SUBSTITUTED BENZYLOXYARYLACETIC ACIDS: SYNTHESIS AND QUANTITATIVE RELATIONSHIPS BETWEEN STRUCTURE AND ANTIINFLAMMATORY ACTIVITY

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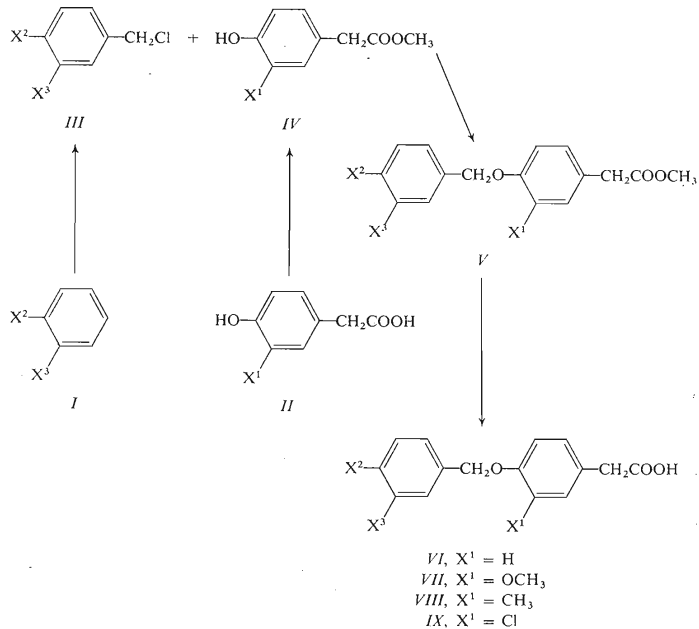
A series of 4-benzyloxyarylacetic acids *VI—IX* either unsubstituted or substituted in position 3 with chlorine, methyl or methoxy groups were prepared by a reaction of methyl 4-hydroxyphenylacetate or of its 3-chloro, 3-methyl and 3-methoxy derivatives with substituted benzyl chlorides and by subsequent hydrolysis of esters *V*. With all the acids *VI—IX* the antiinflammatory activity was assessed from the inhibition of kaolin edema and adjuvant edema. The experimental results were processed by the method of regression analysis. Both types of antiinflammatory effects show a parabolic dependence on the lipophilicity of all the variable substituents and they are also affected by the electronic effects of substituents in the *meta*-position with respect to the acetic acid residue. In agreement with these conclusions, the most potent compound of the series is 3-chloro-4-benzyloxyphenylacetic acid.

Working with a series of cinnamic acids[1] we have recently studied the quantitative relationships between the physico-chemical properties and the activity in a test of stabilizing the erythrocyte membrane toward hypotonic hemolysis. On the basis of the regression equations obtained we reached the conclusion that the optimal substitution of the aromatic ring is given by a halogen in the *meta* position and an alkoxy group in the *para* position. At the same time, most of such substituted acids were better inhibitors of kaolin edema inflammation. It was apparent, however, that the principal structure of cinnamic acids is invested with a highly lipophilic character which, in a system *in vivo*, may diminish its transport toward the target site.

The Hansch equation[2-4] expressing the dependence between biological activity and physico-chemical parameters, shows clearly that application of a given set of results from one series to another is possible only if the mechanism of action of the two series is the same. The mechanism of action of antiinflammatory agents of acid character has not been elucidated satisfactorily. For most compounds of this type, there exist some similar structural elements which underlie their antiinflammatory effect[5-7], such as the aromatic ring, an acidic hydrogen and a connecting or lateral aliphatic chain. This similarity of the basic structures led to the application

of the results obtained with cinnamic acids to the less lipophilic but structurally related arylacetic acids. Some derivatives of phenylacetic acid, substituted with chlorine in the *meta*-position and with a benzyloxy group in the *para* position were prepared. For comparison, the series was extended to include acids without substitution in the *meta* position or substituted with a methoxy or a methyl group. These acids were prepared in a reaction of sodium salts of the methyl esters of the appropriate *p*-hydroxyarylacetic acids *IV* with substituted benzyl chlorides *III* in dimethyl sulfoxide and by hydrolysis of the esters formed *V*. The benzyl chlorides *III* were prepared by chloromethylation of the appropriate aromatic compounds[8–10] *I*. The arylacetic acids *II* (X^1 = H, CH_3, Cl) were prepared from *p*-methoxybenzyl chloride or from its *m*-methyl and *m*-chloro derivatives using a modified method[10] based on the reaction with sodium cyanide and subsequent hydrolysis and on the demethylation of the



SCHEME 1

arylacetonitriles formed by boiling in hydrobromic acid. Acid *II* ($X^1 = OCH_3$) was prepared from vanillin by rhodanine synthesis according to Fischer and Hibbert[11].

With all the acids *VI–IX*, antiinflammatory activity was examined in two tests, *viz.* by inhibition of kaolin edema[12] and by inhibition of Freund's adjuvant edema[13]. In both tests the effect was expressed by an activity index. This index I^K or I^F was calculated as a ratio of the effect of the tested compound to that of the standard in a given experimental edema. The standard used was 3-chloro-4-allyloxyphenylacetic acid (Mervan)[10,14]. The experimental results are summarized in Table I. The antiinflammatory effect of acids *VI–IX* was evaluated as a function of the physico-chemical properties of these acids using the Hansch method of correlation analysis[3,4,15]. The general equation in which the biological activity is treated as a function of changes of free energy, has the form

$$\log (BR) = \Delta G_H + \Delta G_E + \Delta G_S + \text{const.}, \qquad (1)$$

where BR is biological response and ΔG_H, ΔG_E and ΔG_S are changes of free energy of hydrophobic, electronic and steric nature in the course of transport of the substance and its interaction with a suitable receptor at the target site. These changes in free energy are usually expressed by suitable physico-chemical parameters[16].

The biological effect expressed in our case by a variable biological response at a given dose of drug differs from the usual description of biological activity by a variable concentration bringing about a constant response. Even if the first method of describing biological activity may be less suitable it was used in regression analysis by other authors[17,18] even in the case of correlating antiinflammatory effects[19] with physico-chemical parameters.

	n	s	r	F	
$\log I^K = -0{\cdot}110\,\Sigma\pi - 0{\cdot}067$	28	0·172	0·386	4·72	(2)
$\log I^K = 0{\cdot}611\,\Sigma\pi - 0{\cdot}293(\Sigma\pi)^2 - 0{\cdot}394$	28	0·093	0·871	40·94	(3)
$\log I^K = 0{\cdot}613\,(\pm 0{\cdot}248)\,\Sigma\pi - 0{\cdot}303\,(\pm 0{\cdot}097)\,(\Sigma\pi)^2 + 0{\cdot}268\,(\pm 0{\cdot}264)\,\sigma(X^1) - 0{\cdot}413\,(\pm 0{\cdot}153)$	28	0·080	0·909	39·88	(4)

(n is the number of compounds tested, s is the standard deviation, r the regression coefficient and F the Fischer–Snedecor criterion.)

The results of regression analysis of kaolin edema inhibition are summarized in equation (2)–(4), the correlation including only those results that have been

obtained at the level of confidence $\alpha = 0{\cdot}05$ at the least (Table I). From a comparison of equations (*2*) and (*3*) it follows that this effect shows a square dependence on lipophilicity which is expressed as a sum of parameters π of all the variable substituents X^1, X^2 and X^3. By introducing the polar constants $\sigma(X^1)$ of substituents X^1 equation (*4*) was obtained. Comparison of the statistical criteria of equations (*3*) and (*4*) shows that the studied effect is also influenced by the electronic effect of these substituents. Likewise, the *t*-test demonstrates that the selected parameters are statistically significant at a confidence level of $\alpha = 0{\cdot}005$. Application of the polar constants σ of substituents X^2 and X^3, whether alone or in sum with constants $\sigma(X^1)$, or of molar refractions[20] of these substituents did not improve the correlation.

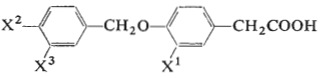
	n	s	r	F	
$\log I^F = -0{\cdot}133\,\Sigma\pi - 0{\cdot}083$	25	0·154	0·471	6·57	(*5*)
$\log I^F = 0{\cdot}271\,\Sigma\pi - 0{\cdot}185\,(\Sigma\pi)^2 - 0{\cdot}239$	25	0·131	0·685	9·71	(*6*)
$\log I^F = 0{\cdot}235\,(\pm 0{\cdot}223)\,\Sigma\pi - 0{\cdot}187\,(\pm 0{\cdot}115)\,(\Sigma\pi)^2 + 0{\cdot}511\,(\pm 0{\cdot}288)\,\sigma(X^1) - 0{\cdot}255\,(\pm 0{\cdot}154)$	25	0·099	0·841	16·93	(*7*)

The analogous equations (*5*)–(*7*) were derived for the inhibition of adjuvant edema, using again experimental results with a minimum level of confidence $\alpha = 0{\cdot}05$. The equations show that the dependence of this effect on the physico-chemical parameters used is similar to that for the inhibition of kaolin edema. The level of confidence of all the parameters in equation (*7*) determined by the *t*-test has an α of 0·025. Like in the case of kaolin edema, introduction of other physico-chemical parameters does not improve the statistical significance of the correlation.

Using the above physico-chemical parameters the kaolin edema inhibition is optimally expressed by equation (*4*) ($F_{3,24} = 5{\cdot}52$ for $\alpha = 0{\cdot}005$) and the adjuvant edema inhibition by equation (*7*) ($F_{3,21} = 3{\cdot}82$ for $\alpha = 0{\cdot}025$). The square dependence of the antiinflammatory effect on lipophilicity permits in both cases to calculate the optimum value of lipophilicity of all the variable substituents. By setting the first derivative of the equation with respect to $\Sigma\pi$ equal to zero one can calculate $(\Sigma\pi)_{opt}$ from equation (*3*) to be $(\Sigma\pi)^K_{opt} = 1{\cdot}01$ and from equation (*7*) to be $(\Sigma\pi)^F_{opt} = 0{\cdot}63$. The regression equations obtained thus permit to determine in a series of acids *VI*–*IX* the compound that was optimally active in both tests of antiinflammatory activity. The optimum is determined by the general lipophilicity of the substituents between 0·6 and 1·1 and by the presence of chlorine which shows the maximum value of σ of all the X^1 substituents in *meta*-position with respect to acetic acid. These requirements are met by 3-chloro-4-benzyloxyphenylacetic acid (*IXa*) and by its

TABLE I

Antiinflammatory Activity of Acids *VI*—*IX*



Number	X^2	X^3	$\Sigma\pi$	Kaolin edema[a,b]			Adjuvant edema[c,d]		
				I^K	$\log I^K_{exp}$	$\log I^K_{calc}$	I^F	$\log I^F_{exp}$	$\log I^F_{calc}$
VIa	H	H	0	0·38	−0·420	−0·413	0·46	−0·337	−0·255
VIb	C_2H_5	H	0·98	0·85	−0·071	−0·103	0·61	−0·215	−0·205
VIc	i-C_3H_7	H	1·40	0·75	−0·125	−0·149	0·36	−0·444	−0·293
VIg	i-C_3H_7O	H	0·80	0·91	−0·041	−0·117	0·65	−0·187	−0·187
VIh	iC_4H_9O	H	1·30	0·80	−0·097	−0·127	0·48	−0·319	−0·266
VIi	CH_3O	CH_3	0·50	0·58	−0·234	−0·182	0·76	−0·119	−0·184
VIj	i-C_3H_7O	CH_3	1·30	0·71	−0·149	−0·129	0·36	−0·444	−0·266
VIn	i-C_3H_7O	Cl	1·64	0·45	−0·347	−0·224	0·32[e]	—	—
VIp	Cl	Cl	1·70	0·70	−0·155	−0·248	0·46	−0·337	−0·397
VIIa	H	H	0·04	0·35	−0·456	−0·356	0·68	−0·167	−0·184
VIIc	i-C_3H_7	H	1·44	0·74	−0·131	−0·127	0·68	−0·167	−0·244
VIIg	i-C_3H_7O	H	0·84	1·18	0·072	−0·082	0·94	−0·027	−0·128
VIIm	CH_2=$CHCH_2O$	Cl	1·58	0·59	−0·229	−0·170	0·52	−0·284	−0·290
VIIo	i-C_4H_9O	Cl	2·18	0·25[e]	—	—	0·21	−0·678	−0·571
VIIIa	H	H	0·49	0·70	−0·155	−0·204	0·60	−0·222	−0·221
VIIIb	C_6H_5	H	1·47	0·66	−0·180	−0·186	0·70	−0·155	−0·350
VIIIi	CH_3O	CH_3	0·99	0·80	−0·097	−0·122	0·46	−0·337	−0·242
VIIIm	CH_2=$CHCH_2O$	Cl	2·03	0·30	−0·523	−0·438	0 36	−0·444	−0·585
VIIIn	i-C_3H_7O	Cl	2·13	0·29	−0·538	−0·503	0·20[e]	—	—
IXa	H	H	0·68	1·18	0·072	−0·037	1·35	0·130	0·007
IXb	C_2H_5	H	1·66	0·68	−0·168	−0·132	0·48	−0·319	−0·192
IXd	i-C_4H_9	H	2·58	0·18	−0·745	−0·738	0·16[e]	—	—
IXe	CH_3O	H[f]	0·68	0·82	−0·085	−0·037	1·03	0·012	0·007
IXf	CH_2=$CHCH_2O$	H	1·38	0·70	−0·155	−0·046	0·81	−0·091	−0·096
IXg	i-C_3H_7O	H	1·48	0·76	−0·119	−0·071	0·82	−0·086	−0·129
IXh	i-C_4H_9O	H	1·98	0·52	−0·284	−0·278	0·38[e]	—	—
IXi	CH_3O	CH_3	1·18	0·70	−0·155	−0·132	0·77	−0·113	−0·050

TABLE I
(*Continued*)

Number	X^2	X^3	$\Sigma\pi$	Kaolin edema[a,b]			Adjuvant edema[c,d]		
				I^K	$\log I^K_{exp}$	$\log I^K_{calc}$	I^F	$\log I^F_{exp}$	$\log I^F_{calc}$
IXj	i-C_3H_7O	CH_3	1·98	0·47	−0·328	−0·290	0·46	−0·337	−0·335
IXk	CH_3O	Cl	1·52	0·76	−0·119	−0·083	0·74	−0·131	−0·142
IXm	CH_2=$CHCH_2O$	Cl	2·22	0·58	−0·237	−0·448	0·36	−0·444	−0·467
IXn	i-C_3H_7O	Cl	2·32	0·25[e]	—	—	0·28[e]	—	—

[a] Hind foot edema was brought about by a subplantar injection of 10% kaolin suspension (0·1 ml) to Wistar female rats (Rosice breed). The compounds tested were applied *per os* in the form of aqueous suspension with gum arabic (25 mg/kg) 1 h before kaolin injection. The size of the edema was followed volumetrically in comparison with a control untreated group, 1·5, 3, 4·5 and 6 h after kaolin injection. The results were evaluated by the t-test at a confidence level of $\alpha = 0{\cdot}05$. The effect of the substance was expressed in % inhibition of inflammation and the activity index *I* was calculated as the ratio of effects of the compound tested and of the standard. [b] Values of $\log I^K_{calc}$ were computed from the regression equation (*4*). [c] The inflammation was brought about by a subplantar injection of 0·1 ml Freund's adjuvant into the hind foot of female rats (Wistar strain, Rosice breed). The compounds were administered for 4 days in 50 mg/kg daily doses, *per os*, in the form of an aqueous suspension with gum arabic. The size of the edema was measured always 4 h after application of the compound. The results were evaluated as under [a]. [d] Values of $\log I^F_{calc}$ were calculated from equation (*7*); [e] Experimental values I^K and I^F are not significant at the chosen significance level. [f] The effect of this acid is not included in the regression equations.

4-(4′-methoxybenzyloxy) derivative *IXe*. Acid *IXa* was prepared in connection with the original series of acids *VI*–*IX*; acid *IXe* is not included in the regression equations because it was prepared after the regression analysis had been completed. The antiinflammatory effect of both acids and especially of acid *IXa* supports the conclusions following from the regression equations. Acid *IXe* has an antiinflammatory effect corresponding to that of Mervan, acid *IXa* is more efficient in both tests. Table II indicates that even in other tests, such as inhibition of a carageenan edema[21] and inhibition of formation of granulation tissue[22], its effect is comparable with that of α-(4-isobutylphenyl)propionic acid, or Brufen[23], which is at present one of the most important antiinflammatory drugs. 3-Chloro-4-benzyloxyphenylacetic acid was then selected for further testing.

TABLE II

Antiinflammatory Effect (inhibition in percent) of 3-Chloro-4-benzyloxyphenylacetic Acid

Acid	Kaolin edema[a]	Adjuvant edema[b]	Implanted pellets[c]	Pleuritis[d]
3-Chloro-4-benzyloxyphenylacetic (VÚFB 9682)	49	61	34	71
α-(4-Isobutylphenyl)propionic (Brufen)	52	48	21	78
3-Chloro-4-allyloxyphenylacetic (Mervan)	47	45	18	—

[a] See note [a] in Table I; dose of 50 mg/kg. [b] See note [b] in Table I. [c] Wistar strain SPF rats were subjected to an abdominal subcutaneous implantation of two pellets of Whatman 4 paper impregnated with 5% carageenan. The compounds were applied *per os* at daily doses of 50 mg/kg. After 7 days the animals were killed, the pellets with granulation tissue were excised and dried at 60°C. The weight of dried granulation tissue was determined. The effect of the compounds was expressed in % inhibition of granulation tissue formation as compared with untreated control group. [d] Wistar male rats were given ether narcosis and then injected with 5 ml 0·075% Evans Blue and 0·025% carageenan into the pleural cavity. The compounds were administered *per os* 1 h before the treatment at a dose of 50 mg/kg. After 6 h, the chest was opened under ether narcosis and the volume of unabsorbed liquid was measured. The effect was expressed in % as compared with untreated control group.

EXPERIMENTAL

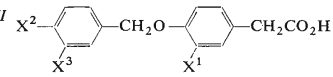
Methods

The IR spectra of benzyloxyacrylacetic acids *VI*—*IX* were registered between 400 and 4000 cm^{-1} in a KBr pellet using an UR-20 (Zeiss Jena) spectrophotometer. The ^{1}H-NMR spectra of the compounds were registered in a BS 487C-80 MHz (Tesla, Czechoslovakia) spectrometer, using a 6% solution in deuteriochloroform and tetramethylsilane as internal standard. With all the compounds these spectra correspond to the suggested structure. Purity of the alkylaryl ethers (*I*, X^2 = OR), substituted benzyl chlorides *III* and esters *IV* was checked by gas chromatography in a Fractometer (Perkin-Elmer F7). A stainless-steel column (3 mm diameter, 2 m length) filled with Gas-Ghrom Q 125—150 μm and moistened with 3% polyethylene glycol (mol. wt. about 20 000) was used. The melting points were determined in a Boetius M block and are not corrected.

The values of the polar constants σ for aromatic substituents were taken from ref.[24], the value for the allyloxy group was considered to be identical with that for the isopropoxy group. The π parameters of the aromatic substituents were taken from ref.[3], using here for X^1 substituents the values of arylacetic acids, for X^2 and X^3 substituents those of substituted benzyl alcohols. With higher alkoxy groups the π parameters were calculated from the value for the *p*-methoxy group ($\pi = 0$) and increments $\Delta\pi = 0{\cdot}5$ for CH_2, $\Delta\pi = -0{\cdot}2$ for branching and $\Delta\pi = -0{\cdot}3$ for a double

TABLE III

Physico-chemical Properties of Acids *VI*



Number	X^2 / X^3	M.p., °C solvent	Calculated/Found % C	% H	% Cl	Yield[a]
VIa	H	120—121·5[b]	74·45	5·82	—	87·4
	H	50% CH_3OH	74·15	6·11	—	
VIb	C_2H_5	122·5—124	75·53	6·71	—	40·0
	H	80%CH_3OH	75·83	6·63	—	
VIc	i-C_3H_7	102—104	75·98	6·95	—	46·0
	H	65% CH_3OH	76·27	7·22	—	
VIg	i-C_3H_7O	111—112·5	71·98	6·71	—	27·4
	H	65% CH_3OH	72·22	6·83	—	
VIh	i-CgH_9O	121—122	72·58	7·06	—	41·6
	H	65% CH_3OH	72·86	7·37	—	
VIi	CH_3O	150—151	71·31	6·34	—	38·2
	CH_3	CH_3OH	71·09	6·51	—	
VIj	i-C_3H_7O	100—103	72·80	7·18	—	48·8
	CH_3	80% CH_3OH	72·59	7·05	—	
VIn	i-C_3H_7O	96—98	64·52	5·72	10·58	63·5
	Cl	80% CH_3OH	64·42	5·74	10·78	
VIp	Cl	99—101	57·90	3·89	22·79	35·0
	Cl	80% CH_3OH	57·96	3·65	22·59	
VIIa	H	108—109·5[c]	70·61	5·92	—	64·8
	H	50% CH_3OH	70·41	5·82	—	
VIIc	i-C_3H_7	129·5—131	72·50	7·04	—	58·5
	H	65% CH_3OH	72·72	7·30	—	
VIIg	i-C_3H_7O	132—134	69·05	6·71	—	30·2
	H	50% CH_3OH	69·26	6·80	—	
VIIm	CH_2=$CHCH_2O$	97—99	62·96	5·28	9·77	62·2
	Cl	80% CH_3OH	62·71	5·29	9·97	
VIIo	i-C_4H_9O	86—87·5	63·13	6·13	9·37	49·8
	Cl	50% CH_3OH	63·47	6·24	9·63	
VIIIa	H	92—94	74·98	6·29	—	65·0
	H	80% CH_3OH	75·14	6·15	—	
VIIIb	C_2H_5	107—109	76·03	7·09	—	45·0
	H	80% CH_3OH	76·26	7·26	—	

TABLE III
(*Continued*)

Number	X^2 X^3	M.p., °C solvent	Calculated/Found % C	% H	% Cl	Yield[a]
VIIIi	CH_3O	127–128	71·98	6·71	–	45·0
	CH_3	70% CH_3OH	72·13	6·82	–	
VIIIm	$CH_2{=}CHCH_2O$	114–116	65·80	5·52	10·23	60·0
	Cl	75% CH_3OH	66·07	5·53	10·48	
VIIIn	i-C_3H_7O	89–91	65·42	6·07	10·16	45·0
	Cl	90% CH_3OH	65·49	6·07	10·00	
IXa	H	122–123	65·05	4·74	12·82	66·0
	H	60% CH_3OH	65·03	4·88	13·06	
IXb	C_2H_5	103–105	67·00	5·62	11·63	48·0
	H	65% CH_3OH	67·02	5·79	11·43	
IXd	i-C_4H_9	93–95	68·56	6·36	10·65	30·0
	H	80% CH_3OH	68·85	6·33	10·89	
IXe	CH_3O	150·5–152	62·65	4·93	11·56	32·0
	H	60% CH_3OH	62·61	4·91	11·63	
IXf	$CH_2{=}CHCH_2O$	105–107	64·96	5·15	10·66	36·8
	H	ethyl acetate	64·84	5·37	10·90	
IXg	i-C_3H_7O	115–116	64·57	5·72	10·59	30·8
	H	65% CH_3OH	64·94	5·59	10·36	
IXh	i-C_4H_9O	107–108	65·42	6·07	10·14	49·6
	H	75% CH_3OH	65·67	5·92	10·03	
IXi	CH_3O	141–143	63·65	5·34	11·05	62·5
	CH_3	90% CH_3OH	63·80	5·49	10·88	
IXj	i-C_3H_7O	99·5–101	65·42	6·07	10·14	25·2
	CH_3	65% CH_3OH	65·72	6·28	9·98	
IXk	CH_3O	151–152	56·38	4·13	20·80	73·4
	Cl	CH_3OH	56·51	4·27	20·96	
IXm	$CH_2{=}CHCH_2O$	132–133·5	58·87	4·39	19·31	50·0
	Cl	$CH_3COOC_2H_5$	58·73	4·52	19·43	
IXn	i-C_3H_7O	128–130	58·55	4·91	19·20	55·0
	Cl	85% CH_3OH	58·66	4·90	19·14	

[a] The total yield of benzylation of ester *VI* and of hydrolysis of ester *V*, [b] Ref.[41] reports a m.p. of 122°C. [c] Ref.[42] reports a m.p. of 116°C.

bond[25]. The coefficients in the regression equations were calculated from experimental data by the least-squares method in a Hewlett-Packard (USA) computer of type 9820. The statistical significance of the regression equations was evaluated by the F-test; in equations (*4*) and (*7*) the *t*-test parameters were employed.

Alkylaryl Ethers *I* (X^2 = OR)

These were prepared from phenol, *o*-cresol or *o*-chlorophenol in a reaction with the appropriate alkyl bromide in ethanol in the presence of sodium ethylate[26] (method *A*) or in a reaction with allyl bromide in acetone in the presence of potassium carbonate[10] (method *B*). Shown below are X^2, X^3, method, yield (%), b.p. (°C/Torr), b.p. found in the literature, elementary analysis: i-C_3H_7O, H, *A*, 55·4, 59–60/6, 178/760 (ref.[27]); CH_2=$CHCH_2O$, H, *B*, 77–79/10, 82/11 (ref.[28]); i-C_4H_9O, H, *A*, 56·8, 76–78/9, 196/760 (ref.[26]); CH_3O, CH_3, *A* 83·0, 55–58/8, 77/29 (ref.[29]); i-C_3H_7O, CH_3, *A*, 65·5, 64–66/8, 192/760 (ref.[31]); CH_3O, Cl, *A*, 76·6, 59–60·5/1, 99·5/12 (ref.[30]); i-C_3H_7O, Cl, *A*, 63·5, 87–89/8, 93/12 (ref.[32]); CH_2=$CHCH_2O$, Cl, *B*, 92·0, 75–77/1·5, 108–110/15 (ref.[33]); i-C_4H_9O, Cl *A*, 62·0, 102–104/7, for $C_{10}H_{13}ClO$ (184·7) calculated: 65·01% C, 7·09% H, 19·23% Cl; found: 64·97% C, 7·02% H, 19·36% Cl.

Substituted Benzyl Chlorides *III*

These were prepared from *I* in three different ways depending on the character of X^2 and X^3. Method *A* (ref.[8]): Reaction of *I* with paraformaldehyde and gaseous hydrogen chloride in benzene at 20°C. Method *B* (ref.[9]); Reaction of *I* with paraformaldehyde and 37% hydrochloric acid in the presence of 85% phosphoric acid in acetic acid at 100°C. Method *C* (ref.[10]): Reaction of *I* with paraformaldehyde and hydrogen chloride in the presence of arsenous oxide in acetic acid at 40°C. Shown below are X^2, X^3, method, yield (%), b.p. (°C/Torr), b.p. found in the literature, elementary analysis: CH_3O, H; *A*, 62·7; 108–110/12, 92·5/1·5 (ref.[34]). i-C_3H_7O, H; *A*, 46·9; 75–77/0·6, 126–128/14 (ref.[35]). CH_2=$CHCH_2O$, H; *A*, 44·9; 113–115/2; for $C_{10}H_{11}ClO$ (182·6) calculated: 65·77% C, 6·07% H, 19·42% Cl; found: 65·89% C, 5·94% H, 19·26% Cl (polymerizes during gas chromatography). i-C_4H_9O, H; *A*, 45·3; 102–104/0·9, 98/0·8 (ref.[35]). C_2H_5, H; *B*, 61·0; 102–104/16, 111/25 (ref.[9]). i-C_3H_7, H; *B*, 23·8; 108–110/14, 108–109/14 (ref.[36]). i-C_4H_9, H; *B*, 45·3; 123–124/15; for $C_{11}H_{15}Cl$ (182·7) calculated: 72·20% C, 8·28% H, 19·49% Cl; found: 72·12% C, 8·47% H, 19·21% Cl. CH_3O, CH_3; *A*, 73·0; 109–111/8, 119/12 (ref.[37]). iC_3H_7O, CH_3; *A*, 48·0; 98–100/0·3; for $C_{11}H_{15}ClO$ (198·7) calculated: 66·49% C, 7·61% H, 17·85% Cl, found: 66·55% C, 7·78% H, 17·99% Cl. CH_3O, Cl; C, 70·7; 140–142/10 (m.p. 39°C), 150–158/12 (m.p. 38°C) (ref.[38]). i-C_3H_7O, Cl; C, 78·3; 92·94/0·1; for $C_{10}H_{12}Cl_2O$ (219·1) calculated: 54·85% C, 5·52% H, 32·38% Cl; found: 54·63% C, 5·72% H, 32·08% Cl. CH_2=$CHCH_2O$, Cl; C, 46·9; 132–135/1·1, 122–130/1 (ref.[10]) (polymerizes during gas chromatography). i-C_4H_9O, Cl; C, 89·1; 106–108/0·5; for $C_{11}H_{14}Cl_2O$ (233·1) calculated: 56·65% C, 6·05% H, 30·40% Cl; found: 56·89% C, 5·84% H, 30·68% Cl. 3,4-Dichlorobenzyl chloride (*III*, $X^2 = X^3$ = Cl) was prepared by chlorination of 3,4-dichlorotoluene with chlorine according to ref.[38]; b.p. 85 to 87°C/10 Torr (ref.[39] reports a b.p. of 241°C/760 Torr).

Methyl 4-Hydroxyphenylacetate (*IV*, X^1 = H)

156·6 g (1·0 mol) *p*-methoxybenzyl chloride was added under stirring at 20°C to a suspension of 53·9 g (1·1 mol) sodium cyanide in 350 ml dimethyl sulfoxide and the mixture was heated for 2 h to 40°C. After pouring into 1 000 ml ice-cold water, the separated oil was extracted into 500 ml ether. After washing with twice 200 ml hydrochloric acid (1 : 1), twice 200 ml water, and drying

with magnesium sulfate, the ether was evaporated *in vacuo*. The crude *p*-methoxybenzyl cyanide obtained was hydrolyzed by boiling with 240 ml 50% hydrobromic acid. Further 240 ml 50% hydrobromic acid was added in four portions in two-hour intervals; after the last portion, the mixture was boiled for 4 h. After cooling to 10°C, a precipitate formed, which was filtered and dissolved in 1 200 ml 1,2-dichloroethane. Concentration at normal pressure yielded 137 g crude *p*-hydroxyphenylacetic acid (*II*, X^1 = H), m.p. 140–145°C (ref.[40] reports a m.p. of 148°C). Crude acid *II* was boiled for 6 h in 900 ml 5% methanolic hydrogen chloride. The solution was evaporated *in vacuo* to an oil which was extracted into 500 ml ether after adding 300 ml water to it. The ether extract was washed twice with 200 ml water, dried with magnesium sulfate, evaporated and distilled *in vacuo*. A total of 90·8 g (58%) ester *IV* (X^1 = H) was obtained as a fraction boiling a 166–168°C/8 Torr which is homogeneous in gas chromatography. For $C_9H_{10}O_3$ (166·2) calculated: 65·05% C, 6·07% H; found: 64·92% C, 6·16% H.

The same technique was used for the preparation of:

Methyl 3-*methyl*-4-*hydroxyphenylacetate* (*IV*, X^1 = CH_3) from 3-methyl-4-methoxybenzyl chloride; it was isolated by distillation as a fraction boiling at 128–129°C/1 Torr, homogeneous in gas chromatography. For $C_{10}H_{12}O_3$ (180·2) calculated: 66·65% C, 6·72% H; found: 66·79% C, 6·78% H.

Methyl 3-*chloro*-4-*hydroxyphenylacetate* (*IV*, X^1 = Cl) from 3-chloro-4-methoxybenzyl chloride with the difference that 3-chloro-4-methoxybenzyl cyanide precipitated after pouring into water and was isolated by filtration (m.p. 49–51°C). *IV* (X^1 = Cl) was isolated by distillation as a fraction boiling at 106–108°C/0·15 Torr (ref.[10] reports a b.p. 124–130°C/1 Torr).

Methyl 3-*methoxy*-4-*hydroxyphenylacetate* (*IV*, X^1 = OCH_3) 50 g crude acid *II* (X^1 = OCH_3), m.p. 138–140°C (ref.[11] gives a m.p. of 142–143°C) was boiled for 6 h in 250 ml methanol in the presence of 1·0 g *p*-toluenesufonic acid. Ester *IV* (X^1 = OCH_3) was isolated by distillation as a fraction boiling at 120–122°C/0·7 Torr, homogeneous in gas chromatography. For $C_{10}H_{12}O_4$ (196·2) calculated: 61·18% C, 6·17% H; found: 61·36% C, 6·45% H.

Substituted Benzyloxyarylacetic Acids *VI–IX*

Ester *IV* (50·0 mmol) was added at 20°C to a solution of sodium ethylate in ethanol (from 65·0 mmol sodium in 75 ml ethanol), the solution was stirred for 30 min and then evaporated *in vacuo*. The residue was dissolved in 50 ml dimethyl sulfoxide and, after adding 65·0 mmol of the appropriate benzyl chloride *III*, the mixture was heated for 4 h to 100°C. After evaporation of the solvent *in vacuo* the oil obtained was poured into 50 ml water and extracted twice with 100 ml ether. The ether solution was washed with 50 ml 5% sodium hydroxide, three times with 100 ml water and dried with magnesium sulfate. The crude ester *V* obtained by concentrating the solution was boiled for 10 h in an aqueous–ethanolic solution of sodium hydroxide (prepared from 14 g potassium hydroxide, 14 ml water and 80 ml ethanol). Ethanol was then distilled from the mixture, the residue was diluted with 250 ml water and the solution filtered with charcoal. Acidification of the filtrate with 10% sulfuric acid yielded the crude product which crystallized from a suitable solvent to obtain the substituted benzyloxyarylacetic acid *VI–IX*.

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