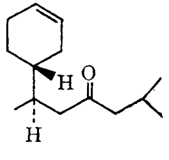
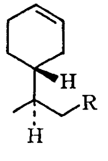
Stereospecific Synthesis and Absolute Stereochemistry of Natural (+)-Juvabione

By BEVERLY A. PAWSON,* H.-C. CHEUNG, SATLOO GURBAXANI, and G. SAUCY
(*Chemical Research Department, Hoffmann-La Roche, Nutley, New Jersey* 07110)

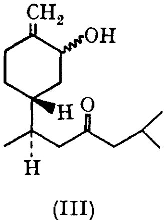
RECENT reports[1] of the isolation from Balsam fir and structure determination of (+)-juvabione and (+)-dehydrojuvabione, compounds having insect juvenile hormone activity, have stimulated research and several syntheses of (±)-juvabione and (±)-dehydrojuvabione have been published.[2] We report the stereospecific synthesis of natural (+)-juvabione and elucidation of the absolute configuration of the two asymmetric centres by chemical correlation.



(Ia) R = CO_2Me
(Ib) R = CO_2H
(Ic) R = Me
(Id) R = CHO



(IIa) R = OH
(IIb) R = OTs
(IIc) R = CN



(III)

(+)-Juvabione (Ia) is the methyl ester of (+)-todomatuic acid (Ib), a compound found in sulphite-treated pulp wood. Based upon the comparison of molecular rotations ($[M]_D$) of (+)-todomatuic acid, and its conversion products, with similar sesquiterpenes of known absolute configuration. Nakazaki and Isoe[3] assigned the *R*-configuration to both asymmetric centres of

(+)-todomatuic acid (Ib). The chemical correlation described confirms this assignment.

Hydroboronation[4] of *R*-(+)-limonene ($[\alpha]_D$ + 116°, neat) with bis-(1,2-dimethylpropyl)borane (disiamylborane) afforded, after oxidative work-up, a mixture of 4(*R*),8(*R*)- and 4(*R*),8(*S*)-*p*-menth-1-en-9-ol. Fractional crystallization of the 3,5-dinitrobenzoates followed by hydrolysis of the less soluble ester gave 4(*R*),8(*S*)-*p*-menth-1-en-9-ol (IIa) of known absolute configuration.[5]

The alcohol (IIa) was converted into (+)-3(*R*)-[4-methylcyclohex-3-en-1(*R*)-yl]butyronitrile (IIc) *via* the toluene-*p*-sulphonate (IIb) by displacement with sodium cyanide in dimethyl sulphoxide. Alkylation of (IIc) with isobutyl-lithium afforded (+)-2(*R*)-[4-methylcyclohex-3-en-1(*R*)-yl]-6-methylheptan-4-one (Ic). Photo-oxygenation[6] of (Ic) in pyridine solution, with hematoporphyrin as sensitizer, afforded, after reduction of the initially formed hydroperoxides, a mixture of secondary and tertiary alcohols including (III). Oxidation of the mixture of secondary alcohols with chromic acid–sulphuric acid–acetic acid in benzene gave the aldehyde (Id) which was further oxidized to the acid (Ib) with silver oxide. Treatment of (Ib) with diazomethane gave the ester (Ia), the spectral properties of which were identical with those of natural (+)-juvabione. In particular, the o.r.d. spectrum of synthetic ester (Ia) (*c* 0·209, ethanol, 23°) had $[\phi]_{700}$ + 153°, $[\phi]_{589}$ + 209°, $[\phi]_{303}$ + 2116°, $[\phi]_{266}$ + 1397°, $[\phi]_{226}$ + 12,065°, $[\phi]_{200}$ 0°, and $[\phi]_{190}$ − 9525°; the c.d. spectrum (*c* 0·00786M, ethanol, 23°) $[\theta]_{320}$ 0, $[\theta]_{292}$ + 1511, $[\theta]_{260}$ + 671, $[\theta]_{215}$ + 13,433, and $[\theta]_{196}$ 0. Corresponding spectra for natural (+)-juvabione were o.r.d. (*c* 0·126, ethanol, 23°) $[\phi]_{700}$ + 136°, $[\phi]_{589}$ + 168°, $[\phi]_{305}$ + 1974°, $[\phi]_{275}$ + 1176°, $[\phi]_{229}$ + 14,700°, and $[\phi]_{196}$ 0°; c.d. (*c* 0·01167M, ethanol, 23°), $[\theta]_{326}$ 0, $[\theta]_{289}$ + 1639, $[\theta]_{260}$ + 735, $[\theta]_{218}$ + 12,438, and $[\theta]_{194}$ 0. Hydrolysis of the synthetic ester (Ia) afforded the crystalline acid (Ib) (m.p. 64·0—65·5°) which did not depress the melting point of (+)-todomatuic acid prepared by hydrolysis of natural (+)-juvabione. The o.r.d. and c.d. spectra of the two acids were in agreement.

We thank Professor V. Cerny for a sample of natural (+)-juvabione, Dr. G. Ohloff for samples of the 3,5-dinitrobenzoates of the diastereoisomeric (+)-*p*-menth-1-en-9-ols, and the Physical Chemistry Department, Hoffmann-La Roche Inc., for spectral measurements.

(*Received, June* 21*st*, 1968; *Com.* 817.)

---

[1] W. S. Bowers, H. M. Fales, M. J. Thompson, and E. C. Uebel, *Science*, 1966, **154**, 1020; V. Cerny, L. Dolejs, L. Labler, F. Šorm, and K. Slama, *Tetrahedron Letters*, 1967, 1053; V. Cerny, L. Dolejs, L. Labler, F. Šorm, and K. Slama, *Coll. Czech. Chem. Comm.*, 1967, **32**, 3926.

[2] K. Mori and M. Matsui, *Tetrahedron*, 1968, **24**, 3127, and references cited therein; K. S. Ayyar and G. S. K. Rao, *Tetrahedron Letters*, 1967, 4677.

[3] M. Nakazaki and S. Isoe, *Bull. Chem. Soc. Japan*, 1963, **36**, 1198.

[4] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, 1961, **83**, 1241.

[5] K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, 1966, **49**, 2150.

[6] G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Annalen*, 1964, **674**, 93.