NATURAL AND SYNTHETIC MATERIALS WITH THE INSECT HORMONE ACTIVITY. XIV.*

SYNTHESIS OF SUBSTITUTED PHENYL GERANYL ETHERS AND RELATED COMPOUNDS

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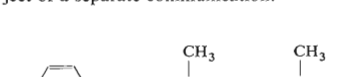
A number of derivatives supposed to exhibit the juvenile hormone activity was prepared from the corresponding phenyl geranyl ethers by addition of alcohols, oxidation with perphthalic acid and other reactions.

In connection with our investigations in the field of juvenile hormone bioanalogues, we prepared some time ago a considerable number of substituted phenyl geranyl ethers and other related types of compounds. Some of these compounds which we had hitherto described only in patent applications[1,2] were mentioned recently among compounds prepared in other Laboratories[3]. This prompts us to describe our results concerning the synthesis and characterisation of the compounds of the aforementioned type whereas their biological activity, already preliminarily described[4], will be the subject of a separate communication.



XXIX, R = Cl, $R^1 = CH_2CH_3$
XXX, R = Br, $R^1 = CH_2CH_3$
XXXI, R = NO_2, $R^1 = CH_2CH_3$

The substituted phenyl geranyl ethers *I*–*XII* which represent the parent type of compounds studied by us were prepared (Table I) by the reaction of corresponding alkali metal phenoxides with geranyl bromide[5] in dimethylformamide. The compounds obtained in this way are mixtures of stereoisomers with the *trans*-isomer predominating, as shown by the NMR spectra. In some cases (*e.g. VII*, *XII*), the pure crystalline *trans*-isomer was isolated from this stereoisomeric mixture, however, since there was no significant difference in the biological activity, the question of ste-

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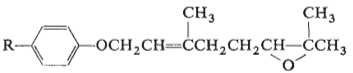
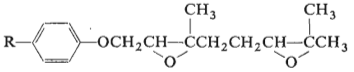
reoisomeric purity was not pursued further. We prepared also some citronellyl phenyl ethers using the less reactive citronellyl bromide as the alkylation agent.

Since some of the compounds exhibited a remarkable biological activity, we synthesized a number of new derivatives by addition of water and alcohols on the geranyl moiety of phenyl geranyl ethers, particularly of the *p*-chloro and *p*-nitro derivatives (*V* and *VII*, respectively). The addition was carried out by treatment of the olefinic compound with mercuric acetate in the presence of the hydroxylic component,

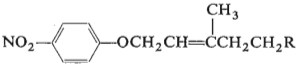


XXXII, R = Cl
XXXIII, R = Br
XXXIV, R = NO_2

followed by a reduction with sodium borohydride[6,7]. The addition took place preferably on the terminal double bond of the geranyl moiety (Table II), only small amount of product of bis-addition (*XXIX*–*XXXI*) being formed (Table III). The addition of secondary alcohols, *e.g.* the reaction of 2-propanol with the compound *VII*, proved to be difficult and satisfactory yields were obtained only when mercuric acetate was replaced with mercuric trifluoroacetate. For the addition we also used some less common hydroxylic components such as *e.g.* methyl glycolate. The reaction of phenyl geranyl ethers with perphthalic acid afforded monoepoxides *XXXII* to



XXXV, R = Cl
XXXVI, R = Br
XXXVII, R = NO_2

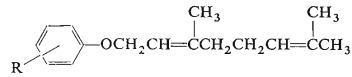


XLIV, R = CHO
XLV, R = CO_2H
XLVI, R = CO_2CH_3
XLVII, R = $CON(CH_3)_2$
XLVIII, R = $CON(C_2H_5)_2$

XXXIV accompanied with a small amount of diepoxides *XXXV*–*XXXVII* (Table III). Two cyclopropane derivatives, *XLI* and *XLII*, were prepared from the ether *V* by its respective reactions with diazomethane in the presence of zinc iodide[8], and with ethyl diazoacetate. Hydration of the epoxide *XXIV* with water in the presence of perchloric acid gave the corresponding diol *XLIII*; this was oxidized with periodic acid to the aldehyde *XLIV* which upon reaction with silver oxide[9] gave the acid *XLV*. Its reaction with diazomethane afforded the methyl ester *XLVI*. The acid *XLV* was transformed into its dimethylamide *XLVII* and diethylamide *XLVIII* by treatment with N,N-dimethylchloromethylenammonium chloride followed by reaction with the corresponding amines[10].

TABLE I

Physical Constants, Yields and Analytical Values of Compounds *I*–*XII* of the Type

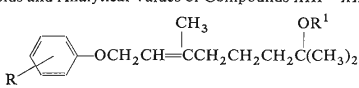


No R	Method[a] conditions, °C/h	Yield, % b.p./Torr, °C	Formula (m.w.)	Calculated/Found % C	 % H	 % N
I[b]	B	42	$C_{12}H_{22}O$	79·05	12·16	
	78/8	100–105/0·5	(182·3)	79·34	12·06	—
II	A	43·5	$C_{16}H_{22}O$	83·47	9·56	
H	70/8	180–182/0·5	(230·3)	83·29	9·73	
III	A	43	$C_{18}H_{26}O$	83·67	10·14	—
3,4-$(CH_3)_2$	20/2[c]	130–131/0·1	(242·4)	83·67	10·27	
IV	A	51	$C_{20}H_{30}O$	83·86	10·56	—
4-t-C_4H_9	20/2[c]	150/0·2	(286·5)	83·99	10·30	
V	A	49·1	$C_{16}H_{21}ClO$	72·58	8·00	13·39[e]
4-Cl	70/8[d]	145–150/0·7	(264·7)	72·85	8·09	13·48[e]
VI	A	51	$C_{16}H_{21}BrO$	62·14	6·84	—
4-Br	30/0·5[d]	—	(309·3)	61·07	6·81	
VII	A	51·8	$C_{16}H_{21}NO_3$	69·79	7·69	5·09
4-NO_2	70/8[d]	140/0·2	(275·3)	70·01	8·00	5·18
VIII	A	54	$C_{16}H_{21}NO_3$	69·79	7·69	5·09
3-NO_2	70/8	158–160/0·5	(275·3)	69·89	8·06	4·68
IX	A	51·9	$C_{16}H_{21}NO_3$	69·79	7·69	5·09
2-NO_2	70/8	153–155/0·5	(275·3)	70·20	7·72	5·08
X	A	23	$C_{16}H_{22}O_2$	78·00	9·00	—
4-OH	70/8[f]	—	(246·3)	77·89	9·29	
XI	C	35·9	$C_{16}H_{23}NO$	78·32	9·44	5·72
4-NH_2	—[a,g]	—	(245·3)	78·62	9·70	5·69
XII[i]	A	55	$C_{20}H_{24}O$	85·67	8·63	
3,4-benzo	30/0·5[h]	—	(280·4)	86·10	8·52	—

[a] *cf.* Experimental; [b] 3,7-dimethyl-1-ethoxy-2,6-octadiene; [c] chromatography on silica gel, eluted with light petroleum +4% ether; [d] chromatography on silica gel, light petroleum +5% ether; [e] % Cl; [f] chromatography on silica gel, ether–light petroleum 1 : 4; [g] chromatography on silica gel, ether–light petroleum 1 : 1; [h] chromatography on silica gel, ether–light petroleum 1 : 9; [i] 2-(3,7-dimethyl-2,6-octadienyloxy)naphthalene.

TABLE II

Physical Constants, Yields and Analytical Values of Compounds *XIII*—*XXVIII* of the Type



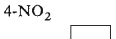
No	R R[1]	Method[a] conditions, °C/h	Yield, % b.p./Torr, °C	Formula (m.w.)	Calculated/Found % C	% H	% N
XIII	4-Cl	E	38	$C_{16}H_{23}ClO_2$	67·95	8·20	—
	—H	20/1[b]	155/0·01	(282·8)	67·74	8·21	
XIV	4-Cl	D	56	$C_{18}H_{27}ClO_2$	69·55	8·75	—
	$-C_2H_5$	20/0·75[c]	146—150/0·7	(310·9)	70·33	8·61	
XV	4-Cl	D	36·5	$C_{19}H_{29}ClO_3$	66·94	8·58	—
	$-CH_2CH_2OCH_3$	20/1[d]	—	(340·9)	67·32	8·75	
XVI	4-Cl	D	31·5	$C_{20}H_{31}ClO_3$	67·68	8·80	—
	$-CH_2CH_2OC_2H_5$	20/1[b]	—	(354·9)	67·78	8·85	
XVII	4-Cl	D	15·5	$C_{19}H_{27}ClO_4$	64·30	7·67	—
	$-CH_2COOCH_3$	20/1[b]	—	(354·9)	64·11	7·32	
XVIII	4-Br	D	20	$C_{18}H_{27}BrO_2$	60·84	7·66	—
	$-CH_2CH_3$	20/3[e]	—	(355·3)	60·85	7·64	
XIX	4-NO_2	E	30	$C_{16}H_{23}NO_4$	65·51	7·90	4·78
	—H	20/0·25[f]	180/0·2[g]	(293·3)	65·39	8·13	4·41
XX	4-NO_2	D	70·6	$C_{17}H_{25}NO_4$	66·43	8·20	4·56
	$-CH_3$	20/0·5[e]	180—200/0·3	(307·4)	66·48	8·30	4·80
XXI	4-NO_2	D	41·5	$C_{18}H_{27}NO_4$	67·26	8·44	4·36
	$-CH_2CH_3$	0/0·5[e]	190—200/0·3	(321·4)	67·16	8·53	4·05
XXII	4-NO_2	D	35	$C_{19}H_{29}NO_4$	68·03	8·71	4·18
	$-CH_2CH_2CH_3$	0/0·5[e]	190—200/0·3	(335·4)	67·89	8·82	4·31
XXIII	4-NO_2	F	30	$C_{19}H_{29}NO_4$	68·03	8·71	4·18
	$-CH(CH_3)_2$	0/05[e]	190—200/0·3	(335·4)	68·07	9·05	4·14
XXIV	4-NO_2	D	19	$C_{20}H_{31}NO_4$	68·74	8·94	4·01
	$-CH_2CH_2CH_2CH_3$	20/0·5[e]	215/0·1[g]	(349·5)	68·70	8·90	4·34
XXV	4-NO_2	D	50	$C_{18}H_{26}ClNO_4$	60·75	7·36	3·94
	$-CH_2CH_2Cl$	20/0·2[d]	210/0·2[g]	(355·9)	60·57	7·23	4·05
XXVI	4-NO_2	D	50	$C_{19}H_{29}NO_5$	64·93	8·32	3·99
	$-CH_2CH_2OCH_3$	20/0·25[d]	200—210/0·2[g]	(351·4)	65·30	8·44	4·24
XXVII	4-NO_2	D	30	$C_{21}H_{31}NO_5$	66·82	8·28	3·71
		20/0·66[h]	—	(377·5)	66·75	8·31	3·86
XXVIII	3,4-benzo[i]	D	31	$C_{22}H_{30}O_2$	80·94	9·26	—
	$-CH_2CH_3$	25/0·5[e]	—	(326·5)	81·07	9·31	

TABLE III

Physical Constants and Analytical Values of Dialkoxy, Monoepoxy and Diepoxy Derivatives *XXIX—XXXVII*

No	Yield, % (m.p., °C)	Formula (m.w.)	Calculated/Found	
			% C	% H
XXIX	10 (47—49)	$C_{20}H_{33}ClO_3$ (356·9)	67·30 67·87	9·32 9·44
XXX	20 (53—54)	$C_{20}H_{33}BrO_3$ (401·4)	59·84 59·85	8·29 8·19
XXXI	21[a,i]	$C_{20}H_{33}NO_5$ (367·5)[b]	65·37 65·49	9·05 9·14
XXXII	34[c,d,i]	$C_{16}H_{21}ClO_2$ (280·8)	68·43 68·73	7·54 7·65
XXXIII	25[c,d,i]	$C_{16}H_{21}BrO_2$ (325·3)	59·08 59·24	6·51 6·64
XXXIV	32·5[e,f,i]	$C_{16}H_{21}NO_4$ (291·4)[g]	65·96 65·80	7·27 7·08
XXXV	22[c,d,i]	$C_{16}H_{21}ClO_3$ (296·8)	64·75 65·07	7·13 7·32
XXXVI	34[c,d,i]	$C_{16}H_{21}BrO_3$ (341·4)	56·30 57·39	6·22 6·63
XXXVII	45[e,f,i]	$C_{16}H_{21}NO_5$ (307·3)[h]	62·53 62·29	6·89 6·99

[a] Distilled at 190—210°C/0·3 Torr (bath temperature); [b] calculated: 3·81% N; found: 3·72% N; [c] prepared by treatment with 1·1 equivalent of perphthalic acid in ether, 20°C/24 h; [d] chromatography on SiO_2, ether–light petroleum (1 : 4); [e] prepared from 2 equivalents of perphthalic acid, 20°C/24 h; [f] chromatography on SiO_2, ether–light petroleum (1 : 1); [g] calculated: 4·81% N; found: 4·76% N; [h] calculated: 4·56% N; found: 4·68% N; [i] oily compound, isolated by evaporation of solvent from chromatographic fractions.

(*Continued*) TABLE II

[a] *cf.* Experimental Part; [b] chromatography on silica gel, eluent ether–light petroleum 1 : 1; [c] chromatography on silica gel, light petroleum +5% ether; [d] chromatography on silica gel, ether–light petroleum 1 : 4; [e] chromatography on silica gel, ether–light petroleum 1 : 9; [f] chromatography on silica gel, benzene +5% acetone; [g] bath temperature; [h] chromatography on silica gel, ether–light petroleum 1 : 2; [i] 2-(3,7-dimethyl-7-ethoxy-2-octenyl)naphthalene.

EXPERIMENTAL

The melting and boiling points are uncorrected. The structure of the compounds was proved, in addition to their analyses, by the NMR spectra taken on a Varian HA-100 instrument.

4-Nitro-1-(3,7-dimethyl-2,6-octadienyloxy)benzene (*VII*) (Method A)

To a solution of sodium hydroxide (0·56 g; 0·014 mol) in anhydrous dimethylformamide (7 ml) was added *p*-nitrophenol (2 g, 0·014 mol) followed by geranyl bromide (3·04 g, 0·014 mol), and the resulting mixture was heated to 70°C for 8 h. The reaction mixture was cooled, diluted with water, the product was taken up in ether, the ethereal layer washed with 10% aqueous NaOH and with water, and dried. The solvent was taken down under diminished pressure and the residue chromatographed on silica gel (light petroleum containing 5% ether) affording thus 2 g (51·8%) of the product *VII* (Table I). Upon standing in a refrigerator for several days, the product deposited crystals which were separated and distilled. According to NMR spectrum, this crystalline portion was the pure *trans*-isomer (simpler signals of the protons at $C_{(1)}$, $C_{(2)}$ and the methyl at $C_{(3)}$). NMR: δ 1·59 s and 1·66 s, 2 × CH_3 at $C_{(7)}$; 1·75 s, CH_3 at $C_{(3)}$; 2·10, 4 H at $C_{(4)}$ and $C_{(5)}$; 4·63 d, $J = 6$ Hz, 2 H at $C_{(1)}$; 5·08 m, 1 H at $C_{(6)}$; 5·46 bt, $J = 6$ Hz, 2 H at $C_{(2)}$; 6·95 and 8·18, AA'XX' system of four aromatic protons.

3,7-Dimethyl-1-ethoxy-2,6-octadiene (*I*) (Method B)

Geranyl bromide (7 g, 0·03 mol) was added to a solution of sodium ethoxide (prepared from 0·7 g, 0·03 mol, of sodium in 20 ml of ethanol) and the mixture was refluxed for 8 h. Ethanol was evapotated under diminished pressure, the residue was diluted with water, the product taken into ether, washed with water, dried over magnesium sulphate and the ether was distilled off under diminished pressure. Distillation *in vacuo* afforded 2·3 g (42%) of the product *I*, b.p. 100—105°C/0·5 Torr.

4-Amino-1-(3,7-dimethyl-2,6-octadienyloxy)benzene (*XI*) (Method C)

A solution of *p*-aminophenol (2·2 g, 0·02 mol) in 85% formic acid (5 ml, 0·1 mol) was refluxed for 1 h. The reaction mixture was taken between ether and an aqueous 10% $NaHCO_3$, washed with water and dried over magnesium sulphate. Evaporation of the solvent under diminished pressure gave 1·55 g (63%) of 4-hydroxyformanilide, m.p. 138—138·5°C. A mixture of 4-hydroxyformanilide (1·55 g, 0·012 mol), anhydrous K_2CO_3 (1·66 g, 0·012 mol), and geranyl bromide (2·6 g, 0·012 mol) in dimethylformamide (7 ml) was heated to 70°C for 8 h. After dilution with water, the reaction mixture was extracted with ether, dried and taken down under diminished pressure. The residue was heated with a 20% NaOH (5 ml) and extracted with benzene. The benzene layer was taken down and the residue upon chromatography on a silica gel column (eluent ether–light petroleum 1 : 1) afforded 1·7 g (35·9%, based on the starting *p*-aminophenol) of the product *XI*.

4-Chloro-1-(7-ethoxy-3,7-dimethyl-2-octenyloxy)benzene (*XIV*) and 4-Chloro-1-(3,7-diethoxy-3,7-dimethyloctyloxy)-benzene (*XXIX*) (Method D)

A mixture of the compound *V* (0·55 g, 2 mmol) and mercuric acetate (0·96 g, 3 mmol) in abs. ethanol (3 ml) was stirred at room temperature. After 45 min, a 3M-NaOH (3 mmol) followed by a solution of sodium borohydride (60 mg) in 3 ml of 3M-NaOH was added to the reaction mixture and the stirring was continued for additional 2 h. The mixture was diluted with water, the compound taken into light petroleum, the organic layer washed with water, dried with magnesium sulphate

and taken down. Chromatography of the residue on silica gel (150 g) using light petroleum–ether (9 : 1) as eluent afforded 350 mg (56%) of the compound *XIV* and 70 mg (10%) of the compound *XXIX*, m.p. 47–49°C.

4-Chloro-1-(7-hydroxy-3,7-dimethyl-2-octenyloxy)benzene (*XIII*) (Method E)

Mercuric acetate (1·4 g) in water (10 ml) was added to a stirred solution of *V* (1·06 g, 4 mmol) in tetrahydrofuran (20 ml) at ambient temperature. The reaction mixture was stirred for 1 h, then cooled to 0°C, treated with 3M-NaOH (4 ml) and with a solution of sodium borohydride (100 mg) in 4 ml of 3M-NaOH, and stirred for an additional hour. The mixture was diluted with water, extracted with ether, the organic layer washed with water, dried over magnesium sulphate and taken down. Chromatography of the residue on silica gel (100 g), using ether–light petroleum (1 : 1) as eluent, afforded *XIII* (430 mg, 38%), b.p. 155°C/0·01 Torr (bath temperature).

4-Nitro-1-(7-isopropoxy-3,7-dimethyl-2-octenyloxy)benzene (*XXIII*) (Method F)

To a solution of *VII* (825 mg, 3 mmol) in 2-propanol (10 ml) a solution of mercuric trifluoroacetate (1·4 g, 3 mmol) in 2-propanol (10 ml) was added under stirring and cooling with ice. After stirring for 0·5 h, the reaction mixture was treated with 3M-NaOH (3 ml) and sodium borohydride (63 mg) in 3M-NaOH (3 ml), and the stirring was continued for 1 h. After dilution with water the compound was taken up in light petroleum, washed with water, dried over magnesium sulphate, taken down and chromatographed on silica gel (100 g). Elution with ether–light petroleum (1 : 9) gave 300 g (30%) of compound *XXIII*, b.p. 190–200°C/0·3 Torr.

4-Nitro-1-(3,7-dimethyl-6-octenyloxy)benzene (*XXXVIII*)

A mixture of *p*-nitrophenol (2·0 g, 0·014 mol), sodium hydroxide (0·56 g, 0·014 mol) and citronellyl bromide[11] (3·1 g, 0·014 mol) in dimethylformamide (7 ml) was heated to 70°C for 8 h. The reaction mixture was diluted with water, extracted with ether, washed with a 10% NaOH solution and with water, and dried over magnesium sulphate. The solvent was distilled off under diminished pressure and the residue was distilled affording 2·0 g (51·5%) of *XXXVIII*, boiling at 166–170°C/0·5 Torr. For $C_{16}H_{23}NO_3$ (277·3) calculated: 69·29% C, 8·36% H, 5·05% N; found: 69·45% C, 8·40% H, 5·17% N.

4-Nitro-1-(6,7-epoxy-3,7-dimethyloctyloxy)benzene (*XXXIX*)

The compound *XXXVIII* (1·0 g, 3·6 mmol) was treated with perphthalic acid (0·72 g, 4 mmol) in ether at 0°C for 16 h. Then the separated phthalic acid was filtered off and the filtrate was taken between ether and a 10% $NaHCO_3$. The ethereal layer was washed with water, dried over magnesium sulphate and taken down under diminished pressure. Chromatography of the residue on silica gel (eluent ether–light petroleum 1 : 4) afforded *XXXIX* (0·85 g, 80%). For $C_{16}H_{23}NO_4$ (293·3) calculated: 65·51% C, 7·90% H, 4·77% N; found: 65·70% C, 7·85% H, 4·90% N.

2,4-Dinitro-1-(3,7-dimethyl-6-octenyloxy)benzene (*XL*)

A solution of 2,4-dinitrophenol (1·7 g, 0·01 mol), citronellyl bromide (2·2 g, 0·01 mol) and triethylamine (1·0 g, 0·01 mol) in benzene was refluxed for 8 h. The reaction mixture was then taken between 1M-HCl and ether. The product *XL* was isolated by distillation, b.p. 184–186°C/0·2 Torr, yield 1·2 g (37·2%). For $C_{16}H_{22}N_2O_5$ (322·3) calculated: 59·62% C, 6·88% H, 8·69% N; found: 59·58% C, 6·75% H, 8·69% N.

1,1-Dimethyl-2-(5-(4-chlorophenoxy)-3-methyl-3-pentenyl)cyclopropane (*XLI*)

An ethereal solution of diazomethane (1·8 g in 60 ml) followed by the compound *V* (1·0 g, 5·4 mmol), was added to a solution of anhydrous zinc iodide (3·0 g) in dioxane (20 ml), and the mixture was refluxed for 40 h, further 5 ml of ethereal solution of diazomethane being added in 10 h intervals. After decomposition with dilute ammonia solution, the ethereal layer was twice washed with water, dried, taken down and the residue distilled, b.p. 130°C/0·3 Torr affording 0·9 g of the crude product containing, according to vapour-phase chromatography, about 40% of the starting material. Repeated chromatography on silica gel (light petroleum containing 2% of ether) gave the compound *XLI*. For $C_{17}H_{23}ClO$ (278·8) calculated: 73·23% C, 8·31% H; found: 72·72% C, 8·21% H. NMR-spectrum: δ 1·00, 1·02 s, 2 × CH_3; 1·71 mt, 3 H, sp^2-CH_3; 2·12 mt, 2 H, allylic CH_2; 4·50 d, $J = 6$ Hz, 2 H, $ArOCH_2$—CH=; 5·46 mt, 1 H, sp^2-H; 6·82 and 7·20, AA'BB' system of 4 aromatic protons.

Ethyl 2,2-dimethyl-2-(5-(4-chlorophenoxy)-3-methyl-3-pentenyl)cyclopropanecarboxylate (*XLII*)

Copper acetylacetonate[12] (30 mg) was added to a solution of *V* (0·8 g, 3 mmol) in hexane (3 ml), the mixture was heated to the boil and ethyl diazoacetate (0·36 g, 3·15 mmol) was added under stirring. The mixture was refluxed for 3 h (till the disappearance of the diazoacetate), cooled, diluted with ether, washed with dilute hydrochloric acid and with water, the solvent was evaporated and the residue chromatographed on silica gel (50 g). Elution with light petroleum, followed by light petroleum containing 10% of ether, afforded 0·55 g of the starting compound and 110 mg (10%) of the product *XLII*. For $C_{20}H_{27}ClO_3$ (350·9) calculated: 68·43% C, 7·76% H, 10·15% Cl; found: 68·75% C, 7·66% H, 10·39% Cl.

4-Nitro-1-(6,7-dihydroxy-3,7-dimethyl-2-octenyloxy)-benzene (*XLIII*)

A solution of *XXXIV* (2·9 g) in dioxane (20 ml) was treated with water (5 ml) and perchloric acid (0·1 ml). After standing at room temperature for 15 min, the mixture was diluted with a saturated $NaHCO_3$, the product was taken up in ether, washed with water, dried over magnesium sulphate and taken down. Purification of the residue by chromatography on silica gel (100 g) using ether as eluent gave 2·3 g (74·5%) of *XLIII*, m.p. 88—89°C (benzene–light petroleum). For $C_{16}H_{23}NO_5$ (309·4) calculated: 62·12% C, 7·49% H, 4·53% N; found: 62·56% C, 7·77% H, 4·53% N.

3-Methyl-5-(4-nitrophenoxy)-3-pentenecarbaldehyde (*XLIV*)

An aqueous solution (10 ml) of sodium periodate (1·6 g) was added to a solution of the diol *XLIII* (1·55 g) in 50% ethanol (100 ml), the mixture was set aside for 2 h at room temperature, then diluted with water and the product taken up in ether. The ethereal solution was washed with water, dried over magnesium sulphate and taken down. Chromatography of the residue on silica gel (50 g), using ether–light petroleum (1 : 1) as eluent, afforded 1·2 g (96·3%) of the aldehyde *XLIV*, m.p. 32—36°C. For $C_{13}H_{15}NO_4$ (249·3) calculated: 62·64% C, 6·07% H, 5·62% N; found: 62·68% C, 6·03% H, 5·78% N.

3-Methyl-5-(4-nitrophenoxy)-3-pentenecarboxylic Acid (*XLV*)

An aqueous solution of silver nitrate (5·1 g in 25 ml) was added to a solution of the aldehyde *XLIV* (2·49 g) in ethanol (10 ml). KOH (3·4 g) in water (25 ml) was added dropwise in the course

of 3/4 h under stirring and cooling with ice and the stirring was continued for 2 h. The precipitate which separated was filtered and washed with water, the filtrate acidified with H_2SO_4 and extracted with ether. The ethereal layer was washed with water, dried and taken down leaving 2·15 g (81%) of the acid *XLV*, m.p. 129—130°C (acetone–light petroleum). For $C_{13}H_{15}NO_5$ (265·3) calculated: 58·86% C, 5·70% H, 5·28% N; found: 59·00% C, 5·73% H, 5·18% N. *Methyl ester* XLVI, m.p. 63—64°C (methanol), was prepared by treatment with diazomethane. For $C_{14}H_{17}NO_5$ (279·3) calculated: 60·21% C, 6·14% H, 5·02% N; found: 60·26% C, 6·14% H, 5·33% N.

N,N-Dimethyl-3-methyl-5-(4-nitrophenoxy)-3-pentenecarboxamide (*XLVII*)

A solution of the acid *XLV* (265 mg) in dimethylformamide (4 ml) was treated with a 2M solution of N,N-dimethylchloromethyleneammonium chloride[13] (1 ml) under stirring and cooling. The mixture was stirred at 0°C for 1 h and then a 4M dimethylamine solution in benzene (4 ml) was added and the stirring was continued for 2 h. The mixture was diluted with water, the product taken into ether, the organic layer was washed, dried over magnesium sulphate and the solvent evaporated. The dimethylamide *XLVII* was obtained by chromatography on silica gel (25 g); elution with ether yielded 230 mg (79%), m.p. 68—70°C (ligroin). For $C_{15}H_{20}N_2O_4$ (292·3) calculated: 61·63% C, 6·90% H, 9·58% N; found: 61·92% C, 7·13% H, 9·36% N.

The same procedure, *i.e.* the reaction with diethylamine, was used for the preparation of the oily diethylamide *XLVIII*. For $C_{17}H_{24}N_2O_4$ (320·4) calculated: 63·73% C, 7·55% H, 8·74% N; found: 64·09% C, 7·84% H, 8·60% N.

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