PREPARATION OF SOME ACYCLIC JUVENOIDAL ANALOGUES*

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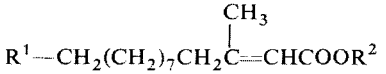
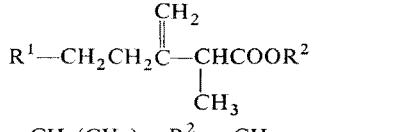
Several esters of branched (1–4 methyl substituents on the chain) unsaturated (1–4 double bonds) aliphatic acids of various chain length have been prepared.

In investigations on the relationship between the biological activity of the insect juvenile hormone analogues and chemical structure, attention has been paid to the influence of chain-length, number of double bonds, position and number of methyl substituents. A contribution in this respect is reported in the present paper.

In the preparation of compounds *I*–*V*, aliphatic acids possessing a suitable number of carbon atoms were converted by the action of thionyl chloride to the corresponding acyl halides which were subjected to the reaction with diethyl ethoxymagnesiummalonate and the subsequent acidolysis with the formation of the appropriate methyl ketones[1]. With the use of the modified Wittig reaction[2] and dimethyl methoxycarbonylmethanephosphonate or diethyl ethoxycarbonylmethanephosphonate as agents, 2-tridecanone was converted into methyl 3-methyl-2-tetradecenoate[3] and the corresponding ethyl ester *I*. Methyl 3-methyl-2,13-tetradecadienoate (*II*) was prepared analogously from 12-tridecen-2-one. Methyl 3-methyl-2-tridece-



I, $R^1 = R^2 = C_2H_5$
II, $R^1 = CH{=}CH_2$, $R^2 = CH_3$
III, $R^1 = R^2 = CH_3$
V, $R^1 = H$, $R^2 = C_2H_5$



IV, $R^1 = CH_3(CH_2)_7$, $R^2 = CH_3$
X, $R^1 = (CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH$, $R^2 = CH_3$
XI, $R^1 = (CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$, $R^2 = C_2H_5$
XV, $R^1 = (CH_3)_2CH(CH_2)_3CH(CH_3)CH_2$, $R^2 = CH_3$

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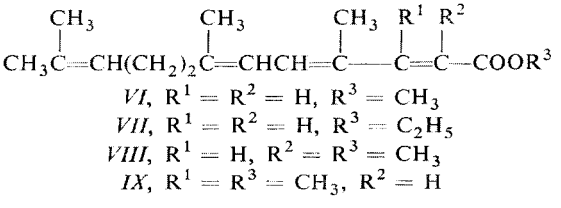
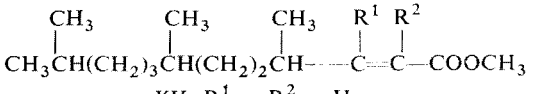
noate (*III*) and methyl 3-decyl-2-methyl-3-butenoate (*IV*) were obtained from 2-dodecanone as follows. Reaction with dimethyl methoxycarbonylmethanephosphonate yielded the ester *III*; the Reformatsky reaction with methyl 2-bromopropionate and the subsequent dehydration of the resulting hydroxy compound by the action of phosphorus oxychloride in pyridine afforded the ester *IV*. Ethyl 3-methyl-2-dodecenoate (*V*) was prepared from 2-undecanone by the Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane[4].

Compounds *VI*–*IX* and *XIV* were prepared from 2,5,9-trimethyl-2,4,8-decatrienal[5] as follows. Reaction with methoxy- and ethoxycarbonylmethylenetriphenylphosphorane afforded the corresponding methyl (*VI*) and ethyl (*VII*) ester of 4,7,11-trimethyl-2,4,6,10-dodecatetraenoic acid. Reaction with methoxycarbonylethylidenetriphenylphosphorane[6] yielded methyl 2,4,7,11-tetramethyl-2,4,6,10-dodecatetraenoate (*VIII*). When treated with methylmagnesium bromide, the above trienal afforded a secondary alcohol which was oxidised with manganese dioxide[7] to 3,6,10-trimethyl-3,5,9-undecatrien-2-one. This ketone was hydrogenated over palladium on active charcoal as catalyst to the corresponding hexahydro derivative; the reaction of methoxycarbonylmethylenetriphenylphosphorane with the original and hydrogenated ketone afforded methyl 3,4,7,11-tetramethyl-2,4,6,10-dodecatetraenoate (*IX*) and methyl 3,4,7,11-tetramethyl-2-dodecenoate (*XIV*), resp., in a low yield. The esters *IX* and *XIV* were also prepared from the appropriate ketones by the Reformatsky reaction with methyl bromoacetate and dehydration of the resulting hydroxy compounds by the action of phosphorus oxychloride in pyridine, but were accompanied (as shown by infrared spectra) by isomers, the double bond of which is not conjugated.



VI, $R^1 = R^2 = H$, $R^3 = CH_3$
VII, $R^1 = R^2 = H$, $R^3 = C_2H_5$
VIII, $R^1 = H$, $R^2 = R^3 = CH_3$
IX, $R^1 = R^3 = CH_3$, $R^2 = H$



XII, $R^1 = R^2 = H$
XIII, $R^1 = H$, $R^2 = CH_3$
XIV, $R^1 = CH_3$, $R^2 = H$

Compounds *X*, *XI*, and *XV* were prepared from the corresponding methyl ketone by the Reformatsky reaction with methyl or ethyl 2-bromopropionate, followed by dehydration of the resulting hydroxy compounds by the action of phosphorus oxychloride in pyridine. Thus, 6,10-dimethyl-5,9-undecadien-2-one afforded methyl

2,7,11-trimethyl-3-methylene-6,10-dodecadienoate (*X*), 6,10-dimethyl-9-undecen-2-one yielded ethyl 2,7,11-trimethyl-3-methylene-10-dodecenoate (*XI*), and 6,10-dimethyl--2-undecanone furnished methyl 3-(4,8-dimethylnonyl)-2-methyl-3-butenoate (*XV*). The Wittig reaction of 2,5,9-trimethyldecanal with methoxycarbonylmethylenetriphenylphosphorane or methoxycarbonylethylidenetriphenylphosphorane was used in preparation of methyl 4,7,11-trimethyl-2-dodecenoate (*XII*) and methyl 2,4,7,11-tetramethyl-2-dodecenoate (*XIII*), resp. The starting 2,5,9-trimethyldecanal was prepared by hydrogenation of 2,5,9-trimethyl-2,4,8-decatrienal diethyl acetal over Pd on active charcoal as catalyst and the subsequent liberation of the free aldehyde. Methyl 5,9-dimethyl-2,4,8-decatrienoate (*XVI*) was prepared from citral and methoxycarbonylmethylenetriphenylphosphorane. From 6,10,14-trimethyl-5,9,13-pentadecatrien-2-one and ethoxycarbonylmethylenetriphenylphosphorane, the ethyl 3,7,11,15--tetramethyl-2,6,10,14-hexadecatetraenoate (*XVII*) was obtained. The preparation of esters *XVI* and *XVII* has been performed earlier[8-10].

Compounds *IV*, *X*, *XI* and *XV* obtained by the Reformatsky reaction of ketones with alkyl 2-bromopropionates and the subsequent dehydration of the resulting hydroxy compounds, were not homogeneous. As shown by infrared spectra, the main reaction product is represented by esters, the carbonyl group of which is not conjugated with the double bond; the presence of a methylene[11] double bond was established. The esters of α,β-unsaturated acids constitute the minor reaction product (10–20%). The structure of compound *XI* was established by ^{1}H-NMR spectral measurements.

EXPERIMENTAL

The IR spectra were taken in tetrachloromethane. The ^{1}H-NMR spectrum was measured in deuteriochloroform (tetramethylsilane as internal standard). The chemical shifts are expressed in δ (p.p.m.), the coupling constants are given in Hz. Column chromatographies were performed on silica gel partially deactivated with 12% water. Gas chromatography was carried out on a Pye Argon Chromatograph with a radioactive ionisation detection.

3,6,10-Trimethyl-3,5,9-undecatrien-2-ol

Bromomethane was introduced into a mixture of magnesium shavings (1·22 g), 1,2-dibromoethane (0·1 g), and ether (50 ml). When the reaction was over, a solution of 2,5,9-trimethyl--2,4,8-decatrienal (9·6 g) in ether (50 ml) was added dropwise, the whole mixture refluxed for 1 h, cooled down, decomposed with aqueous ammonium chloride, and processed as usual to afford 9·5 g of the title trienol, which was redistilled at 100–110°C/0·05 Torr (bath temperature).

3,6,10-Trimethyl-3,5,9-undecatrien-2-one

A mixture of 3,6,10-trimethyl-3,5,9-undecatrien-2-ol (6·0 g), powdered active manganese dioxide[7] (50 g), and light petroleum (b.p. 40–45°C; 150 ml) was stirred at 20–25°C for 10 h. The reaction

course was checked by thin-layer chromatography. When the reaction was over, the solid portion was filtered off and washed with light petroleum. The filtrate and washings were evaporated and the residue distilled at 100—110°C/0·05 Torr (bath temperature) to afford 4 g of the title ketone.

3,6,10-Trimethyl-2-undecanone

3,6,10-Trimethyl-3,5,9-undecatrien-2-one (2·0 g) was hydrogenated over 5% palladium on active charcoal catalyst (0·2 g) in ethanol (20 ml). Usual work-up yielded 1·8 g of the title ketone distilling at 100—105°C/0·05 Torr (bath temperature).

Preparation of Esters *I*, *II* and *III*

A solution prepared from sodium (0·12 g) and methanol or ethanol (2 ml each) was added dropwise in an inert atmopshere at 20—30°C to a solution of dimethyl methoxycarbonylmethanephosphonate (1·0 g) or diethyl ethoxycarbonylmethanephosphonate (1·23 g) in dimethylformamide (15 ml). The mixture was stirred at room temperature for 1 h and then the appropriate ketone (5 mmol) was added. The whole mixture was heated at 70—80°C for 4—6 h, decomposed with water, and extracted with light petroleum. The extract was processed as usual to afford the crude ester which was purified by chromatography on 30 parts (by weight) of silica gel with the use of 95 : 5 light petroleum–ether as eluant. Yields, about 75%. This procedure was used to prepare ethyl 3-methyl-2-tetradecenoate (*I*), methyl 3-methyl-2,13-tetradecadienoate (*II*), and methyl 3-methyl-2-tridecenoate (*III*).

Preparation of Esters *V*, *IX*, *XIV*, and *XVII*

A mixture of the appropriate ketone (4 mmol), ethoxycarbonylmethylenetriphenylphosphorane (2·3 g) or methoxycarbonylmethylenetriphenylphosphorane (2·2 g), benzoic acid (0·2 g), and dry benzene (20—30 ml) was refluxed under nitrogen for 20 h. Another portion of ethoxy- or methoxycarbonylmethylenetriphenylphosphorane (1·1 g each) and benzoic acid (0·1 g) was then added and the reflux continued for 20 h. The reaction course was checked by thin-layer chromatography. When the starting ketone disappeared or when the composition of the reaction mixture was constant, the benzene was evaporated and the viscous residue repeatedly triturated with light petroleum. The extracts were processed as usual and the crude residues chromatographed on 30 parts (by weight) of silica gel with the use of 95 : 5 light petroleum–ether as eluant. Yields, 25—60%. This procedure was used to prepare ethyl 3-methyl-2-dodecenoate (*V*), methyl 3,4,7,11-tetramethyl-2,4,6,10-dodecatetraenoate (*IX*), methyl 3,4,7,11-tetramethyl-2-dodecenoate (*XIV*), and ethyl 3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoate (*XVII*).

Preparation of Esters *VI*, *VII*, *VIII*, *XII*, *XIII*, and *XVI*

A mixture of the appropriate aldehyde (4 mmol), methoxy- or ethoxycarbonylmethylenetriphenylphosphorane (2·2 g and 2·3 g, resp.), benzoic acid (0·2 g), and benzene (20—30 ml) was refluxed under nitrogen for 8 h and then processed analogously to the preceding paragraph. The resulting crude esters *XII*, *XIII*, and *XVI* were purified by chromatography on silica gel (30 parts by weight) with the use of 95 : 5 light petroleum–ether as eluant. The crude esters *VI*, *VII*, and *VIII* were subjected to fractional distillation. Yields, 50—80%. This procedure was used to prepare methyl (*VI*) and ethyl (*VII*) 4,7,11-trimethyl-2,4,6,10-dodecatetraenoate, methyl 2,4,7,11-tetramethyl-2,4,6,10-dodecatetraenoate (*VIII*), methyl 4,7,11-trimethyl-2-dodecenoate (*XII*), methyl 2,4,7,11-tetramethyl-2-dodecenoate (*XIII*), and methyl 5,9-dimethyl-2,4,8-decatrienoate (*XVI*).

TABLE I

Elemental Analyses and Boiling Points of Esters *I*–*XVII*

Ester	Formula (m.w.)	Calculated/Found % C	% H	B.p.[a] °C/Torr
I	$C_{17}H_{32}O_2$ (268·4)	76·06 76·00	12·02 11·93	125–135 0·01
II	$C_{16}H_{28}O_2$ (252·4)	76·14 76·28	11·18 11·36	120–130 0·01
III	$C_{15}H_{28}O_2$ (240·4)	74·95 74·87	11·74 11·80	110–115 0·01
IV	$C_{16}H_{30}O_2$ (254·4)	75·53 75·88	11·89 11·97	110–120 0·01
V	$C_{15}H_{28}O_2$ (240·4)	74·95 75·05	11·74 11·78	105–115 0·01
VI	$C_{16}H_{24}O_2$ (248·4)	77·37 77·25	9·74 9·77	115–125 0·01
VII	$C_{17}H_{26}O_2$ (262·4)	77·81 77·55	9·99 9·87	115–125 0·01
VIII	$C_{17}H_{26}O_2$ (262·4)	77·81 77·56	9·99 9·93	120–130 0·01
IX	$C_{17}H_{26}O_2$ (262·4)	77·81 78·14	9·99 9·97	125–135 0·01
X	$C_{17}H_{28}O_2$ (264·4)	77·22 77·52	10·67 10·67	117–125 0·01
XI	$C_{18}H_{32}O_2$ (280·4)	77·09 76·86	11·50 11·39	98–110 0·008
XII	$C_{16}H_{30}O_2$ (254·4)	75·53 75·26	11·89 11·76	105–110 0·01
XIII	$C_{17}H_{32}O_2$ (268·4)	76·06 76·30	12·02 12·00	110–115 0·01
XIV	$C_{17}H_{32}O_2$ (268·4)	76·06 76·32	12·02 11·90	115–120 0·01
XV	$C_{17}H_{32}O_2$ (268·4)	76·06 76·09	12·02 11·93	115–120 0·01
XVI	$C_{13}H_{20}O_2$ (208·3)	74·95 75·30	9·68 9·47	95–105 0·01
XVII	$C_{22}H_{36}O_2$ (332·5)	79·46 79·73	10·91 11·07	140–150 0·01

[a] Bath temperature was measured.

Preparation of Esters *IV*, *IX*, *X*, *XI*, *XIV*, and *XV*

To a suspension of activated zinc (0·65 g) in benzene (20 ml) there was added a portion (with heating, to induce the reaction) and then the remainder of a mixture of the appropriate ketone and the corresponding alkyl bromoalkanoate (0·01 mol each). The mixture was refluxed for 2—3 h and processed as usual to afford the crude hydroxy compound which was added dropwise into a mixture of phosphorus oxychloride (1·6 ml), pyridine (12 ml), and benzene (20 ml). The whole mixture was heated at 70—80°C for 2 h, poured into iced water, extracted with ether, and the extract worked up. The crude product was purified by chromatography on silica gel (30 to 60 parts by weight) with the use of 95 : 5 light petroleum–ether as eluant; a partial separation of the conjugated and nonconjugated ester was observed. Yields, 35—50%. This procedure was used to prepare methyl 3-decyl-2-methyl-3-butenoate (*IV*), methyl 3,4,7,11-tetramethyl-2,4,6,10-dodecatetraenoate (*IX*), methyl 2,7,11-trimethyl-3-methylene-6,10-dodecadienoate (*X*), ethyl 2,7,11-trimethyl-3-methylene-10-dodecenoate (*XI*), methyl 3,4,7,11-tetramethyl-2-dodecenoate (*XIV*), and methyl 3-(4,8-dimethylnonyl)-2-methyl-3-butenoate (*XV*). Compounds *IV*, *X*, *XI*, and *XV* contained as admixture the following isomeric esters: methyl 2,3-dimethyl-2-tridecenoate (*IVa*), methyl 2,3,7,11-tetramethyl-2,6,10-dodecatrienoate (*Xa*), ethyl 2,3,7,11-tetramethyl-2,10-dodecadienoate (*XIa*), and methyl 2,3,7,11-tetramethyl-2-dodecenoate (*XVa*).

Characterisation

Compounds shown in Table I were characterised by elemental analysis, IR spectra, and ^{1}H-NMR spectra. The purity of specimens was checked by thin-layer chromatography and gas chromatography (Cellite impregnated with 10% Apiezon L; 160—210°C).

The IR spectra of compounds *I*, *V*, *VI*, *VIII*, *XII*, and *XVII* contained absorption bands due to the ester group in conjugation with double bond (at about 1710—1720, 1650, and 1160 cm^{-1}). The IR spectra of compounds *IX* and *XIV* (prepared by the Reformatsky reaction and dehydration of the resulting hydroxy compounds) exhibited absorption bands due to an ester of the α,β-unsaturated acid (1720, 1650, and 1160 cm^{-1}) along with an absorption band attributable to a nonconjugated ester group (at about 1740 cm^{-1}). In the nonhomogeneous IR spectra of compounds *IV*, *X*, *XI*, and *XV*, there were observed absorption bands of an ester group which was not conjugated with the double bond (at about 1740, 1200, and 1170 cm^{-1}) and absorption bands belonging to the methylene double bond (at about 900, 3070, and 3015 cm^{-1}). The absorption bands at 1720 and 1640—1650 cm^{-1} corresponded to the minor component of the mixture, *i.e.*, to the ester of an α,β-unsaturated acid. The structure of ethyl 2,7,11-trimethyl-3-methylene-10-dodecenoate (*XI*) was confirmed by measurements of ^{1}H-NMR spectrum.

Biological Activity of Esters *I*—*XVII**

The insect juvenile hormone activity of esters *I*—*XVII* was expressed in ID-50 Morph units designating such an amount of the test substance in microgrammes per specimen which when topically applied to larvae of the last instar causes formation of half-imaginal species. A weak juvenile activity on *Pyrrhocoris apterus* (10—100 ID-50 Morph units) and *Dysdercus cingulatus* (5 to 1000) was observed with all esters *I*—*XVI* in the range given; the esters were almost inactive on *Graphosoma italicum* (100 to 1000) and *Tenebrio molitor* (500 to 1000). The ester *XVII* with an isoprenoid chain system was the most active.

* The biological activity of the present esters will be reported in detail elsewhere in collaboration with coworkers of the Institute of Entomology, Czechoslovak Academy of Sciences, Prague.

Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) by Mrs V. Rusová and Mr V. Štěrba. The IR spectra were measured by Mrs K. Matoušková and interpreted by Dr J. Smolíková. The ^{1}H-NMR *spectrum was measured and interpreted by Dr M. Masojídková. The insect juvenile hormone activity assays were performed by Dr K. Sláma, Institute of Entomology, Czechoslovak Academy of Sciences, Prague.*

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