SOME OTHER CYCLIC ANALOGUES OF THE INSECT JUVENILE HORMONE*

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The preparation of ethyl 3-methyl-7-ethyl-10-(2-oxolanyl)-2-decenoate (*I*), some derivatives of 3-methyl-9-(5-methyloxolan-2-yl)-2-nonenoic acid (*XXIe*), and ethyl 3-methyl-9-(2-oxolanyl)--2-nonenoate (*XXIII*) has been described.

In connection with investigations on cyclic analogues of the insect juvenile hormone in which the oxirane ring is replaced by the more stable oxolane ring, ethyl 3-methyl-7--ethyl-10-(2-oxolanyl)-2-decenoate (*I*) and related compounds have been prepared** for purposes of a detailed biological evaluation and comparison.

The readily accessible (by hydrogenation of ethyl furylacrylate) ethyl 3-(2-oxolanyl)propionate (*II*) was used as the starting material. The lithium aluminium hydride reduction of the ester *II* afforded 3-(2-oxolanyl)propanol (*III*) which was converted to 1-bromo-3-(2-oxolanyl)propane (*IV*) and the corresponding Grignard reagent. By reaction of this agent with propanal there was obtained 6-(2-oxolanyl)-3-hexanol (*V*) which was transformed into 3-bromo-6-(2-oxolanyl)hexane (*VI*). Reaction of the bromide *VI* with diethyl sodiomalonate yielded the expected ethyl 2-ethoxycarbonyl-3-ethyl-6-(2-oxolanyl)hexanoate (*VII*) along with a small amount of ethyl 2-ethoxycarbonyl-5-(6-ethyloxan-2-yl)pentanoate (*VIII*). Compound *VIII* was probably formed by a cyclic mechanism (Scheme 1). The structures *VII* and *VIII* were confirmed by spectroscopy. The mass spectrum of the oxolane *VII* exhibits a base peak at the mass 71, corresponding to a five-membered oxonium ion *a* whereas the base peak of compound *VIII* is situated at the mass 113 (a six-membered oxonium ion *b*). In the NMR spectrum of compound *VII*, a complex multiplet at 3·76 p.p.m. corresponds to three protons of the $-CH_2OCH=$ grouping; the multiplet of compound *VIII* at 3·59 p.p.m. is attributable to two protons of the $=CHOCH=$ grouping. The decarbethoxylation[1,2] of compound *VII* afforded ethyl 3-ethyl-6-(2-oxolanyl)-hexanoate (*IX*) which was reduced to 3-ethyl-6-(2-oxolanyl)hexanol (*X*) and this

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** The biological activity of the present substances will be reported elsewhere.

$RCH_2CH(C_2H_5)CH_2CH_2CH_2C(CH_3)=CHCO_2C_2H_5$
I

$RCO_2C_2H_5$
II

RCH_2OH
III

RCH_2Br
IV

$RCH_2CH(C_2H_5)OH$
V

$RCH_2CH(C_2H_5)CH(CO_2C_2H_5)_2$
VII

$RCH_2CH(C_2H_5)CH_2CO_2C_2H_5$
IX

$RCH_2CH(C_2H_5)CH_2CH_2OH$
X

$RCH_2CH(C_2H_5)CH_2CH_2Br$
XI

$RCH_2CH(C_2H_5)CH_2CH_2CH_2COCH_3$
XII

$RCH(CH_3)OH$
XIII

$RCH(CH_3)CH(CO_2C_2H_5)_2$
XVI

$R^1CH_2CH_2COX$
XVII

$R^1CH_2CH_2CH_2OH$
XVIII

$R^1CH_2CH_2CH_2Br$
XIX

$R^1CH_2CH_2CH_2CH_2COCH_3$
XX

$R^1CH_2CH_2CH_2CH_2C(CH_3)=CHCOX$
XXIa, X = OCH_3
XXIb, X = OC_2H_5
XXIc, X = NHC_2H_5
XXId, X = $N(C_2H_5)_2$
XXIe, X = OH
XXIf, X = Cl

$R^1CH_2CH_2CH_2CH_2C(CH_3)=CHCN$
XXII

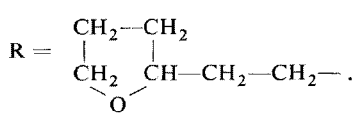
RCO_2H
XXIV

$RCH_2CH_2CH_2CH_2COX$
XXV X = OCH_3
XXVI X = OH
XXVII X = Cl

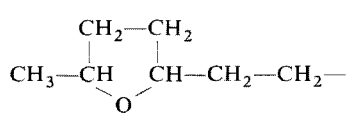
$RCH_2CH_2CH_2CH_2COCH_3$
XXVIII

$RCH_2CH_2CH_2CH_2C(CH_3)=CHCO_2C_2H_5$
XXIII

In formulae: *I*—*V*, *VII*, *IX*—*XIII*, *XVI*, *XXIII*—*XXVIII*:



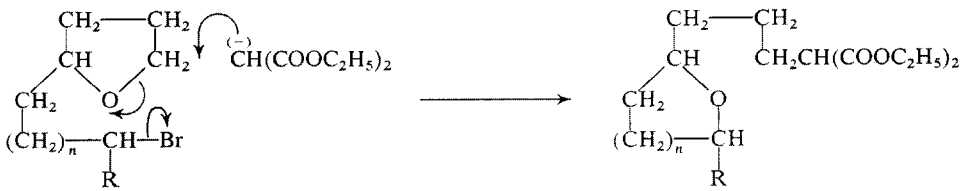
In formulae: *XVII*—*XXII*:



SCHEME 1

compound converted to 1-bromo-3-ethyl-6-(2-oxolanyl)hexane (*XI*). Alkylation of ethyl acetoacetate with the bromide *XI* and the subsequent ketonic hydrolysis afforded 6-ethyl-9-(2-oxolanyl)-2-nonanone (*XII*). The required ester *I* was finally prepared by reaction of the ketone *XII* with triphenylethoxycarbonylmethylenephosphorane under acidic catalysis[3].

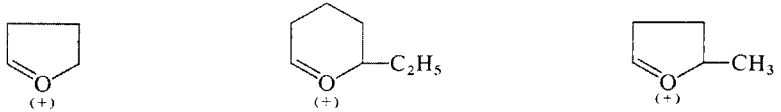
The above mentioned rearrangement was utilised in the preparation of some earlier reported[4] derivatives (*XXIa*–*XXId* and *XXII*) of 3-methyl-9-(5-methyloxolan-2-yl)-2-nonenoic acid (*XXIe*), namely, from 4-(2-oxolanyl)-2-butanol (*XIII*) which is accessible by catalytic hydrogenation of furfurylideneacetone[5]. The alcohol *XIII* was converted into 2-bromo-4-(2-oxolanyl)butane (*XIV*). Alkylation (Scheme 1) of diethyl sodiomalonate with the bromide *XIV* afforded ethyl 2-ethoxycarbonyl-5-(5-methyloxolan-2-yl)pentanoate (*XV*) as the predominant product whereas the normal alkylation product, ethyl 2-ethoxycarbonyl-3-methyl-5-(2-oxolanyl)pentanoate (*XVI*) was formed to a negligible extent only. The isomers *XV* and *XVI* could be separated by gas chromatography; their identification was effected by mass spectroscopy. The oxolane *XVI* exhibits a characteristic base peak *a* at *m/e* 71 whereas the spectrum of compound *XV* contains a homologous base peak *c* at *m/e* 85 (Scheme 1).



VI; R = C_2H_5, $n = 2$
XIV; R = CH_3, $n = 1$

VIII; R = C_2H_5, $n = 2$
XV; R = CH_3, $n = 1$

SCHEME 1



a *m/e* 71 *b* *m/e* 113 *c* *m/e* 85

The ester *XV* was saponified and thermally decarboxylated to 5-(5-methyloxolan-2-yl)pentanoic acid (*XVII*) which was esterified with diazomethane and the methyl ester reduced with lithium aluminium hydride to afford 5-(5-methyloxolan-2-yl)pentanol (*XVIII*). The alcohol was converted to 1-bromo-5-(5-methyloxolan-2-yl)pentane (*XIX*). Alkylation of ethyl acetoacetate with the bromide *XIX* and the subsequent

ketonic hydrolysis afforded 8-(5-methyloxolan-2-yl)-2-octanone (*XX*) which was used in the preparation of the required derivatives *XXIa*–*XXIc* and *XXII* with the use of the reaction with cyanomethylene- or alkoxycarbonylmethylenetriphenylphosphoranes[3] or diethyl ethylaminocarbonylmethanephosphonate[6]. The N,N-diethylamide of 3-methyl-9-(5-methyloxolan-2-yl)-2-nonenoic acid (*XXId*) was prepared from the ester *XXIb* by saponification to the acid *XXIe*, conversion to the chloride *XXIf*, and reaction with diethylamine.

For purposes of comparison, ethyl 3-methyl-9-(2-oxolanyl)-2-nonenoate (*XXIII*) was also prepared. Thus, 3-(2-oxolanyl)propionic acid (*XXIV*) as the starting compound (obtained from the ester *II*) was subjected to electrolysis with monomethyl adipate to afford methyl 7-(2-oxolanyl)heptanoate (*XXV*) which was converted[7] *via* the free acid *XXVI* and its chloride *XXVII* to 8-(2-oxolanyl)-2-octanone (*XXVIII*). Reaction of the ketone *XXVIII* with triphenylethoxycarbonylmethylenephosphorane afforded the required ester *XXIII*.

EXPERIMENTAL

Column chromatography was performed on the Pitra[8] silica gel (particle size, 60–120 micron unless stated otherwise; produced by Service Laboratories of this Institute) previously extracted with 1 : 1 chloroform–methanol mixture, activated at 120°C for 24 h, and partially deactivated by the addition of 12% of water. Thin-layer chromatography was carried out on the Merck silica gel G. The homogeneity of substances and ratio of isomers (if any) was determined by gas chromatography on a Pye Argon Chromatograph with ionisation detection (^{90}Sr) on columns packed with 10% butanediol succinate or QF 1 on Chromosorb W. The IR spectra were taken on a UR 10 apparatus (Carl Zeiss, Jena, German Democratic Republic). The mass spectra were recorded on an A.E.I. MS 902 A apparatus combined with Model 64 Pye Series 104 gas chromatograph. The NMR spectra were measured on a Varian HA-100 apparatus in deuteriochloroform and with the use of tetramethylsilane as internal standard; δ in p.p.m., J in cycles per s.

Ethyl 3-(2-Oxolanyl)propionate (*II*)

Ethyl furylacrylate (152·2 g) was hydrogenated in ethanol (100 ml) over Raney nickel (1·5 g) under the pressure of 125 atm first at 110–120°C and then at 150°C until the uptake of hydrogen ceased. Usual work-up and distillation afforded 143 g (90·6%) of the ester *II*, b.p. 100–106°C : : 9 Torr (reported[9], b.p. 110°C/15 Torr).

3-(2-Oxolanyl)propanol (*III*)

Lithium aluminium hydride (20·6 g) was refluxed in ether (1 000 ml) for 1 h, the solution treated at 20°C over 65 min under stirring with the ester *II* (143 g), the whole mixture refluxed for 1 h, kept at room temperature overnight, and decomposed[10] by successive additions of water (20·6 ml), 15% aqueous sodium hydroxide (20·6 ml), and water (61·8 ml) again. The precipitated was filtered off with suction and washed with ether. The filtrate and washings were combine and processed as usual to afford 79·8 g (74%) of the alcohol *III*, b.p. 105°C/9 Torr to 109·5°/10 Torr (reported[11], b.p. 106–107°C/2 Torr).

1-Bromo-3-(2-oxolanyl)propane (*IV*)

To a solution of the alcohol *III* (85·1 g) and triphenylphosphine (188·55 g) in dry dimethylformamide (655 ml) there was added dropwise under argon with stirring and occasional cooling dry bromine[12] (11·49 g) over 70 min at such rate to keep the temprature below 55°C. The stirring was then continued at room temperature for 1 h and the reaction mixture distilled under diminished pressure. The fraction boiling up to 96°C/11 Torr was poured into ice-cold water and extracted with light petroleum. The extract was worked up as usual to afford 89·9 g (71%) of the bromide *IV*, b.p. 91—94°C/11·5 Torr (reported[13], b.p. 115—116°C/27 Torr).

6-(2-Oxolanyl)-3-hexanol (*V*)

A solution of the bromide *IV* (71·2 g) in ether (50 ml) was gradually added to magnesium shavings (9·4 g) in ether (100 ml), the mixture refluxed for 1 h, and cooled down. Freshly distilled propanal (21·5 g) in dry ether (25 ml) was then added dropwise at room temperature with stirring over 40 min. The mixture was stirred 1 h at room temperature and 2 h at the reflux temperature, allowed to stand overnight, and decomposed with a solution of ammonium chloride (99 g) in water (300 ml). Usual work-up, drying over anhydrous magnesium sulfate, and evaporation yielded 56·1 g of the residue which was distilled under diminished pressure. Yield, 39·6 g (62%) of the alcohol *V*, b.p. 90·5—98·5°C/0·5 Torr. For purposes of analysis, the alcohol was chromatographed on silica gel in 95 : 5 light petroleum–acetone and redistilled. For $C_{10}H_{20}O_2$ (172·3) calculated: 69·72% C, 11·70% H; found: 69·91% C, 11·76% H.

3-Bromo-6-(2-oxolanyl)hexane (*VI*)

A. The alcohol *V* (9·1 g) and triphenyl phosphite (18·9 g) was dissolved in dry ether (35 ml) and the solution cooled down externally with ice. Bromine[14] (9·75 g) was then added dropwise with stirring over 25 min, the cooling bath removed, and the stirring continued at room temperature for additional 2 h. The ether was evaporated and the residue distilled under diminished pressure. The distillate (6·3 g) boiling up to 70°C/0·02 Torr was dissolved in light petroleum, the solution washed with three portions of ice-cold 1M aqueous sodium hydroxide and water, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure at the bath temperature of 40°C. The residual crude bromide (5·4 g) was chromatographed on silica gel (200 g) in 96 : 4 light petroleum–ether to afford 2·7 g (22%) of the bromide *VI*. Mass spectrum: M^+ 234 (for ^{79}Br), 233, 205, 192, 191, 155, 71 (base peak). IR spectrum (cm^{-1}): 1 071.

B. An ice-cooled solution of the alcohol *V* (52 g) in dry benzene (52 ml) was saturated with gaseous hydrogen bromide. The reaction mixture was kept at 0°C for 17 h and at room temperature for 54 h, poured onto a mixture of ice and water, and extracted with ether. Usual work-up of the extract and evaporation afforded 98 g of the crude bromide which underwent decomposition when distilled under diminished pressure. The distillate (b.p. up to 120°C/0·7 Torr; 37·6 g) was dissolved in light petroleum and the insoluble portions discarded. The solution was processed as usual and evaporated to afford 33·6 g (47%) of the crude bromide *VI* which was used directly without purification in the next step.

Ethyl 2-Ethoxycarbonyl-3-ethyl-6-(2-oxolanyl)hexanoate (*VII*)

To a stirred ethanolic sodium ethoxide (from 4 g of sodium and 120 ml of absolute ethanol) there was added dropwise over 20 min at room temperature diethyl malonate (28·7 g). The mixture was treated with sodium iodide (0·5 g) and then the crude bromide *VI* (33·6 g) was added drop-

wise over 50 min. The whole mixture was stirred at room temperature for 1 h and at 100°C for 4 h, kept overnight, and adjusted to pH 6·5 by the addition of acetic acid. The alcohol was taken down on a rotatory evaporator under diminished pressure, the residue diluted with water, and the product extracted with ether. The extract was washed with aqueous sodium thiosulfate, aqueous sodium hydrogen carbonate, and water till neutral, dried over anhydrous magnesium sulfate, and the ether evaporated. Diethyl malonate was then removed by distillation up to 135°C/13·5 Torr. The residue (40·1 g) was chromatographed on silica gel (1 660 g) in 9 : 1 light petroleum–ether to afford 12 g of compound *VII*, 0·09 g of compound *VIII*, and 10 g of the *VII*—*VIII* mixture. Mass spectrum of compound *VII*: M^+ 314, 285, 269, 201, 161, 160, 71. Mass spectrum of compound *VIII*: M^+ 314, 285, 269, 173, 160, 161, 113. NMR spectrum of compound *VII*: 0·875 (t ~ 3 H, $J \approx 7$), 1·245 (t ~ 6 H, $J \approx 7$), 3·40 (d ~ 1 H, $J \approx 7{\cdot}5$), 4·18 (q ~ 4 H, $J \approx 7$), 3·76 (cm ~ 3 H), 1·10—2·35 (overlapping multiplets, all other protons). NMR spectrum of compound *VIII*: 0·88 (t ~ 3 H, $J \approx 7$), 1·24 (t ~ 6 H, $J \approx 7$), 3·32 (t ~ 1 H, $J \approx 7{\cdot}5$), 4·185 (q ~ 4 H, $J \approx 7$), 3·59 (m ~ 2 H), 1·10—2·05 (overlapping multiplets, all other protons).

Ethyl 3-Ethyl-6-(2-oxolanyl)hexanoate (*IX*)

A mixture of the ester *VII* (8·6 g), dry solid sodium cyanide (2·7 g), and dimethyl sulfoxide (50 ml) was heated at 160°C with stirring for 4 h, cooled down, poured into water acidified with acetic acid, and extracted with light petroleum. The extract was processed as usual to afford 4·7 g (71%) of compound *IX* boiling at the bath temperature of 170—180°C/10 Torr. The distillate was chromatographed on silica gel (400 g) in 9 : 1 light petroleum–ether and redistilled at 10 Torr (bath temperature, 175—180°C). Yield, 4·5 g of the ester *IX*. For $C_{14}H_{26}O_3$ (242·4) calculated: 69·38% C, 10·81% H; found: 69·47% C, 10·88% H.

3-Ethyl-6-(2-oxolanyl)hexanol (*X*)

To a stirred solution of lithium aluminium hydride (0·7 g) in ether (80 ml) there was added dropwise over 10 min the ester *IX* (4·5 g) in ether (10 ml), the mixture stirred at room temperature for 2 h and then at the reflux temperature for 1 h, cooled down, and decomposed by successive additions[10] of water (0·7 ml), 15% aqueous sodium hydroxide (0·7 ml), and water (2·1 ml) again. The precipitated salts were filtered off with suction and washed with ether. The filtrate and washings were combined and processed as usual to afford 3·7 g of the crude alcohol *X* which was directly used in the next step.

1-Bromo-3-ethyl-6-(2-oxolanyl)hexane (*XI*)

To a solution of the crude alcohol *X* (3·7 g) and triphenylphosphine (5·4 g) in dry dimethylformamide (25 ml) there was added dropwise under argon with stirring over 30 min dry bromine (3·26 g) at such a rate to keep the temperature below 40°C. The mixture was stirred at room temperature for 1 h and extracted with five 25 ml portions of light petroleum. The extract was washed with dimethylformamide (1 ml) and small portions of water until neutral, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure to afford 4·7 g of the crude bromide *XI* which was used directly without purification in the next step.

6-Ethyl-9-(2-oxolanyl)-2-nonanone (*XII*)

Into ethanolic sodium ethoxide (from 0·82 g of sodium and 17 ml of ethanol) there was added dropwise with stirring at room temperature ethyl acetoacetate (5·1 g) and then the crude bromide

XI (4·7 g). The mixture was stirred at room temperature for 30 min and at 90°C for 10 h. Aqueous sodium hydroxide (10%, 60 ml) was then added dropwise, the mixture heated at 90°C with stirring for additional 4 h, cooled down, diluted with water, and extracted with light petroleum. The extract was processed as usual to afford 1·1 g of the crude product containing (as determined by thin-layer chromatography on silica gel G in 9 : 1 light petroleum–acetone) the ketone *XII* along with a considerable amount of the nonketonic portion. The residue was therefore dissolved in absolute ethanol (22·5 ml) and the solution treated with glacial acetic acid (1·8 g) and Girard reagent[16] T (2·5 g). The mixture was refluxed for 1 h, diluted with ethylene glycol (22·5 ml), and the ethanol removed by distillation under diminished pressure from a steam bath. The remaining ethylene glycol solution was washed with four 20 ml portions of ether and diluted with water (previously acidified with 9·75 ml of 96% sulfuric acid) to the volume of 350 ml. After 1 h at room temperature, the ketone *XII* was extracted with ether and the extract processed as usual to afford 0·26 g of the ketone *XII* boiling at the bath temperature of 115—125°C/0·005 Torr. Mass spectrum: M^+ 314.

Ethyl 3-Methyl-7-ethyl-10-(2-oxolanyl)-2-decenoate (*I*)

A mixture of the ketone *XII* (210 mg), ethoxycarbonylmethylenetriphenylphosphorane[17] (457 mg), benzoic acid (100 mg) and benzene (3 ml) was refluxed under argon for 24 h. Another portion of the phosphorane (152 mg), benzene (1 ml), and benzoic acid (33 mg) was then added and the reflux continued for additional 24 h. This procedure was repeated once more. The benzene was then evaporated under diminished pressure and the oily residue extracted by repeated triturations with light petroleum. The extract was processed as usual to afford 0·19 g of the crude ester which was chromatographed on a column of silica gel (particle size, 30—60 micron; 30 g) in 96 : 4 light petroleum–acetone. Yield, 140 mg (52%) of the ester *I*, boiling at the bath temperature of 135—145°C/0·006 Torr. For $C_{19}H_{34}O_3$ (310·5) calculated: 73·50% C, 11·04% H; found: 73·58% C, 10·91% H. IR spectrum (cm^{-1}): 1 710, 1 649, 1 223, 1 149, 1 050.

2-Bromo-4-(2-oxolanyl)butane (*XIV*)

A. Into a stirred solution containing 4-(2-oxolanyl)-2-butanol[5] (*XIII*) (15·5 g), light petroleum (30 ml), and dry pyridine (2·6 ml) there was added dropwise at —20°C over 20 min a solution of phosphorus tribromide (13 g) in light petroleum (18 ml). The freezing bath was removed and the mixture stirred for 1·5 h at room temperature and then for 4 h almost at the boiling point temperature. The mixture was cooled down, poured into ice and water, and extracted with light petroleum (the insoluble layer in petroleum ether was discarded). The extract was processed as usual to afford 12·1 g (54%) of the bromide *XIV*, b.p. 89—91°C/8·5 Torr (reported[15], b.p. 79·5—80·0°C/4 Torr).

B. Into a stirred solution of the alcohol *XIII* (14·4 g) and triphenylphosphine (28 g) in dimethylformamide there was added dropwise under argon dry bromine[12] (17·1 g) at such rate to keep the temperature below 55°C. The mixture was then stirred at room temperature for 2 h, distilled under diminished pressure, the distillate (b.p. 40—85°C/8 Torr) poured into water, and extracted with light petroleum. The extract was processed as usual to afford 13·3 g (64·5%) of the bromide *XIV*, b.p. 89—91°C/9 Torr, the properties of which corresponded to those of the specimen obtained by procedure A.

Ethyl 2-Ethoxycarbonyl-(5-methyloxolan-2-yl)pentanoate (*XV*)
and Ethyl 2-Ethoxycarbonyl-3-methyl-5-(2-oxolanyl)pentanoate (*XVI*)

Into stirred ethanolic sodium ethoxide (from 4·9 g of sodium and 106 ml of ethanol) there was added dropwise over 25 min diethyl malonate (37·3 g) and then the bromide *XIV* (43·8 g) over 20 min. The mixture was stirred at room temperature for 1 h, kept overnight, and heated at 110 to 115°C for 6 h. After this period of time, the pH value was 6·5. Most ethanol was evaporated under diminished pressure, the cold residue diluted with water, and extracted with ether. The extract was processed as usual to afford 61·2 g of the crude reaction product. A portion of the product was distilled under diminished pressure; the distillate, b.p. 96—97°C/0·007 Torr was shown by gas chromatography to represent a mixture of two substances (the component with the shorter elution time predominated). The attempted separation of the two substances by column chromatography on silica gel (100 parts by weight) in 95 : 5 light petroleum–ether failed. Mass spectrum of compound *XV* (shorter elution time): 286, 241, 213, 173, 161, 160, 85. Mass spectrum of the minor compound *XVI* (longer elution time): 286, 71.

5-(5-Methyloxolan-2-yl)pentanoic Acid (*XVII*, X = OH)*

A mixture of the esters *XV* and *XVI* (58·4) g) was added into a solution of potassium hydroxide (34·4 g) in water (310 ml), the mixture refluxed with stirring for 3 h, and the reflux condenser replaced by a descending (Liebig) condenser. The reflux was then continued until the boiling point value of the distillate was 98°C (the volume of the content of the distillation flask was maintained constant by addition of water). The neutral portion was cooled down, washed with ether, acidified with dilute (1 : 3) sulfuric acid to Congo Red paper, and the organic acid extracted with ether. The extract was processed as usual and the residue dried by coevaporation with benzene. The residual benzene was removed under diminished pressure. Glass powder (particle size, 0·5—1·0 mm; 3·5 g) was added to the residue (39·3 g), the air replaced by argon, and the flask immersed into a bath kept at 140°C. The bath temperature was gradually raised to 150°C. After 30 min at 150°C, the evolution of carbon dioxide ceased. The content of the flask was cooled down, dissolved in ether, the glass powder filtered off, and the filtrate thoroughly shaken with excess 10% aqueous sodium hydroxide. The ethereal layer was separated and the non-acidic portion extracted with ether once more. The alkaline solution was acidified with 25% aqueous sulfuric acid to Congo Red paper and the liberated organic acid extracted with ether. The extract was processed as usual to afford 31 g of the crude acid *XVII* (X = OH).

Methyl 5-(5-Methyloxolan-2-yl)pentanoate (*XVII*, X = OCH_3)*

To a solution of the crude acid *XVII* (X = OH, 31 g) in ether (30 ml) there was added a solution of diazomethane (from 30·9 g of N-nitrosomethylurea and 300 ml of ether) and the mixture kept at 0°C overnight. The ether and excess diazomethane were evaporated under diminished pressure and the residue distilled to afford (in addition to a small amount of the forerun) 26·35 g of the methyl ester *XVII* (X = OCH_3), b.p. 122·7—126·8°C/9·5 Torr. For $C_{11}H_{20}O_3$ (200·3) calculated: 65·96% C, 10·07% H; found: 66·33% C, 10·12% H. IR spectrum (cm^{-1}): 1742, 1438, 1157, and 1096.

* All compounds marked with an asterisk are contaminated with a small amount of the corresponding isomer derived from the ester *XVI*.

5-(5-Methyloxolan-2-yl)pentanol (*XVIII*)*

To a stirred suspension of lithium aluminium hydride (2·81 g) in ether (25 ml) there was added dropwise over 1 h the ester *XVII* (X = OCH_3; 19·6 g) in ether (100 ml). The mixture was stirred at room temperature for 2 h and at the reflux temperature for 90 min, kept overnight, decomposed with water and 4M-HCl, and the ethereal layer separated. The aqueous phase was extracted with ether. The ethereal solutions were combined and processed as usual to afford 15·7 g (93%) of the alcohol *XVIII*, b.p. 100·5–101·5°C/0·8 Torr. For $C_{10}H_{20}O_2$ (172·3) calculated: 69·72% C, 11·70% H; found: 69·90% C, 11·74% H.

1-Bromo-5-(5-methyloxolan-2-yl)pentane (*XIX*)*

Into a stirred solution containing the alcohol *XVIII* (32·4 g), light petroleum (55 ml), and pyridine (4·4 g) there was added dropwise at −10°C over 30 min a solution of phosphorus tribromide (22·75 g) in light petroleum (30 ml) and the whole mixture stirred at −7°C for additional 30 min. The freezing bath was then removed and the stirring continued until the temperature of the reaction mixture was equal to room temperature. The mixture was then kept at room temperature overnight, poured onto ice, and extracted with light petroleum. The extract was processed as usual to afford 20·65 g (47%) of the bromide *XIX*, b.p. 128–132°C/11·5 Torr. For $C_{10}H_{19}BrO$ (235·2) calculated: 51·07% C, 8·15% H, 33·98% Br; found: 51·03% C, 8·07% H, 33·98% Br.

8-(5-Methyloxolan-2-yl)-2-octanone (*XX*)

To ethanolic sodium ethoxide (from 2·2 g of sodium and 30 ml of ethanol) there was added dropwise at room temperature with stirring over 15 min ethyl acetoacetate (12·5 g) and then the bromide *XIX* (20·5 g). The reaction mixture was stirred at room temperature for 1 h and at 90°C for 12 h, and then allowed to stand overnight. The mixture was heated to 85°C and 10% aqueous sodium hydroxide (140 ml) was added dropwise over 35 min. The stirring at 85°C was continued for 4 h, the mixture cooled down, diluted with water, and extracted with light petroleum. The extract was processed as usual to afford 13·2 (71%) of the ketone *XX*, b.p. 106–110°C/0·6 Torr, which was chromatographed on a column of silica gel (1 000 g) in 95 : 5 light petroleum–acetone. The appropriate fractions (as determined by thin-layer chromatography) were pooled and the predominating component isolated by preparative gas chromatography (3 m column with 15% LAC 6R-860). Yield, 7·8 g of the ketone *XX* boiling at the bath temperature of 110–120°C : : 0·01 Torr. For $C_{13}H_{24}O_2$ (212·3) calculated: 73·53% C, 11·40% H; found: 73·30% C, 11·40% H. IR spectrum (cm^{-1}): 1 720, 1 359, 1 096. Mass spectrum: 212, 85.

Methyl 3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoate (*XXIa*)

A mixture of the ketone *XX* (1·06 g), methoxycarbonylmethylenetriphenylphosphorane[17] (1·67 g), benzoic acid (300 mg), and dry benzene (15 ml) was refluxed under argon for 20 h. Another portion of the phosphorane (1·67 g), benzoic acid (250 mg), and benzene (6 ml) was then added and the reflux continued for additional 24 h. The benzene was then evaporated under diminished pressure and the residual oil extracted by repeated triturations with light petroleum. The extract was processed as usual, the residue (1·02 g) chromatographed on a column of silica gel (particle size, 30–60 micron; 174 g) in 97·5 : 2·5 tetrachloromethane–acetone to recover 0·45 g of the starting ketone *XX* and to obtain 0·38 g (49%, with respect to the recovered ketone *XX*) of the methyl ester *XXIa* boiling at the bath temperature of 130–135°C/0·006 Torr. For $C_{15}H_{26}O_3$ (254·4) calculated: 70·82% C, 10·31% H, 18·87% O; found: 71·10% C, 10·17% H, 19·20% O.

Ethyl 3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoate (*XXIb*)

A mixture of the ketone *XX* (1·06 g), ethoxycarbonylmethylenetriphenylphosphorane[17] (3·48 g), benzoic acid (300 mg), and dry benzene (15 ml) was refluxed under argon for 16 h. Another portion of the phosphorane (1·74 g) and benzoic acid (174 mg) was then added, the whole mixture refluxed for additional 16 h, and processed analogously to the methyl ester *XXIa* to afford 1·29 g of the crude ester *XXIb* which was chromatographed on a column of silica gel (117 g) in 93 : 7 light petroleum–acetone. Recovery, 0·3 g of the ketone *XX*. Yield, 0·8 g (57%) of the ethyl ester *XXIb* boiling at the bath temperature of 135°C/0·007 Torr. For $C_{17}H_{30}O_3$ (282·4) calculated: 72·30% C, 10·71% H; found: 72·45% C, 10·95% H. IR spectrum (cm^{-1}): 1718, 1649, 1150, and 1086.

N-Ethylamide of 3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoic Acid (*XXIc*)

Into a stirred solution of diethyl ethylaminocarbonylmethanephosphonate[18] (1·34 g) in dry dimethylformamide (120 ml) there was added dropwise under argon over 3 min ethanolic sodium ethoxide (from 0·14 g of sodium and 4 ml of absolute ethanol). The mixture was stirred at room temperature for 1 h and than the ketone *XX* (1·06 g) was added dropwise over 5 min. The whole mixture was then stirred for 1 h at room temperature and for 8 h at 75—85°C, cooled down, poured into water (previously acidified with acetic acid), and extracted with light petroleum. The extract was processed as usual to afford 1·3 g of the crude amide *XXIc* which was chromatographed on a column of silica gel (110 g) in 9 : 1 light petroleum–acetone. The appropriate chromatographic fractions were pooled and distilled to afford 0·02 g, 0·40 g, and 0·38 g of fractions boiling at the bath temperature of 160—170°C/0·007 Torr and differing by the content of the particular isomers. For $C_{17}H_{31}NO_2$ (281·4) calculated: 72·55% C, 11·10% H, 4·98% N; found: 72·20% C, 11·09% H, 5·27% N. IR spectrum (cm^{-1}): 3450, 3325, 1666, 1640, 1535, 1504, and 1094.

3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoic Acid (*XXIe*)

The crude ester *XXIb* (2·60 g) was saponified with potassium hydroxide (1·55 g) in water (1·55 ml) and methanol (15·5 ml by keeping the mixture for 48 h at room temperature and for 1 h at the reflux temperature. The methanol was then evaporated under diminished pressure, the residue diluted with water, and the non-acidic portion extracted with ether. The aqueous phase was acidified with aqueous sulfuric acid, the liberated organic acid extracted with ether, and the extract processed as usual to afford 1·53 (65%) of the crude acid *XXIe*.

Chloride of 3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoic Acid (*XXIf*)

A solution of the crude acid *XXIe* (1·53 g) in dry benzene (10 ml) containing one drop of dimethylformamide was treated with thionyl chloride (1·43 g), the mixture kept at room temperature for 24 h, the benzene and excess reagent evaporated, the residue coevaporated with fresh absolute benzene (10 ml), finally under diminished pressure. Yield, 1·64 g of the crude chloride *XXIf* which was immediately used in the next step.

N,N-Diethylamide of 3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoic Acid (*XXId*)

A solution of the crude chloride *XXIf* (1·64 g) in dry ether (25 ml) was added dropwise with stirring over 20 min into a solution of diethylamine (1·32 g) in dry ether (50 ml), the stirring continued at room temperature for 90 min, and the mixture kept overnight. Water was added

to dissolve the precipitate, the ethereal layer separated and processed as usual to afford 1·8 g of a dark residue which was chromatographed on a column of silica gel (particle size, 30–60 μ, 230 g) in 95 : 5 light petroleum–acetone. The appropriate fractions (as determined by thin layer chromatography) were processed to yield 0·79 g of the N,N-diethylamide *XXId* boiling at the bath temperature of 150°C/0·007 Torr to 155°C/0·004 Torr. For $C_{19}H_{35}NO_2$ (309·5) calculated: 73·73% C, 11·40% H, 4·53% N; found: 73·71% C, 11·30% H, 4·74% N. IR spectrum (cm^{-1}): 3070, 1645, 1097.

Nitrile of 3-Methyl-9-(5-methyloxolan-2-yl)-2-nonenoic Acid (*XXII*)

A mixture of the ketone *XX* (1·06 g), cyanomethylenetriphenylphosphorane[19] (3·01 g), and benzoic acid (0·30 g) was refluxed under argon for 24 h. Another portion of the phosphorane (0·75 g) and benzoic acid (75 mg) was then added, the mixture refluxed for additional 8 h, and processed analogously to compound *XXI*. Yield, 1·63 g of the crude nitrile *XXII* which was chromatographed on a column of silica gel (100 g) in 30 : 1 : 20 chloroform–acetone–hexane. The appropriate fractions (as determined by thin-layer chromatography) yielded 1·03 g (85·5%) of the nitrile *XXII* boiling at the bath temperature of 118°C/0·009 to 125°C/0·007 Torr. For $C_{15}H_{25}NO$ (235·4) calculated: 76·54% C, 10·71% H, 5·95% N; found: 76·45% C, 10·71% H, 6·27% N. IR spectrum (cm^{-1}): 2220, 1633, and 1095. Mass spectrum: 235, 85.

3-(2-Oxolanyl)propionic Acid (*XXIV*)

Saponification of the ester *II* with aqueous-methanolic potassium hydroxide afforded the acid *XXIV*, b.p. 118°C/0·25 Torr to 124°C/0·4 Torr (reported[20], 118–120°C/2 Torr).

Methyl 7-(2-Oxolanyl)heptanoate (*XXV*)

The acid *XXIV* (14·42 g) and monomethyl adipate (32·02 g) were added into methanolic sodium methoxide (from 0·21 g of sodium and 90 ml of absolute methanol) and the mixture electrolysed in an apparatus described by Seher and Kühnast[21] (initial intensity 3 A gradually dropped to 1·75 A) until the electrolyte was alkaline to phenolphthalein (tor 4 h). Portions insoluble in methanol were filtered off with active charcoal, the filtrate acidified with acetic acid, the methanol evaporated under diminished pressure, and the residue dissolved in ether. Usual work-up yielded 25·4 g of crude esters which were chromatographed on a column of silica gel (900 g) in 9 : 1 light petroleum–ether. Yield, 6·65 g of the crude ester *XXV*.

7-(2-Oxolanyl)heptanoic Acid (*XXVI*)

The crude ester *XXV* (6·65 g) was saponified by standing for 48 h in a solution of potassium hydroxide (5·23 g) in water (5·2 ml) and methanol (52·3 ml). The methanol was then evaporated under diminished pressure, the residue diluted with water, the non-acidic portion extracted with ether, the aqueous phase acidified with aqueous sulfuric acid to Congo Red paper, the liberated organic acid extracted with ether, and the extract processed as usual to afford 5·03 g of the crude acid *XXVI*.

Chloride of 7-(2-Oxolanyl)heptanoic Acid (*XXVII*)

Into a stirred solution of the crude acid *XXVI* (5·03 g) in dry benzene (50 ml) there was added dropwise at room temperature thionyl chloride (4·52 g) and the stirring continued for 1 h at room

temperature. Excess thionyl chloride and benzene were then evaporated and the residue coevaporated with two portions of fresh dry benzene, finally under diminished pressure. Yield, 5·8 g of the crude chloride *XXVII*.

8-(2-Oxolanyl)-2-octanone (*XXVIII*)

The crude chloride *XXVII* (5·8 g) in dry benzene (20 ml) was added dropwise over 30 min to a stirred solution of diethyl ethoxymagnesiummalonate in benzene (obtained[7] from 2 g of magnesium, 12·8 g of diethyl malonate, and 5·4 ml of ethanol in the presence of benzene) at room temperature. The reaction mixture was refluxed for 1 h, cooled down, poured onto ice, acidified with 5% aqueous sulfuric acid, and the benzene layer set aside. The aqueous layer was extracted with ether, the extract combined with the benzene layer, washed with 1M-H_2SO_4 and then water till neutral, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. Excess diethyl malonate was removed by distillation at 115–120°C/9 Torr. To the residual crude ethyl 7-(2-oxolanyl)heptanoylmalonate (8 g) there was added propionic acid (17·5 g) and sulfuric acid (0·25 g). The whole mixture was refluxed for 3 h, allowed to cool, treated with 2M-H_2SO_4 (2·2 ml), refluxed for additional 2 h, cooled down, poured onto ice and water, made alkaline with 30% aqueous sodium hydroxide, and extracted with ether. The extract was processed as usual and dried over anhydrous magnesium sulfate to afford 4·5 g of the crude ketone *XXVIII* which was chromatographed on a column of silica gel (140 g) in 95 : 5 light petroleum–acetone. Yield, 1·87 g of the ketone *XXVIII* boiling at the bath temperature of 105–115°C/0·006 Torr. For $C_{12}H_{22}O_2$ (198·3) calculated: 72·68% C, 11·18% H; found: 72·43% C, 11·16% H. IR spectrum (cm^{-1}): 1721, 1094, 1067, and 1050.

Ethyl 3-Methyl-9-(2-oxolanyl)-2-nonenoate (*XXIII*)

Into a solution of the ketone *XXVIII* (1·75 g) and diethyl ethoxycarbonylmethanephosphonate[22] (2·28 g) in absolute ethanol (13 ml) there was added dropwise at room temperature over 5 min under argon and with stirring ethanolic sodium ethoxide (from 0·22 g of sodium and 6 ml of absolute ethanol). The whole mixture was stirred for additional 2 h and kept at room temperature for 16 h. The ethanol was evaporated at room temperature under diminished pressure, the residue poured into water (previously acidified with acetic acid), and extracted with ether. The extract was processed as usual and the residue chromatographed on a column of silica gel (120 g) in 97 : 3 light petroleum–acetone to afford 2·16 g (91%) of the ester *XXIII* boiling at the bath temperature of 135°C/0·006 Torr to 142°C/0·005 Torr. For $C_{16}H_{28}O_3$ (268·4) calculated: 71·60% C, 10·52% H; found: 71·47% C, 10·49% H. IR spectrum (cm^{-1}): 1719, 1651, 1221, 1148, 1096, and 1067.

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