CYCLIC ANALOGUES OF INSECT JUVENILE HORMONE

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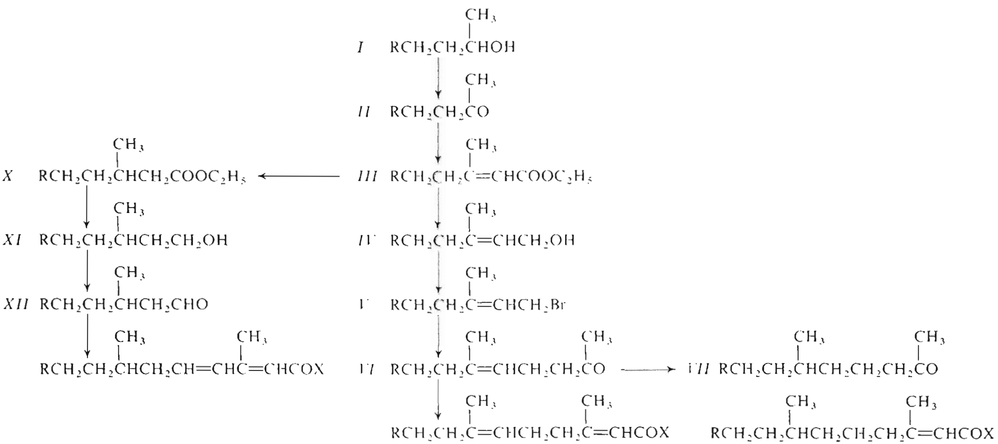
The preparation and the juvenilization effect of some derivatives of 3,7-dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoic, 3,7-dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoic (methyl, ethyl and isopropyl ester, monomethyl and dimethylamide) and 3,7-dimethyl-9-(5-methyl-2-oxolanyl)-2,4-nonadienoic acid (methyl, ethyl and isopropyl ester) have been described.

In connection with the research in the field of juvenile hormone and especially the relationships between chemical structure and biological effect we described some time ago the preparation of bioanalogues[1] in which the oxirane ring of the juvenile hormone has been substituted with an oxolane ring. Since some of the substances described displayed considerable activity, we have focussed our attention in this study on the praparation of similar substances in which the oxolane ring is substituted with the 5-methyloxolane ring. Their preparation has been described only in patent literature so far[2,3].

4-(5-Methyl-2-oxolanyl)-2-butanol (*I*) served as the starting substance for the synthesis of the compounds described, prepared by catalytic hydrogenation of 5-methylfurfurylideneacetone[4]. Oxidation of alcohol *I* with Jones' reagent[5,6] afforded 4-(5-methyl-2-oxolanyl)-2-butanone (*II*) which reacted[7] with diethyl ethoxycarbonylmethylphosphonate under formation of ethyl 3-methyl-5-(5-methyl-2-oxolanyl)-2-pentenoate (*III*). This was reduced with lithium aluminum hydride to 3-methyl-5-(5-methyl-2-oxolanyl)-2-penten-1-ol (*IV*) which was converted to 1-bromo-3-methyl-5-(5-methyl-2-oxolanyl)-2-pentene (*V*) affording on reaction with ethyl acetoacetate and subsequent ketone-forming cleavage 6-methyl-8-(5-methyl-2-oxolanyl)-5-octen-2-one (*VI*). Catalytic hydrogenation of the latter compound gave 6-methyl-8-(5-methyl-2-oxolanyl)-2-octanone (*VII*).

Reaction of ketones *VI* and *VII* with dialkyl esters of alkoxycarbonylmethyl- or alkylaminocarbonylmethyl and dialkylaminocarbonylmethylphosphonic acids[7,8] gave corresponding derivatives of 3,7-dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoic acid (*VIIIa*–*VIIIe*) and 3,7-dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoic acid (*IXa*–*IXe*).

The esters of 3,7-dimethyl-9-(5-methyl-2-oxolanyl)-2,4-nonadienoic acid (*XIIIa*



XIIIa, X = $-OCH_3$
XIIIb, X = $-OC_2H_5$
XIIIc, X = $-OCH(CH_3)_2$

VIIIa, X = $-OCH_3$
VIIIb, X = $-OC_2H_5$
VIIIc, X = $-OCH(CH_3)_2$
VIIId, X = $-NHC_2H_5$
VIIIe, X = $-N(C_2H_5)_2$

IXa, X = $-OCH_3$
IXb, X = $-OC_2H_5$
IXc, X = $-OCH(CH_3)_2$
IXd, X = $-NHC_2H_5$
IXe, X = $-N(C_2H_5)_2$

R = 5-methyl-2-oxolanyl-

SCHEME 1

to *XIIIc*) were prepared from 3-methyl-5-(5-methyl-2-oxolanyl)pentanal (*XII*) on reaction with corresponding dialkyl esters of 2-methyl-3-alkoxycarbonyl-2-propenylphosphonic acid. The required aldehyde *XII* was prepared by catalytic hydrogenation of ester *III* to the corresponding ethyl 3-methyl-5-(5-methyl-2-oxolanyl)pentanoate (*X*), its reduction to 3-methyl-5-(5-methyl-2-oxolanyl)pentanol (*XI*) and final oxidation with the chromium trioxide–pyridine complex in dichloromethane[9]. Individual reaction steps are shown in Scheme 1.

The prepared substances were submitted to the test on juvenile hormone activity described earlier[10]. For the tests freshly cast-off last larval instars of *Dysdercus* and *Graphosoma* and freshly cast-off chrysalids of *Tenebrio* were used. The substances were applied topically in 1 µl of acetone. The activity was evaluated according to the degree of inhibition of metamorphosis judged on the basis of morphological symptoms in the epidermis. The data on ID-50 Morph., given in Table I, represent the dose of substance in µg per individual, just eliciting the formation of a half-larval or half-chrysalid adultoids (in *Tenebrio*).

TABLE I

ID-50 Morph Values in Tests on Juvenile Hormone Activity

Compound	Caterpillars of the 5th instar chrysalids		
	Dysdercus cingulatus	*Graphosoma italicum*	*Tenebrio molitor*
VIIIa	0·1	100·0	100·0
VIIIb	4·0	10·0	100·0
VIIIc	1·0	100·0	3·0
VIIId	0·05	[a]	0·006
VIIIe	1·0	[a]	4·0
IXa	4·0	100·0	[a]
IXb	0·05	5·0	50—100·0
IXc	0·01	10·0	4·0
IXd	0·008	[a]	0·1
IXe	0·09	[a]	3·0
XIIIa	0·1	100·0	5·0
XIIIb	0·3	5·0	7·0
XIIIc	0·007	100·0	0·1

[a] The substance had no activity on application of 500 µg and 1000 µg per individual insect.

EXPERIMENTAL

Column chromatographies were carried out on silica gel according to Pitra[11], particle size 60 – 120 µm, deactivated with 12% of water (a product of the service laboratory of this Institute) and thin-layer chromatographies on silica gel G (Merck). The homogeneity of the substances and the ratio of isomers were determined by gas chromatography on a Pye Argon Chromatograph provided with an ionization detector (^{90}Sr), on columns with 10% of 1,4-butanediol succinate, 15% of QFI on Chromosorb W or 10% of Apiezon L on Cellite. The infrared spectra were measured on a UR 10 or UR 20 spectrometer (C. Zeiss, Jena, GDR) in tetrachloromethane. The mass spectra were measured on an AEI MS 902 spectrometer, coupled with a gas chromatograph of the Pye Series 104 Model 64. The light petroleum used in this paper was a fraction boiling between 30 and 60°C.

4-(5-Methyl-2-oxolanyl)-2-butanol (*I*)

5-Methylfurfurylideneacetone (85·26 g; 567·8 mmol, b.p. 66–68°C/1·6 – 1 Pa, prepared according to[4] from acetone and 5-methylfurfural[12]) was dissolved in ethanol (85 ml), Raney nickel was added (3–4 g) and the mixture hydrogenated at 180°C and 14·5–21·5 MPa until absorption of hydrogen ceased. After filtration off of the catalyst through a layer of charcoal the mixture was worked up in the conventional manner affording 6.61 g (7.4%) of a fore-run of b.p. up to 105.7°C/ /1470 Pa and 78.32 g (87·2%) of *I*, b.p. 105·7–107·7°C/1470 Pa. For $C_9H_{18}O_2$ (158·2) calculated: 68·31% C, 11·47% H; found: 68·26% C, 11·41% H. IR spectrum (cm^{-1}): 3625, 1138, 1090.

4-(5-Methyl-2-oxolanyl)-2-butanone (*II*)

Compound *I* (84·59 g; 534·5 mmol) was dissolved in acetone (320 ml) and the solution was cooled with water and ice. A precooled solution of chromium trioxide (37.42 g) in water (160 ml) and conc. sulfuric acid (32·61 ml) was added dropwise to it over 40 min, so that the temperature was maintained at 20°C. After 3 h stirring at 20°C the starting compound *I* disappeared from the mixture (monitored by thin-layer chromatography in light petroleum–acetone, 9 : 1). Solid sodium hydrogen sulphite was then added under stirring until the yellow-brown coloration of the acetone layer disappeared. The lower phase was separated and extracted with light petroleum (120 ml), the extract was combined with the original acetone upper layer and shaken. Thus two layers were formed again of which the lower one was separated, combined with the original lower phase and extracted with light petroleum (two 120 ml portions and one 100 ml portion). The extracts were combined with the original upper phase, washed with two 25 ml portions of saturated sodium chloride solution, two 25 ml portions of saturated sodium hydrogen carbonate solution and two 25 ml portions of saturated sodium chloride solution. After drying over sodium sulfate and distillation 4.15 g (5%) of a forerun of b.p. 88°C/1470 Pa were obtained in addition to 71·12 g (85·2%) of ketone *II*, b.p. 88–93°C/1470 Pa. For $C_9H_{16}O_2$ (156·2) calculated: 69·19% C, 10·33% H; found: 69·42% C, 10·38% H. IR spectrum (cm^{-1}): 1720, 1365, 1163, 1092.

Ethyl 3-Methyl-5-(5-methyl-2-oxolanyl)-2-pentenoate (*III*)

Ketone *II* (73·26 g; 468·9 mmol) and diethylester of ethoxycarbonylmethylphosphonic acid[13] (115·65 g; 515·8 mmol) were dissolved in ethanol (650 ml). Sodium (11·86 g, 515·8 gat) dissolved in ethanol (300 ml) was added under argon over 135 min to the above stirred solution, kept at 22–30°C. After two additional hours of stirring at room temperature and 18 h standing the mixture was evaporated on a rotary evaporator at 60°C/2000 Pa, acetic acid (31·8 g; 530 mmol) in water (1 l) was added to the residue and the ester *III* was extracted with light petroleum. The extract was washed successively with water, 2M potassium hydrogen carbonate and then water to neutrality, further with a saturated sodium chloride solution and then dried over magnesium sulfate. Distillation gave 90·83 g (85·6%) of ester *III*, b.p. 83—95°C/0·9—0·8 Pa, in addition to a forerun (4·37 g; 4·1%) of b.p. up to 83%C/0·9 Pa. For $C_{13}H_{22}O_3$ (226·3) calculated: 68·99% C, 9·80% H; found: 68·88% C, 9·80% H. IR spectrum (cm^{-1}): 1719, 1650, 1248, 1244, 1092, 1042.

3-Methyl-5-(5-methyl-2-oxolanyl)-2-pentenol (*IV*)

Ester *III* (20·37 g; 90 mmol), dissolved in ether (35 ml) was added dropwise and under stirring over 30 min to a solution or suspension of lithium aluminum hydride (2·56 g; 67·5 mmol) in ether (275 ml) at −22°C. After additional 60 min of stirring at −22°C and 90 min at room temperature the mixture was decomposed[14] by gradual dropwise addition of water (2·56 ml), 15% aqueous sodium hydroxide solution (2·56 ml) and water (7·68 ml), the precipitate was filtered off and washed with ether. After washing, drying over Drierite and distillation 15.6 g (90·8%) of *IV* were obtained. b.p. 102—107°C/37—35 Pa. For analytical purposes a part of the substance (1 g) was chromatographed on silica gel with light petroleum containing 10% of acetone. On distillation of the fractions which were identical according to thin-layer chromatograms (light petroleum–acetone 4 : 1) 0·66 g of *IV* boiling at 135—145°C/1260 Pa, (bath temperature), were obtained. For $C_{11}H_{20}O_2$ (184·3) calculated: 71·69% C, 10·94% H; found: 71·42% C, 10·81% H. IR spectrum (cm^{-1}): 3625, 1680, 1668, 1095, 1006. Mass spectrum: $M^+ = 184$ (for both isomers), 166, 98, 85, 67.

1-Bromo-3-methyl-5-(5-methyl-2-oxolanyl)-2-pentene (*V*)

A solution of 14·93 g (81·02 mmol) of alcohol *IV* in light petroleum (30 ml) was mixed with pyridine (0·8 ml) and cooled to −30°C. Phosphorus tribromide (8·74 g; 32·4 mmol) in light petroleum (8 ml) was then added to it under stirring over 20 min while keeping the temperature between −25 and −20°C. After another 60 min of stirring at this temperature the mixture was poured into water with ice and extracted with light petroleum. The combined extracts were washed gradually with water, 2M potassium hydrogen carbonate solution and water to a neutral reaction, then with saturated sodium bromide solution, and dried over Drierite. Distilling off of the solvent on a rotary evaporator at 22°C (bath temperature) and 2000 Pa gave 16·68 g (83·3%) of crude *V* which was used, in view of its instability for the next reaction step without further purification.

6-Methyl-8-(5-methyl-2-oxolanyl)-5-octen-2-one (*VI*)

A mixture of crude bromide *V* (16·68 g; 67·48 mmol) and ethyl acetoacetate (12·30 g; 94·51 mmol) was cooled at −15°C and a solution of sodium ethoxide (from 1·86 g, *i.e.* 80·88 mgat of sodium) in ethanol (40·5 ml) was added to it over 30 min keeping the temperature between −12°C and −8°C. After an additional 3 h of stirring at −12°C to −5°C and 16 h standing at room temperature the mixture was stirred at 80—90°C for another 1 h. An aqueous solution of 10% sodium hydroxide (115 ml) was added to it dropwise over 45 min and the mixture heated for another 4 h. The cooled mixture was extracted with light petroleum, the extract washed until neutral, dried over magnesium sulfate and distilled to afford 12·57 g of crude *VI*, b.p. 85—90°C/1·20 Pa, which was chromatographed on 400 g of silica gel with a mixture of light petroleum with 5% of acetone as eluent. The fractions which were identical according to thin-layer chromatography in light petroleum–acetone (9 : 1) were combined and distilled, to give 10·08 g (66·6%) of *VI*, b.p. 92·5 to 97°C/1—0·9 Pa. For $C_{14}H_{24}O_2$ (224·3) calculated: 74·95% C, 10·79% H; found: 74·70% C, 10·71% H. IR spectrum (cm^{-1}): 1722, 1670, 1410, 1359, 1159, 1095.

6-Methyl-8-(5-methyl-2-oxolanyl)-2-octanone (*VII*)

Ketone *VI* (11·56 g; 51·53 mmol) was dissolved in ethanol (35 ml), 1 g of 5% palladium on charcoal was added and the mixture hydrogenated until the absorption of hydrogen ceased. Crude *VII*, obtained after a conventional workup, was chromatographed on silica gel (320 g) with light petroleum containing 4% of acetone. The fractions containing the required product according to thin-layer chromatography (in light petroleum–acetone, 9 : 1) were combined and distilled to give 9·42 g (80·8%) of ketone *VII*, boiling at 110—120°C (bath temperature) and 0·9 Pa. For $C_{14}H_{26}O_2$ (226·4) calculated: 74·28% C, 11·58% H; found: 74·30% C, 11·42% H. IR spectrum (cm^{-1}): 1 720, 1 357, 1 096.

Ethyl 3-Methyl-5-(5-methyl-2-oxolanyl)-pentanoate (*X*)

Compound *III* (11·49 g; 50·77 mmol) in ethanol (15 ml) was hydrogenated on 0·60 g of 5% palladium on charcoal. After filtration and evaporation of ethanol the crude product was dissolved in light petroleum, washed, dried over magnesium sulfate and distilled to afford 10·64 g (91·8%) of *X*, b.p. 77—82°C/0·5 Pa. For $C_{13}H_{24}O_3$ (228·3) calculated: 68·38% C, 10·60% H; found: 68·45% C, 10·51% H. IR spectrum (cm^{-1}): 1 736, 1 165, 1 095.

3-Methyl-5-(5-methyl-2-oxolanyl)pentanol (*XI*)

Ester *X* (10·54 g; 46.16 mmol) dissolved in ether (30 ml) was added dropwise under stirring and over 50 min to a solution or suspension of lithium aluminum hydride (1·75 g; 46·1 mmol) in ether (70 ml). After 30 min stirring at room temperature and 60 min under reflux the mixture was cooled and decomposed[14] by gradual dropwise addition of water (1·75 ml), 15% aqueous sodium hydroxide (1·75 ml) and again water (5·25 ml). The precipitated material was filtered off under suction and washed with ether. The filtrate was washed in the usual manner and dried over magnesium sulfate to give crude *XI*, which was chromatographed on silica gel (230 g) with light petroleum containing 10% of acetone. Combination of the fractions identical according to thin-layer chromatography in light petroleum–acetone 4 : 1 and distillation gave 6·37 g (74·2%) of alcohol *XI* boiling at 105—110°C (bath temperature) and 6·7—1·3 Pa. For $C_{11}H_{22}O_2$ (186·3) calculated: 70·92% C, 11·90% H; found: 71·13% C, 11·83% H. IR spectrum (cm^{-1}): 3 635, 1 095, 1 065.

3-Methyl-5-(5-methyl-2-oxolanyl)pentanal[9] (*XII*)

Chromium trioxide (19·75 g; 197·5 mmol) dried in a vacuum over phosphorus pentoxide was added under argon to a stirred mixture of pyridine (31·23 g; 394·8 mmol) and dichloromethane (495 ml). After 20 min stirring at room temperature alcohol *XI* (6·13 g; 32·91 mmol) dissolved in dichloromethane (5 ml) was added and the mixture stirred for another 30 min. The dichloromethane solution was poured off and the remaining gummy precipitate was washed with three 220 ml portions of ether. The combined dichloromethane and ether solutions were washed with three 330 ml portions of 5% aqueous sodium hydroxide, water, 330 ml of 5% hydrochloric acid, water, 330 ml of 5% sodium hydrogen carbonate and again water until neutral, and finally with a saturated sodium chloride solution. After drying over magnesium sulfate and filtering the filtrate was distilled to give 4·70 g (77·5%) of aldehyde *XII* boiling at 135—148°C (bath temperature) at 1500 Pa. A part of *XII* (0·82) was chromatographed on silica gel (50 g) with light petroleum containing 3% of acetone for analysis. Fractions of *XII*, identical according to thin-layer chromatography in light petroleum–acetone (9 : 1), were combined and distilled to give 0·39 g of *XII*, boiling at 125°—135°C/1470 Pa (bath temperature). For $C_{11}H_{20}O_2$ (184·3) calculated: 71·69% C, 10·94% H; found: 71·47% C, 10·85% H. IR spectrum (cm^{-1}): 1 729, 1 095.

Methyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoate (*VIIIa*)

Ketone *VI* (2·24 g; 10 mmol) and dimethyl ester of methoxycarbonylmethylphosphonic acid (2·28 g; 12·5 mmol) (b.p. 95·5 – 103·5°C/40 Pa, prepared analogously as ethyl ester[13] from analogous methyl compounds) were dissolved in methanol and a sodium methoxide solution (prepared on dissolution of 0·31 g, *i.e.* 13·5 mgat of sodium in 6 ml of methanol) was added to it dropwise over 5 min under argon. After another 10 h of stirring at room temperature and standing overnight the mixture was evaporated on a rotary evaporator at 30°C/2000 Pa, diluted with water acidified with a small excess of sulfuric acid and the product was extracted with light petroleum. The extract was washed with water, 2M potassium hydrogen carbonate solution and water to neutrality. After drying over magnesium sulfate, filtration and evaporation of the solvent the crude product *VIIIa* was chromatographed on silica gel (130 g) from light petroleum containing 2·5% of acetone. Fractions which were identical according to thin-layer chromatography (light petroleum–acetone 9 : 1) were combined and distilled, affording 1·68 g (59·5%) of ester *VIIIa*, boiling at 132 – 142°C/1·20 Pa (bath temperature). For $C_{17}H_{28}O_3$ (280·4) calculated: 72·81% C, 10·07% H; found: 72·98% C, 10·13% H. IR spectrum (cm^{-1}): 1711, 1650, 1436, 1224, 1152, 1095.

Ethyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoate (*VIIIb*)

This was prepared analogously as *VIIIa* from ketone *VI* (2·24 g; 10 mmol), diethyl ethoxycarbonylmethylphosphonate[13] (2·47 g; 11 mmol) in ethanol (14 ml) and sodium ethoxide solution in ethanol (dissolution of 0·25 g or 11 mgat of sodium in 7 ml of ethanol) by 7 h stirring at room temperature and standing overnight. Chromatography of the crude product on silica gel (130 g) with light petroleum containing 2% of acetone, combination of identical fractions (according to thin-layer chromatography in light petroleum–acetone 9 : 1) and distillation gave 1·84 g (62·5%) of ester *VIIIb* boiling at 138 – 145°C/1.2 Pa (temperature of the bath). For $C_{18}H_{30}O_3$ (294·4) calculated: 73·43% C, 10·27% H; found: 73·22% C, 10·30% H. IR spectrum (cm^{-1}): 1715, 1650, 1222, 1154, 1145, 1095, 1060.

Methyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoate (*IXa*)

This was prepared analogously as *VIIIa* from ketone VII (2.26 g; 10 mmol) and dimethyl methoxycarbonylmethylphosphonate (2 g; 11 mmol) in methanol (14 ml) by dropwise addition of a sodium methoxide solution (0·25 g of sodium, *i.e.* 11 mgat, dissolved in 6 ml of methanol) over 15 min, stirring for 4 h and standing overnight. Chromatography of the crude product on silica gel (130 g) with light petroleum containing 2% of acetone, combination of the fractions containing according to thin-layer chromatography in light petroleum–acetone 9 : 1 the required product, and distillation gave 1·86 g (65·9%) of ester *IXa* boiling at 120 – 130°C/0·7 Pa (bath temperature). For $C_{17}H_{30}O_3$ (282·4) calculated: 72·29% C, 10·71% H; found: 72·15% C, 10·69% H. IR spectrum (cm^{-1}): 1724, 1651, 1436, 1225, 1151, 1096.

Ethyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoate (*IXb*)

This was prepared analogously as *VIIIb*, from ketone *VII* (2·26 g; 10 mmol) and diethyl ethoxycarbonylmethylphosphonate (2·47 g; 11 mmol) in ethanol (14 ml) on dropwise addition of a solution of sodium (0·25 g; 11 mgat) in ethanol (7 ml) over 15 min, 3 h stirring and standing overnight. The crude product was chromatographed on silica gel (130 g) with light petroleum containing 2% of acetone, the corresponding fractions (analysed by thin-layer chromatography in light petroleum acetone 9 : 1) were combined and distilled. Yield 2·76 g (93·1%) of ester *IXb*, boiling at 135—142°C/0·7 Pa (temperature of the bath). For $C_{18}H_{32}O_3$ (296·4 calculated: 72·93% C, 10·88% H; found: 72·76% C, 10·70% H. IR spectrum (cm^{-1}): 1 719, 1 650, 1 244, 1 149, 1 096.

General Procedure for the Preparation of *VIIIc—VIIIe*, *IXc—IXe* and *XIIIa—XIIIe*

The respective substituted phosphonic acid ester (12·5 mmol) was added dropwise and under argon to a stirred suspension of sodium hydride (1·30 g of 80%; 10 mmol) in dry, peroxide-free 1,2-dimethoxyethane (20 ml) at room temperature over 5 min. The mixture was stirred for T_1 min at room temperature, or for T_2 min at 40°C, depending on the ease of formation of the respective ylide. The carbonyl compound (10 mmol) was then added dropwise at room temperature over 5 min and the mixture stirred for T_3 min at room temperature and for T_4 min at 50 to 60°C. The reaction course was followed by thin-layer chromatography on silica gel. When the starting compound disappeared from the reaction mixture or the composition of the latter remained unchanged, it was poured into water (500 ml), acidified with a small excess of sulfuric acid, and extracted with light petroleum. The extract was washed with water, 2M potassium hydrogen carbonate solution, water and saturated sodium chloride solution. After drying over magnesium sulfate, filtration and evaporation of the light petroleum the residue was chromatographed on silica gel as described below.

Isopropyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoate (*VIIIc*)

This was obtained from the diisopropyl ester of isopropoxycarbonylmethylphosphonic acid (3·33 g) prepared from corresponding isopropyl derivatives analogously as in ref.[13] (b.p. 94·5 to 97·5°C/30 Pa) and ketone *VI* (2·24 g); $T_1 = 60$ min, $T_2 = 0$ min $T_3 = 20$ min, $T_4 = 240$ min. Crude *VIIIc* was chromatographed on silica gel (170 g) from light petroleum with 2% of acetone. The fractions containing according to thin-layer chromatography in light petroleum–acetone 93 : 7 the required product were combined and distilled, to yield 2·12 g (68·7%) of *VIIIc*, boiling at 130—140°C/1 Pa (bath temperature). For $C_{19}H_{32}O_3$ (308·4) calculated: 73·98% C, 10·46% H; found: 74·00% C, 10·39% H. IR spectrum (cm^{-1}): 1 712, 1 650, 1 225, 1 158, 1 447, 1 111, 1 095.

Monoethylamide of 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoic Acid (*VIIId*)

This was prepared from diethyl monoethylaminocarbonylmethylphosphonate[15] (2·79 g) and ketone *VI* (2·24 g); $T_1 = 60$ min, $T_2 = 0$ min, $T_3 = 20$ min, $T_4 = 150$ min. Crude *VIIId* was chromatographed on silica gel (130 g) with light petroleum containing 10% of acetone. The fractions of identical composition (according to thin-layer chromatography in light petroleum–acetone 4 : 1) were combined, the solvent evaporated at 97°C/1 500 Pa yielding 2·5 g (85·2%) of *VIIId*. For $C_{18}H_{31}NO_2$ (293·4) calculated: 73·67% C, 10·65% H, 4·77% N; found: 73·46% C, 10·42% H, 4·63% N. IR spectrum (cm^{-1}): 3 460, 3 330, 1 666, 1 640, 1 633, 1 536, 1 504, 1 094.

Diethylamide of 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,6-nonadienoic Acid (*VIIIe*)

Prepared from diethyl ester of diethylaminocarbonylmethylphosphonic acid[16] (3·14 g) and ketone *VI* (2·24 g); $T_1 = 60$ min, $T_2 = 0$ min, $T_3 = 15$ min, $T_4 = 180$ min. Crude *VIIIe* was chromatographed on silica gel (130 g) with light petroleum containing 10% acetone. The fractions were combined according to thin-layer chromatography analysis in light petroleum–acetone 4 : 1 and the solvent evaporated on a rotary evaporator at 97°C/1 500 Pa. Yield 2·66 g (82·7%) of *VIIIe*.

For $C_{20}H_{35}NO_2$ (321·5) calculated: 74·71% C, 10·98% H, 4·36% N; found: 74·57% C, 10·81% H, 4·15% N. IR spectrum (cm^{-1}): 1 650, 1 630, 1 134, 1 096.

Isopropyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoate (*IXc*)

Prepared from diisopropyl isopropoxycarbonylmethylphosphonate (3·33 g) and ketone *VII* (2·26 g) T_1 = 60 min, T_2 = 0 min, T_3 = 60 min, T_4 = 180 min. The crude product was chromatographed on silica gel (130 g) with light petroleum containing 2% of acetone. The fractions of identical composition according to thin-layer chromatography in light petroleum–acetone 9 : 1 were combined and distilled, yielding 2·27 g (73·1%) of ester *IXc*, boiling at 138—148°C/1·2 Pa (bath temperature). For $C_{19}H_{34}O_3$ (310·5) calculated: 73·50% C, 11·04% H; found: 73·64% C, 11·10% H. IR spectrum (cm^{-1}): 1 712, 1 650, 1 225, 1 153, 1 111, 1 095.

Monoethylamide of 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoic Acid (*IXd*)

Prepared from diethyl monoethylaminocarbonylmethylphosphonate[15] (2·79 g) and ketone *VII* (2·26 g); T_1 = 60 min, T_2 = 0 min, T_3 = 15 min, T_4 = 180 min. The crude product was chromatographed on silica gel (130 g) with light petroleum containing 10% of acetone. The fractions of identical composition according to thin-layer chromatography in light petroleum–acetone 4 : 1 were combined and the solvent evaporated on a rotary evaporator at 97°C/1 600 Pa. Yield 2·65 g (89·7%) of *IXd*. For $C_{18}H_{33}NO_2$ (295·5) calculated: 73·17% C, 11·26% H, 4·74% N; found: 72·94% C, 11·35% H, 4·58% N. IR spectrum (cm^{-1}): 3 460, 3 335, 1 699, 1 641, 1 538, 1 505, 1 095.

Diethylamide of 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2-nonenoic Acid (*IXe*)

Prepared from diethyl diethylaminocarbonylmethylphosphonate[16] (3·14 g) and ketone *VII* (2·26 g); T_1 = 60 min, T_2 = 0 min, T_3 = 15 min, T_4 = 180 min. The crude product was chromatographed on silica gel (130 g) with light petroleum containing 7% acetone. The fractions which were identical according to thin-layer chromatography in light petroleum–acetone 4 : 1 were combined and the solvent evaporated on a rotary evaporator at 97°C/1 600 Pa. Yield 3·02 g (93·4%) of *IXe*. For $C_{20}H_{37}NO_2$ (323.5) calculated: 74·25% C, 11·53% H, 4·33% N; found: 74·18% C, 11·58% H, 4·39% N. IR spectrum (cm^{-1}): 1 650, 1 630, 1 096.

Methyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,4-nonadienoic Acid (*XIIIa*)

Prepared from dimethyl 2-methyl-3-methoxycarbonyl-2-propenylphosphonate[17] (2·78 g) and aldehyde *XII* (1·84 g); T_1 = 60 min, T_2 = 0 min, T_3 = 20 min, T_4 = 60 min. The crude product was chromatographed on silica gel (220 g) with light petroleum containing 2% of acetone. The fractions which were identical according to thin-layer chromatography in light petroleum–acetone 9 : 1 were combined and distilled. Yield 1·71 g (61%) of *XIIIa*, boiling at 135—145°C/0·9—0·5 Pa (bath temperature). For $C_{17}H_{28}O_3$ (280·4) calculated: 72·81% C, 10·07% H; found: 72·88% C, 10·23% H. IR spectrum (cm^{-1}): 1 719, 1 649, 1 611, 1 607 (sh), 1 436, 1 242, 1 157, 1 095, 1 048.

Ethyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,4-nonadienoate (*XIIIb*)

Prepared from diethyl 2-methyl-3-ethoxycarbonyl-2-propenylphosphonate (prepared analogously as in ref.[17]) from corresponding ethyl derivatives (b.p. 98—108°C/0·8 Pa; ref.[18] gives b.p. 157—158°C/1 070 Pa) and aldehyde *XII* (1·84 g); T_1 = 60 min, T_2 = 0 min, T_3 = 60 min, T_4 = 120 min. The crude product was chromatographed on silica gel (135 g) using light petroleum with 8% of ether for elution. The fractions which were identical according to thin-layer chromatography in light petroleum–acetone 95 : 5 were combined and distilled. Yield 2·61 g (88·6%) of *XIIIb*, boiling at 135°C/0·9 Pa—143°C/0·5 Pa (bath temperature). For $C_{18}H_{30}O_3$ (294·4) calculated: 73·43% C, 10·27% H; found: 73·66% C, 10·11% H. IR spectrum (cm^{-1}): 1712, 1639, 1614, 1240, 1155, 1097, 1050.

Isopropyl 3,7-Dimethyl-9-(5-methyl-2-oxolanyl)-2,4-nonadienoate (*XIIIc*)

Prepared from diisopropyl ester of 2-methyl-3-isopropoxycarbonyl-2-propenylphosphonic acid[17] (3·84 g) and aldehyde *XII* (1·84 g); T_1 = 30 min, T_2 = 30 min, T_3 = 80 min, T_4 = 120 min. The crude product was chromatographed on silica gel (130 g) with light petroleum with 2% of acetone. The fractions which were identical according to thin-layer chromatography in light petroleum–acetone 9 : 1 were combined and distilled to yiled 1·46 g (47·3%) of *XIIIc*, boiling at 143—153°C/0·8 Pa (bath temperature). For $C_{19}H_{32}O_3$ (308·4) calculated: 73·98% C, 10·46% H; found: 73·89% C, 10·46% H. IR spectrum (cm^{-1}): 1711, 1640, 1615, 1241, 1160, 1111, 1036.

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