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

SYNTHESIS OF METHYL 3,7,11,11-TETRAMETHYL-2-DODECENOATE AND SOME OF ITS HOMOLOGUES

M.Romañuk, L.Streinz and F.Šorm

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 6

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Using Kolbe anodic synthesis several esters of aliphatic α,β-unsaturated C_{14}—C_{17} acids with a terminal quaternary C-alkyl group have been prepared.

In recent years ever greater attention is being devoted to substances imitating the effect of the insect juvenile hormone in the insect organism. Some of these substances were isolated from natural sources, but a much larger number of them were prepared synthetically[1-3]. Both cecropia juvenile hormones *I*, *II* were isolated and identified[1,4-6] some time ago, and some of their analogues were prepared synthetically[1-3,7-10], similarly to juvabione[2,3,11] (*III*) and related aromatic derivatives with juvenilizing activity[12,13]. Substances similar to farnesylic acid[2,3,14-20] (*IV*) constitute another group of synthetic analogues.

In our laboratories the selectivity of action of different analogues in dependence on structural changes in their molecule has been investigated.** In connection with the interesting physiological results obtained with methyl 11-chloro-3,7,11-trimethyl-2-dodecenoate (*V*) (ref.[20]) we decided to synthetise its carbon analogues in which chlorine was substituted by a methyl group. This paper presents only chemical results. The relationship between the structure and activity has been discussed elsewhere[21]. As a key reaction we made use of Kolbe's anodic synthesis; this reaction was used for the preparation of some terpenic derivatives by Burrell and coworkers[22]. In principle the reaction represents the construction of the isoprenoid skeleton from several components; in each of them one of the tertiary alkyl substituted carbons is present (Scheme 1). For the synthesis of methyl 3,7,11,11-tetramethyl-2-dodecenoate (*VI*) we took 4,4-dimethylpentanoic acid (*VII*) (ref.[23]) as the starting material which we obtained from the aldehyde *VIII* (ref.[24]) by oxidation with silver oxide. Cross coupling of acid *VII* with monoester of β-methylglutaric acid (*IX*) (ref.[25])

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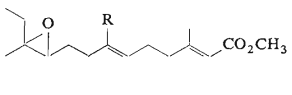
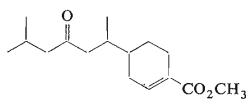
afforded 3,7,7-trimethyloctanoic acid (*X*). The third reaction component was *cis*, *trans*-4-methyl-5-methoxycarbonyl-4-pentanoic acid* (*XI*) (ref.[26]). Its anodic reaction with acid *X* gave ester *VI*.

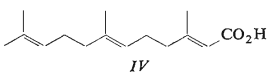
A number of homologues of ester *VI* can be prepared by this method. If instead of monoester *IX* its β-ethyl homologue (*XII*) (ref.[27]) is used for the electrolysis, 7,7-dimethyl-3-ethyloctanoic acid (*XIII*) is formed first, and from it by anodic reaction with acid *XI* methyl 3,11,11-trimethyl-7-ethyl-2-dodecenoate (*XIV*) is synthetised.



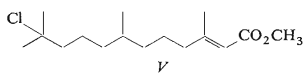
I, R = C_2H_5
II, R = CH_3



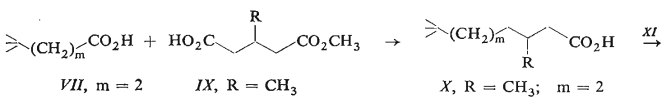
III



IV

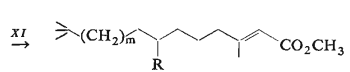


V



VII, m = 2 *IX*, R = CH_3
XV, m = 1 *XII*, R = C_2H_5

X, R = CH_3; m = 2
XIII, R = C_2H_5; m = 2
XVI, R = CH_3; m = 1
XVIII, R = C_2H_5; m = 1



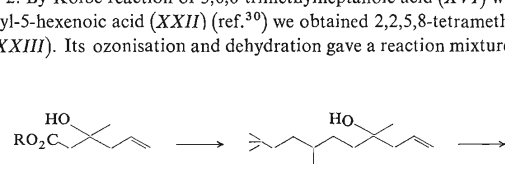
VI, R = CH_3; m = 2
XIV, R = C_2H_5; m = 2
XVII, R = CH_3; m = 1
XIX, R = C_2H_5; m = 1

SCHEME 1

* Burrell[22] states that the *cis* isomer prevails in the mixture. Our analysis of ester *VI* by gas–liquid chromatography shows that the approximate ratio of *cis* and *trans* isomers is 60 : 40. Similar results were also obtained with other homologues of ester *VI*.

The use of 3,3-dimethylbutanoic acid (*XV*) (ref.[28]) instead of homologue *VII* permitted us to prepare by the same reaction sequence shorter homologues of both esters *VI* and *XIV*. From acid *XV* and half-ester *IX* we thus obtained 3,6,6-trimethylheptanoic acid (*XVI*) which on Kolbe reaction with acid *XI* gave methyl 3,7,10,10-tetramethyl-2-undecenoate (*XVII*). In a similar manner 6,6-dimethyl-3-ethylheptanoic acid (*XVIII*), obtained from acid *XV* and monoester of β-ethylglutaric acid (*XII*), afforded in the presence of acid *XI* methyl 3,10,10-trimethyl-7-ethyl-2-undecenoate (*XIX*).

In connection with this work the preparation of methyl 3,6,9,9-tetramethyl-2-decenoate (*XX*) also became interesting, because it is, in actual fact, a bisnor derivative of ester *VI*. However, for its synthesis according to Scheme 1, the lower homolog of acid *XI*, *cis*, *trans*-3-methyl-4-methoxycarbonyl-3-butenoic acid (*XXI*) could not be used because the anodic synthesis with α,β- or β,γ-unsaturated acids does not take place in the expected manner[29]. Therefore we employed a procedure represented in Scheme 2. By Kolbe reaction of 3,6,6-trimethylheptanoic acid (*XVI*) with 3-hydroxy-3-methyl-5-hexenoic acid (*XXII*) (ref.[30]) we obtained 2,2,5,8-tetramethyl-10-undecen-8-ol (*XXIII*). Its ozonisation and dehydration gave a reaction mixture containing

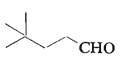


XXII, R = H
XXXI, R = t—C_4H_9

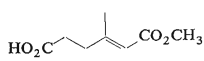
XXIII

XX, R = CH_3
XXIV, R = H

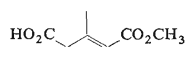
SCHEME 2



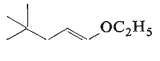
VIII



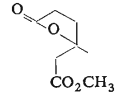
XI



XXI



XXV



XXIX

TABLE I
Anodic Synthesis

Product	Reaction components	B.p., °C/Torr	IR spectrum cm^{-1}	n_t^D (t, °C)	Formula (mol.w.)	Calculated/Found % C	Calculated/Found % H
3,7,7-Trimethyloctanoic acid[a] (*X*)	*VII* *IX*[c]	85—88 0·5	1 412, 1 710 2 400—3 400	1·4300 (23)	$C_{11}H_{22}O_2$ (186·3)	70·92 70·70	11·90 12·01
7,7-Dimethyl-3-ethyloctanoic acid[a] (*XIII*)	*VII* *XII*[d]	89—93 0·2	—	1·4301 (22)	$C_{12}H_{24}O_2$ (200·3)	71·95 72·23	12·08 12·21
3,6,6-Trimethylheptanoic acid[a] (*XVI*)	*IX*[c] *XV*[e]	86—90[g] 1·0	1 412, 1 709 2 400—3 400	1·4304 (24)	$C_{10}H_{20}O_2$ (172·3)	69·72 69·46	11·70 11·53
6,6-Dimethyl-3-ethylheptanoic acid[a] (*XVIII*)	*XII*[d] *XV*[e]	85—88 0·3	1 410, 1 710 2 400—3 400	1·4300 (23)	$C_{11}H_{22}O_2$ (186·3)	—	—
Methyl 3,7,11,11-Tetramethyl-2-dodecenoate[b] (*VI*)	*X* *XI*[f]	110 0·3	1 154, 1 226 1 366, 1 395 1 438, 1 650, 1 723	1·4533 (22)	$C_{17}H_{32}O_2$ (268·4)	76·06 75·75	12·02 11·99
Methyl 3,11,11-Trimethyl-7-ethyl-2-dodecenoate[b] (*XIV*)	*XI*[f] *XIII*	106—108 0·4	1 153, 1 227 1 365, 1 395 1 438, 1 650, 1 723	1·4557 (23)	$C_{18}H_{34}O_2$ (282·5)	76·54 76·37	12·13 12·01
Methyl 3,7,10,10-Tetramethyl-2-undecenoate[b] (*XVII*)	*XI*[f] *XVI*	135—137 10	1 152, 1 367 1 396, 1 650 1 721	1·4529 (23)	$C_{16}H_{30}O_2$ (254·4)	75·53 75·57	11·89 11·83
Methyl 3,10,10-Trimethyl-7-ethyl-2-undecenoate[b] (*XIX*)	*XI*[f] *XVIII*	113—115 0·5	1 225, 1 366 1 390, 1 435 1 650, 1 720	1·4530 (23)	$C_{17}H_{32}O_2$ (268·4)	76·06 76·26	12·02 12·05

[a] Prepared by procedure A; [b] prepared by procedure B; [c] see ref.[25]; [d] see ref.[27]; [e] commercial preparation from Koch and Light; [f] see ref.[26]; [g] m.p. 24—25°C.

in addition to other products 3,6,9,9-tetramethyl-2-decenoic acid (*XXIV*) and its methyl ester *XX*. The pure ester *XX* was obtained by esterification of this mixture with diazomethane and preparative chromatography on silica gel.

EXPERIMENTAL

Analytical thin-layer chromatography was carried out on silica gel (Merck, Kieselgel G nach Stahl), using a spray of phosphomolybdic acid in ethanol for detection. For column chromatography silica gel according to Pitra[31] was used. For Kolbe anodic synthesis an apparatus was used consisting of a reaction vessel, cooling spiral, platinum electrodes according to Dolejš and Novotný[32], a magnetic stirrer, and a thermometer. The course of the electrolysis was appreciably accelerated by stirring the reaction mixture during electrolysis, as well as by increased voltage of the direct current. The same effect was achieved by the occasional switching over of the electrodes. Such an acceleration of the electrolysis was necessary especially during work with unsaturated acids *XI* and *XXII*.

1-Ethoxy-4,4-dimethyl-1-pentene (*XXV*)

This[24] was prepared on reaction of tert-butylmagnesium chloride (from 74·8 g of tert-butyl chloride and 19·2 g of magnesium) with acrolein diethyl acetal (*XXVI*; 48·8 g). Fractional distillation through a column of 15 TP gave 23·7 g of product *XXV*, b.p. 75—78°C/55 Torr. For $C_9H_{18}O$ (142·2) calculated: 75·99% C, 12·76% H; found: 76·21% C, 12·75% H.

4,4-Dimethylpentanoic Acid (*VII*)

A mixture of ether *XXV* and 10% sulfuric acid (200 ml) was refluxed for 1 hour. The formed 4,4-dimethylpentanal (*VIII*) was distilled off from the reaction mixture together with 100 ml of water into a flask in which it was immediately oxidised with silver oxide prepared from 10·4 g of silver nitrate and 6·4 g of potassium hydroxide. The reaction mixture was worked up in the conventional manner. The whole procedure was repeated four times. Totally 11·28 g of acid *VII* were obtained, b.p. 75—78°C/12 Torr, n_D^{20} 1·4159. For $C_7H_{14}O_2$ (130·2) calculated: 64·58% C, 10·84% H; found: 64·86% C, 11·01% H.

Anodic Syntheses

Procedure A: A solution of methyl hydrogen β-alkylglutarate (25 mmol) and the monocarboxylic acid (40 mmol) in methanol (30 ml) in which 50 mg of sodium were dissolved was electrolysed at 6 V and 30—35°C. The end of the electrolysis was indicated by the change of the pH walue of the reaction mixture to higher values. After the evaporation of methanol the sample was taken into ether and chromatographed on a 100 fold amount of silica gel. Elution with a mixture of light petroleum–ether 9 : 1 gave a methyl ester which after 2 hours saponification with aqueous ethanolic potassium hydroxide afforded the corresponding saturated monocarboxylic acid (Table I).

Procedure B: Equimolar mixture of the monocarboxylic acid obtained by procedure A and *cis*, *trans*-4-methyl-5-methoxycarbonyl-4-pentenoic acid (*XI*) was electrolysed in methanol at 24 V and 35—45°C. After electrolysis the excess methanol was evaporated and the product purified by column chromatography on a 100 fold amount of silica gel with light petroleum–ether mixture (5 : 1) (Table I).

3-Hydroxy-3-methyl-5-hexenoic Acid (*XXII*)

Using tert-butyl acetoacetate (26·3 g), allyl bromide (26·5 g), and zinc shavings (14·9 g) tert-butyl 3-hydroxy-3-methyl-5-hexenoate (*XXXI*; 23·01 g) was obtained which on saponification with

aqueous alcoholic potassium hydroxide gave hydroxy acid *XXII* (ref.[30]) (14·2 g), b.p. 94°C/1 Torr and n_D^{24} 1·4625. For $C_7H_{12}O_3$ (144·2) calculated: 58·31% C, 8·39% H; found: 58·33% C, 8·46% H.

2,2,5,8-Tetramethyl-10-undecen-8-ol (*XXIII*)

Anodic synthesis was carried out by a procedure similar to the preceding cases from 3,6,6-trimethylheptanoic acid (*XVI*; 3·50 g) and 3-hydroxy-3-methyl-5-hexenoic acid (*XXII*; 3·50 g). Chromatography on a 100 fold amount of silica gel with light petroleum–ether 7 : 1 and distillation gave 0·82 g of substance *XXIII*, b.p. 87–90°C/0·5 Torr and n_D^{23} 1·4500. The substance had in its IR spectrum characteristic maxima at 918, 1000, 1367, 1393, 1639, 3005, 3070, and 3610 cm^{-1}. For $C_{15}H_{30}O$ (226·4) calculated: 79·57% C, 13·36% H; found: 79·76% C, 13·49% H.

Methyl 3,6,9,9-Tetramethyl-2-decenoate (*XX*)

Alcohol *XXIII* (400 mg) was ozonised at −20°C in ethyl acetate (15 ml) until the reaction mixture turned blue. It was acidified with acetic acid (50%; 30 ml) and additioned with hydrogen peroxide (30%; 3 ml) and refluxed for one hour. After cooling and dilution with water (20 ml) the reaction mixture was extracted with ether (totally 100 ml). The combined ethereal fractions were dried over sodium sulfate and esterified with diazomethane. The crude dry residue (310 mg) was heated with formic acid (98%; 4·0 g) at 80–85°C for 2 hours and then allowed to stand overnight at room temperature. After evaporation of the major part of formic acid *in vacuo* the residue was esterified with ethereal diazomethane solution. Ether was evaporated and the residue chromatographed on a silica gel column (50 g). Elution with a light petroleum–ether mixture (4 : 1) and subsequent distillation gave 46 mg of ester *XX*, b.p. 90°C/1 Torr. Principal bands in the IR spectrum occured at 1370, 1395, 1655, and 1715 cm^{-1}. Mass spectrum: molecular ion $M^+ = 240$ *m/e*, further 184*m/e* ($M^+ - C_4H_8$), 209*m/e* ($M^+ - CH_3O$), 59*m/e* ($COOCH_3$), and 57*m/e* (C_4H_9).

Elemental analyses were carried out in our laboratories by Mrs V. Rusová, E. Sýkorová, and Mr V. Štěrba. Infrared spectra were measured by Mrs K. Matoušková on a Zeiss UR 10 apparatus. We thank Dr J. Smolíková for help in their interpretation. The purity of compounds was controlled with a Perkin Elmer F 11 gas chromatograph provided with FID. The columns were filled with silicone elastomer E 301 (2·5% on AW DCMS Chromosorb G) and the analysis was performed by Dr V. Lukeš and Mrs S. Holubová. Mass spectra were measured by Dr L. Dolejš, and Mrs M. Vokáčová on a MS 902 mass spectrometer, and we also thank Dr L. Dolejš for their interpretation.

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