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SYNTHESIS OF (±)-JUVABIONE (METHYL (±)-TODOMATUATE), A SESQUITERPENE ESTER WITH JUVENILE HORMONE ACTIVITY

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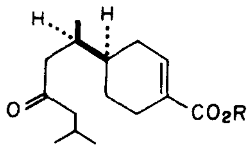
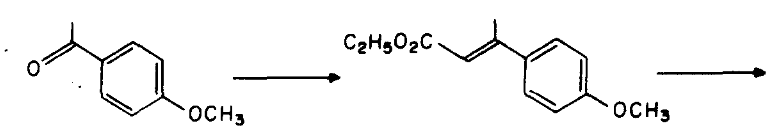
Juvabione, a sesquiterpene ester isolated from balsam fir (*Abies balsamea* (L.) Miller), shows strong juvenile hormone activity in the hemipteran bug, *Pyrrhocoris apterus* (L.) (1,2). Direct comparison with an authentic sample revealed that this biologically interesting substance was the methyl ester (Ib) of todomatuic acid (Ia) (1), of which chemistry had been studied by several Japanese workers (3,4,5). We now wish to describe the total synthesis of racemic acid (Ia) and ester (Ib).

Ethyl β-(*p*-methoxyphenyl)-crotonate (III)(6), prepared from *p*-methoxyacetophenone (II) by the Reformatsky reaction, was hydrogenated over Raney nickel W-7 to give ethyl (±)-β-(*p*-methoxyphenyl)-butyrate (IVa), b.p. 129-132°/3mm, n_D^{20} 1.4988(7). The corresponding acid (IVb), m.p. 66-67°, was successively treated with thionyl chloride and dimethyl amine to give an amide (IVc), b.p. 162-163°/3mm, n_D^{21} 1.5290. Its reduction by lithium triethoxyaluminohydride (8) gave (±)-β-(*p*-methoxyphenyl) butyraldehyde (IVd), b.p. 130-132°/7mm, n_D^{19} 1.5218; 2,4-dinitrophenylhydrazone, m.p. 126-127°. Addition of isobutyl magnesium bromide to the aldehyde (IVd) afforded 2-(*p*-methoxypenyl)-6-methylheptan-4-ol (V)(9), b.p. 118-120°/0.4mm, n_D^{17} 1.5062.

The Birch reduction (Dryden's modification (10)) of this alcohol gave a diene (VI) b.p. 148-150°/0.8mm, n_D^{17} 1.4886. This was converted to a β,γ-unsaturated ketone (VII), b.p. 130-132°/0.3mm, n_D^{16} 1.4835, by treatment with oxalic acid in methanol-water. Hydrogenation of the enone (VII) over palladium-charcoal gave 2-(4'-oxocyclohexyl)-6-methylheptan-4-ol (VIIIa), b.p. 132-135°/0.4mm, n_D^{19} 1.4770. Acetylation of this ketol with acetyl chloride-pyridine gave an acetate (VIIIb), b.p. 125-127°/0.2mm, n_D^{19} 1.4630. Addition of hydrogen cyanide to it yielded a cyanohydrin (IX) as a viscous oil which was dehydrated with phosphorus oxychloride and pyridine to give 2-(4'-cyanocyclohex-3'-enyl)-4-acetoxy-6-methylheptane (X), b.p. 140-142°/0.4mm. n_D^{21} 1.4738. Hydrolysis of the nitrile with concomittant removal of the acetyl group was effected by heating the nitrile with potassium hydroxide in diethylene glycol-water to afford a hydroxy acid (XI) somewhat contaminated with a β,γ-unsaturated acid. This was treated with sodium

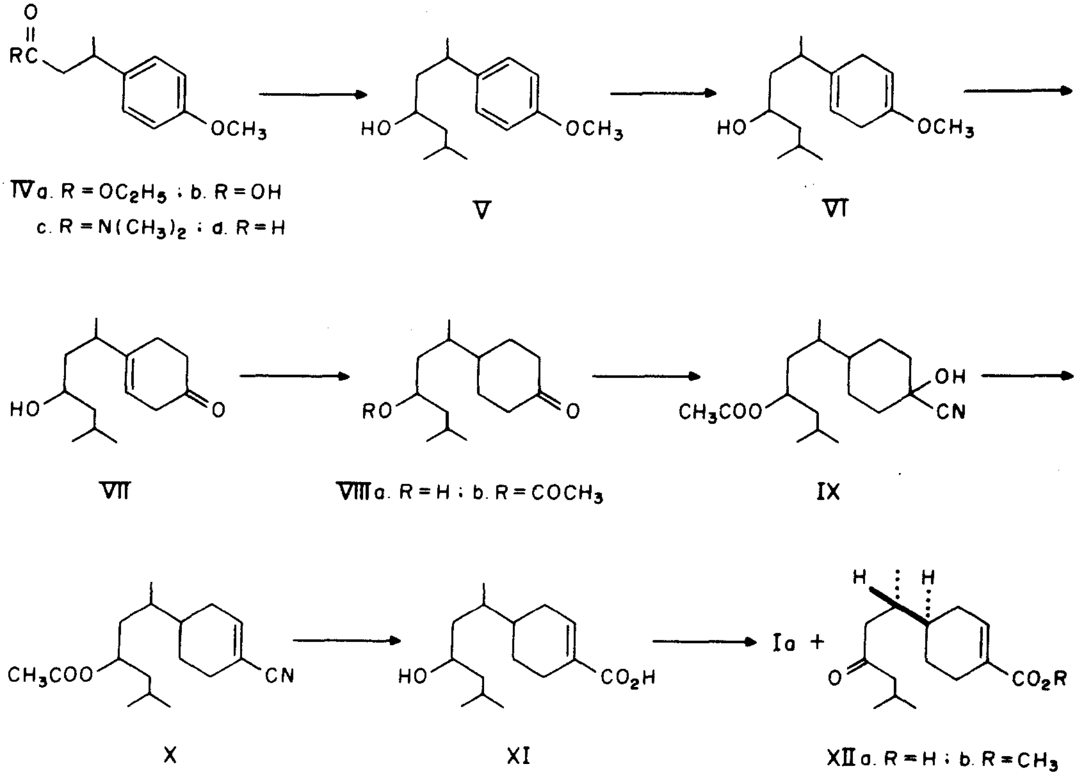


Ia. R = H ; b. R = CH_3



II

III



IVa. R = OC_2H_5 ; b. R = OH

c. R = $N(CH_3)_2$; d. R = H

V

VI

VII

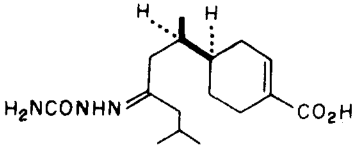
VIIIa. R = H ; b. R = $COCH_3$

IX

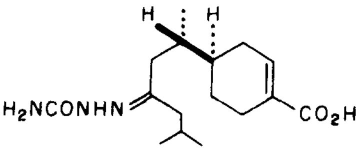
X

XI

XIIa. R = H ; b. R = CH_3



XIII



XIV

ethoxide in ethanol to give a purer hydroxy acid (XI). This, upon Jones oxidation, yielded a mixture of the racemates of todomatuic acid (Ia) and its stereoisomer (XIIa) as a viscous oil, b.p. 182-185°/0.6mm, n_D^{15} 1.4952. The amount of the obtained oil was 11.4g starting from 100g of p-methoxyacetophenone.

Separation of the two racemates was successfully carried out when it was found that one isomer gave a highly crystalline semicarbazone (XIII), m.p. 186-187°, ν 3470, ~3200-~2600, 1695, 1660, 1575. This was hydrolyzed by heating with dilute sulfuric acid to give back the parent acid as pure crystals, m.p. 66-67° (sinter at 59°), ν ~3200-~2500, 1714, 1694, 1652 (sh.), 1648, 1278, 950, 940, 920, 783, 740, 708, ν (CS_2) ~3200-~2500, 1720, 1694, 1654 (sh.), 1650, 1275, 935, 920, δ 0.83 (3H, d, J=6cps), 0.88 (6H, d, J=6cps), 7.02 (1H, C=C$\underline{H}$), λmax (EtOH) 215 mμ (ε 10200) (11, 12). The fact that the natural acid (Ia, m.p. 58-58.5°) (2) and its semicarbazone (XIII, m.p. 193.2-193.7°) (2) were crystalline suggested that this crystalline racemate was the desired isomer (Ia)(13). Comparison of its spectral properties with those of an authentic sample of the natural product (Ia) proved that the crystalline isomer was indeed (±)-todomatuic acid (Ia). The infrared (CS_2) and n.m.r. spectra of natural and synthetic acids were identical in every detail. The racemic acid was methylated with diazomethane to give (±)-juvabione (Ib), b.p. 140-141°/0.1mm, n_D^{19} 1.4818, ν 1726, 1718, 1654, 1256, 1084, 1034, 922, 805, 745, 715, ν (CS_2) 1724,(sh.), 1718, 1654, 1254, 1076, 1032, 920, 804, 742, 714, δ ($CDCl_3$) 0.88 (3H, d, J=6cps), 0.92 (6H, d, J=6cps), 1.0~1.85 (~5H), 1.85~2.5 (~8H, 2.22 (2H, s)), 3.68 (3H, s), 6.94 (1H), λmax (EtOH) 218 mμ (ε 12800). This racemate was indistinguishable from the natural isomer (Ib) by i.r., n.m.r. and g.l.c.

An oily semicarbazone (XIV) remaining in the mother liquor after removal of the crystalline isomer was hydrolyzed with dilute sulfuric acid to give (±)-epitodomatuic acid (XIIa) as an oil, b.p. 160-164°/0.2mm, n_D^{20} 1.4930. The infrared and n.m.r. spectra of these isomeric acids (Ia) and (XIIa) differred only very slightly and almost superimposable to each other. The oily epimer (XIIa) was treated with diazomethane to afford methyl (±)-epitodomatuate (XIIb), b.p. 142-143°/0.1mm, n_D^{18} 1.4832. Here again, the spectral properties of the two epimeric esters (Ib) and (XIIb) were almost identical. Moreover, they could not be separated by gas chromatography.

It is of interest to know whether methyl (±)-epitodomatuate (XIIb) is biologically as active as (±)-juvabione (Ib) or not, in view of their very similar physical properties (14).

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10. H.L. Dryden, Jr., G.M. Webber, R.R. Burtner and J.A. Cella, *J. Org. Chem.* **26**, 3237 (1961)
11. Infrared spectra were determined as films for liquids and as nujol pastes for solids unless otherwise stated and expressed in wave number (cm^{-1}).
12. N.m.r. spectra were taken in CCl_4 with TMS as internal standard at 100 Mc except where stated otherwise and expressed in δ (p.p.m.).
13. Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in the case of synthetic products.
14. The bioassay is now under way in Dr. Bower's laboratory.