Synthesis of Compounds with Juvenile Hormone Activity

Part III.¹⁾ ($\pm$)-Demethyljuvabione and Demethyl-*ar*-juvabione

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Received May 20, 1969

Two juvabione analogues (III and IV) were synthesized and one (IV) of them was shown to possess the juvenile hormone activity.

We recently reported a synthesis of ($\pm$)-juvabione (I), a sesquiterpene ester with high juvenile hormone activity.²⁾ Since then three independent syntheses have been carried out by the Indian,³⁾ the American⁴⁾ and the Australian⁵⁾ workers, respectively. The Indian group pointed out that *ar*-($\pm$)-juvabione (II) was also biologically active.³⁾ Almost simultaneously Sláma *et al.*⁶⁾ in Czechoslovakia found that certain derivatives of methyl *p*-(1,5-dimethylhexyl) bezoate showed high juvenile hormone activity, some of them being more active than juvabione itself. We also noted the biological activity of the stereoisomer of ($\pm$)-juvabione.²⁾ In view of these findings it is now clear that the observed high juvenile hormone activity of juvabione and dehydro-

juvabione^{7,8)} is not their peculiar characteristics but common to the analogous sesquiterpene-like esters. This paper describes the synthesis of two new juvabione analogues, III and IV, without a methyl group on the side chain.

Synthesis of ($\pm$)-demethyljuvabione (III)

The gross carbon skeleton of this compound was constructed by the condensation of ethyl isovalerylacetate (V)⁹⁾ with *p*-methoxybenzyl chloride (VI)¹⁰⁾ in the presence of sodium ethoxide. The resulting β -keto ester (VII) was refluxed with hydrochloric acid to give a ketone (VIII). This was reduced with sodium borohydride to afford an alcohol (IX). Hereafter we followed the route used in the synthesis of ($\pm$)-juvabione.²⁾

The modified Birch reduction¹¹⁾ of this al-

* Undergraduate Research Participants: 1967~1968 (T. M.); 1968~1969 (I. Y.).

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cohol gave a diene (X). This was converted to a β , γ -unsaturated ketone (XI) by treatment with oxalic acid in aqueous methanol. Hydrogenation of the unsaturated ketone over palladium-charcoal gave a ketol (XIIa). The corresponding acetate (XIIb) was prepared from the alcohol by the action of acetyl chloride and pyridine. Addition of hydrogen cyanide to the acetoxy ketone (XIIb) gave a cyanohydrin (XIII), which was dehydrated with phosphorus oxychloride and pyridine to give an unsaturated nitrile (XIV). Hydrolysis of the nitrile with concomitant removal of the acetyl group was effected by heating the nitrile (XIV) with potassium hydroxide in aqueous diethylene glycol to afford a hydroxy acid (XV). This, upon Jones oxidation,¹² yielded a crystalline keto acid (demethyltodomatuic acid; XVI). This was methylated with ethereal diazomethane to give ($\pm$)-demethyljuvabione (III).

Synthesis of demethyl-*ar*-juvabione (IV)

p-Carbethoxybenzyl bromide (XVII), one of the starting materials, was prepared from ethyl *p*-toluate by bromination with N-bromosuccinimide.* The bromide (XVII) was condensed with ethyl isovalerylacetate (V) in the presence of sodium ethoxide to give a diester (XVIII). This was heated with hydrochloric acid to give a crystalline keto acid (demethyl-*ar*-todomatuic acid; XIX). Its esterification with ethereal diazomethane gave demethyl-*ar*-juvabione (IV).

Juvenile hormone activity of the products

The juvenile hormone activity of the two synthetic products 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. ($\pm$)-Demethyljuvabione (III) was shown to be inactive up

to 10 μ g dosage per insect. With demethyl-*ar*-juvabione (IV), however, 10 μ g was sufficient to produce a supernumerary nymph. This might be compared to our synthetic juvabione in activity.²¹ It is interesting to notice that the structural similarity between III and IV does not necessarily mean the similarity in the degree of biological activity.

EXPERIMENTAL

All mp values and bp values were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for liquids. UV spectra were determined in ethanol. NMR spectra were recorded at 100 MHz in carbon tetrachloride with tetramethylsilane as an internal standard unless otherwise stated.

*Ethyl α -isovaleryl- β -(*p*-methoxyphenyl) propionate (VII).* Ethyl isovalerylacetate (V, 21.3 g) in dry benzene (75 ml) was added to a solution of sodium ethoxide (from 3.0 g of sodium) in absolute ethanol (35 ml). To this mixture *p*-methoxybenzyl chloride (VI, 19.3 g) in dry benzene (75 ml) was added with stirring at 0–5°C. After the addition, the mixture was heated under reflux for 2 hr, cooled and poured into ice-water. The organic layer was separated and the aqueous layer was extracted with ether. The combined extract was washed with water, dried with magnesium sulfate and concentrated. The residue was distilled *in vacuo* to give 19.5 g (53.8%) of VII, bp 135–137°C/0.07 mm; n_D^{20} 1.5022. *Anal.* Found: C, 69.75; H, 8.28. *Calcd.* for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27%. $\nu_{\max}$ 1730, 1700, 1610, 1515, 1255 cm^{-1} . δ 0.88 (6 H, d, $J=6$ Hz), 1.20 (3 H, t, $J=6$ Hz), 3.66 (3 H, s), 4.02 (2 H, q, $J=6$ Hz), 6.58, 6.66, 6.89, 6.98 (4 H) ppm.

*1-(*p*-Methoxyphenyl)-5-methylhexan-3-one (VIII).* A mixture of the β -keto ester (VII, 19.4 g) and conc. hydrochloric acid (50 ml) was heated under reflux for 50 hr, diluted with water and extracted with ether. The ethereal extract was washed with water and sodium bicarbonate solution, dried (MgSO_4) and concentrated. The residue was distilled *in vacuo* to give 11.6 g (79%) of VIII, bp 135–138°C/0.15 mm; n_D^{20} 1.5026. *Anal.* Found: C, 75.98; H, 9.26. *Calcd.* for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%. $\nu_{\max}$ 1700, 1250 cm^{-1} . δ 0.83–0.89 (6 H, q), 3.66 (3 H, s), 6.63, 6.72, 6.94, 7.02 (4 H) ppm.

* A crystalline dibromide (i) was obtained as a by-product.

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1-(p-Methoxyphenyl)-5-methylhexan-3-ol (IX). A suspension of sodium borohydride (5 g) in ethanol (100 ml) was added portionwise to an ice-cooled solution of the ketone (VIII, 47 g) in ethanol (300 ml). The mixture was left to stand overnight at room temperature, acidified with dilute hydrochloric acid and concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed with water and brine, dried (MgSO₄) and concentrated. The residue was distilled *in vacuo* to give 33.4 g (70%) of IX, bp 115~125°C/0.06 mm; n_D^{19} 1.5085. *Anal.* Found: C, 75.21; H, 9.56. *Calcd.* for C₁₄H₂₂O₂: C, 75.63; H, 9.97%. $\nu_{\max}$ 3400, 1240 cm⁻¹.

1-(4'-Oxocyclohex-1'-enyl)-5-methylhexan-3-ol (XI). A solution of the alcohol (IX, 16.5 g) in dry tetrahydrofuran (150 ml) and *t*-butanol (150 ml) was added to liquid ammonia (350 ml) cooled in a dry ice-acetone bath. Lithium (7 g) was added portionwise during 1 hr to the stirred solution. After the addition, the mixture was stirred for 4 hr at dry ice-acetone temperature. Then the excess lithium was destroyed by the addition of ethanol (50 ml). The mixture was left at room temperature to evaporate ammonia. Water (200 ml) was added to the residue with stirring. The mixture was then concentrated *in vacuo* to remove tetrahydrofuran, *t*-butanol and ethanol. The remaining aqueous solution was extracted with ether. The extract was washed with water and brine, dried (MgSO₄) and distilled to give 10.0 g (61%) of crude diene X, bp 120~130°C/0.06 mm. The oily X, (20.0 g), without further characterization, was dissolved in methanol (150 ml) and mixed with an aqueous solution of oxalic acid (3 g in 40 ml). The mixture was heated at 40~50°C for 1 hr. Then the mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution and brine, dried (MgSO₄) and distilled to give 9.0 g (48%) of an oil, bp 110~113°C/0.08 mm; n_D^{19} 1.4851. *Anal.* Found: C, 74.78; H, 10.68. *Calcd.* for C₁₃H₂₂O₂: C, 74.29; H, 10.48%. $\nu_{\max}$ 3520, 1715 cm⁻¹ δ 0.88 (3 H, d, $J=7$ Hz), 0.94 (3 H, d, $J=7$ Hz), 5.45 (1 H, C=CH) ppm.

1-(4'-Oxocyclohexyl)-5-methylhexan-3-ol (XIIa). The oily unsaturated ketone (XI, 8.5 g) dissolved in ethyl acetate (50 ml) was hydrogenated over 10% palladium-charcoal (4 g) at room temperature under atmospheric pressure. The hydrogen uptake ceased after 3 hr. The catalyst was filtered off and the filtrate was distilled to

give 6.5 g (76%) of an oil, bp 120~125°C/0.06 mm; n_D^{18} 1.4773. *Anal.* Found: C, 73.29; H, 11.06. *Calcd.* for C₁₃H₂₄O₂: C, 73.53; H, 11.39%. $\nu_{\max}$ 3500, 1715 cm⁻¹. δ 0.88 (3 H, d, $J=7$ Hz), 0.92 (3 H, d, $J=7$ Hz) ppm.

1-(4'-Oxocyclohexyl)-3-acetoxy-5-methylhexane (XIIb). To a solution of the alcohol (XIIa, 6.4 g) in ether (30 ml) and pyridine (10 ml) was added portionwise a solution of acetyl chloride (4 g) in ether (15 ml) at 0~5°C. The mixture was stirred for 30 min at 0~5°C and then heated under reflux for 30 min with stirring. The mixture was diluted with ice-water and extracted with ether. The ethereal solution was washed successively with dilute hydrochloric acid, water, sodium bicarbonate solution and brine, dried (MgSO₄) and concentrated to give 6.1 g of crude acetate (XIIb), $\nu_{\max}$ 1740, 1720, 1240 cm⁻¹. This was employed for the next step without further purification.

1-(4'-Hydroxy-4'-cyanocyclohexyl)-3-acetoxy-5-methylhexane (XIII). To a stirred and ice-cooled solution of the acetoxy ketone (XIIb, 6 g) in 95% ethanol (40 ml) was added powdered potassium cyanide (9 g). Then acetic acid (10 ml) was added to the mixture during about 10 min. 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 hydrogen cyanide was removed *in vacuo* after the addition of 2~3 drops of conc. hydrochloric acid. The mixture was diluted with water and extracted with ether. The extract was washed with dilute hydrochloric acid and brine, dried (MgSO₄) and concentrated *in vacuo* to give 6 g of an oil, $\nu_{\max}$ 3420, 2230, 1720, 1695, 1238 cm⁻¹, which was employed for the next reaction without further characterization.

1-(4'-Cyanocyclohex-3'-enyl)-3-acetoxy-5-methylhexane (XIV). To a solution of the cyanohydrin (XIII, 6 g) in pyridine (30 ml) was added phosphorus oxychloride (8 g). The dark-colored mixture was left to stand at room temperature for several days, heated under reflux for 1 hr and finally poured into ice-water containing conc. hydrochloric acid (100 ml). The mixture was extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution and brine, dried (MgSO₄) and concentrated to give 3.8 g (46% from XIIb) of the crude XIV, $\nu_{\max}$ 2320, 1740, 1630, 1240 cm⁻¹.

1-(4'-Carboxycyclohex-3'-enyl)-5-methylhexan-3-ol (XV). A solution of the crude nitrile (XIV, 3.7 g) in die-

thylene glycol (40 ml) was mixed with aqueous potassium hydroxide (15 g in 50 ml) and the mixture was heated under reflux for 48 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 conc. hydrochloric acid (50 ml) and extracted with ether. The ethereal solution was washed with water and brine, dried (MgSO_4) and evaporated. Water was removed from the residual oily acid by repeated addition and distillation of dry benzene. The residual oil was dissolved in absolute ethanol (50 ml). A solution of sodium ethoxide (from 2 g of sodium) in absolute ethanol (50 ml) was added to the acid in ethanol and the mixture was heated under reflux for 3 hr. Water (100 ml) was added to the mixture. Then it was concentrated *in vacuo*, acidified with conc. hydrochloric acid and extracted with ether. The extract was washed with water and brine, dried (MgSO_4) and concentrated to give 1.85 g (54%) of the product. This was employed for the next step without further purification; $\nu_{\text{max}} \sim 3400 \sim 2600$, 1680, 1640, 1275, 950 cm^{-1} .

1-(4'-Carboxycyclohex-3'-enyl)-5-methylhexan-3-one ($\pm$)-*demethyltodomatiic acid* (XVI). To a solution of the hydroxy acid (XV, 1.85 g) in acetone (35 ml) was added Jones reagent¹²⁾ (1.63 ml) at $0 \sim 5^\circ\text{C}$. After 10 min methanol was added to destroy the excess oxidant. The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ethereal solution was washed with water and brine, dried (MgSO_4) and concentrated to give a crystalline keto acid (XVI). This was recrystallized from petroleum ether to give 0.9 g (49%) of plates, mp $93 \sim 94^\circ\text{C}$. *Anal.* Found: C, 70.36; H, 9.22. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_3$: C, 70.63; H, 9.24%. $\nu_{\text{max}} \sim 3200 \sim 2600$, 1705, 1672, 1643, 1290, 940 cm^{-1} . δ 0.92 (6 H, d, $J=7$ Hz), 7.13 (1 H, broad, $\text{C}=\text{CH}$) (CDCl_3 soln) ppm. λ_{max} 215 m μ (ϵ 8970). Semicarbazone: mp $191 \sim 192.5^\circ\text{C}$. *Anal.* Found: C, 60.79; H, 8.25; N, 13.71. Calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_3\text{N}_3$: C, 61.02; H, 8.47; N, 14.24%. ν_{max} 3530, $\sim 3250 \sim 2600$, 1689, 1660, 1580 cm^{-1} .

1-(4'-Carbomethoxycyclohex-3'-enyl)-5-methylhexan-3-one ($\pm$)-*demethyljuvabione* (III). The crystalline acid (XVI, 0.7 g) was esterified with ethereal diazomethane to give 0.55 g (74%) of the corresponding ester (III), bp $124 \sim 127^\circ\text{C}/0.06$ mm; n_D^{18} 1.4801. *Anal.* Found: C, 72.22; H, 9.31. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_3$: C, 71.43; H,

9.52%. ν_{max} 1700, 1644, 1249 cm^{-1} . δ 0.94 (6 H, d, $J=7$ Hz), 3.66 (3 H, s), 6.90 (1 H, broad, $\text{C}=\text{CH}$) ppm. λ_{max} 217 m μ (ϵ 11400). GLC retention time: 6.9 min, 2% SE-30. column (2 m $\times$ 0.45 mm) temp.: 190°C . Carrier gas: He, 20 ml/min.

p-Carbethoxybenzyl bromide (XVII) and ethyl *p*-dibromomethylbenzoate (i). To a refluxing solution of ethyl *p*-toluate (45.3 g) in carbon tetrachloride (44 ml) a mixture of *N*-bromosuccinimide (52.6 g) and a trace of benzoyl peroxide was added portionwise. After the addition, the mixture was heated under reflux for 3 hr to complete the reaction. After cooling, it was filtered to remove succinimide and the imide was washed with a small amount of carbon tetrachloride. The combined filtrate and washings were concentrated *in vacuo*. The residue was distilled to give 57.0 g (85%) of crude XVII, bp $110 \sim 115^\circ\text{C}/0.07$ mm, n_D^{18} 1.5494. ν_{max} 1725, 1630, 1395, 1140, 807, 740 cm^{-1} . Repeated redistillation afforded an analytical sample, mp $36 \sim 37^\circ\text{C}$. *Anal.* Found: C, 49.43; H, 4.59. Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_2\text{Br}$: C, 49.43; H, 4.55%. The crude distillate was contaminated with a crystalline dibromide (i) which was removed by filtration. The dibromide (i) crystallized from *n*-hexane as rhombs, mp $97 \sim 98^\circ\text{C}$. *Anal.* Found: C, 37.82; H, 2.85; Br, 48.89. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{Br}_2$: C, 37.29; H, 3.13; Br, 49.64%. ν_{max} 1695, 1620, 1485, 1430, 1381, 1300, 1150, 1042, 845, 723 cm^{-1} . δ 1.40 (3 H, t, $J=6$ Hz), 4.34 (2 H, q, $J=6$ Hz), 6.63 (1 H, s, CHBr_2), 7.56, 7.65, 7.98, 8.06 (4 H) ppm.

Ethyl α -isovaleryl- β -(*p*-carbethoxyphenyl) propionate (XVIII). Ethyl isovalerylacetate (V, 17.2 g) in dry benzene (75 ml) was added to a solution of sodium ethoxide (from 2.3 g of sodium) in absolute ethanol (30 ml). To this mixture crude *p*-carbethoxybenzyl bromide (XVII, 23.8 g) in dry benzene (75 ml) was added with stirring at $0 \sim 5^\circ\text{C}$. After the addition the mixture was heated under reflux for 2 hr, cooled and poured into water. The organic layer was separated and the aqueous layer was extracted with ether. The combined extract was washed with water and brine, dried (MgSO_4) and concentrated. The residue was distilled *in vacuo* to give 28.7 g (86%) of XVIII, bp $154 \sim 160^\circ\text{C}/0.07$ mm, contaminated with a small amount of i; n_D^{18} 1.5032. *Anal.* Found: C, 69.15; H, 7.97. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_6$: C, 68.24; H, 7.84%. ν_{max} 1730, 1700, 1605, 1380, 1285, 1130, 980, 790 cm^{-1} . δ 0.83 (6 H, d, $J=6$ Hz), 1.18 (3 H, t, $J=7$ Hz), 1.35 (3 H, t, $J=7$ Hz), 2.0 $\sim$ 2.4 (2 H, m, CH_2CO), 3.05 $\sim$

3.13 (2 H, d, $C_6H_5CH_2$), 4.06 (2 H, q, $J=7$ Hz), 4.26 (2 H, q, $J=7$ Hz), 7.13, 7.20, 7.84, 7.92 (4 H) ppm.

1-(p-Carboxyphenyl)-5-methylhexan-3-one = demethyl-ar-todomatuic acid (XIX). A mixture of the β -keto ester (XVIII, 25 g) and conc. hydrochloric acid (75 ml) was heated under reflux for 40 hr, diluted with water and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$), decolorized (activated charcoal) and concentrated to give 14.1 g (80%) of crystalline XIX. Recrystallization from ethyl acetate-*n*-hexane gave needles, mp $124\sim 125^\circ C$. *Anal.* Found: C, 71.38; H, 7.75. Calcd. for $C_{14}H_{18}O_5$: C, 71.77; H, 7.74%. $\nu_{max}\sim 2940\sim 2670$, 1700, 1610, 1470, 1440, 1335, 1306, 1196, 1102, 1050, 788, 730 cm^{-1} . δ 0.89 (6 H, d, $J=6$ Hz), ~ 2.0 (1 H, m), 2.16 (2 H, broad s), 2.55 $\sim$ 2.95 (4 H), 7.18, 7.26, 7.96, 8.04 (4 H) ppm.

1-(p-Carbomethoxyphenyl)-5-methylhexan-3-one = demethyl-ar-juvabione (IV). The acid (XIX, 9.8 g) was methylated with ethereal diazomethane and the product was distilled to give 9.9 g (93%) of IV, bp $143\sim 144^\circ C$ /

0.09 mm; n_D^{18} 1.5052. *Anal.* Found: C, 72.65; H, 8.07. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%. ν_{max} 1720, 1610, 1445, 1295, 1130, 1044, 788, 725 cm^{-1} . δ 0.85 (6 H, d, $J=6$ Hz), ~ 2.0 (1 H, m), 2.13 (2 H, broad s), 2.50 $\sim$ 2.95 (4 H), 3.79 (3 H, s), 7.10, 7.18, 7.80, 7.88 (4 H) ppm.

Bioassay. Data are based on topical treatment of last instar nymphs of *Pyrhocoris apterus* (10 insects per assay).

Compound	Dosage (μg)			
	0.01	0.1	1.0	10.0
($\pm$)-Demethyljuvabione (III)	A	A	A	A
Demethyl-ar-juvabione (IV)	A	A	A	SN

A=Normal adult (no activity)

SN=Supernumerary nymphs (high activity)

Acknowledgement. Our thanks are due to Dr. W. S. Bowers, USDA Agricultural Research Service, Beltsville, U. S. A., for bioassay.