

## SYNTHESIS OF 8-OXA ANALOGUES OF ACYCLIC JUVENOIDAL SUBSTANCES\*

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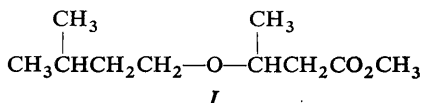
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Some esters and amides of substituted 8-oxa-2-dodecenoic acids have been prepared.

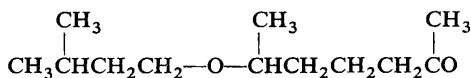
In connection with investigations on relations between the chemical structure and biological activity in the field of insect juvenile hormone analogues, we wish to report in the present paper preparation of esters, amides, and a nitrile of substituted 8-oxa-2-dodecenoic acids.\*\* The corresponding syntheses have been so far described in a patent application only<sup>1</sup>.

The required ethereal intermediates have been prepared by solvomercuration of the appropriate double-bond-containing compounds in the presence of alcohol and the subsequent demercuration with sodium borohydride<sup>2,3</sup>. In the preparation of 7-methyl-8-oxa-2-dodecenoic acid derivatives, methyl crotonate was used as the starting material. Thus, solvomercuration by the action of mercuric trifluoroacetate in the presence of 3-methylbutanol and demercuration afforded methyl 3,7-dimethyl-4-oxaoctanoate (*I*). The lithium aluminum hydride reduction of compound *I* yielded 3,7-dimethyl-4-oxaoctanol which was converted on treatment with triphenylphosphine dibromide<sup>4</sup> into 1-bromo-3,7-dimethyl-4-oxaoctane yielding 6,10-dimethyl-7-oxa-2-undecanone (*II*) by reaction with ethyl acetoacetate and ketonic hydrolysis. In the preparation of 7,7-dimethyl-8-oxa-2-dodecenoic acid derivative, 2-methyl-2-(4-methyl-3-pentenyl)-1,3-dioxolane (*III*) was converted to 6,6,10-trimethyl-7-oxa-2-undecanone (*IV*) by mercuration with mercuric acetate in the presence of 3-methylbutanol, demercuration, and deketalisation.

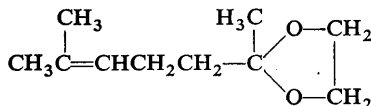


\* Part XXIV in the series Natural and Synthetic Materials with the Insect Hormone Activity; Part XXIII: This Journal 40, 1070 (1975).

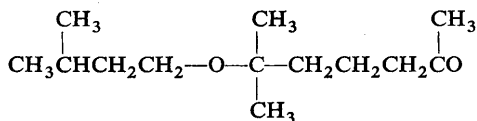
\*\* The biological activity of these substances will be reported elsewhere in collaboration with workers of the Entomological Institute, Czechoslovak Academy of Sciences, Prague.



II

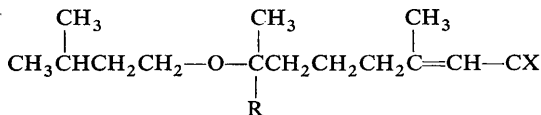


III



IV

The required esters, amides and the nitrile were finally prepared from ketones II and IV by reaction with the corresponding phosphorane under catalysis of benzoic acid<sup>5</sup> or from the appropriate phosphonates in dimethylformamide<sup>6</sup>.

Va: R = H, X = -OOC<sub>2</sub>H<sub>5</sub>Vb: R = H, X = -OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>Vc: R = H, X = -ONHC<sub>2</sub>H<sub>5</sub>Vd: R = H, X = -ON(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>

Ve: R = H, X = ≡N

Vf: R = CH<sub>3</sub>, X = -OOC<sub>2</sub>H<sub>5</sub>

## EXPERIMENTAL

Column chromatography was performed on the Pitra<sup>7</sup> silica gel (produced by Service Laboratories of this Institute; particle size 60–120 μ unless stated otherwise) extracted before use with a mixture of 1 : 1 chloroform-methanol, activated at 120°C for 24 h, and deactivated partially by the addition of 12% water. Thin-layer chromatography was carried out on silica gel G (Merck). Purity of substances and ratio of isomers were determined by gas chromatography on a Pye Argon Chromatograph apparatus with ionisation detector (<sup>90</sup>Sr) on columns packed with 10% LAC-6R-860 on Chromosorb W or 10% Apiezon L on Celite. The mass spectra were taken on a A.E.I. MS 902 apparatus. The IR spectra were measured on a UR 10 apparatus (Carl Zeiss, Jena) in tetrachloromethane.

Methyl 3,7-Dimethyl-4-oxaocanoate (*I*)

Into a solution of mercuric trifluoroacetate (106.66 g; 0.25 mol) in 3-methylbutanol (250 ml) there was added dropwise under exclusion of atmospheric moisture and stirring methyl crotonate (25 g; 0.25 mol) over 20 min. The mixture was stirred at 17–18°C for 60 min and then treated dropwise with stirring over 10 min at the temperature below 10°C with a solution of potassium hydroxide (98 g; 1.75 mol) in methanol (650 ml). Solid sodium borohydride (4.74 g; 0.125 mol) was then added portionswise at 10°C over 20 min. The whole mixture was stirred at 2–3°C for 60 min, adjusted to pH 6.5 by the addition of acetic acid, and kept at room temperature overnight. The mercury was separated and the methanol removed by distillation under diminished pressure. The residue was diluted with water and extracted with ether. The extract was washed with water until neutral, dried over anhydrous magnesium sulfate, and the ether evaporated. Excess 3-methylbutanol was removed by distillation through a 20 cm column up to the boiling point of 43.2°C/11.5 Torr (bath temperature 70°C). The final residue (41.5 g) was saponified by keeping for 24 h in a mixture of potassium hydroxide (28 g; 0.5 mol), water (28 ml), and methanol (280 ml). The mixture was then diluted with water and distilled under diminished pressure to remove methanol along with a portion of 3-methylbutanol. The non-acidic components were removed by extraction with ether. The aqueous layer was acidified with dilute (1 : 2) sulfuric acid, the liberated organic acid extracted with ether, the extract washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residual crude acid (33.89 g) was dissolved in ether and esterified with diazomethane obtained from *N*-nitrosomethylurea (36 g) and 50% aqueous potassium hydroxide (110 ml) in ether (360 ml). Yield, 33.17 g (70%) of the methyl ester *I*, b.p. 90–90.5°C/12 Torr. For  $C_{10}H_{20}O_3$  (188.3) calculated: 63.79% C, 10.71% H; found: 63.88% C, 10.65% H. IR spectrum ( $cm^{-1}$ ): 1741, 1199, 1180, 1095.

## 3,7-Dimethyl-4-oxaocanol

Into a solution prepared by refluxing lithium aluminum hydride (6.53 g; 172.3 mmol) in ether (300 ml) for 1 h and cooling down, there was added dropwise at room temperature over 50 min the methyl ester *I* (32.43 g; 172.3 mmol) with stirring which was continued for 90 min. The mixture was then kept at room temperature for 48 h, refluxed for 60 min, cooled down, and decomposed<sup>8</sup> by the successive dropwise additions of water (6.53 ml), 15% aqueous sodium hydroxide (6.53 ml), and water (19.59 ml). The salts were filtered off and washed with ether. The filtrate and washings were combined, washed with water as usual, dried over magnesium sulfate, evaporated through Vigreux column, and the residue distilled to afford 24.02 g (87%) of 3,7-dimethyl-4-oxaocanol, b.p. 92–93°C/9 Torr. For  $C_9H_{20}O_2$  (160.3) calculated: 67.45% C, 12.58% H; found: 67.59% C, 12.31% H.

1-Bromo-3,7-dimethyl-4-oxaocane<sup>4</sup>

3,7-Dimethyl-4-oxaocanol (17.70 g; 110.4 mmol) and triphenylphosphine (31.85 g; 121.4 mmol) were dissolved in dry dimethylformamide (115 ml) and the solution treated dropwise under argon with dry bromine (19.41 g; 121.4 mmol) over 35 min (stirring) at the temperature below 50°C. The mixture was stirred at room temperature for 1 h and distilled under diminished pressure (up to the boiling point temperature of 95°C/11 Torr) the bath temperature being gradually increased. The distillate was poured into water and extracted with light petroleum. The extract was washed as usual, dried over anhydrous magnesium sulfate, and evaporated. Distillation of the residue yielded 19.96 g (81%) of 1-bromo-3,7-dimethyl-4-oxaocane, b.p. 83–84°C/10 Torr. For  $C_9H_{19}BrO$  (223.2) calculated: 48.44% C, 8.58% H, 35.81% Br; found: 48.65% C, 8.71% H, 35.86% Br.

6,10-Dimethyl-7-oxa-2-undecanone (*II*)

Ethyl acetoacetate (19.26 g; 0.148 mol) was added dropwise with stirring over 15 min into ethanolic sodium ethoxide (from 3.40 g *i.e.* 0.148 gramatom of sodium and 60 ml of ethanol). The mixture was stirred for additional 15 min at room temperature and treated with sodium iodide (0.85 g). 1-Bromo-3,7-dimethyl-4-oxa-octane (29.95 g; 0.132 mol) was then added dropwise over 45 min. The whole mixture was stirred at room temperature for 1 h and then at 90°C for 10 h; 10% aqueous sodium hydroxide (208 ml) was added at 90°C over 45 min, the whole mixture stirred at 90°C for 4 h, cooled down, poured into water, and extracted with ether. The extract was washed as usual, dried over anhydrous magnesium sulfate, and distilled to afford 21.49 g of the crude ketone *II*, b.p. 95–114°C/9 Torr, which was dissolved in ethanol (307 ml) and the solution refluxed with the Girard reagent T (27 g) and 98% acetic acid (24.8 g) for one hour<sup>9</sup>. The whole mixture was then cooled down and poured into ice-cold water (1228 ml) containing 19.31 g of anhydrous sodium carbonate. The non-ketonic components were removed by extraction with four portions of ether. The remaining aqueous phase was acidified with dilute (1 : 1) sulfuric acid (80 ml) and kept at room temperature for 1 h. The liberated ketone was extracted with ether, the extract washed, dried over anhydrous magnesium sulfate, and distilled through a Vigreux column to afford 13.59 g (50%) of compound *II*, b.p. 112.5–113.0°C/10 Torr. For C<sub>12</sub>H<sub>24</sub>O<sub>2</sub> (200.3) calculated: 71.95% C, 12.08% H; found: 71.83% C, 11.96% H. IR spectrum (cm<sup>-1</sup>): 1718, 1360, 1165, 1140, 1100, 1084. The extract of the reaction mixture prior to its acidification yielded 6.88 g of a mixture of the ketone *II* and non-ketonic components (b.p. 90–114°C/9 Torr.)

Ethyl 3,7,11-Trimethyl-8-oxa-2-dodecenoate (*Va*)

A mixture of the ketone *II* (3 g; 15 mmol), ethoxycarbonylmethylenetriphenylphosphorane<sup>10</sup> (8.71 g; 25 mmol), and benzene (45 ml) was refluxed under argon in the presence of benzoic acid<sup>5</sup> (1.48 g) for 31 h. Further portions of the phosphorane (3.48 g; 10 mmol), benzoic acid (0.35 g), and benzene (5 ml) were then added and the reflux continued for additional 24 h. The benzene was evaporated under diminished pressure and the residue repeatedly extracted with light petroleum. The extracts were washed, dried over anhydrous magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (188 g) in light petroleum–ether (9 : 1). Pure fractions were combined, evaporated, and the residue distilled from a Hickman flask packed with glass wool to afford 2.25 g (55%) of the ethyl ester *Va*, boiling at the bath temperature of 105–110°C and at 0.01–0.008 Torr, along with an additional less pure crop (0.96 g; 25%). For C<sub>16</sub>H<sub>30</sub>O<sub>3</sub> (270.4) calculated: 71.07% C, 11.18% H; found: 71.36% C, 11.19% H. IR spectrum (cm<sup>-1</sup>): 1715, 1649, 1250, 1100.

## Diethyl 2-Methoxyethoxycarbonylmethanephosphonate

A mixture of 2-methoxyethyl chloroacetate (18.18 g; 119 mmol) and triethyl phosphite (25.72 g; 154.8 mmol) was gradually heated up to 135–140°C. As soon as the reaction was over, the temperature was increased to 150°C and maintained for 5 h. Excess triethyl phosphite was evaporated at 10 Torr and the residue distilled to afford 25.30 g (83.5%) of the title phosphonate, b.p. 123.0–125.5°C/0.25 Torr.

2-Methoxyethyl 3,7,11-Trimethyl-8-oxa-2-dodecenoate (*Vb*)

Into a solution of diethyl 2-methoxyethoxycarbonylmethanephosphonate (2.80 g; 11 mmol) in dry dimethylformamide<sup>6</sup> (20 ml) there was added dropwise with stirring at room temperature

in argon atmosphere over 10 min the alkoxide prepared from sodium (0.252 g; 11 milligramatom) and 2-methoxyethanol (6 ml). The mixture was stirred at room temperature for 1 h and then treated dropwise with compound *II* (2.0 g; 10 mmol) in such a manner that the temperature did not exceed 30°C. The stirring was continued until the temperature dropped to room temperature and additional 7 h at 70–80°C. The mixture was cooled down, poured into water, and extracted with light petroleum. The extract was washed, dried over anhydrous magnesium sulfate, evaporated, and the residue chromatographed on silica gel (120 g) in light petroleum–ether (95 : 5). Initial fractions yielded 0.48 g of compound *Va*, formed by transesterification. The remaining fractions were pooled, evaporated, and the residue distilled from a Hickman flask packed with glass wool to afford 1.98 g (66%) of compound *Vb*, boiling at the bath temperature of 125–130°C and at 0.008 Torr. For  $C_{17}H_{32}O_4$  (300.4) calculated: 67.96% C, 10.74% H; found: 68.28% C, 10.74% H. IR spectrum ( $cm^{-1}$ ): 1735i, 1720, 1649, 1150, 1100.

#### N-Monoethylamide of 3,7,11-Trimethyl-8-oxa-2-dodecenoic Acid (*Vc*)

The title compound was prepared analogously to compound *Vb* from compound *II* (2.00 g; 10 mmol), diethyl monoethylaminocarbonylmethanephosphonate<sup>11</sup> (2.45 g; 11 mmol), and ethanolic sodium ethoxide prepared from sodium (0.25 g; 11 milligramatom) and ethanol (6 ml). Chromatography on silica gel (125 g) in light petroleum–acetone (92 : 8) yielded 1.87 g (69%) of compound *Vc*, boiling at the bath temperature from 135°C (0.004 Torr) to 145°C (0.003 Torr). For  $C_{16}H_{31}NO_2$  (269.4) calculated: 71.32% C, 11.60% H, 5.20% N; found: 71.45% C, 11.64% H, 5.90% N. Molecular weight (by high resolution mass spectrometry) calculated: 269.2355; found: 269.2355. IR spectrum ( $cm^{-1}$ ): 3450, 1655, 1640, 1535, 1502.

#### N,N-Diethylamide of 3,7,11-Trimethyl-8-oxa-2-dodecenoic Acid (*Vd*)

The title compound was prepared analogously to compound *Vc* from substance *II* (2.00 g; 10 mmol) and diethyl diethylaminocarbonylmethanephosphonate<sup>12</sup> (2.76 g; 11 mmol). Chromatography on silica gel (126 g; particle size, 30–60  $\mu$ ) in light petroleum–acetone (92.5 : 7.5) yielded 2.31 g (78%) of compound *Vd*, boiling at the bath temperature 142–147°C and at 0.007 Torr. For  $C_{18}H_{35}NO_2$  (297.5) calculated: 72.67% C, 11.86% H, 4.71% N; found: 72.44% C, 11.92% H, 4.83% N. IR spectrum ( $cm^{-1}$ ): 1648, 1630, 1099, 1038.

#### Nitrile of 3,7,11-Trimethyl-8-oxa-2-dodecenoic Acid (*Ve*)

The title compound was prepared analogously to compounds *Vb*, *c*, *d* from substance *II* (2.00 g; 10 mmol) and diethyl cyanomethanephosphonate (purchased from Aldrich; 1.95 g; 11 mmol). Chromatography of the crude product on silica gel (125 g) in light petroleum–ether (93 : 7) yielded 1.76 g (79%) of compound *Ve*, boiling at the bath temperature from 95°C (0.007 Torr) to 100°C (0.005 Torr). For  $C_{14}H_{25}NO$  (223.4) calculated: 75.28% C, 11.29% H, 6.27% N; found: 75.43% C, 11.38% H, 6.52% N. IR spectrum ( $cm^{-1}$ ): 2225, 1633, 1131, 1100, 1084.

#### 2-Methyl-2-(4-methyl-3-pentenyl)-1,3-dioxolane (*III*)

Usual dioxolanation of 6-methyl-5-hepten-2-one yielded 72% of compound *III*, b.p. (*cf.*<sup>13,14</sup>) 86–89°C/12 Torr. For  $C_{10}H_{18}O_2$  (170.2) calculated: 70.54% C, 10.66% H; found: 70.87% C, 10.82% H. IR spectrum ( $cm^{-1}$ ): 1675, 1220, 1205, 1140, 1061.

6,6,10-Trimethyl-7-oxa-2-undecanone (*IV*)

To a suspension of mercuric acetate<sup>2</sup> (15.94 g; 50 mmol) in 3-methylbutanol (50 ml) there was added compound *III* (8.51 g; 50 mmol) and the mixture vigorously stirred for 5 h. During this period of time, the mixture got yellow but did not become homogeneous. The mixture was then treated under cooling with ice-cold water with aqueous 3M-NaOH (50 ml) and 0.5M solution of sodium borohydride in 3M-NaOH (50 ml). The mixture was stirred for 2.5 h and then kept overnight. The mercury was separated and the supernatant extracted with ether. The extract was washed, dried over anhydrous potassium carbonate, and evaporated under ordinary pressure. Excess 3-methylbutanol was removed under diminished pressure (b.p. of the distillate up to 47°C at 12 Torr). The residue was refluxed in dry acetone (200 ml) in the presence of *p*-toluenesulfonic acid (60 mg) for 3 h, the acetone evaporated under diminished pressure, the residue dissolved in ether, the ethereal solution washed, dried over anhydrous magnesium sulfate, and distilled to afford 4.75 g of a liquid, boiling at the bath temperature 115–145°C and at 13 Torr, which was chromatographed on silica gel (700 g) in light petroleum–ether (92 : 8). The homogeneous fractions were combined, evaporated, and the residue distilled from a Hickman flask packed with glass wool to afford 3.43 g (32%) of compound *IV*, boiling at the bath temperature 125–130°C and at 12 Torr. For C<sub>13</sub>H<sub>26</sub>O<sub>2</sub> (214.3) calculated: 72.84% C, 12.23% H; found: 72.91% C, 12.10% H. IR spectrum (cm<sup>-1</sup>): 1719, 1365, 1083.

Ethyl 3,7,7,11-Tetramethyl-8-oxa-2-dodecenoate (*Vf*)

A mixture of compound *IV* (1.07 g; 5 mmol), ethoxycarbonylmethylenetriphenylphosphorane<sup>10</sup> (3.48 g; 10 mmol), benzoic acid<sup>5</sup> (300 mg), and benzene (20 ml) was refluxed under argon for 24 h. Another portion of the phosphorane (1.74 g; 5 mmol) and benzoic acid (150 mg) was then added and the reflux continued for 24 h more. The mixture was processed analogously to compound *Va*. Chromatography on silica gel (106 g) in light petroleum–ether (97 : 3) and distillation from a Hickman flask packed with glass wool yielded 0.82 g (58%) of compound *Vf*, boiling at the bath temperature 110–115°C and at 0.007 Torr. For C<sub>17</sub>H<sub>32</sub>O<sub>3</sub> (284.4) calculated: 71.78% C, 11.34% H; found: 72.12% C, 11.45% H. IR spectrum (cm<sup>-1</sup>): 1719, 1650, 1225, 1152, 1080. The remaining chromatographic fractions yielded the unreacted compound *IV*.

*Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) of this Institute by Mrs V. Rusová, Mrs A. Froňková, Mrs L. Pejchová, Mrs E. Šipová, and Mr V. Štěrba. The IR spectra were measured by Mrs K. Matoušková and Mr P. Formánek, and interpreted by Dr J. Smolíková. The mass spectrum was measured and interpreted by Dr K. Ubík. The technical assistance of Miss J. Jahelková and Mrs V. Kalvodová is gratefully acknowledged.*

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