# A NEW METHOD OF PREPARATION OF α,β-γ,δ-UNSATURATED SECONDARY ALCOHOLS*

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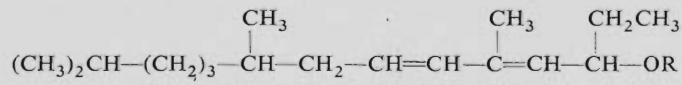
A method of preparation of β-hydroxy-γ,δ-unsaturated nitriles used as intermediates for the synthesis of α,β-γ,δ-unsaturated ketones and alcohols, and having the activity of insect juvenile hormone is described.

In view of their biological properties the synthetic analogues of the insect juvenile hormone (juvenoids) are classified among potential modern pesticides[1,2]. Their wider practical use is hampered by their low stability in the insect organism and in the field, and a relatively high volatility. One of the routes leading to the elimination of these disadvantages is the orientation to the so-called juvenogens. *i.e.* compounds which in the insect organism set free the active component under the effect of enzymatic systems[3-5]. The types of active components of juvenogens which were prepared and described in our laboratory include the unsaturated alcohol *I*. Its stearate *II* was then used in the study of the conditions of enzymatic hydrolysis in some insect species[3]. Favourable biological properties of the alcohol *I* induced us to undertake a deeper study of the question of the preparation of substances of this type.



*I*, R = H *II*, R = —$CO(CH_2)_{16}CH_3$

The most advantageous route for the preparation of α,β-γ,δ-unsaturated secondary alcohols seems to lead *via* the corresponding α,β-γ,δ-unsaturated ketones, with subsequent reduction with sodium borohydride. Till now the reactions of organometallic compounds with α,β-γ,δ-unsaturated acids[6], or with their S-alkyl and S-aryl thioesters[7] have been used for their preparation. In an effort to find a more economical way of preparing these dienones we tried to utilize corresponding nitriles as possible intermediates. For example, the reaction of saturated ketones leads to unsaturated nitriles *via* Scheme 1.

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$$R^1CH_2COR^2 + {}^{(-)}CH_2CN \rightarrow \underset{III}{R^1CH_2C(R^2)(OH)CH_2CN} \rightarrow \underset{IV}{R^1CH_2C(R^2)=CHCN}$$

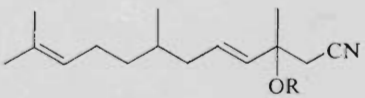
SCHEME 1

$$R^1CH{=}CHCOCH_3 \xrightarrow{{}^{(-)}CH_2CN} \underset{V}{RCH{=}CHCH_3(C)(OH)CH_2CN} \xrightarrow{R^2MgX} \rightarrow \underset{VII}{[R^1CH{=}CHC(CH_3){=}CHCN]} \rightarrow \underset{VI}{R^1CH{=}CHC(CH_3){=}CHCOR^2}$$

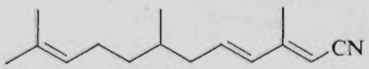
SCHEME 2

3-Hydroxy nitrile *III* formed in this reaction can be isolated from the reaction mixture in the majority of cases[8-10] and then converted by dehydration to the unsaturated nitrile *IV* (ref.[8,9,11]).

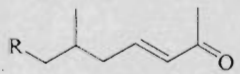
We made use of this fact for the preparation of α,β-γ,δ-unsaturated ketones in agreement with reaction Scheme 2.



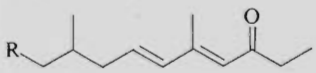
*VIII*, R = —O—CH(—O—$(CH_2)_3CH_2$)—
*IX*, R = H



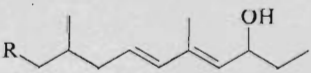
*X*



*XI–XIV*



*XV–XVIII*



*I*, *XIX–XXI*

*XI*, *XV*, *XIX*, R = $(CH_3)_2C{=}CH$—
*I*, *XII*, *XVI*, R = $(CH_3)_2CHCH_2$—
*XIII*, *XVII*, *XX*, R = $CH_2(CH_2)_4CHCH_2$—
*XIV*, *XVIII*, *XXI*, R = $CH_3CH(CH_2)_4CHCH_2$—

On reaction with n-butyllithium in ether at −60°C to −70°C we prepared its lithium salt which was allowed to react *in situ* at −70°C with α,β-unsaturated ketone. We obtained thus the β-hydroxy-γ,δ-unsaturated nitrile *V* as a relatively stable compound which, as a rule, can be isolated and purified chromatographically and by vacuum distillation. Its reaction with an excess of alkylmagnesium halide, first in ether at about 0°C and then in benzene at boiling point temperature afforded the corresponding dienone *VI* in an approximate ratio of 65% of 4*E*- and 35% of 4*Z*-isomer. The preparation of β-hydroxy-γ,δ-unsaturated nitriles in the described manner has also been published by Sauverte and coworkers[12].

The advantage of the unsaturated hydroxy nitriles used for the preparation of α,β-γ,δ-unsaturated ketones consists especially in the easy accessibility of the starting α,β-unsaturated ketones, prepared from aldehydes by condensation with acetone in the presence of barium hydroxide[16] or by Wittig's reaction of aldehydes with acetonylidenetriphenylphosphorane[17], and the ensuing accessibility of the unsaturated hydroxy nitrile. We found that on reaction of such a nitrile with alkylmagnesium bromide dehydration to unsaturated 2,4-diene nitrile *VII* takes place first, which is then converted to the corresponding dienone. This course was checked by the direct effect of ethylmagnesium bromide on α,β-γ,δ-unsaturated nitrile which was obtained from the corresponding β-hydroxy-γ,δ-unsaturated nitrile on reaction with ethylmagnesium bromide at room temperature in ether. When alkyllithium is used instead of the Grignard reagent polymerization of the unsaturated nitrile mostly takes place and the yield of ketone *VI* is negligible. The reaction of nitrile *VIII* also has a similar course. This β-tetrahydropyranyloxy-γ,δ-unsaturated nitrile, obtained from hydroxynitrile *IX* using the method described by Miyashita and coworkers[13], gives on reaction with ethylmagnesium bromide at room temperature and under the conditions described by us for the reduction of β-hydroxynitriles, the saturated nitrile *X* and then, at boiling temperature of benzene, the corresponding dienone *XV*.

Table I includes ketone *XI*–*XIV* described by us and α,β-γ,δ-unsaturated ketones *XV*–*XVIII* which we obtained from them according to Scheme 2. The corresponding secondary alcohols *I*, *XIX*–*XXI*, obtained on reduction of ketones *XV*–*XVIII* with sodium borohydride are given in Table II. Compounds *I*, *XV*–*XXI*, analogues of juvenile hormone, were found to possess a distinct group-specific effect in insects.

## EXPERIMENTAL

The substances described were characterized by IR spectroscopy (UR-20, $CCl_4$) mass spectrometry (AEI MS-902) and $^1$H-NMR spectroscopy (Varian XL-200, $CDCl_3$, tetramethylsilane) The chemical shifts are expressed in δ-units and the ratio of the 4*E*- and 4*Z*-isomers was also evaluated from the spectra (preparation of compounds *XV*—*XVIII*). Column chromatography was carried out on silica gel (Gebr. Herrmann, Köln-Ehrenfeld, GFR).

TABLE I
Properties of Compounds *XI—XVIII*

| Compound[a] B.p., °C | Method of preparation | Mass sp. $M^+$ | IR sp. $cm^{-1}$ | Formula (m.w.) | Calc./Found % C | Calc./Found % H |
|---|---|---|---|---|---|---|
| *XI*[b,d] 148—160 | *A* | 194 | 1 679, 1 629 1 378, 1 369 980 | $C_{13}H_{22}O$ (194·3) | 80·35 80·43 | 11·41 10·78 |
| *XII*[c] 151—158 | *A* | 196 | 3 040, 1 680 1 630, 1 478 980 | $C_{14}H_{24}O$ (196·3) | 79·53 79·01 | 12·32 12·12 |
| *XIII* 154—166 | *B* | 222 | 1 681, 1 630 1 450, 1 360 | $C_{15}H_{26}O$ (222·4) | 81·02 80·51 | 11·79 11·74 |
| *XIV* 154—160 | *B* | 236 | 1 680, 1 630 1 450, 1 360 | $C_{16}H_{28}O$ (236·4) | 81·29 80·72 | 11·94 11·24 |
| *XV*[e,g] 128—136 | — | 248 | 1 686, 1 634 1 589, 1 379 969 | $C_{17}H_{28}O$ (248·4) | 82·20 81·79 | 11·36 10·97 |
| *XVI*[f] 131—138 | — | 250 | 1 694, 1 632 1 590, 1 383 1 366, 970 | $C_{17}H_{30}O$ (250·4) | 81·53 81·32 | 12·08 12·28 |
| *XVII* 133—140 | — | 276 | 1 685, 1 634 1 589, 969 | $C_{19}H_{32}O$ (276·5) | 82·54 81·91 | 11·66 11·36 |
| *XVIII* 135—151 | — | 290 | 1 688, 1 632 1 589, 970 | $C_{20}H_{34}O$ (290·5) | 82·67 81·85 | 11·80 11·17 |

[a] Bath temperature; vacuum: 1·6 kPa (*XI—XIV*), 13 Pa (*XV—XVIII*); [b] see ref.[14]; [c] see ref.[15]; [d] $^1$H-NMR spectrum: $C_{(2)}$—$CH_3$ 2·25 (br s), $C_{(3)}$—H 6·08 (br d) $J = 16$, $C_{(4)}$—H 6·79 (pent) $J_{3,4} = 15·8$, $J_{4,5} = 7·5$, $C_{(6)}$—$CH_3$ 0·92 (d) $J = 6·6$, $C_{(6)}$—H 1·50—1·70 (m), $C_{(9)}$—H 5·085 (br t) $J = 7$, $C_{(10)}$—2 × $CH_3$ 1·61 1·69 (2 × br s); [e] see ref.[18]; [f] see ref.[19]; [g] $^1$H-NMR spectrum: $C_{(1)}$—$CH_2$ 2·48 (q) $J = 7·3$, $C_{(2)}$—$CH_3$ 1·09 (t) $J = 7·3$, $C_{(4)}$—H 6·06 (br s), $C_{(5)}$—$CH_3$ 2·25 (d) $J = 1·1$, $C_{(6)}$—H, $C_{(7)}$—H 6·00—6·20 (m), $C_{(9)}$—$CH_3$ 0·89 (d) $J = 6·6$, $C_{(12)}$—H 5·10 (br t) $J$ × 7·7, $C_{(13)}$—2 × $CH_3$ 1·60 1·68 (s × br s).

Preparation of Ketones *XI—XIV*

*Method* A: A mixture of 0·54 mol of aldehyde, 222 g of acetone, 150 ml of water and 30 g of ground barium hydroxide was refluxed under argon for 3 h. Acetone was evaporated on a vacuum rotatory evaporator, the residue was diluted with 350 ml of water and extracted with three 150 ml portions of hexane. The combined organic extracts were washed with 100 ml of a saturated sodium chloride solution and filtered through a column of 10 g of Celite 545. After evaporation of hexane the residue was distilled on a glass column (Vigreux, 20 cm). The yields were about 50% (referred to the starting aldehyde).

*Method* B: 17·3 mmol of aldehyde and 18 mmol of acetonylidenetriphenylphosphorane were refluxed in benzene under argon for 4 h. The solvent was evaporated on a rotatory evaporator, the residue was diluted with 15 ml of pentane and the solution decanted from the solid residue. The latter was extracted with three 15 ml portions of pentane and the combined extracts were evaporated to dryness. The residue was percolated through a five-fold amount of silica gel and finally distilled at reduced pressure. Yield, 70—90%.

α,β-γ,δ-Unsaturated Ketones *XV—XVIII*

*a*) *Preparation of* 3-*hydroxynitriles*: An ethereal solution of n-butyllithium was prepared from n-butyl bromide (40 mmol) and lithium wire (80 gat) in 110 ml of ether. which was then diluted

TABLE II

Properties of compounds *I*, *XIX—XXI*

| Compound[a] B.p., °C | Mass sp. $M^+$ | IR spectrum $cm^{-1}$ | Formula (m.w.) | Calc./Found | |
|---|---|---|---|---|---|
| | | | | % C | % H |
| *XIX* | | | | | |
| 131—145 | 250 | 3 625, 3 030, 1 609, 1 570, 1 377, 1 000, 968 | $C_{17}H_{30}O$ (250·4) | 81·53<br>81·19 | 12·08<br>11·98 |
| *I* | | | | | |
| 130—141 | 252 | 3 640, 3 625, 3 035, 1 383, 1 367, 1 000, 968 | $C_{17}H_{32}O$ (252·4) | 80·88<br>80·27 | 12·78<br>12·10 |
| *XX*[b] | | | | | |
| 139—143 | 278 | 3 620, 3 035, 1 646, 1 625, 1 000, 968 | $C_{19}H_{34}O$ (278·5) | 81·95<br>81·64 | 12·31<br>12·12 |
| *XXI* | | | | | |
| 139—152 | 292 | 3 625, 3 035, 1 650, 1 625, 1 000, 968 | $C_{20}H_{36}O$ (292·5) | 82·12<br>81·43 | 12·40<br>12·10 |

[a] Bath temperature; vacuum: 13 Pa; [b] $^1$H-NMR spectrum: $C_{(2)}$—$CH_3$ 1·02 (t), $C_{(2)}$—H 1·57 (pent), $C_{(3)}$—H 4·20 (m), $C_{(4)}$—H 5·50 (br m), $C_{(5)}$—$CH_3$ 1·80 (br s) (4*E*-isomer) 1·77 (d) $J$ = 1·2 (4*Z*-isomer), $C_{(6)}$—H 5·90 (d) $J$ = 12·6 (4*Z*-isomer) 5·96 (d) $J$ = 12·6 (4*E*-isomer), $C_{(7)}$—H 6·20—6·40 (m,) $C_{(9)}$—$CH_3$ 0·98 (d) $J$ = 6·8, $C_{(9)}$—H 1·50—1·70 (m).

with 120 ml of ether and cooled to —70°C. Acetonitrile (80 mmol) in 20 ml of ether was then added to the solution at —70°C under argon over 15 min. The mixture was stirred for 45 min and ketone *XI*—*XIV* (20 mmol) was then added dropwise over 5 min. The mixture was further stirred at —70°C for 5 min and at 0°C (cooling with ice and water) for another 15 min. It was then decomposed with ice and worked up. The crude β-hydroxynitrile obtained can be purified by chromatography on silica gel and drying *in vacuo* at 60°C and 13 Pa for 30 min, or it can be worked up directly. Yields are about 59—71%.

*b*) *Preparation of ketones* XV—XVIII: β-Hydroxynitrile in 20 ml of ether was added to a solution of ethylmagnesium bromide (prepared from ethyl bromide, 60 mmol, and magnesium shavings, 60 gat) in 80 ml of ether under cooling and stirring and under argon over 30 min. The mixture was allowed to warm up at room temperature, then diluted with 60 ml of benzene and refluxed for at least 90 min (control by TLC). After cooling the mixture was poured onto a mixture of 20 ml of 1M-$H_2SO_4$ and 15 g of ice, the organic phase was separated and the aqueous phase extracted with 30 ml of benzene. The combined organic extracts were washed with two 50 ml portions of a saturated sodium hydrogen carbonate solution and worked up. Yield, 38 to 51%. The ratio of the isomers 4*E*/4*Z* ranges from 60—73% and 40—27%.

2,6,10-Trimethyl-1,3,9-undecatrienyl cyanide (*X*)

n-Butyllithium was prepared from butyl bromide (5·5 g, 40 mmol) and lithium wire (0·56 g, 80 mmol) in 110 ml of ether. Under the conditions already mentioned acetonitrile (3·3 g, 80 mmol) and then 6,10-dimethyl-3,9-undecadien-2-one (*XI*, 3·89 g, 20 mmol) were then added consecutively to the mixture, in a total of 16 ml of ether. The mixture was worked up to afford 2·9 g of compound *IX* (62%). IR spectrum: 3615, 1380, 978; NMR spectrum: $C_{(1)}$—H 2·57 (s); $C_{(2)}$—$CH_3$ 1·455 (s); $C_{(3)}$—H 5·57 (d) $J_{3,4} = 16$; $C_{(4)}$—H 5·80 (dt) $J_{4,3} = 16$, $J_{4,5} = 6·6$; $C_{(6)}$—$CH_3$ $C_{(10)}$—2 × $CH_3$ 0·865 (d) $J = 6·5$.

A solution of compound *IX* (2·9 g, 12·3 mmol) in 15 ml of ether was added dropwise and under stirring and cooling with ice and water to a solution of ethylmagnesium bromide in 60 ml of ether, prepared from ethyl bromide (4·4 g, 40 mmol) and magnesium shavings (0·97 g, 40 gat). The mixture was allowed to warm to room temperature and then poured onto ice. The organic phase was separated and the aqueous phase extracted with ether. The combined organic phases were dried over sodium sulfate and then percolated through a 5-fold amount of silica gel. The residue was dried at 50°C for 30 min in a vacuum (13 Pa), affording 2·0 g of product (75%). For $C_{15}H_{23}N$ (217·4) calculated: 82·89% C, 10·67% H, 6·44% N; found: 82·12% C, 10·64% H, 7·22% N. IR spectrum: 2220, 1677, 1642, 1394, 970 $cm^{-1}$. Mass spectrum: $M^+ = 217$ *m/z*. NMR spectrum: $C_{(1)}$—H 5·20 (br s); $C_{(2)}$—$CH_3$ 2·00 (d) $J = 1·6$ (1*Z*-isomer); 2·14 (d) $J = 0·9$ (1*E*-isomer); $C_{(3)}$—H 6·05—6·15 (m) (1*E*-isomer); 6·67 (d) $J_{3,4} = 15·4$ (1*Z*-isomer); $C_{(4)}$—H 6·05 to 6·15 (m) (1*E*-isomer); 6·18 (pent) $J_{4,3} = 15·3$; $J_{4,5} = 7·2$; $C_{(6)}$—$CH_3$ 0·89 (d) $J = 6·8$ (1*E*-isomer); 0·91 (d) $J = 6·8$ (1*Z*-isomer); $C_{(9)}$—H 5·08 (m); $C_{(10)}$—2 × $CH_3$ 1·61 (2 × br s). From the integrals the ratio of the isomers 1*E*/1*Z* = 2/1 was determined.

2,6,10-Trimethyl-2-tetrahydropyranyloxyundeca-3,9-dienyl cyanide (*VIII*)

A mixture of compound *IX* (6·0 g, 25·5 mmol) and pyridinium toluenesulfonate (0·64 g, 2·55 mmol) in 40 ml of dihydropyran was refluxed for 90 min. After elimination of the excess of dihydropyran by distillation and chromatographic purification of the residue on a 20-fold amount of silica gel a fraction was obtained which contained 2 substances which were separated by distillation:

*a*) 2·4 g (30%) of compound *VIII*, b.p. 163—179°C/13 Pa (temperature of the bath). For $C_{20}H_{33}NO_2$ (319·5) calculated: 75·19% C, 10·41% H; found: 75·15% C, 10·77% H. Mass spectrum: $M^+ = 319m/z$. IR spectrum: 2255, 1670, 1125, 1117, 1080, 1036, 1025, 994 $cm^{-1}$.

*b*) 0·9 g (21%) of $CH_2(CH_2)_3CH(O)—CH(CH_2)_3CH_2$ (O), boiling at 115—121°C (bath temperature). Mass spectrum: $M^+ = 186$ ($C_{10}H_{18}O_3$); 168 ($C_{10}H_{16}O_2$), 144 ($C_7H_{12}O_3$), 140 ($C_9H_{16}O$), 85 (BP). NMR spectrum: 1·32—1·91 (12 H, m), 3·44—4·18 (4 H, m), 4·94 (2 H br s).

Preparation of Unsaturated Alcohols *I*, *XIX—XXI*

From ketones *XV—XVIII* the corresponding alcohols *I*, *XIX—XXI* were obtained by reduction with a two-molar excess of sodium borohydride in methanol at 0°C. The isolation of the product and the purification was carried out by working up the reaction mixture and chromatography on a 10-fold amount of silica gel and distillation. Yield, 96%.

Biological Activity of the Substances Prepared

The juvenilizing activity of substances *I*, *XV—XXI* is expressed in ID-50 Morph. units[1], meaning the amount of the substance in micrograms, that — when applied topically on an individual — caused the formation of an adultoid in which one half of the characters of the preceding developmental stage remained unchanged. The above mentioned juvenoids were extremely active on the beetle *Tenebrio molitor* (activity interval 0·1—0·0007).

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