Tetrahedron Letters No.48, pp. 4853-4856, 1967. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF A MIXTURE OF (±)-DEHYDROJUVABIONE AND ITS STEREOISOMER

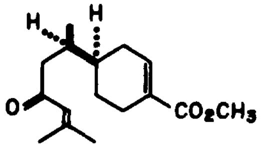
Kenji Mori and Masanao Matsui
Department of Agricultural Chemistry, The University of Tokyo
Bunkyo-ku, Tokyo, Japan

(Received in Japan 22 August 1967)

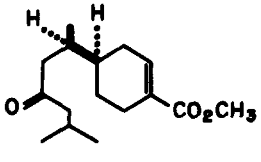
Dehydrojuvabione (I) is a compound with high juvenile hormone activity isolated from Czechoslovak balsam fir (Abies balsamea L.) by Šorm and his co-workers (1). After the completion of the synthesis of (±)-juvabione (II) (2), a congener of dehydrojuvabione (1)(3), we turned our attention to the synthesis of this sesquiterpene ester which has now been accomplished.

β-(p-Methoxyphenyl)butyryl chloride (IIIa)(2) was condensed with diethyl ethoxymagnesiomalonate to give an ester (IIIb)(4), which was hydrolyzed and decarboxylated to give a ketone (IIIc), b.p. 94-95°/0.15mm, n_D^{24}1.5104; 2,4-dinitrophenylhydrazone, m.p. 109-111°. Carbethoxylation of the ketone (IIIc) with diethyl carbonate and sodium amide gave a β-keto ester (IIId), b.p. 130-132°/0.1mm, n_D^{25}1.5048. This was hydrogenated over Raney nickel W-7 to give a hydroxy ester (IV), b.p. 145-147°/0.1mm, n_D^{27}1.5020. Addition of methyl magnesium iodide to this ester yielded 2-methyl-6-(p-methoxyphenyl)-heptane-2,4-diol (V), b.p. 149°/0.15mm, n_D^{27}1.5072.

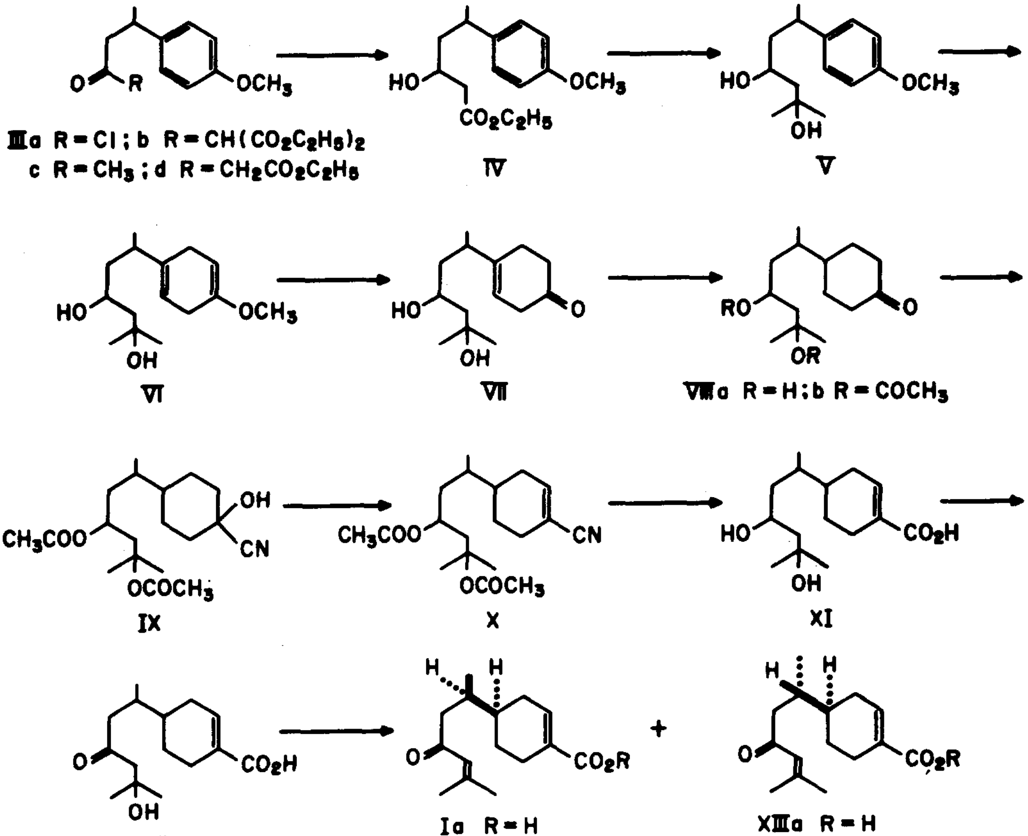
The Birch reduction (Dryden's modification (5)) of this diol gave a diene (VI), b.p. 133-135°/0.08mm, n_D^{27}1.4902. This was converted to a β,γ-unsaturated ketone (VII) by treatment with oxalic acid in methanol-water. Hydrogenation of the enone (VII) over palladium-charcoal gave a dihydroxy ketone (VIIIa), b.p. 125-127°/0.1mm, n_D^{25}1.4784, which was acetylated with acetyl chloride-pyridine to give a diacetate (VIIIb), b.p. 155-157°/0.15mm, n_D^{27} 1.4748. Addition of hydrogen cyanide to it yielded a cyanohydrin (IX) as a viscous oil which was dehydrated with phosphorus oxychloride and pyridine to give an unsaturated nitrile (X), b.p. 155-160°/0.08mm. n_D^{25}1.4800. Hydrolysis of the nitrile with concomitant removal of the acetyl group was effected by heating the nitrile with potassium hydroxide in diethylene



Ib



II



IIIa R = Cl ; b R = $CH(CO_2C_2H_5)_2$
c R = CH_3 ; d R = $CH_2CO_2C_2H_5$

IV

V

VI

VII

VIIIa R = H ; b R = $COCH_3$

IX

X

XI

XII

Ia R = H
b R = CH_3

XIIIa R = H
b R = CH_3

glycol-water to give a dihydroxy acid (XI). This was oxidized with 8N-chromic acid reagent to give a stereoisomeric mixture of hydroxytodomatuic acid (XII).

This β-hydroxy ketone (XII) dissolved in benzene was heated in the presence of a small amount of hydrochloric acid and iodine to give a mixture of (±)-dehydrotodomatuic acid (Ia) and its stereoisomer (XIIIa), b.p. 170-175°/0.08mm, n_D^{30}1.5184, $\nu_{max.}$ (film)~2600, 1685, 1645, 1620, 1280, ~930 cm^{-1}; δ (ppm from TMS at 100 Mc, CCl_4 soln.) 0.92 (3H,d,J=6cps), 1.92 (3H,s), 2.15 (3H,s), 6.02 (1H,s), 7.10 (1H, broad); λmax (EtOH) 224 mμ (ε 13,000) (6). This was esterified with diazomethane to give a mixture of (±)-dehydrojuvabione (Ib) and its stereoisomer (XIIIb), b.p. 140-143°/0.08mm, n_D^{29}1.5025; $\nu_{max.}$ (CCl_4) 1722, 1694, 1652, 1620, 1435, 1380, 1252, 1082, 1034 cm^{-1}; δ (ppm from TMS at 100 Mc, $CDCl_3$ soln.) 0.88 (3H,d,J=6cps), 1.85 (3H,s), 2.10 (3H,s), 3.65 (3H,s), 6.04 (1H,s), 6.93 (1H, broad); λmax. (EtOH) 224 mμ (ε 15,000). The spectral properties of the synthetic product agreed well with those of the natural product kindly provided by Prof. Šorm. Small differences are obviously due to the presence of the isomer (XIIIb). The synthetic and natural products were indistinguishable by g.l.c. The biological activity of the synthetic product is now under estimation in Dr. Bowers' and in Dr. Sláma's laboratories (7).

Acknowledgments. We are indebted to Professor F. Šorm (Institute of Organic Chemistry and Biochemistry, Prague) for a sample of dehydrojuvabione. Our thanks are also due to Dr. N. Ikekawa (Institute of Physical and Chemical Research, Japan) for gas chromatographic analysis.

REFERENCES

1. V. Černý, L. Dolejš, L. Lábler, F. Šorm and K. Sláma, Tetrahedron Letters 1053 (1967).
2. K. Mori and M. Matsui, ibid. 2515 (1967).
3. W.S. Bowers, H.M. Fales, M.J. Thompson and E.C. Uebel, Science **154**, 1020 (1966).
4. Satisfactory spectral data (m.m.r. and/or i.r.) were obtained for all the

compounds specified with b.p. or m.p.

5. H.L. Dryden, Jr., G.M. Webber, R.R. Burtner and J.A. Cella, *J. Org. Chem.* **26**, 3237 (1961).

6. This acid partly crystallised after standing in a refrigerator. Separation of the two isomers, however, was impossible because of the limited amount of the semi-solid acid. The crystalline acid is probably the desired stereoisomer (cf. 2).

7. (±)-Juvabione showed high activity (about a half as active as natural juvabione) in the bug *Pyrrhocoris apterus*.