

JUVENOIDS WITH A FIVE-MEMBERED CARBON CYCLE IN THE MOLECULE*

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In connection with the studies of the structure activity relationships within a group of substances with insect juvenile hormone activity, the preparation of homologous series of esters derived from 3,11-dimethyl-7,8-propano-2-dodecenoic acid as well as of the *cis* and *trans* isomers of its 6-oxa analogue is described.

In recent years great attention has been devoted to the chemistry and biology of substances imitating the effect of insect juvenile hormone¹⁻³ (JH). In connection with the investigation of the mechanism of action of these JH bioanalogues (juvenoids), the structure-activity relationships between the chemicals are also being studied in our laboratories in collaboration with the Entomological Institute of the Czechoslovak Academy of Sciences^{2,4,6}.

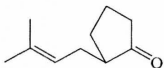
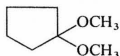
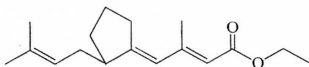
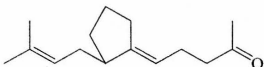
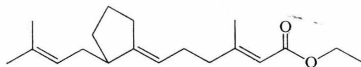
In substances derived from pharneoic acid it has been observed that the changes in the structure of α,β -unsaturated functional group and its closest proximity (especially such changes as lead to a certain fixation of this grouping) usually greatly affect their biological properties^{2,4,7}. The same is true of the changes in the structure of the "terminal" part of the molecule of juvenoids⁶. In contrast to this relatively little is known about what effect similar changes in the central part of the aliphatic molecule of juvenoids have on the juvenilizing activity.

Studying this problem we have prepared a series of unsaturated esters with a five-membered ring in the central part of the molecule. Similar juvenoids have been prepared recently in two other laboratories^{7,8}. The key intermediate for the preparation of our substances was the still undescribed 2-(3-methyl-2-butenyl)cyclopentan-1-one (*I*) prepared by Claisen reaction⁹ from cyclopentanone dimethyl ketal (*II*) and 2-methyl-3-buten-2-ol (*III*), by heating at 150°C in a pressure vessel, in the presence of a small amount of phosphoric acid. The structure of ketone *I* was confirmed by elemental analysis and mass and infrared spectra.

The reactions of this ketone with triethylphosphoseneoate¹⁰ (*IV*) in the pre-

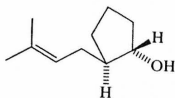
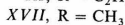
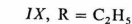
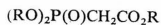
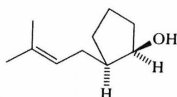
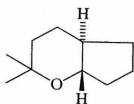
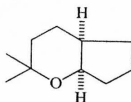
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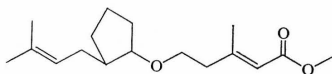
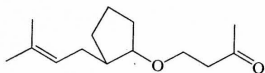
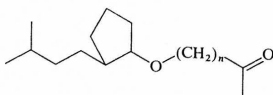
sence of sodium hydride in 1,2-dimethoxyethane afforded ethyl 3,9-dimethyl-5,6-propano-2,4,8-decatrienoate (*V*). Reaction of vinylmagnesium bromide with ketone *I* gave 7-methyl-3,4-propano-1,6-octadien-3-ol (*VI*) from which 10-methyl-6,7-propano-5,9-undecadien-2-one (*VII*) was obtained by Carrol reaction with diethyl acetylmalonate¹¹. Ethyl 3,11-dimethyl-7,8-propano-2,6,10-dodecatrienoate (*VIII*) was prepared from *VII* by Wadsworth–Emmons reaction¹² with triethyl phosphonoacetate (*IX*).

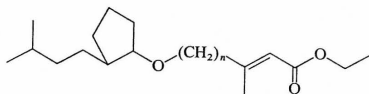
*I**II**III**IV**V**VI**VII**VIII*

On reduction of ketone *I* with lithium aluminium hydride two new diastereoisomeric alcohols, *X* and *XI*, were obtained which were easily separated by column chromatography on neutral alumina. On cyclisation with boron trifluoride etherate both racemic alcohols *X* and *XI* gave corresponding bicyclic ethers *XII* and *XIII*. Comparison of the ¹H-NMR data of these ethers enabled the determination of the relative configurations of both starting alcohols. The differences in the width of the multiplets that approximately correspond to the sums of three vicinal interactions of the —CH—O protons in the molecule ($W \approx 30$ Hz, or 10 Hz, respectively), as well as the differences in the chemical shifts of these protons ($\delta = 3.36$, or 4.20 respectively), show unambiguously that the methine proton —CH—O is bound in the first case (*XII*) axially, and in the second (*XIII*) equatorially. From these data it can be deduced that the alcohol with the lower R_F value (in TLC) and a longer

retention time (in GLC), corresponding to ether *XII*, is *trans*-2-(3-methyl-2-butenyl)-cyclopentan-1-ol (*X*), while the alcohol *XI* with the higher R_F value and shorter retention time, corresponding to ether *XIII*, is *cis*-isomer of *X*.


X

XI

XII

XIII

XIV, XX

XVIII

XV

XVI, XXI ($n = 2$)

XXIII, XXV ($n = 1$)

XIX, XXII ($n = 2$)

XXIV, XXVI ($n = 1$)

The alcohol *X* and its dihydro derivative *XIV* (obtained from the former by hydrogenation on palladium catalyst in methanol) afforded on reaction with 3-buten-2-one

and catalysis with a mixture of boron trifluoride etherate and mercuric oxide¹³ 6,7-*trans*-10-methyl-6,7-propano-5-oxa-9-undecen-2-one (XV) or its 9,10-dihydro derivative XVI, respectively. Reaction of ketone XV with trimethyl phosphonoacetate XVII gave methyl 7,8-*trans*-3,11-dimethyl-7,8-propano-6-oxa-2,10-dodecadienoate (XVIII), while from ketone XVI ethyl 7,8-*trans*-3,11-dimethyl-7,8-propano-6-oxa-2-dodecenoate (XIX) was prepared on reaction with triethyl phosphonoacetate (IX). A similar reaction sequence was also carried out with alcohol XI that is a *cis* isomer of alcohol X. Dihydro derivative XX obtained on hydrogenation of alcohol XI gave with methyl vinyl ketone 6,7-*cis*-10-methyl-6,7-propano-5-oxaundecan-2-one (XXI). The latter was reacted with phosphonoacetate IX to give ethyl 7,8-*cis*-3,11-dimethyl-7,8-propano-6-oxa-2-dodecenoate (XXII). The 7,8-*cis*-isomer of the unsaturated ester XVIII could not be prepared by this route, because under these conditions the formation of cyclic ether XIII and other unidentified substances mostly took place.

Shorter homologues of esters XIX and XXII were also prepared. Thus, on reaction with diazoacetone, alcohol XIV in the presence of BF₃ etherate gave 5,6-*trans*-9-methyl-5,6-propano-4-oxa-2-decanone (XXIII) which on reaction with triethyl phosphonoacetate afforded ethyl 6,7-*trans*-3,10-dimethyl-6,7-propano-5-oxa-2-undecenoate (XXIV). In the same manner 5,6-*cis* isomer of ketone XXIII, ketone XXV, and 6,7-*cis* isomer of ester XXIV, ester XXVI, were prepared from alcohol XX.

EXPERIMENTAL

Column chromatography was carried out on silica gel (Gebr. Herrmann, Köln-Ehrenfeld, GFR) or neutral alumina (Woelm, act. III according to Brockmann). The purity of the substances was checked both by analytical thin-layer chromatography on silica gel G (Merck) or by gas chromatography on a Perkin-Elmer F-11 instrument, with FID. The IR spectra were measured in tetrachloromethane on a UR-20 (Carl Zeiss, Jena) instrument. The ¹H-NMR spectra were measured on a Varian HA-100 apparatus, in deuteriochloroform, using tetramethylsilane as internal reference. The mass spectra were measured on a AEI MS-902 spectrometer.

2-(3-Methyl-2-butenyl)cyclopentan-1-one (I)

A mixture of 2-methyl-3-buten-2-ol (11.50 g), dimethyl ketal of cyclopentanone¹⁴ (27.10 g), and phosphoric acid (85%, 50 mg) was heated in a sealed tube at 150°C for 16 h. After working up it was distilled through a column with a glass helix (the length of the effective part was 20 cm), affording 7.70 g of ketone I, b.p. 118–120°C/45 Torr and n_D^{21} 1.4785. IR spectrum: 1378, 1408, 1673, 1740, 3040 cm⁻¹. Mass spectrum: M⁺ 152, 97, 84 (base peak). For C₁₀H₁₆O (152.2) calculated: 78.89% C, 10.59% H; found 78.76% C, 10.60% H.

Ethyl 3,9-Dimethyl-5,6-propano-2,4,8-decatrienoate (V)

A solution of triethyl phosphonosencioate (1.01 g) in tetrahydrofuran (1 ml) and then of ketone I (600 mg) in tetrahydrofuran (1 ml) was added dropwise under nitrogen and stirring to a suspension of sodium hydride (a 50% suspension in paraffin oil; 190 mg) in tetrahydrofuran (10 ml)

kept at -5 to -10°C . The mixture was stirred for 4 h at 20°C , diluted with a five-fold amount of brine and extracted with ether (3×20 ml). After working up the product was chromatographed on a column of alumina. By elution with hexane-10% ether mixture ester *V* (550 mg) was obtained, b.p. $112-115^{\circ}\text{C}/0.5$ Torr, n_{D}^{23} 1.5113, IR spectrum: 1155, 1602, 1710 cm^{-1} . For $\text{C}_{17}\text{H}_{26}\text{O}_2$ (262.4) calculated: 77.82% C, 9.99% H; found: 78.03% C, 10.29% H.

10-Methyl-6,7-propano-5,9-undecadien-2-one (*VII*)

Using the procedure described earlier¹⁵ 0.59 g of ketone *VII*, b.p. $85-88^{\circ}\text{C}/0.5$ Torr, (IR spectrum: 1360, 1410, 1673, 1720 cm^{-1} ; mass spectrum: $\text{M}^+ = 220, 177, 162, 151, 133$ (base peak)) was prepared from 1.00 g of 7-methyl-3,4-propano-1,6-octadien-3-ol (*VI*; prepared from 1.60 g of ketone *I* according to Normant¹⁶) and diethyl acetylmalonate¹⁷ (1.80 g).

Preparation of Esters *VIII*, *XVIII*, *XIX*, *XXII*, *XXIV*, *XXVI*

A solution of 8.4 mmol of sodium in 5 ml of ethanol¹⁸ was added dropwise at a temperature not exceeding 40°C into a solution of 8 mmol of corresponding ketone (*VII*, *XV*, *XVI*, *XXI*, *XXIII*, *XXV*, respectively) and phosphonoacetate *IX* or *XVII*, (8.4 mmol) respectively, in ethanol (10 ml). The mixture was allowed to stand at 20°C and the reaction course was followed by thin-layer chromatography. The reaction was over, as a rule, after 4-6 h. The mixture was concentrated

TABLE I

Properties of Compounds *VIII*, *XVIII*, *XIX*, *XXII*, *XXIV*, *XXVI* (mixtures of geometrical isomers on the double bonds conjugated with the ester group)

Products ^a B.p., $^{\circ}\text{C}$	Reaction components	IR Spectrum cm^{-1}	Formula (mol. w.)	Calculated/Found	
				% C	% H
<i>VIII</i> 114-115	<i>VII</i> , <i>IX</i>	1 649, 1 719	$\text{C}_{19}\text{H}_{30}\text{O}_2$ (290.4)	78.57 78.65	10.41 10.35
<i>XVIII</i> 126-130	<i>XV</i> , <i>XVII</i>	1 099, 1 110 1 154, 1 226, 1 437 1 654, 1 724	$\text{C}_{17}\text{H}_{28}\text{O}_3$ (280.4)	(280 <i>m/e</i>) ^b	
<i>XIX</i> 131-132	<i>XVI</i> , <i>IX</i>	1 090, 1 098, 1 115 1 149, 1 370, 1 653 1 718	$\text{C}_{18}\text{H}_{32}\text{O}_3$ (296.4)	72.92 72.81	10.88 11.22
<i>XXII</i> 131-134	<i>XXI</i> , <i>IX</i>	1 098, 1 150, 1 223 1 369, 1 653, 1 720	$\text{C}_{18}\text{H}_{32}\text{O}_3$ (296.4)	(296 <i>m/e</i>) ^b	
<i>XXIV</i> 123-126	<i>XXIII</i> , <i>IX</i>	1 150, 1 660, 1 716	$\text{C}_{17}\text{H}_{30}\text{O}_3$ (282.4)	(282 <i>m/e</i>) ^b	
<i>XXVI</i> 125-126	<i>XXV</i> , <i>IX</i>	1 099, 1 150, 1 170 1 225, 1 662, 1 720	$\text{C}_{17}\text{H}_{30}\text{O}_3$ (282.4)	(282 <i>m/e</i>) ^b	

^a At 0.3 Torr; ^b mass spectrum M^+ .

under reduced pressure and the residue extracted with pentane. The combined pentane fractions were worked up and chromatographed on a 100-fold amount of alumina with light petroleum–5% ether, and the product was vacuum distilled. The esters obtained in this manner represented mixtures of 2*E* : 2*Z* isomers in an approximately 1–1.5 : 1 ratio. The constants of individual esters are listed in Table I.

cis and *trans*-2-(3-Methyl-2-butenyl)cyclopentan-1-ol (*XI*, *X*, respectively)

A solution of ketone *I* (1.52 g) in ether (15 ml) was added dropwise at 5°C to a suspension of lithium aluminum hydride (0.30 g) in ether (8 ml). The mixture was refluxed for 1 h, cooled to room temperature and worked up. Chromatography of the product (residue) on a 100-fold amount of alumina with light petroleum–20% ether mixture, and subsequent vacuum distillation, gave 0.40 g of alcohol *XI* in the fore-fractions; b.p. 145–150°C/100 Torr, n_D^{21} 1.4785, IR spectrum: 988, 1030, 1671, 3025, 3045, 3620 cm^{-1} . For $\text{C}_{10}\text{H}_{18}\text{O}$ (154.2) calculated: 77.86% C, 11.76% H; found: 77.93% C, 11.90% H.

From the later fractions 0.65 g of alcohol *X* was obtained, b.p. 147–151°C/100 Torr, n_D^{21} 1.4770, and IR spectrum: 1671, 3025, 3045, 3620 cm^{-1} . For $\text{C}_{10}\text{H}_{18}\text{O}$ (154.2) calculated: 77.86% C, 11.76% H; found: 77.93% C, 11.90% H.

trans-1-Oxa-2,3-dimethyl-[4.3.0]-bicyclononane (*XII*)

A solution of *trans*-isomer *X* (0.50 g) and BF_3 etherate (0.25 g) in 1,2-dimethoxyethane (10 ml) was allowed to stand in a closed flask under nitrogen at 20°C for 48 h. The reaction course was followed by means of thin-layer chromatography and gas chromatography. After 20 h 75% of the starting alcohol could be detected in the reaction mixture. The mixture was washed with an aqueous sodium hydrogen carbonate solution and worked up. The residue was chromatographed on a 100-fold amount of alumina affording 125 mg of ether *XII*, b.p. 135–138°C/160 Torr, n_D^{21} 1.4599. IR spectrum: 1098, 1114 cm^{-1} ; $^1\text{H-NMR}$ spectrum: 1.25 (s) $(\text{CH}_3)_2\text{C}$, 3.36 (m) W = 40 Hz $(-\text{O}-\underset{\text{|}}{\text{C}}-\text{H})$. For $\text{C}_{10}\text{H}_{18}\text{O}$ (154.2) calculated: 77.86% C, 11.76% H; found: 77.58% C, 11.62% H.

cis-1-Oxa-2,2-dimethyl-[4.3.0]-bicyclononane (*XIII*)

Using a procedure similar to that employed for compound *XII* a 20 hours' reaction of *XI* (0.50 g) and BF_3 etherate (0.25 g) in 1,2-dimethoxyethane (10 ml) gave ether *XIII* (0.25 g), b.p. 132 to 135°C/150 Torr, n_D^{21} 1.4562. IR spectrum: 1050, 1130 cm^{-1} ; $^1\text{H-NMR}$ spectrum: 1.18, 1.20 (s) $(\text{CH}_3)_2\text{C}$, 4.20 (m) W 1/2 = 8 Hz $(-\text{O}-\underset{\text{|}}{\text{C}}-\text{H})$. For $\text{C}_{10}\text{H}_{18}\text{O}$ (154.2) calculated: 77.86% C, 11.76% H; found: 78.00% C, 11.92% H.

trans-2-(3-Methylbutyl)cyclopentan-1-ol (*XIV*)

trans-Isomer *X* (2.00 g) was hydrogenated in methanol (15 ml) under atmospheric pressure and catalysis with 5% Pd/ CaCO_3 (0.30 g). Evaporation of the solvent under reduced pressure gave product *XIV* (1.60 g) b.p. 161–165°C/70 Torr, n_D^{21} 1.4538. For $\text{C}_{10}\text{H}_{20}\text{O}$ (156.3) calculated: 76.86% C, 12.90% H; found: 76.99% C, 12.92% H.

cis-2-(3-Methylbutyl)cyclopentan-1-ol (*XX*)

cis-Alcohol *XX* (0.45 g), b.p. 155–158°C/100 Torr, n_D^{21} 1.4537, was prepared from *XI* (0.51 g) in a manner analogous to that described above, using 5% Pd/CaCO₃ (80 mg) in methanol (5 ml). IR spectrum of the product: 990, 1020, 1367, 1385, 3620 cm⁻¹.

Compounds *XV*, *XVI*, *XXI*

A mixture of boron trifluoride etherate (40 mg) and mercuric oxide (13 mg) was heated at 70°C for 1/2–1 min under stirring. The brownish viscous liquid was mixed with 8.3 mmol of alcohol *X*, *XIV* or *XX*, respectively, and 5.4 mmol of 3-buten-2-one and allowed to stand at 25°C for 24 h. The mixture was poured into icy water, neutralized with solid potassium carbonate, and extracted with ether (30 ml). After working up the residue was chromatographed on a 100-fold amount of silica gel. Elution with light petroleum containing 30% of ether, and subsequent distillation in a vacuum gave corresponding ketones *XV*, *XVI*, *XXI* in about 50% yield. Their constants are given in Table II.

5,6-*trans*-9-Methyl-5,6-propano-4-oxa-2-decanone (*XXIII*)

A mixture of corresponding alcohol (*XIV*, 0.62 g), BF₃ etherate (10 mg) and diazoacetone (6.0 g) was allowed to stand at 0°C for 2 h and at 25°C for 30 min and then worked up as in the preceding case. Ketone *XXIII* was thus obtained in pure state (102 mg). Its constants are given in Table II. In the same manner its *cis* isomer, ketone *XXV*, was prepared from alcohol *XX*.

Biological Activity of the Prepared Substances

The juvenile hormone activity of substances *V*, *VIII*, *XVIII*, *XIX*, *XXII*, *XXIV* and *XXVI*, determined by Dr K. Sláma, Entomological Institute, Czechoslovak Academy of Sciences.

TABLE II

Properties of Compounds *XV*, *XVI*, *XXI*, *XXIII*

Product ^a B.p., °C	Starting material	IR Spectrum cm ⁻¹	Formula (mol. w.)	Calculated/Found	
				% C	% H
<i>XV</i> 145–150	<i>X</i>	1 108, 1 360 1 678, 1 720	C ₁₄ H ₂₄ O ₂ (224.3)	74.95 75.05	10.78 10.78
<i>XVI</i> 146–150	<i>XIV</i>	1 115, 1 361, 1 723	C ₁₄ H ₂₆ O ₂ (226.4)	74.28 74.33	11.58 11.69
<i>XXI</i> 149–151	<i>XX</i>	1 100, 1 360, 1 721	C ₁₄ H ₂₆ O ₂ (226.4)	74.28 74.55	11.58 11.48
<i>XXIII</i> 129–132	<i>XIV</i>	1 122, 1 367 1 385, 1 721	C ₁₃ H ₂₄ O ₂ (212.3)	73.53 73.22	11.39 11.32

^a 12 Torr.

ces, is expressed in ID-50 Morph. units² meaning the amount of the substance in micrograms, that — when applied topically on an individual — caused the formation of an adultoid in which one half of the characters of the preceding developmental stage remained unchanged. The above mentioned juvenoids were active in the bug *Dysdercus cingulatus* in the 100—0.1 units interval; they were less active in the bug *Graphosoma italicum* (activity interval 500—1) and the beetle *Tenebrio molitor* (activity interval 1000—10). The differences in the activities between the corresponding *cis* and *trans* isomers ranged from one half to one order of magnitude.

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