·01 2·000	2·416 2·118	nd	nd

TABLE IV
(*Continued*)

Number X	Log P^a	Activation of fibrinolysis		Anti-inflammatory efficacy[b]	
		C^F(mol l^{-1}) Log $(1/C^F)_{exp}$	Log $(1/C^F)_{calc}$[c] Log $(1/C^F)_{calc}$[f]	KE[d]	FA[e]
IId 2-CH_3	2·97	0·09 1·046	1·517 1·030	nd	nd
IIg 2-$C_6H_5CH_2$	4·41	0·008 2·097	2·410 2·115	21	23
IIh 3-C_6H_5[h]	4·10	<0·01[g] <2·000	— 1·950	20	18
IIk 3-(4′-i- -$C_3H_7OC_6H_4$)[h]	4·59	0·006 2·222	2·522 2·194	nd	nd
III 3-(4′-i- -$C_3H_7C_6H_4$)[h,k]	5·63	ud[i] —	— —	34	na
IIIa C_6H_5	3·95	0·02 1·699	2·125 1·856	na	na
IIIb 4-$CH_3C_6H_4$	4·51	ud[i] —	— —	30	12
IIId 4-i-$C_3H_7C_6H_4$	5·48	ud[i] —	— —	31	46
IIIe 4-i-$C_4H_9C_6H_4$	5·98	ud[i] —	— —	26	28
IIIf 4-ClC_6H_4	4·66	0·007 2·155	2·565 2·221	na	na
IIIg 4-FC_6H_4	4·09	0·009 2·046	2·212 1·944	nd	nd
4-Cyclohexyl- phenylacetic acid	3·91 3·91	0·005 2·301	— —	39	32
2′-(4′-Iso- butylphenyl)- propanoic acid	3·60	0·01 2·000	— —	46	42

[a] Values of log *P* were calculated by the fragment method, see Experimental; [b] na denotes inactive compounds, nd denotes compounds that were not tested; [c] values calculated from Eq. (*1*) and consistent with the dependence of activation of fibrinolysis on lipophilicity in the group of aryl-aliphatic acids; [d] % of inhibition of kaolin-induced oedema; [e] % of inhibition of oedema induced by the Freund adjuvans; [f] values calculated from Eq. (*2*); [g] not soluble to a high concentration; [h] tested as cyclohexylammonium salt; [i] insoluble under the conditions of the test. Compounds *IIe*, *IIf*, and *IIIc* were not biologically tested and are therefore omitted.

capacity can be expressed by the quadratic equation:

$$\log (1/C^{F}) = 2{\cdot}200 \log P - 0{\cdot}196 (\log P)^2 - 3{\cdot}775 , \qquad (2)$$

$$n = 12, r = 0{\cdot}979, s = 0{\cdot}116, F = 101{\cdot}3 ,$$

the optimum of lipophilicity corresponding to $\log P_{opt} = 5{\cdot}55$. Cyclohexylaliphatic acids, unlike arylaliphatic acids, did not exhibit a steep decrease in fibrinolytic capacity with an increase in lipophilicity beyond the optimum value. A similar parabolical dependence of fibrinolytic capacity on lipophilicity had been observed by us[8] in a series of aryloxoaliphatic acids.

The anti-inflammatory efficacy of the acids *I*–*III* was tested on two experimental models of inflammation. Not even one derivative out of the whole group matched 2-(4′-isobutylphenyl)propanoic acid (ibuprofen) as standard in either model. The importance of position of the aromatic or cyclohexyl ring to the carboxyl group is apparent from comparison of the anti-inflammatory effects of arylcyclohexylacetic acids with that of 4-cyclohexylphenylacetic acid (Table IV). In contrast to the arylaliphatic acids, the optimum lipophilicity of the acids *I*–*III* is obviously higher. Salts of the considerably lipophilic acids *Ik*, *IIl*, *IIId*, and *IIIe* with $\log P \gg 3{\cdot}5$ had a marked anti-inflammatory activity. The acids *I*–*III* seem to differ from the arylaliphatic acids in the mechanism of the anti-inflammatory action or in the site of this action. The presence of one or two double bonds diminished the anti-inflammatory efficacy of the low-lipophilicity acids (*cf. Ie* and *IId*, *Ig* and *IIh*, *IIIa*). At an elevated lipophilicity the differences in saturation degree of the cycloaliphatic moiety in the acids *Ik*, *IIk*, and *IIId* had only a negligible effect on the antiinflammatory efficacy.

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