SYNTHESIS OF N-[(3-SUBSTITUTED PHENOXY)ALKYL]-ACETOHYDROXAMIC ACIDS, POTENTIAL INHIBITORS OF THE ENZYME 5-LIPOXYGENASE

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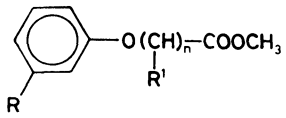
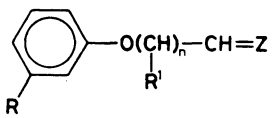
The synthesis of the title compounds starts from methyl (3-subst. phenoxy)alkanoates *II* which are reduced to the corresponding aldehydes and then transformed to oximes *V* by reaction with hydroxylamine. Reduction with borane–pyridine complex gives the hydroxylamines *VI* which on diacetylation and partial deacetylation provide the hydroxamic acids *VIII*.

The leucotrienes[1] (LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4) formed in organism by the bioconversion of arachidonic ((all-*Z*)-5,8,11,14-eicosatetraenoic) acid catalyzed by the enzyme 5-lipoxygenase[2] are considered to be significant mediators of inflammatory and allergic reactions[3]. Thus e.g. LTC_4 and LTD_4 are efficient bronchoconstrictors of human bronchi[4] and LTB_4 exhibits a strong chemotactic factor for leucocytes[5] and causes inflammatory skin diseases such as psoriasis[6] and contact dermatitis[7]. Hence, an inhibition of the enzyme 5-lipoxygenase, i.e. the initial step of formation of leucotrienes in organism, can possess therapeutic effect. From the mechanism of action of iron in the lipoxygenase from soya beans[8] it was deduced that the active site of 5-lipoxygenase from mammals contains iron. On this basis a hypothesis has been formulated that substances containing groups able to form strong chelates with iron (such as e.g. hydroxamic acids) will be efficient inhibitors of this enzyme. With regard to this presumption there were prepared a number of efficient (both in vitro and in vivo) inhibitors of 5-lipoxygenase: analogues of arachidonic acid[9,10], hydroxamic acids derived from arylalkanoic acids[11,12], and substituted benzo-[13] and acetohydroxamic acids[14]. In connection with our earlier studies[15–20] in the area of antiinflammatory agents based on arylpropionic acids, the present paper describes the synthesis of N-[(3-substituted phenoxy)alkyl]acetohydroxamic acids *VIII* (Scheme 1). The aim of the work is to verify the effect of 3-alkoxy or 3-phenoxy group in the aromatic ring (compounds *VIIIb* – *VIIIf*) as well as the effect of the length of and substituents in the N-[(3-butoxyphenoxy)]alkyl chain of the compound (*VIIIg* – *VIIIj*) on the inhibition of the enzyme 5-lipoxy-

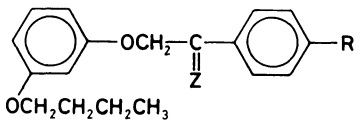
genase and/or cyclooxygenase. The introduction of *p*-isobutylphenyl group in compound *VIIIj* was meant as an attempt at incorporation of the skeleton of well-known antiinflammatory agent – ibuprofen. All reaction steps of the synthesis were verified



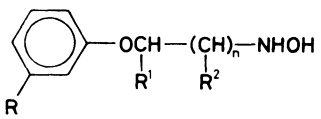
IIa–IIh



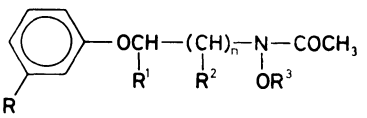
IIIa–IIIh, Z = O
IVa–IVh, Z = $NNHCONH_2$
Va–Vh, Z = NOH



IIi, IIj, Z = O
IVi, IVj, Z = NOH



VI



VII, VIII

	n	R	R^1	R^2	R^3
IIa – VIIIa	1	H	H	H	
IIb – VIIIb	1	CH_3O	H	H	
IIc – VIIIc	1	$n\text{-}C_4H_9O$	H	H	
IId – VIIId	1	$n\text{-}C_8H_{17}O$	H	H	
IIe – VIIIe	1	$C_6H_5CH_2O$	H	H	
IIf – VIIIf	1	C_6H_5O	H	H	
IIg – VIIIg	1	$n\text{-}C_4H_9O$	CH_3	H	
IIh – VIIIh	4	$n\text{-}C_4H_9O$	H	H	
IIi, IVi		H			
IIj, IVj		$(CH_3)_2CH_2$			
VI	1	$n\text{-}C_4H_9O$	H	C_6H_5	
VI	1	$n\text{-}C_4H_9O$	H	$p\text{-}(CH_3)_2CHCH_2C_6H_4$	
VII					$COCH_3$
VIII					H

SCHEME 1

by simultaneously carrying out the transformations with the nonsubstituted compounds *IIa*–*VIIIa*. Detailed description of syntheses of compounds *IIb*–*VIIIb* is given in Experimental. The other substances were synthesized in the same way.

The aldehydes *IIIa*–*IIIh* and ketones *IIi*–*IIj* represent key intermediates in the syntheses of compounds *VIII*. In contrast to the ways described for syntheses of phenoxyacetaldehyde (*IIIa*, refs[21–23]) or 2-methoxyphenoxyacetaldehyde[24], we synthesized the aldehydes *IIIa*–*IIIh* from the readily available phenoxyalkylesters *IIa*–*IIh* which were prepared in the usual way[25–27]. i.e. by alkylation of the respective 3-alkoxy- (*Ia*–*Id*) or 3-phenoxyphenol (*Ie*) with methyl chloroacetate, 2-bromopropanoate, or 5-bromovalerate in refluxing acetone in the presence of anhydrous potassium carbonate and a catalytic amount of sodium iodide. The esters *IIa*–*IIh* were obtained in good yields (Table I) and characterized by their IR and ^{1}H NMR spectra (Table II).

In next step the esters *IIa*–*IIh* were reduced[29] with diisobutylaluminium hydride in toluene at −78°C. At the given conditions the reduction selectively produces the

TABLE I
Conditions and results of syntheses of esters *II*

Ester	Reaction time, h	Yield, %	B.p., °C/kPa	Formula (Mol. mass)	Calculated/Found	
					% C	% H
IIa[a]	10	96	123–126/1·9[b]			
IIb	6	86	157–162/2·0[c]			
IIc	10	77	145–150/0·27	$C_{13}H_{18}O_4$ (238·3)	65·52 65·41	7·61 7·48
IId	10	91	165–170/0·27	$C_{17}H_{26}O_4$ (294·4)	69·36 69·11	8·90 8·86
IIe	10	90	173–177/0·13	$C_{16}H_{16}O_4$ (272·3)	70·57 70·43	5·92 5·84
IIf	10	91	150–156/0·13	$C_{15}H_{14}O_4$ (258·3)	69·75 69·58	5·46 5·28
IIg	40	60	150–154/0·27	$C_{14}H_{20}O_4$ (252·3)	66·65 66·44	7·99 7·81
IIh	3	62	150–155/0·67	$C_{16}H_{24}O_4$ (280·4)	68·54 68·37	8·63 8·49

[a] Mass spectrum: 166 (68) M^+, 108 (8), 107 (100) (M − $COOCH_3$), 79 (26), 78 (13), 77 (87), 65 (11), 59 (4), 51 (26); [b] b.p. from ref.[28] 130°C/1·86 kPa; [c] ref.[25] gives b.p. 134°C/0·053 kPa.

corresponding aldehydes *IIIa–IIIh*. The reaction mixture from the reduction of ester *IIa* was analyzed by means of GC-MS: It contained the raw aldehyde *IIIa*, a small amount of the starting ester *IIa*, and about 2% 2,4-diphenoxy-3-hydroxybutanal (*IX*) formed by aldolization of *IIIa*. Therefore, the aldehydes *IIIb–IIIh* were not isolated as analytically pure substances but, instead, were submitted to subsequent reaction without purification. Only a small part of the aldehydes was purified by flash chromatography and used for spectral characterization (Table III) and for transformations to the corresponding semicarbazones (Table IV). The ketones *IIi* and *IIj* were prepared by heating 3-butoxyphenol with ω-bromoacetophenone and ω-chloro-4-isobutylacetophenone, respectively, in acetone in the presence of potassium carbonate.

TABLE II
Spectral characteristics of the esters *II*

Ester	IR spectrum, cm^{-1}	^1H NMR spectrum[a]
IIb	1 758, 1 740, 1 602, 1 595 1 493, 1 155	3·77 s (OCH_3), 3·80 s (OCH_3), 4·62 s (CH_2), 6·48–6·58 m and 7·19 dd (4 H, arom.), $J_{4,5}$ = 8·2
IIc	1 759, 1 740, 1 602, 1 593 1 493, 1 155	0·97 t (CH_3); J = 7·0, 1·47 m (CH_2), 1·74 m (CH_2) 3·81 s (OCH_3), 3·92 t (CH_2O), 4·62 s (CH_3), 6·45–6·58 m and 7·16 dd (4 H, arom.), $J_{4,5}$ = 8·2
IId	1 755, 1 736, 1 598, 1 500 1 489, 1 174, 1 152	0·88 t (CH_3), 1·30 m (($CH_2)_4$), 1·44 m (CH_2), 1·76 m (CH_2), 3·80 s (OCH_3), 3·90 t (CH_2O), J = 7·6, 4·61 s (CH_2), 6·44–6·56 m and 7·16 dd (4 H, arom.)
IIe	1 748, 1 738, 1 598, 1 592 1 490, 1 173, 1 152	3·79 s (OCH_3), 4·61 s (CH_2), 5·03 s (CH_2O), 6·49–6·66 m and 7·18 dd (4 H), 7·31–7·43 m (5 H, arom.)
IIf	1 749, 1 739, 1 608, 1 586 1 168, 1 143	3·78 s (OCH_3), 4·60 s (CH_2), 6·58–6·67 m and 7·00–7·37 m (9 H, arom.)
IIg	1 750, 1 735, 1 600, 1 590 1 491, 1 178, 1 155	0·96 t (CH_3), J = 7·4, 1·47 m (CH_2), 1·60 t (CH_3), J = 7·0, 1·74 m (CH_2), 3·75 s (OCH_3), 3·92 t (CH_2O), 4·75 q (CH), 6·40–6·53 m and 7·14 dd (4 H, arom.), $J_{4,5}$ = 8·2
IIh	1 730, 1 600, 1 588, 1 490 1 178, 1 150	0·97 t (CH_3), 1·48 m (CH_2), 1·74 m (CH_2), 1·81 m (($CH_2)_2$), 2·39 t (CH_2), 3·68 s (OCH_3), 3·92 m (2 × CH_2O), 6·45 m and 7·15 dd (4 H, arom), $J_{4,5}$ = 8·1

[a] J in Hz.

In the third step of reaction the carbonyl compounds *III* were converted[31,32] into the corresponding oximes *Va*–*Vj* by reaction with hydroxylamine hydrochloride in ethanol–pyridine medium; the oximes were purified by recrystallization or by

TABLE III
Spectral characteristics of the aldehydes *III* and ketones *IIi*, *IIj*

Aldehyde	IR spectrum, cm^{-1}	^1H NMR spectrum[a]
IIIa[b]	2 840, 2 730, 1 609, 1 599, 1 493, 1 170	4·52 s (CH_2), 6·85–6·97 m and 7·25 dd (5 H, arom.), $J_{4,5}$ = 8·2, 9·80 s (CH=O)
IIIb	2 840, 1 728, 1 603, 1 590, 1 491, 1 196, 1 153	3·78 s (OCH_3), 4·56 s (CH_2), 6·50 m and 7·18 dd (4 H, arom.), 9·82 s (CH=O)
IIIc	2 845, 1 735, 1 603, 1 590, 1 489, 1 167, 1 143	0·96 t (CH_3), 1·45 m (CH_2), 1·72 m (CH_2), 3·91 t 4·48 s (CH_2), 6·48 m and 7·13 dd (4 H, arom.), 9·78 s (CH=O)
IIId	2 840, 2 725, 1 730, 1 585 1 490, 1 180, 1 159	0·89 t (CH_3), J = 6·8, 1·29 m ($(CH_2)_4$), 1·43 m (CH_2), 1·73 m (CH_2), 3·88 t (CH_2O), 4·46 s (CH_2), 6·48 m and 7·11 dd (4 H, arom.), 9·70 s (CH=O)
IIIe	2 848, 1 735, 1 597, 1 485, 1 181, 1 160	4·51 s (CH_2), 4·95 s (CH_2), 6·52 m, 7·13 dd and 7·33 m (9 H, arom.), 9·72 s (CH=O)
IIIf	2 840, 2 735, 1 730, 1 598, 1 480, 1 181, 1 156	4·42 s (CH_2), 6·55 m and 7·00–7·30 m (9 H, arom.), 9·70 s (CH=O)
IIIg	2 850, 2 720, 1 734, 1 603, 1 587, 1 492, 1 179, 1 160	0·97 t (CH_3), J = 7·3, 1·23 m (CH_2), 1·47 d (CH_3), J = 6·9, 1·75 m (CH_2), 3·93 t (CH_2O), 4·61 dq (CH), 6·41–6·58 m and 7·17 dd (4 H, arom.), 9·72 s (CH=O)
IIIh	2 890, 2 720, 1 724, 1 603, 1 590, 1 495, 1 182, 1 158	0·97 t (CH_3), J = 7·3, 1·48 m (CH_2), 1·74 m (CH_2), 1·81 m ($(CH_2)_2$), 2·38 t (CH_2), 3·90 m (2 × CH_2O), 6·40–6·60 m and 7·13 dd (4 H, arom.), $J_{4,5}$ = 8·2, 9·78 s (CH=O)
IIi	1 703, 1 595, 1 490, 1 174, 1 156	0·98 t (CH_3), J = 7·4, 1·47 m (CH_2), 1·72 m (CH_2), 3·91 t (CH_2O), 5·26 s ($3H_2$), 6·51 m and 7·16 dd (4 H), 7·50 t, 7·60 t and 8·00 m (5 H, arom.)
IIj	1 702, 1 605, 1 595, 1 493, 1 176, 1 157	0·92 d ($(CH_3)_2$), J = 6·2, 0·96 t (CH_3), J = 7·4, 1·47 m (CH_2), 1·72 m (CH_2), 1·90 m (CH), 3·91 t (CH_2O), 5·26 s (CH_2), 6·54 m and 7·18 dd (4 H), 7·30 d and 7·90 d (4 H, arom.), $J_{4,5}$ = 8·3

[a] J in Hz; [b] mass spectrum: 136 (46) (M^+, 108 (15), 107 (62) (M – CHO), 94 (7), 70 (21), 78 (17), 77 (100), 65 (14), 51 (29).

column chromatography (Table V). The mother liquor after the recrystallization of the crude oxime *Va* was submitted to chromatography to give small amount of 2,4-diphenoxy-3-hydroxybutanal oxime (*X*), i.e. the oxime of the aldehyde *IX*, whose structure was confirmed by comparison (IR, MS) with the standard prepared from compound *IX*.

The analysis of ^{1}H NMR spectra of oximes *Vd* and *Ve* showed that the products are mixtures of configurational isomers. It is known[34-37] that with the (*E*)-isomer the chemical shifts of protons at α-position and in CH=N group are higher and lower, respectively, than those in the (*Z*)-isomer. Also the chemical shift of the proton in OH group of (*E*)-isomer is higher than that in the corresponding (*Z*)-isomer. Using these facts we could assign the geometry configuration to the respective oximes *Vd* and *Ve* (Table VI). The resulting characteristic values of the vicinal coupling constant in CH—CH_α group were 3·60 and 5·50 Hz for the (*E*)- and (*Z*)--isomers, respectively. Thus it was also possible to assign the configuration to the

TABLE IV
Physico-chemical characteristics of the semicarbazones *IV*

Semicarbazone	M.p., °C (Solvent)	Formula (Mol. mass)	Calculated/Found		
			% C	% H	% N
IVa	148·5—151·5[a] (*i*-PrOH)	$C_9H_{11}N_3O_2$ (193·2)	55·95 55·86	5·74 5·78	21·75 21·36
IVb	146—148 (EtOH)	$C_{10}H_{13}N_3O_3$ (223·2)	53·81 53·82	5·87 6·03	18·82 18·86
IVc	146—149 (EtOH)	$C_{13}H_{19}N_3O_3$ (265·3)	58·85 58·81	7·22 7·24	15·84 15·44
IVd	139—142 (EtOH)	$C_{17}H_{27}N_3O_3$ (321·4)	63·53 64·00	8·47 8·51	13·07 13·33
IVe	169—172 (EtOH)	$C_{16}H_{17}N_3O_3$ (299·3)	64·21 64·40	5·73 5·94	14·04 14·21
IVf	125—128 (EtOH/H_2O)	$C_{15}H_{15}N_3O_3$ (285·3)	63·15 62·58	5·30 5·50	14·73 14·69
IVg	152·5—154·5 (EtOH)	$C_{14}H_{21}N_3O_3$ (279·3)	60·21 60·20	7·58 7·58	15·04 15·34
IVh	113—115 (EtOH/H_2O)	$C_{16}H_{25}N_3O_3$ (307·4)	62·52 62·40	8·20 8·06	13·67 13·73

[a] Ref.[30] gives m.p. 146°C.

oximes *Va – Vf*. The compounds *Va – Vc* are pure (*E*)-isomers, compound *Vd* is an (*E* + *Z*)-mixture (2 : 1) on the basis of integral intensities of protons of CH_2 and CH groups, respectively, in the oxime *Ve* the ratio is (*E*) : (*Z*) = 9 : 1, and compound *Vf* contains the (*Z*)-isomer in the amount of ca 2%. The configurations were also confirmed by measurements of IR and ^{1}H NMR spectra of oximes *Vd* and *Ve* within a dilution experiment. The IR spectra of the oximes exhibit a distinct increase of the free OH group to the detriment of the associated form; the ^{1}H NMR spectra show a faster shift of signal of oxime OH group in (*E*)-configuration as compared with

TABLE V
Yields and physico-chemical characteristics of oximes *V*

Oxime	Yield, %	M.p., °C	Formula (Mol. mass)	Calculated/Found		
				% C	% H	% N
Va[a]	54[b]	96–98[c,d]	$C_8H_9NO_2$ (151·2)	63·57 64·03	6·00 5·98	9·27 9·18
Vb	56[b]	100–102[e]	$C_9H_{11}NO_3$ (181·2)	59·66 59·43	6·12 6·01	7·73 7·78
Vc	58[b]	63–66[f]	$C_{12}H_{17}NO_3$ (223·3)	64·55 64·36	7·67 7·81	6·27 6·13
Vd	59[b]	64–66[f]	$C_{16}H_{25}NO_3$ (279·4)	68·76 68·46	9·02 9·07	5·01 5·09
Ve	55[b]	105–108[g]	$C_{15}H_{15}NO_3$ (257·3)	70·02 70·36	5·88 5·96	5·44 5·68
Vf	64[b]	78–81[e]	$C_{14}H_{13}NO_3$ (243·3)	69·11 69·44	5·39 5·67	5·76 5·91
Vg	79[b]	104–106[h]	$C_{13}H_{19}NO_3$ (237·3)	65·80 66·09	8·07 8·02	5·90 5·81
Vh	77[b]	105–108[d]	$C_{15}H_{23}NO_3$ (265·3)	67·91 67·48	8·74 8·68	5·28 5·44
Vi	97	70–73[f]	$C_{18}H_{21}NO_3$ (299·3)	72·23 72·16	7·07 6·89	4·68 4·44
Vj	94	oil	$C_{22}H_{29}NO_3$ (355·5)	74·33 74·18	8·22 8·36	3·94 3·81

[a] Mass spectrum: 151 (40) M^+, 134 (12), 119 (14), 107 (42), 104 (15), 94 (100), 91 (12), 77 (60), 65 (25), 57 (24), 51 (22); [b] calculated on starting ester *III*; [c] ref.[33] gives m.p. 95°C (petroleum ether); [d] from ethyl acetate–heptane; [e] from dichloromethane–petroleum ether; [f] from heptane; [g] from chloroform–petroleum ether; [h] from benzene–petroleum ether.

TABLE VI
IR and ^{1}H NMR spectra of the oximes

Oxime	IR spectrum, cm^{-1}	^{1}H NMR spectrum[a]
(*E*)-*Va*	3 590, 3 300, 1 599, 1 588 1 497	5·22 d (CH_2O), 6·85—6·95 m and 7·22 t (5 H, arom.), 7·03 t (CH), J = 3·80, 8·20 s (OH)
(*E*)-*Vb*	3 580, 3 300, 1 598, 1 492 1 196, 1 152	3·81 s (OCH_3), 4·89 d (OCH_2), J = 3·60, 6·50 m and 7·21 dd (4 H, arom.), 7·03 t (CH), 8·93 s (OH)
(*E*)-*Vc*	3 582, 3 300, 1 600, 1 591 1 491, 1 177, 1 155	0·96 t (CH_3), J = 7·4, 1·47 m (CH_2), 1·72 m (CH_2), 3·89 t (2 × CH_2O), J = 6·4, 6·51 m and 7·13 t (4 H, arom.), 7·05 t (CH), J = 3·80, 8·99 s (OH)
Vd	3 580, 3 300, 1 600, 1 590 1 489, 1 170, 1 151	0·90 t (CH_3), 1·28 m ((CH_2)$_5$), 1·43 m (CH_2), 1·77 m (CH_2), 3·92 t and 3·93 t (2 × CH_2O), 4·63 dd (OCH_2-*Z*), J = 5·48, 4·87 dd (OCH_2-*E*), J = 3·59, 6·47—6·58 m and 7·18 dd (4 H, arom.), 7·03 t (CH-*Z*), 7·63 t (CH-*E*), 7·83 s (OH-*E*), 8·17 s (OH-*Z*)
Ve	3 585, 3 284, 1 600, 1 590 1 491, 1 176, 1 153	4·62 d (OCH_2-*E*), J = 5·50, 4·87 d (OCH_2-*Z*), J = 3·60, 5·04 s (CH_2O), 6·52—6·64 m and 7·18 t (4 H), 7·3—7·45 m (5 H, arom.), 7·02 t (CH-*Z*), 7·61 t (CH-*E*), 8·02 s (OH-*E*), 8·43 s (OH-*Z*)
Vf	3 580, 3 285, 1 605, 1 583 1 491, 1 168, 1 140	4·62 d (OCH_2-*E*), J = 5·50, 4·87 d (OCH_2-*Z*), J = 3·60, 6·59—6·70 m and 7·13 t (4 H), 7·23 t and 7·32—7·38 m (5 H, arom.), 7·03 t (CH-*Z*), 7·61 t (CH-*E*), 8·09 s (OH-*E*), 8·48 s (OH-*Z*)
Vg	3 585, 3 307, 1 602, 1 588 1 492, 1 181, 1 157	0·99 t (CH_3), J = 7·4, 1·48 m (CH_2), 1·50 d (CH_3), J = 6·5, 1·76 m (CH_2), 3·93 t (CH_2O), 5·46 q (CH), J = 6·5, 6·45—6·53 m and 7·13 t (4 H, arom.), 6·77 d (CH), J = 6·0, 8·25 s (OH)
Vh	3 598, 3 300, 1 602, 1 590 1 495, 1 182, 1 156	0·97 t (CH_3), J = 7·4, 1·48 m (CH_2), 1·68 m (CH_2), 1·76 m (CH_2), 1·83 m (CH_2), 2·44 m (CH_2), 3·96 m (2 × CH_2O), 6·43—6·51 m and 7·13 t (4 H, arom.), 6·73 t (CH), J = 5·48, 7·92 s (OH)
Vi	3 580, 3 320, 1 600, 1 590 1 490, 1 175, 1 145	0·96 dt (CH_3), 1·47 m (CH_2), 1·73 m (CH_2), 3·90 t (CH_2O), 3·91 t (CH_2O), J = 6·5, 4·89 s (CH_2-*Z*), 5·25 s (CH_2-*E*), 6·45—6·55 m and 7·15 t (4 H), 7·30 to 7·60 m, (5 H, arom.), 8·44 s (OH-*Z*), 8·92 a (OH-*E*)
Vj	3 580, 3 285, 1 595, 1 585 1 484, 1 172, 1 140	0·89 d ((CH_3)$_2$), J = 6·9, 0·95 t (CH_3), J = 7·4, 1·44 m (CH_2), 1·72 m (CH_2), 1·85 m (CH), 2·44 d (CH_2), 3·92 t (CH_2O), 4·87 s (CH_2O-*Z*), 5·24 s (CH_2O-*E*), 6·48—6·57 m and 7·17 t (4 H), 7·12 d and 7·55 d (4 H, arom.), J = 8·4

[a] J in Hz.

the (*Z*)-form. From these results and the data published[38,39] about analogous compounds it is possible to deduce also the configurations of ketoximes *Vi* and *Vj* which represent equimolecular mixtures of (*E*)- and (*Z*)-forms (Table VI).

The next step in the synthesis of the hydroxamic acids *VIII* consisted in the reduction[14,40,41] of oxime *Va* with a complex of borane and tetrahydrofurane or pyridine to give the hydroxylamine *VIa*. This product – without purification – was submitted to acetylation with acetanhydride in pyridine in the presence of catalytic amounts of 4-dimethylaminopyridine to give the N,O-diacetyl derivative *VIIa*. It was found that the borane–pyridine complex gives higher yields of the hydroxylamine *VIa* without formation of undesirable side products. Then the N,O-diacetylhydroxylamines *VIIa*–*VIIj* were obtained in good yields (Table VII). The structure of the

TABLE VII
Yields and physico-chemical characteristics of compounds *VII*

Compound	Yield, %	Formula (Mol. mass)	Calculated/Found		
			% C	% H	% N
VIIa	87	$C_{12}H_{15}NO_4$ (237·3)	60·74 60·44	6·37 6·26	5·90 5·88
VIIb	75	$C_{13}H_{17}NO_5$ (267·3)	58·41 58·18	6·41 6·36	5·24 5·09
VIIc	83	$C_{16}H_{23}NO_5$ (309 4)	62·11 62·01	7·49 7·66	4·53 4·18
VIId[a]	73	$C_{20}H_{31}NO_5$ (365·5)	66·45 66·41	8·55 8·60	3·83 3·68
VIIe	86	$C_{19}H_{21}NO_5$ (343·4)	66·46 66·21	6·16 6·11	4·08 3·89
VIIf	66	$C_{18}H_{19}NO_5$ (329·4)	65·63 65·37	5·81 6·03	4·25 4·11
VIIg	73	$C_{17}H_{25}NO_5$ (323·4)	63·14 63·28	7·79 7·94	4·33 4·16
VIIh	54	$C_{19}H_{29}NO_5$ (351·4)	64·94 64·67	8·32 8·06	3·99 3·88
VIIi	52	$C_{22}H_{27}NO_5$ (385·4)	68·56 68·62	7·06 7·11	3·63 3·48
VIIj[b]	66	$C_{26}H_{35}NO_5$ (441·6)	70·72 70·50	5·71 6·88	3·17 3·02

[a] M.p. 42–43°C (hexane); [b] m.p. 70–73°C (hexane).

TABLE VIII
IR and ^{1}H NMR spectra of the compounds *VII*

Compound	IR spectrum, cm^{-1}	^{1}H NMR spectrum[a]
VIIa[b]	1 796, 1 677, 1 600, 1 589 1 498, 1 155	2·03 bs ($NCOCH_3$), 2·20 s ($OCOCH_3$), 4·07 m (CH_2), 4·12 m (CH_2), 6·86 m, 6·95 t and 7·27 m (5 H, arom.) ,
VIIb	1 796, 1 678, 1 600, 1 495 1 155	2·03 bs ($NCOCH_3$), 2·22 s ($OCOCH_3$), 3·69 s (OCH_3) 4·11 m (CH_2), 4·15 m (CH_2), 6·40—6·55 m and 7·16 t (4 H, arom.)
VIIc	1 794, 1 672, 1 602, 1 590 1 492, 1 182, 1 156	0·97 t (CH_3), J = 7·3, 1·48 m (CH_2), 1·75 m (CH_2), 2·04 bs ($NCOCH_3$), 2·19 s ($OCOCH_3$), 3·92 t (OCH_2), 4·08 m (CH_2), 4·12 m (CH_2), 6·42—6·47 m, 6·51 dd and 7·15 t (4 H, arom.)
VIId	1 793, 1 668, 1 600, 1 590 1 490, 1 179, 1 152	0·89 t (CH_3) J = 7·1, 1·30 m (($CH_2)_5$), 1·44 m (CH_2), 1·75 m (CH_2), 2·04 bs ($NCOCH_3$), 2·18 s ($OCOCH_3$), 3·92 t (OCH_2), 4·11 m (OCH_2CH_2N), 6·41—6·52 and 7·13 t (4 H, arom.)
VIIe	1 795, 1 676, 1 602, 1 590 1 493, 1 183, 1 156	2·03 bs ($NCOCH_3$), 2·20 s ($OCOCH_3$), 4·08 bs (OCH_2CH_2N), 6·53—6·63 m and 6·93—7·36 m (9 H, arom.)
VIIf	1 796, 1 678, 1 583, 1 484 1 170, 1 142	2·03 bs ($NCOCH_3$), 2·17 s ($OCOCH_3$), 4·09 bs (OCH_2CH_2N), 5·04 s (CH_2O), 6·47—6·52 m, 6·59 dd, 7·16 t and 7·29—7·44 m (9 H, arom.)
VIIg	1 795, 1 676, 1 602, 1 588 1 491, 1 180, 1 158	0·97 t (CH_3(J = 7·4, 1·35 d (CH_3) J = 6·2, 1·48 m (CH_2), 1·75 m (CH_2), 2·01 bs ($NCOCH_3$), 2·17 s ($OCOCH_3$), 3·93 t (OCH_2), 4·61 m (CH), 6·41 to 6·52 m and 7·17 t (4 H, arom.)
VIIh	1 792, 1 665, 1 600, 1 583 1 488, 1 175, 1 152	0·97 t (CH_3), 1·48 m (($CH_2)_2$), 1·65 m (CH_2), 1·78 m (($CH_2)_2$), 2·02 bs ($NCOCH_3$), 2·21 s ($OCOCH_3$), 3·71 t (CH_2), 3·94 t (($CH_2O)_2$), 6·43—6·53 m and 7·13 t (4 H, arom.)
VIIi	1 798, 1 668, 1 600, 1 590 1 492, 1 180, 1 157	0·95 t (CH_3) J = 7·4, 1·47 m (CH_2), 1·72 m (CH_2), 1·98 s ($NCOCH_3$), 2·06 s ($OCOCH_3$), 3·88 t (CH_2O), 4·34 dd and 4·45 t (CH_2), J = 8·4, 5·90 bs (CH), 6·45—6·53 m, 7·13 t, and 7·29—7·40 m (9 H, arom.)
VIIj	1 796, 1 665, 1 600, 1 588 1 490, 1 182, 1 155	0·89 d (($CH_3)_2$), 0·97 t (CH_3), 1·47 m (CH_2), 1·74 m (CH_2), 1·84 m (CH), 2·01 bs ($NCOCH_3$), 2·11 s ($OCOCH_3$), 2·45 d (CH_2), 3·91 t (CH_2O), 4·34 dd and 4·45 t (CH_2), 5·90 bs (CH, 6·42—6·52 m and 7·15 t (4 H, arom.), 7·12 d and 7·29 d (4 H, arom.) J = 8·[illegible]

[a] J in Hz; [b] mass spectrum: 237 (6) M^+, 144 (45), 120 (22), 102 (48), 92 (28), 91 (18), 87 (23), 77 (18), 65 (8), 43 (100).

compounds *VII* was proved by spectral methods. The ^{1}H NMR spectra show – in contrast to the hydroxamic acids *VIII* – a coalescence of proton signals of methyl group in acetamide grouping which resulted in a broad singlet in the spectrum (Table VIII). Similar coalescences are observed with peptides.

The partial deacetylation was carried out according to the known procedure[14] applied to a number of N,O-diacetylhydroxamic acids, i.e. action of aqueous lithium hydroxide in 2-propanol. However, an alternative procedure based on a triethylamine-catalyzed transesterification with methanol[42] led (after a simple treatment of the reaction mixture) to better yields of the hydroxamic acids *VIIIa*–*VIIIj* (Table IX). The spectral characteristics of the compounds synthesized are given in Table X.

TABLE IX

Yields and physico-chemical characteristics of the hydroxamic acids *VIII*

Compound	Yield %	M.p., °C	Formula (Mol. mass)	Calculated/Found		
				% w	% H	% N
VIIIa	93	92–95[a]	$C_{10}H_{13}NO_3$ (195·2)	61·53 61·48	6·71 6·66	7·18 7·01
VIIIb	92	62–64[b]	$C_{11}H_{15}NO_4$ (225·2)	58·67 58·46	6·71 6·74	6·22 6·09
VIIIc	89	57–58[c]	$C_{14}H_{21}NO_4$ (267·3)	62·91 62·80	7·92 7·79	5·24 5·31
VIIId	93	55·5–57·5[d]	$C_{18}H_{29}NO_4$ (313·4)	68·98 68·76	9·33 9·07	4·47 4·31
VIIIe	94	63–65[d]	$C_{17}H_{19}NO_4$ (301·3)	67·77 67·60	6·36 6·19	4·65 4·38
VIIIf	93	82–84[b]	$C_{16}H_{17}NO_4$ (287·3)	66·89 66·61	5·96 5·91	4·88 4·53
VIIIg	98	oil	$C_{15}H_{23}NO_4$ (281·4)	64·02 64·24	8·24 8·36	4·98 4·72
VIIIh	98	oil	$C_{17}H_{27}NO_4$ (309·4)	65·99 66·23	8·78 8·98	4·53 5·11
VIIIi	86	58–60[d]	$C_{20}H_{25}NO_4$ (343·4)	69·95 69·81	7·34 7·16	4·08 3·83
VIIIj	79	68–72[d]	$C_{24}H_{33}NO_4$ (399·5)	72·16 72·00	8·33 8·29	3·51 3·29

[a] From heptane–ethanol; [b] from benzene–hexane; [c] from benzene–petroleum ether; [d] from hexane.

TABLE X
IR and ^{1}H NMR spectra of the hydroxamic acids *VIII*

Compound	IR spectrum, cm^{-1}	^{1}H NMR spectrum[a]
VIIIa	3 500, 3 255, 1 625, 1 598 1 582, 1 496, 1 177, 1 152	2·11 s (CH_3), 3·95 m (CH_2), 4·13 m (CH_2), 6·55 m, 7·03—7·35 m (5 H, arom.), 8·87 s (OH)
VIIIb	3 500, 3 245, 1 625, 1 595 1 577, 1 490, 1 174, 1 146	2·10 s (CH_3), 3·87 s (OCH_3), 3·97 d and 4·11 d (OCH_2CH_2N), 6·51—6·64 m and 7·15 t (4 H, arom.), 8·70 s (OH)
VIIIc	3 490, 3 240, 1 620, 1 595 1 585, 1 488, 1 176, 1 148	0·96 t (CH_3) J = 7·3, 1·48 m (CH_2), 1·75 m (CN_2), 2·14 s (CH_3), 3·92 m (2 × CH_2O), 4·14 m (CH_2), 6·40—6·53 m and 7·15 t (4 H, arom.), 8·70 s (OH)
VIIId	3 490, 3 240, 1 620, 1 600 1 588, 1 490, 1 178, 1 150	0·89 t (CH_3), 1·30 m ((CH_2)$_5$), 1·43 m (CH_2), 1·77 m (CH_2), 2·15 s (CH_3), 3·91 t (CH_2O), 4·00 m and 4·18 m (OCH_2CH_2N), 6·40—6·55 m and 7·14 t (4 H, arom.), 8·70 s (OH)
VIIIe	3 500, 3 266, 1 620, 1 590 1 487, 1 177, 1 153	2·06 s (CH_3), 3·90 bd –nd 4·10 bt (OCH_2CH_2N), 4·95 s (CH_2O), 6·45—6·60 m, 7·15 t and 7·30—7·45 m (9 H, arom.), 8·87 s (OH)
VIIIf	3 500, 3 245, 1 625, 1 585 1 475, 1 164, 1 136	2·10 s (CH_3), 3·98 bd and 4·11 bd (OCH_2CH_2N), 6·51—6·62 m and 6·90—7·40 m (9 H, arom.), 8·87 s (OH)
VIIIg	3 500, 3 250, 1 625, 1 590 1 487, 1 170, 1 155	0·97 t (CH_3) J = 7·4, 1·53 d (CH_3) J = 6·2, 1·48 m (CH_2), 1·75 m (CH_2), 2·13 s (CH_3), 3·90 m (CH_2), 3·93 t (CH_2), 4·55 m (CH), 6·48—6·57 m and 7·17 t (4 H, arom.), 8·55 s (OH)
VIIIh	3 500, 3 250, 1 620, 1 600 1 590, 1 490, 1 179, 1 153	0·96 t (CH_3) J = 7·4, 1·48 m (2 × CH_2), 1·75 m 2·12 s (CH_3), 3·62 m (CH_2), 3·93 m (2 × CH_2O), 6·40—6·50 m and 7·16 t (4 H, arom.), 9·40 s (OH)
VIIIi	3 483, 3 235, 1 625, 1 600 1 585, 1 485, 1 180, 1 153	0·95 t (CH_3), J = 7·3, 1·46 m (CH_2), 1·72 m (CH_2), 2·11 s (CH_3), 3·88 t (CH_2O), 4·24 t and 4·45 dd (CH_2), 5·91 bs (CH), 6·43—6·52 m, 7·13 t and 7·24—7·44 m (9 H, arom), 8·40 s (OH)
VIIIj	3 485, 3 240, 1 620, 1 600 1 587, 1 487, 1 187, 1 152	0·89 d ((CH_3)$_2$), 0·97 t (CH_3), 1·47 m (CH_2), 1·74 m (CH_2), 1·83 m (CH), 2·09 s (CH_3), 2·44 d (CH_2), 3·90 t (CH_2O), 4·33 dd and 4·45 bs (CH_2), 5·92 bs (CH), 6·42—6·50 m and 7·15 t (4 H, arom.), 7·12 d and 7·28 d (4 H, arom.) J = 8·5

[a] J in Hz.

The IR spectra of compounds *II*–*VIII* are characterized by the presence of absorption bands of aromatic skeleton at 1 600 cm^{-1}, strong C—H deformation vibrations at 1 400 cm^{-1}, and two distinct C—O bond absorptions from 1 190 to 1 150 cm^{-1}.

The results of pharmacological studies will be presented in a subsequent communication.

EXPERIMENTAL

The temperature data were not corrected. The melting temperatures were determined on a Boetius apparatus. The IR spectra were measured with a Perkin–Elmer 325 apparatus in chloroform. The ^1H NMR spectra were obtained with the help of a Bruker 400 apparatus in deuteriochloroform, using TMS as the internal standard. The mass spectra were measured with a JEOL DX 300 apparatus (the electron energy 70 eV). The gas chromatography was performed on an apparatus Chrom 5, FID, stationary phase carrier Gaschrom Q.

Chemicals: The 3-alkoxyphenols *Ia*–*Ie* were prepared by standard procedures[43–47] from resorcinol and the respective alkyl halogenide or dimethyl sulfate in the presence of sodium hydroxide: 3-methoxyphenol (*Ia*, yield 48%, b.p. 122–123·5°C/1·86 kPa, ref.[45] gives b.p. 85°C/0·53 kPa), 3-butoxyphenol (*Ib*, 44%, b.p. 160–164°C/2·43 kPa, ref.[43] gives b.p. 130°C/0·67 kPa). 3-octyloxyphenol (*Ic*, 24%, b.p. 134·5–136·5°C/0·04 kPa, ref.[43] gives b.p. 170°C/0·67 kPa), 3-benzyloxyphenol (*Id*, 23%, b.p. 160–165°C/0·04 kPa, ref.[44] gives b.p. 202–210°C/1·43 kPa), 3-Phenoxyphenol (*Ie*) was prepared by demethylation of 1-methoxy-3-phenoxybenzene[46] with aluminium chloride and sodium iodide in acetonitrile according to ref.[47] (yield 87%, b.p. 120 to 123°C/0·04 kPa, ref.[43] gives b.p. 150°C/0·67 kPa).

2-Chloro-1-(4-isobutylphenyl)ethanone

A mixture of 25·8 g (0·2 mol) isobutylbenzene and 28·2 g (0·25 mol) chloroacetyl chloride was added dropwise to a mixture of 26·7 g (0·2 mol) aluminium chloride and 100 ml 1,2-dichloroethane with stirring at 0–5°C within 1 h. After 3 h the mixture was poured on ice and conc. HCl (100 ml), the aqueous layer was washed with 1,2-dichloroethane, and the combined organic portions were washed with dilute HCl (1 : 1, 50 ml) and with a solution of sodium hydrogencarbonate (100 ml). After drying with anhydrous magnesium sulfate and evaporation of the solvent the residue was submitted to distillation to give 37·5 g (0·178 mol) product, b.p. 130 to 134°C/0·27 kPa, yield 89%, m.p. 36–38°C. For $C_{12}H_{15}ClO$ (210·9) calculated: 68·41% C, 7·18% H, 16·82% Cl; found: 68·69% C, 7·24% H, 17·08% Cl. IR spectrum (cm^{-1}): ν(C=O) 1 695. ^1H NMR spectrum: ($(CH_3)_2$, J = 6·7 Hz), 1·91 m (CH), 2·54 d (CH_2), 4·69 s (CH_2Cl), 7·26 d and 7·87 d ((4 H, arom.), J = 8·5 Hz).

Methyl (3-Methoxyphenoxy)acetate (*IIb*)

A mixture of 30·0 g (0·242 mol) phenol *Ia*, 26·0 g (0·24 mol) methyl chloroacetate, 26·6 g (0·192 mol) potassium carbonate, 2 g sodium iodide and 100 ml acetone was refluxed with stirring for 6 h. After cooling the suspension was filtered, the acetone was evaporated, and the residue was distilled to give 40·6 g (86%) ester *IIb*, b.p. 157–162°C/2·0 kPa. The esters *IIa*, *IIc*–*IIh* were prepared in the same way (Table I). The IR and ^1H NMR spectra of the products are presented in Table II.

(3-Methoxyphenoxy)acetaldehyde (*IIIb*)

A solution of diisobutylaluminum hydride in hexane (187 ml, 1 mol l^{-1}, 0·187 mol) was added dropwise to a mixture of 33·3 g (0·17 mol) ester *IIb* and 300 ml toluene at −78°C during 4 h. The mixture was stirred 10 min, decomposed with 250 ml 5% methanolic HCl, filtered through alumina, and dried with anhydrous magnesium sulfate. The solvent was evaporated and the crude product was transformed into oxime *IVb* immediately. For analysis, 0·2 g aldehyde was purified by flash chromatography (silica gel, chloroform/methanol as eluent). The physico-chemical characteristics of the aldehydes and semicarbazones are summarized in Tables II–IV. The aldehydes *IIIc*–*IIIh* were prepared in the same way. The crude aldehyde *IIIa* was submitted to GC-MS analysis. It contained a small amount of the starting ester *IIa* and about 2% 2,4-diphenoxy-3-hydroxybutanal (*IX*). Mass spectrum: 254 (43) $(M - H_2O)^+$, 225 (32), 161 (55), 135 (35), 107 (43), 106 (32), 105 (76), 91 (15), 77 (100), 65 (43), 58 (22), 51 (57).

2-(3-Butoxyphenoxy)-1-phenylethanone (*IIi*)

A mixture of 22·7 g (0·137 mol) phenol *Ib*, 27·9 g (0·14 mol) ω-bromoacetophenone, 22·6 g (0·163 mol) potassium carbonate and 250 ml acetone was refluxed with stirring 8 h, cooled, filtered, and the solvent was evaporated. The residue was diluted with toluene (200 ml), washed with 5% NaOH and with water, and dried with anhydrous $MgSO_4$. The solvent was evaporated and the residue was recrystallized from ethanol to give 24·3 g (85·3 mmol) ketone *IIi*, m.p. 60 to 62°C, yield 62%. Ketone *IIj* was obtained similarly from the phenol *Ib* and 2-chloro-1-(4-isobutylphenyl)ethanone, yield 34%, m.p. 45–47°C (ethanol).

(3-Methoxyphenoxy)acetaldoxime (*Vb*)

A mixture of 27·5 g crude aldehyde *IIIb* and 23·7 g (0·34 mol) hydroxylamine hydrochloride was dissolved in a mixture of 75 ml ethanol and 50 ml pyridine. After 3 h at 40°C the solution was evaporated and the dry residue was washed with ether. The ethereal solution was washed with 5% HCl and with water and dried with anhydrous $MgSO_4$. The recrystallization of the residue from a dichloromethane–heptane mixture gave 17·2 g (95 mmol) oxime *Vb* (56% with respect to the ester *IIb*), m.p. 100–102°C. Oximes *Va*, *Vc*–*Vj* were prepared in the same way from *IIIa*, *IIIc*–*IIIh*, *IIi*, *IIj*, respectively; the results are given in Tables V and VI. The mother liquor from isolation of oxime *Va* was evaporated and submitted to column chromatography (silica gel, chloroform–methanol as eluent) to give 0·41 g 2,4-diphenoxy-3-hydroxybutanal oxime (*X*) – the product of oximation of *IX*. IR spectrum (cm^{-1}): 3 580 and 3 350 ν(OH), 1 710 ν(C=N), 1 599, 1 589, 1 492. Mass spectrum: 287 (33) M^+, 269 (6) $(M - H_2O)^+$, 193 (7), $(M - C_6H_5O)^+$, 176 (5), 151 (66), 134 (19), 119 (17), 107 (72), 94 (82), 77 (100), 65 (22), 51 (24).

N-Acetoxy-N-[2-(3-methoxyphenoxy)ethyl]acetamide (*VIIb*)

Borane–pyridine complex (26·6 g, 0·28 mol) was added dropwise to a mixture of 17·1 g (94·3 mmol) oxime *Vb* and 100 ml ethanol with stirring at 0°C. After 10 min 100 ml dilute HCl (1 : 1) was added drop by drop. After 30 min the mixture was neutralized with sodium carbonate (pH 8) and the crude hydroxylamine was extracted with ether (4 × 50 ml), the extract was dried with anhydrous $MgSO_4$, the solvent was evaporated, and the residue was dissolved in 50 ml pyridine. The solution was treated with 0·1 g dimethylaminopyridine added at 5°C and with 28·5 g (0·28 mol) acetanhydride added dropwise during 15 min. After 3 h standing at 20°C the mixture was decomposed with 250 ml water, washed with ether (4 × 50 ml), the ethereal solution was washed with 50 ml 5% hydrochloric acid and with water and dried with anhydrous $MgSO_4$.

The solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexane–ether as eluent). The results are summarized in Table VII. The spectral characteristics of the compounds *VII* synthesized are presented in Table VIII.

N-Hydroxy-N-[(3-methoxyphenoxy)ethyl]acetamide (*VIIIb*)

Compound *VIIb* (2·7 g, 10 mmol) was dissolved in 10 ml methanol, and 0·1 ml triethylamine was added thereto. The mixture was stirred at room temperature 4 h, the solvent was evaporated, the evaporation residue was diluted with 100 ml ether and washed with 5% hydrochloric acid. After drying with anhydrous magnesium sulfate the solvent was evaporated, and the residue was recrystallized from a benzene–hexane mixture to give 2·07 g (9·2 mmol) compound *VIIIb*, yield 92%, m.p. 62—64°C. The hydroxamic acids *VIIIa*, *VIIIc*—*VIIIj* were prepared in the same way. The results and physico-chemical characteristics of the products are summarized in Tables IX and X.

The elemental analyses were carried out in Department of Organic Analysis (Dr L. Helešic, Head), the IR *spectra were measured in Department of Absorption Spectroscopy (Dr A. Kohoutová, Head), the* ^{1}H NMR *spectra were measured in Department of* NMR *Spectroscopy (Dr P. Trška, Head), and the mass spectra were measured in* MS *Department (Dr V. Kubelka, Head), all the departments belonging to Central Laboratories of Prague Institute of Chemical Technology. The authors are indebted to all those mentioned for their kind help.*

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