SYNTHESIS OF SOME *p*-SUBSTITUTED ALKOXYALKYL PHENYL ETHERS*

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As bioanalogues of the insect juvenile hormone, several alkoxyalkyl phenyl ethers have been prepared of various number of carbon atoms in the alkoxyalkyl chain and with various substituents in the *para* position of the phenyl residue.

In connection with the preparation of the insect juvenile hormone bioanalogues containing an aromatic ring in this Institute[1,2], attention has been now paid to the synthesis** of some *p*-substituted alkoxyalkyl phenyl ethers (some results in this respect have been reported in our patent application[3]).

The synthesis of compounds *I*–*VI*, *VIII*, *IX*, and *XI*–*XIV* (Table I and Scheme 1) was performed from alkoxyalkyl alcohols obtained by reduction of esters of corresponding alkoxyalkanoic acids[4–6] or alkoxyalkyl ketones with lithium aluminium hydride. By reaction with phosphorus tribromide in the presence of pyridine or on treatment with bromine and triphenylphosphine, the alkoxyalkanols were converted to the appropriate alkoxyalkyl bromides which afforded the required phenyl ethers by reaction with *p*-substituted phenols. Compound *VII* was prepared analogously from diethylene glycol monomethyl ether. Saponification of the ester *VIII* afforded an acid which was converted to the N,N-diethylamide *X* *via* transformation to the acyl chloride and its reaction with diethylamine.

EXPERIMENTAL

The IR spectra were taken in tetrachloromethane. The gas chromatography was performed on a Pye Argon Chromatograph (radioactive ionisation detection). Column chromatography was carried out on the Pitra silica gel (produced by Service Laboratories of this Institute) partially deactivated by the addition of 12% water. Substances that were not distilled were dried for analytical purposes at 50°C/12 Torr for 1 h. The boiling point data refer to bath temperatures.

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** The biological activity of the present substances will be reported elsewhere.

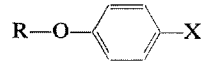
Preparation of Alkoxyalkyl Alcohols

The lithium aluminium hydride reduction was performed analogously[5] to the preparation of 5-(1,1-dimethylethoxy)-3-methyl-2-penten-1-ol and 5-(1,1-dimethylethoxy)-3-methyl-1-pentanol.

TABLE I

Elemental Analyses of Compounds *I*—*XIV*

Compound	Formula (m.w.)	Calculated/Found				B.p., °C/Torr
		% C	% H	% Cl	% N	
I	$C_{16}H_{23}ClO_2$ (282·8)	67·95 68·26	8·20 8·04	12·54 12·61	—	135—140 0·01
II	$C_{16}H_{25}ClO_2$ (284·8)	67·47 67·59	8·85 8·90	12·45 12·48	—	133—138 0·008
III	$C_{14}H_{21}ClO_2$ (256·8)	65·48 65·36	8·24 8·23	13·81 14·04	—	110—120 0·009
IV	$C_{17}H_{25}ClO_2$ (296·8)	68·79 69·09	8·49 8·57	11·95 12·03	—	—
V	$C_{20}H_{29}ClO_2$ (336·9)	71·30 71·15	8·68 8·55	10·52 10·41	—	150—160 0·008
VI	$C_{17}H_{23}ClO_2$ (294·8)	69·26 68·89	7·86 7·85	12·03 12·22	—	—
VII	$C_{11}H_{15}ClO_3$ (230·7)	57·27 57·31	6·55 6·64	15·37 15·35	—	127—135 0·009
VIII	$C_{19}H_{28}O_4$ (320·4)	71·22 70·96	8·81 8·85	—	—	—
IX	$C_{17}H_{26}O_4$ (294·4)	69·36 69·57	8·90 9·02	—	—	—
X	$C_{21}H_{33}NO_3$ (347·5)	72·58 72·61	9·57 9·56	—	4·03 4·30	—
XI	$C_{19}H_{28}O_3$ (304·4)	74·96 74·88	9·27 9·34	—	—	—
XII	$C_{19}H_{30}O_3$ (306·4)	74·47 74·17	9·87 9·82	—	—	—
XIII	$C_{16}H_{26}O_2$ (250·4)	76·75 76·93	10·47 10·32	—	—	90—95 0·01
XIV	$C_{16}H_{23}NO_4$ (293·4)	65·28 65·50	7·90 8·18	—	4·77 4·86	—



	R =	X =
I	$(CH_3)_3C-O-CH_2-CH_2-C(CH_3)=CH-CH_2-$	Cl
II	$(CH_3)_3C-O-CH_2-CH_2-CH(CH_3)-CH_2-CH_2-$	Cl
III	$(CH_3)_3C-O-CH_2-CH_2-CH(CH_3)-$	Cl
IV	$(CH_3)_3C-CH_2-O-CH_2-CH_2-C(CH_3)=CH-CH_2-$	Cl
V	$(CH_3)_2C=CH-CH_2-CH_2-CH(CH_3)-O-CH_2-CH_2-C(CH_3)=CH-CH_2$	Cl
VI	$CH_3-CH=C(CH_3)-CH_2-O-CH_2-C(C_2H_5)=CH-CH_2-$	Cl
VII	$CH_3-O-CH_2-CH_2-O-CH_2-CH_2-O-$	Cl
VIII	$(CH_3)_3C-O-CH_2-CH_2-C(CH_3)=CH-CH_2-$	$-COOC_2H_5$
IX	$(CH_3)_3C-O-CH_2-CH_2-CH(CH_3)-$	$-COOC_2H_5$
X	$(CH_3)_3C-O-CH_2-CH_2-C(CH_3)=CH-CH_2-$	$-CON(C_2H_5)_2$
XI	$(CH_3)_3C-O-CH_2-CH_2-C(CH_3)=CH-CH_2-$	$-CO-C_2H_5$
XII	$(CH_3)_3C-O-CH_2-CH_2-CH(CH_3)-CH_2-CH_2-$	$-CO-C_2H_5$
XIII	$(CH_3)_3C-O-CH_2-CH_2-CH(CH_3)-$	$-C_2H_5$
XIV	$(CH_3)_3C-O-CH_2-CH_2-C(CH_3)=CH-CH_2-$	$-NO_2$

SCHEME 1

This route was used to prepare the following alcohols. 3-[(2-methyl-2-butenyloxy)methyl]-2-penten-1-ol (b.p. 155—160°C/12 Torr). For $C_{11}H_{20}O_2$ (184·3) calculated: 71·68% C, 10·94% H; found: 71·49% C, 10·93% H. 5-(2,2-Dimethylpropoxy)-3-methyl-2-penten-1-ol (b.p. 130—140°C : : 18 Torr). For $C_{11}H_{22}O_2$ (186·3) calculated: 70·91% C, 11·91% H; found: 70·97% C, 11·92% H. 5-(1,5-Dimethyl-4-hexenyloxy)-3-methyl-2-penten-1-ol (b.p. 105—115°C/0·01 Torr). For $C_{14}H_{26}O_2$ (226·3) calculated: 74·30% C, 11·58% H; found: 74·00% C, 11·36% H.

Preparation of Alkoxyalkyl Bromides

The preparation was performed analogously to that[5] of 1-bromo-5-(1,1-dimethylethoxy)-3-methyl-2-pentene and 1-bromo-5-(1,1-dimethylethoxy)-3-methylpentane.

The phosphorus tribromide-pyridine method (light petroleum as solvent) was used in the preparation of the following bromides. 1-Bromo-3-[(2-methyl-2-butenyloxy)methyl]-2-pentene (b.p. 140—145°C/12 Torr), 1-bromo-5-(1,1-dimethylpropoxy)-3-methyl-2-pentene,* 1-bromo-5-(1,5-dimethyl-4-hexenyloxy)-3-methyl-2-pentene,* 3-bromo-1-(1,1-dimethylethoxy)butane (b.p. 120—130°C/30 Torr), and (diethyl ether as solvent) 1-bromo-2-(2-methoxyethoxy)ethane (b.p. 105—110°C/16 Torr).

Preparation of Alkoxyalkyl Phenyl Ethers *I*—*IX* and *XI*—*XIV*

A mixture of the appropriate alkoxyalkyl bromide (50 mmol), the corresponding phenol derivative (55 mmol), and anhydrous potassium carbonate (0·4 g) in methyl ethyl ketone (10—15 ml) was refluxed for 6—16 h. The reaction course was checked by thin-layer chromatography. When the alkoxyalkyl bromide disappeared or when the composition of the reaction mixture remained constant, the reaction mixture was poured into water, extracted with ether, the ethereal extract washed with 5% aqueous sodium hydroxide, and processed as usual. The crude product was purified by chromatography on silica gel (30—50 parts by weight) with the use of the light petroleum–ether mixture (1 : 32 with compounds *I*—*VI* and *XIII*; 1 : 12 with compounds *VIII, IX, XI, XII,* and *XIV*; and 1 : 6 in the case of compound *VII*). Yields, 40—70%. The ratio *cis*-isomer/*trans*-isomer, 1 : 1·5—2.

This route was used to prepare the following compounds. 1-Chloro-4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyloxy)benzene (*I*), 1-chloro-4-(5-(1,1-dimethylethoxy)-3-methylpentyloxy)-benzene (*II*), 1-chloro-4-(3-(1,1-dimethylethoxy)-1-methylpropoxy)benzene (*III*), 1-chloro-4-(5-(2,2-dimethylpropoxy)-3-methyl-2-pentenyloxy)benzene (*IV*), 1-chloro-4-(5-(1,5-dimethyl-4-hexenyloxy)-3-methyl-2-pentenyloxy)benzene (*V*), 1-chloro-4-(3-((2-methyl-2-butenyloxy)methyl)-2-pentenyloxy)benzene (*VI*), 1-chloro-4-(2-(2-methoxyethoxy)ethoxy)benzen e (*VII*), ethyl 4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyloxy)benzoate** (*VIII*), ethyl 4-(3-(1,1-dimethylethoxy)-1-methylpropoxy)benzoate (*IX*), 4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyloxy)propiophenone (*XI*), 4-(5-(1,1-dimethylethoxy)-3-methylpentyloxy)propiophenone (*XII*), 1-ethyl-4-(3-(1,1-dimethylethoxy)-1-methylpropoxy)benzene (*XIII*), and 4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyloxy)-1-nitrobenzene (*XIV*).

The IR spectra of compounds *I*—*III* and *VIII* exhibited absorption bands of the etherified phenolic oxygen atom (at about 1240 cm^{-1}), of the ethereal oxygen atom (at about 1080 and 1100 cm^{-1}) and of the *p*-substituted aromatic system (at about 1490, 1580, 1590, and 830 cm^{-1}).

* The substance was not distilled and used directly in the next step.

** For the preparation of the corresponding methyl ester see ref.[7].

The homogeneity of products and the *cis*/*trans* ratio was determined by gas chromatography on Cellite impregnated with 10% Apiezon L (in the case of compounds *I*—*IV*, *VI*, and *XIII*; at 200 or 225°C) and on Gas Chrom Q impregnated with 3% SE-30 (compounds *V*, *VII*—*IX*, *XI*, *XII*, and *XIV*; at 150—180°C).

N,N-Diethylamide of 4-(5-(1,1-Dimethylethoxy)-3-methyl-2-pentenyloxy)benzoic Acid (*X*)

The ethyl ester *VIII* (1·0 g) was saponified by refluxing for 1 h with 2% ethanolic sodium hydroxide (15 ml) and the mixture processed as usual to afford 0·8 g of the free acid. A solution of this acid (0·8 g), pyridine (2·5 ml), and benzene (10 ml) was treated with thionyl chloride (0·5 ml), the whole kept at room temperature for 2 h, diluted with benzene (10 ml), and treated dropwise with diethylamine (3 ml). After 2 h at room temperature, the mixture was worked up as usual and the crude amide chromatographed on silica gel (30 parts by weight) with the use of light petroleum–acetone (1 : 9) mixture as eluant. Yield, 0·6 g of the amide *X*.

Elemental analyses were performed in the Analytical Department of this Institute by Mrs V. Rusová, Mrs E. Šípová, Mrs Y. Černá, and Mr V. Štěrba under the direction of Dr J. Horáček. The IR spectra were measured by Mr P. Formánek and interpreted by Dr J. Smolíková. The technical assistance was provided by Miss D. Stiborková.

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