Synthesis of Compounds with Juvenile Hormone Activity

Part VI. A Mixture of (±)-Dehydrojuvabione and its Stereoisomer

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A total synthesis of the title compound, a sesquiterpene ester with high juvenile hormone activity, is described.

Dehydrojuvabione is a compound with high juvenile hormone activity isolated from Czechoslovak balsam fir (Abies balsamea L.) by Šorm and his co-workers.1) The structure Ib was assigned to it on the basis of spectroscopic data and its chemical correlation to its congener, juvabione.1,2) In view of the recent revision of the structure of juvabione as depicted in II,3) dehydrojuvabione should now be represented as IIIb.* This paper describes in detail the synthesis of a mixture of (±)-dehydrojuvabione (IIIb) and its stereoisomer (Ib)4) which is the extension of our work on the synthesis of (±)-juvabione.5)**

The synthetic scheme was similar to the previous one5) but somewhat modified owing to the presence of an α,β-unsaturated carbonyl function in the final product (IIIb). In the intermediates VI~XII, this function was in the form of 1,3-diol system. This was oxidized and dehydrated to give the final product (Ib+IIIb).

β-(p-Methoxyphenyl)butyryl chloride(IVa),5) prepared from the corresponding acid, was condensed with diethyl ethoxymagnesioformate to give an ester (IVb). This was hydrolyzed and decarboxylated to give a ketone (IVc, 70% from the acid), characterized as a crystalline 2,4-dinitrophenylhydrazone, mp 109~111°C. Carbethoxylation of the ketone (IVc) with diethyl carbonate and sodium amide gave a β-keto ester (IVd, 73%). This

* The formulas of juvabione and dehydrojuvabione depicted in our previous papers4~7) should be corrected as shown in this paper.

** After the publication of our work three other syntheses of (±)-juvabione have appeared.8~10)
was hydrogenated over Raney nickel W-7 to give a hydroxy ester (V, 98%). Addition of methyl magnesium iodide to this ester yielded 2-methyl-6-(p-methoxyphenyl)-heptane-2,4-diol (VI, 98%).

This was converted to a $\beta,\gamma$-unsaturated ketone (VIII, 91%) by treatment with oxalic acid in methanol-water. Hydrogenation of the enone (VIII) over Pd-C gave a dihydroxy ketone (IXa, 90%), which was acetylated with acetyl chloride-pyridine to give a diacetate (IXb, 87%). Addition of hydrogen cyanide to the CO group gave a cyanohydrin (X, 95%) as a viscous oil. This was dehydrated with phosphorus oxychloride and pyridine to give an unsaturated nitrile

The Birch reduction (Dryden’s modification\(^{\text{11}}\)) of this diol gave a diene (VII, 91%).

Hydrolysis of the nitrile with concomitant removal of the acetyl group was effected by heating with potassium hydroxide in diethylene glycol-water to give a dihydroxy acid (XII, 95%). This was oxidized with the Jones chromic acid reagent to give a stereoisomeric mixture of hydroxytodomatuic acid (XIII, 70%).

This ω-hydroxy ketone (XIII) dissolved in benzene was heated in the presence of a small amount of hydrochloric acid and iodine to give a mixture of (±)-dehydrotodomatuic acid (IIIa) and its stereoisomer (Ia) as a viscous oil. This partly crystallized after standing in a refrigerator. In analogy with the case of (±)-todomatuic acid the crystalline acid, mp 66–67°C, is probably the desired stereoisomer (IIIa) although there is no rigid proof. The solution IR and NMR spectra of the pure crystalline acid was identical with those of the oily mixture (IIIa+Ia). This mixture was esterified with diazomethane to give a mixture of (±)-dehydrojuvabione (IIIb) and its stereoisomer (Ib). The IR and NMR spectral properties of the synthetic product agreed well with those of dehydrojuvabione kindly provided by Professor F. Sorm. Very minor differences are obviously due to the presence of the isomer (Ib) in the synthetic product. The synthetic and natural materials were indistinguishable by GLC on an OV-17 column.

The juvenile hormone activity of the synthetic product (Ib+IIIb) was tested on newly molted last instar nymphs of Pyrrhocoris apterus L. by the courtesy of Dr. W. S. Bowers of USDA Agricultural Research Service. The activity was less than that of (±)-juvabione. At treatment of less than 5 μg no activity was observed. At 5 μg some very slight modifications were evident, but these were chiefly wing deformations and are very difficult to interpret as definite activity. Only three of the eight insects tested at this dose showed wing deformation; the others were normal. At 20 μg very definite nymphal-adult intermediates were produced which corresponded to that which was obtained with 1~2 μg of juvabione. At this treatment (20 μg) three of six insects were definite intermediates, nearly supernumerary nymphs. At 40 μg treatment all insects (seven) gave supernumerary nymphs.

The bioassay with P. apterus L. was also kindly performed by Professor F. Sorm and Dr. K. Sláma of Czechoslovak Academy of Sciences. The results are shown in Table I.

<table>
<thead>
<tr>
<th>Juvabione</th>
<th>Dehydrojuvabione</th>
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<tr>
<td>Natural</td>
<td>Synthetic</td>
</tr>
<tr>
<td>0.1 μg</td>
<td>0</td>
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<tr>
<td>1 μg</td>
<td>2</td>
</tr>
<tr>
<td>10 μg</td>
<td>5</td>
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The activity is expressed in the scores previously described by Williams and Sláma (0—normal adults; 3—adultoids; 5—perfect sixth instar larvae).

**EXPERIMENTAL**

All mps and bps were uncorrected. IR spectra refer to nujol mulls for solid samples and films for liquids. NMR spectra were recorded at 100 MHz in CCl₄ with TMS as an internal standard unless otherwise stated.

Diethyl ω-(p-methoxyphenyl)butyrylmalonate (IVb). A solution of diethyl ethoxymagnesiomalonate was prepared from Mg (18 g), diethyl malonate (120 g) and abs EtOH (85 ml). The mixture was stirred and heated under reflux for 3 hr. The excess of EtOH was thoroughly removed from it by repeated addition and removal of dry benzene. To the residue dissolved in dry ether (250 ml), a solution of IVa (from 130 g of the acid) in ether (100 ml) was added dropwise at 5~10°C with stirring. The mixture was left to stand overnight at room temperature, then stirred and heated under reflux for 15 min, cooled and mixed with ice-
cooled dil H$_2$SO$_4$ (from 40 ml of concd. H$_2$SO$_4$ and 200 ml of water). The ether layer was separated and the aqueous layer was extracted with ether. The combined ethereal solution was washed with water, NaHCO$_3$aq and brine, dried (MgSO$_4$) and concentrated to give crude IVb (260 g). $\nu_{\text{max}}$ 1740, 1720, 1640, 1600, 1230, 1020, 820 cm$^{-1}$. This was employed for the next step without further purification.

4-(p-Methoxyphenyl)pentan-2-one (IVc). A solution of IVb (260 g) in AcOH (240 ml) was mixed with dil H$_2$SO$_4$ (from 30 ml of concd. H$_2$SO$_4$ and 160 ml of water) and the mixture was stirred and heated under reflux for 7 hr. After dilution with water, it was extracted with ether. The extract was washed with water, NaHCO$_3$aq and brine, dried (K$_2$CO$_3$) and concentrated. The residue was distilled to give 106 g (70% from the acid) of IVc, $\delta$ 125$^\circ$-130$^\circ$/3 mm. An analytical sample boiled at 94$^\circ$-95$^\circ$/0.15 mm, $\delta$ 1.5104; $\nu_{\text{max}}$ 1715, 1612, 1585, 1515, 1252, 1180, 1030, 840 cm$^{-1}$; $\delta$ 1.16 (3H, d, J=8Hz), 1.88 (3H, s), 2.48 (2H, q), 3.12 (1H, sext), 3.62 (3H, s), 6.65 (2H, d, J=8Hz), 6.98 (2H, d, J=8Hz) ppm. Anal. Found: C, 75.05; H, 8.21. Calcd. for C$_{12}$H$_{16}$O$_2$: C, 74.97; H, 9.39%.

2,4-Dinitrophenylhydrazone. Orange needles from EtOAc, mp 109$^\circ$-111$^\circ$ (dec). $\nu_{\text{max}}$ 3400, 3100, 1620, 1595, 1515, 1285, 1260 cm$^{-1}$. Anal. Found: C, 55.12; H, 5.58; N, 13.90. Calcd. for C$_{18}$H$_{22}$O$_6$N$_4$: C, 55.38; H, 5.68; N, 14.35%.

Ethyl 3-oxo-5-(p-methoxyphenyl)hexan-1-oate (IVd). A solution of IVc (105 g) in dry ether (200 ml) was added dropwise to a suspension of NaNH$_2$ (45 g) in diethyl carbonate (350 g) and ether (300 ml). After the exothermic reaction had been subsided, the mixture was stirred and heated under reflux for 2.5 hr. It was cooled, poured into ice-water containing AcOH (80 ml) and extracted with ether. The extract was washed with water, NaHCO$_3$aq and brine, dried (MgSO$_4$) and concentrated, The residue was distilled to give 102 g (73% of the acid) of IVd, bp 150$^\circ$-160$^\circ$/0.1 mm, $\delta$ 1.5048; $\nu_{\text{max}}$ 1745, 1712, 1640 (sh), 1612, 1585, 1515, 1250, 1180, 1030, 835 cm$^{-1}$; $\delta$ 1.16 (6H, m), 2.60 (1H, d, J=2Hz), 2.68 (1H, s), 3.15 (2H, s), 3.63 (3H, s), 6.02 (2H, q, J=7Hz), 6.71 (2H, d, J=8Hz), 7.03 (2H, d, J=8Hz) ppm. Anal. Found: C, 73.97; H, 9.39%.

Ethyl 3-hydroxy-5-(p-methoxyphenyl)hexan-1-oate (V). A solution of IVd (46 g) dissolved in 95% EtOH (300 ml) was hydrogenated over Raney nickel W-7 (30 g) at 50$^\circ$C and an initial pressure of 50 kg/cm$^2$ for 4 hr. The catalyst was filtered off and the filtrate concentrated in vacuo to give 45 g (98%) of crude V. An analytical sample boiled at 145$^\circ$-147$^\circ$/0.1 mm, $\delta$ 1.5020; $\nu_{\text{max}}$ 3500, 1740, 1612, 1585, 1515, 1250, 1180, 1030, 830 cm$^{-1}$; $\delta$ 1.20 (6H, m), 1.60 (2H, m), 2.25 (2H, t, J=6Hz), 2.90 (1H, br. -OH), 3.65 (3H, s), 4.00 (2H, m), 6.72 (2H, d, J=7Hz), 7.03 (2H, d, J=7Hz) ppm. Anal. Found: C, 67.89; H, 7.82. Calcd. for C$_{15}$H$_{20}$O$_3$: C, 67.64; H, 7.63%.

2-Methyl-6-(p-methoxyphenyl)heptane-2,4-diol (VI). A solution of V (40 g) in ether (100 ml) was added dropwise to a stirred solution of a Grignard reagent prepared from MeLi (106 g) and Mg (18 g) in ether (400 ml). After the addition the mixture was stirred and heated under reflux for 2 hr, cooled and poured into ice-NH$_4$Claq. It was extracted with ether. The extract was washed with NH$_4$Claq and brine, dried (MgSO$_4$) and concentrated to give 39 g (98%) of crude VI. An analytical sample boiled at 149$^\circ$-150$^\circ$/0.1 mm, $\delta$ 1.5072; $\nu_{\text{max}}$ 3400, 1615, 1585, 1515, 1250, 1180, 1030, 833 cm$^{-1}$; $\delta$ 1.18 (9H, unresolved q), $\sim$ 1.5 (4H, m), $\sim$ 2.80 (1H, m), 3.68 (3H, s), $\sim$ 3.6 (1H, m), 4.28 (2H, br, 2-OH), 6.72 (2H, d, J=7Hz), 7.02 (2H, q) ppm. Anal. Found: C, 71.83; H, 9.52. Calcd. for C$_{15}$H$_{24}$O$_3$: C, 71.39; H, 9.59%.

2-Methyl-6-(4'Methoxycyclohexa-1',4'-dienyl)heptane-2,4-diol (VII). A solution of VI (20 g) in THE (100 ml) and t-BuOH (100 ml) was added to liquid NH$_3$ (350 ml) cooled in a dry ice-acetone bath. Lithium (7 g) was added portionwise during 30 min to the stirred solution. After the addition, the mixture was stirred for 4.5 hr at dry ice-acetone temperature. Then the excess Li was destroyed by the addition of EtOH (30 ml). The mixture was left at room temperature to evaporate NH$_3$. Water (200 ml) was added to the residue with stirring. The mixture was then concentrated in vacuo to remove THF, t-BuOH and EtOH. The remaining aqueous solution was extracted with ether. The ether extract was washed with water and sat brine, dried (K$_2$CO$_3$) and concentrated to give 18.2 g (91% of crude oily VII. An analytical sample boiled at 133$^\circ$-135$^\circ$/0.08 mm, $\delta$ 1.4902; $\nu_{\text{max}}$ 3400, 1692, 1660, 1220, 1170, 790 cm$^{-1}$; $\delta$ 1.00 (3H, d, J=8Hz), 1.18 (3H, s), 1.21 (3H, s), $\sim$ 1.40 (4H, m), $\sim$ 2.00 (1H, m), 2.62
(2H, s), 3.44 (3H, s), ~3.80 (1H, m), 4.25 (2H, br, 2-OH), 4.47 (1H, s), 5.36 (1H, m) ppm. Anal. Found: C, 70.84; H, 10.45. Calcd. for C_{15}H_{26}O_{3}: C, 70.83; H, 10.30.

2-Methyl-6-(4'-oxoeyclohex-1'-enyl)heptane-2,4-diol (VIII). A solution of VII (33 g) in MeOH (200 ml) was mixed with an aqueous solution of oxalic acid (3.5 g in 45 ml). The mixture was left to stand at 25°C for 40 min. Then the mixture was concentrated in vacuo, diluted with water and extracted with ether. The ether extract was washed with water, NaHCO_{3} aq and brine, dried (MgSO_{4}) and concentrated to give 30 g (91%) of crude oily VIII, ν_{max} 3400, 1715 cm^{-1}. This was employed for the next step without further purification.

2-Methyl-6-(4'-oxocyclohexyl)heptane-2,4-diol (IXa). The oily VIII (20 g) dissolved in 99.40% EtOH (200 ml) was hydrogenated over 10% Pd-C (5 g) at room temperature under atmospheric pressure. The H_{2} uptake ceased after 5 hr. The catalyst was filtered off and the filtrate was concentrated to give 18 g (90%) of crude oily IXa. An analytical sample distilled at 125.0-127.0°C/0.1 mm with slight decomposition, δ_{d} 1.4784; ν_{max} 3400, 1715 cm^{-1}; δ 0.88 (3H, d, J=5Hz), 1.18 (3H, s), 1.24 (3H, s), ~3.8 (1H, broad), ~4.25 (2H, broad, 2-OH) ppm. Anal. Found: C, 70.10; H, 10.92. Calcd. for C_{14}H_{26}O_{3}: C, 69.38; H, 10.14%.

2-Methyl-6-(4'-oxocyclohexyl)heptane-2,4-diol diacetate (IXb). Acetyl chloride (40 g) was added portionwise at 0-5°C to a solution of IXa (24 g) in benzene (100 ml) and pyridine (120 ml). The mixture was stirred and heated at 60-80°C for 1.5 hr. Then it was diluted with ice-water and extracted with ether. The ether extract was washed successively with dil HCl, water, NaHCO_{3} aq and sat brine, dried (K_{2}CO_{3}) and concentrated to give 28 g (87%) of oily crude IXb. An analytical sample boiled at 155.5-157°C/0.15 mm with considerable decomposition, δ_{d} 1.4784; ν_{max} 1740, 1720 (sh), 1370, 1250, 1150, 1020 cm^{-1}; δ 0.90 (3H, d, J=6Hz), 1.38 (3H, s), 1.40 (3H, s), 1.88 (3H, s), 1.95 (3H, s), ~5.05 (1H, m, AcOCH) ppm. Anal. Found: C, 71.23; H, 8.94; N, 4.28. Calcd. for C_{18}H_{30}O_{5}: C, 68.03; H, 8.41; N, 4.18%.

2-Methyl-6-(4'-hydroxy-4'-cyanocyclohexyl)heptane-2,4-diol diacetate (X). To a stirred and ice-cooled solution of IX (27 g) in 95% EtOH (140 ml) was added KCl (35 g) followed by AcOH (40 ml). After the addition, the mixture was stirred for 30 min at 0-5°C and then for 30 min at 40-50°C. The excess HCN was removed in vacuo after the addition of 2-3 drops of conc HCl. The mixture was diluted with water and extracted with benzene-ether. The ether extract was washed with dil HCl and sat brine, dried (MgSO_{4}) and concentrated to give 27 g (95%) of crude X, ν_{max} 3400, 2200 (w), 1740 (br), 1250 cm^{-1}. This was employed for the next step without further purification.

2-Methyl-6-(4'-cyanoeyclohex-3'-enyl)heptane-2,4-diol diacetate (XI). To an ice-cooled solution of X (27 g) in pyridine (150 ml) was added POCl_{3} (36 g). The dark-colored mixture was left overnight at room temperature, heated under reflux for 30 min and finally poured into ice-water containing conc HCl (200 ml). The mixture was extracted with ether. The ether extract was washed with dil HCl, water, NaHCO_{3} aq and sat brine, dried (MgSO_{4}) and concentrated to give 17 g (65%) of crude oily XI. An analytical sample boiled at 155.5-160°C/0.08 mm with considerable decomposition to give olefinic product, δ_{d} 1.4800; ν_{max} 2220, 1735, 1680 (sh.), 1640, 1370, 1250 cm^{-1}; δ 0.88 (3H, d, J=5Hz), 1.39 (3H, s), 1.89 (3H, s), 1.95 (3H, s), ~5.05 (1H, m, AcOCH), 6.55 (1H, br) ppm. Anal. Found: C, 71.23; H, 8.94; N, 4.28. Calcd. for C_{18}H_{30}O_{4}N: C, 68.03; H, 8.41; N, 4.18%.

2-Alethyl-6-(4'-carboxycyclohex-3'-enyl)heptane-2,4-diol (XII). A solution of the crude XI (15 g) in diethylene glycol (120 ml) was mixed with KOH aq (30 g in 100 ml) and the mixture heated under reflux for 42 hr. After cooling, the mixture was diluted with water and extracted with ether to remove the neutral impurities. The alkaline aqueous layer was acidified with dil HCl and extracted with ether. The ether extract was washed with water and sat brine, dried (MgSO_{4}) and concentrated to give 11.5 g (95%) of crude XII, ν_{max} ~3400-~2600, 1710 cm^{-1}. This was employed for the next step without further purification.

2-Methyl-6-(4'-carboxycyclohex-3'-enyl)heptane-2-ol-4-one (stereoisomeric mixture of hydroxycoumaric acid, XIII). To a solution of XII (11.5 g) in acetone (200 ml) was added Jones chromic acid reagent (10 ml) at 0-5°C. After 10 min MeOH was added to destroy the excess oxidant. The mixture was concentrated in vacuo. The residue was diluted with water and extracted with ether. The etheral solution was washed with water and sat brine, dried (MgSO_{4}) and concentrated to give 8 g (70%) of crude XIII, ν_{max} ~3400-~2600, 1710 cm^{-1}.
Synthesis of Compounds with Juvenile Hormone Activity. Part VI

2-Methyl-6-(4'-carboxycyclohex-3'-enyl)hept-2-en-4-one (dl-dehydrodopaminic acid (IIIa) and its stereoisomer (Ia)]. To a solution of XIII (5 g) in benzene (100 ml), conc. HCl (1 drop) and iodine (50 mg) were added. The mixture was heated under reflux with a water separator for 2.5 hr. After cooling, the soln was washed with Na$_2$S$_2$O$_3$ aq and sat brine, dried (MgSO$_4$) and concentrated. The residue was distilled to give 2.0 g (41%) of Ia+IIIa, bp 165–180°C/0.1 mm. An analytical sample boiled at 170–175°C/0.08 mm, $n_D^{50}$ 1.5184; $\nu_{\max}$ ~3200–~2600, 1685, 1645, 1280, 930 cm$^{-1}$; $\delta$ 0.92 (3H, d, $J=6$ Hz), 1.92 (3H, s), 2.15 (3H, s), 6.02 (1H, s), 7.10 (1H, br), 11.62 (1H, s) ppm; $\lambda_{\max}$ (EtOH) 224 m$\mu$ ($\varepsilon$ 1.3 $\times$ 10$^4$). Anal. Found: C, 72.13; H, 8.98. Calcd for C$_{15}$H$_{22}$O$_5$: C, 71.97; H, 8.86%.

The oily acid partly crystallized after several days in a refrigerator. Recrystallization from EtOAc-pet. ether gave needles, mp 66–67°C; $\nu_{\max}$ ~3200–~2600, 1678 (va), 1642 (s), 1620 (s), 1320 (m), 1280 (s), 1245 (m), 1215 (m), 1192 (w), 1160 (w), 1130 (m), 1110 (w), 1090 (m), 1040 (m), 1015 (w), ~940, 895 (w), 865 (w), 828 (w), 790 (m), 750 (m), 732 (m), 700 (m), 640 (w) cm$^{-1}$; $\nu_{\max}$ (CCl$_4$) ~3200–~2600, 1692 (s), 1645 (m), 1620 (s), 1270 (s) cm$^{-1}$; $\delta$ 0.90 (3H, d, $J=6$ Hz), 1.88 (3H, s), 2.09 (3H, s), 5.98 (1H, s), 7.06 (1H, br), 11.37 (1H, s) ppm; $\lambda_{\max}$ (EtOH) 224 m$\mu$ ($\varepsilon$ 2 $\times$ 10$^4$). Anal. Found: C, 72.09; H, 8.80. Calcd. for C$_{15}$H$_{22}$O$_5$: C, 71.97; H, 8.86%.

A mixture of (±)-dehydrojuvabione (IIIb) and its stereoisomer (Ib) [2-methyl-6-(4'-carbomethoxy-cyclohex-3'-enyl)hept-2-en-4-one]. The acid Ia+IIIa in ether was esterified with diazomethane. Subsequent work-up gave Ib+IIIb, bp 140–143°C/0.08 mm, $n_D^{20}$ 1.5025; $\nu_{\max}$ 1725 (weak sh), 1715, 1688, 1650, 1630 (sh), 1620, 1430, 1380, 1252, 1083, 920, 820, 804 cm$^{-1}$; $\nu_{\max}$ (CCl$_4$) 1722, 1694, 1652, 1430, 1380, 1252, 1082, 1034 cm$^{-1}$; $\delta$ (CDCl$_3$) 0.88 (3H, d, $J=6$ Hz), 1.85 (3H, s), 2.10 (3H, d, ~3.65 (3H, s), 6.04 (1H), 6.93 (1H, br) ppm; $\lambda_{\max}$ (EtOH) 224 m$\mu$ ($\varepsilon$ 1.5 $\times$ 10$^4$). Anal. Found: C, 72.34; H, 9.20. Calcd for C$_{16}$H$_{24}$O$_3$: C, 72.69; H, 9.15%.

GLC: Column, OV-17 on Shimalite, 3m x 3 mm i.d.; Column temp 220°C; Carrier gas N$_2$, 2 kg/cm$^2$; Rt 12.55 min. The spectral data are in good accord with those of an authentic sample. The GLC retention time is completely identical with that of the natural product.

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