Tetrahedron Letters No.47, pp. 4677–4682, 1967. Pergamon Press Ltd. Printed in Great Britain.

STUDIES IN TERPENOIDS - IV (1): SYNTHESIS OF (±)-JUVABIONE AND (±)-*ar*-JUVABIONE (2). CONVERSION OF TURMERONE TO (+)-*ar*-JUVABIONE

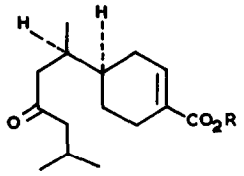
K. SUBRAHMANIA AYYAR(3) and G.S. KRISHNA RAO
Department of Organic Chemistry, Indian Institute of Science, Bangalore-12 (India)

(Received in UK 1 August 1967)

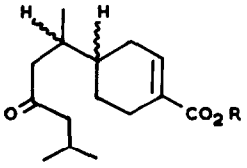
The reported (4) synthesis of (±)-juvabione [methyl (±)-todomatuate] by Mori and Matsui (5) prompts us to place on record our own work on the synthesis of (±)-juvabione and its aromatic (±)- and (+)-analogues.

By hydrolysis of the oil derived from *Abies sachalinensis* Mast., Tuchihashi and Hansawa (6) isolated todomatuic acid and its structure, deduced by Momose (7), was confirmed by Nakazaki and Isoe (8) who also assigned its absolute configuration (Ia). Very recently highly active sesquiterpenoid juvenile hormones called juvabione (9,10) and dehydrojuvabione (10) were isolated from the wood of the balsam fir, *Abies balsamea* L., the former identified as a methyl ester (Ib) of todomatuic acid.

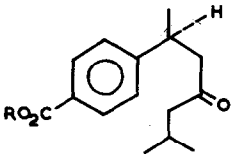
The present communication describes the synthesis of the keto acid IIa, its methyl ester IIb (11) and its aromatic analogues (+)-III (12) [correlated with (±)-VIIId prepared by total synthesis *vide infra*] by conversion of the naturally occurring turmerone fraction from the essential oil of *Curcuma longa* L.



I. a, R = H
b, R = Me

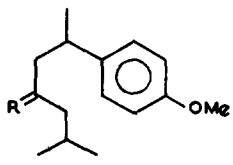


II. a, R = H
b, R = Me

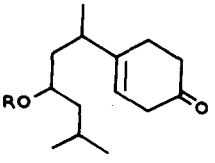


III. a, R = H
b, R = Me

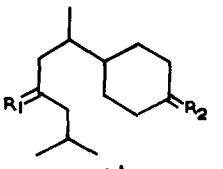
'p-Methoxystyrylisobutyl ketone (13) on conjugate addition (14) with CH_3MgI furnished the 1,4-addition product IVa (15). Birch reduction of the anisyl alcohol IVb and hydrolysis of the resulting dihydroanisole gave the unconjugated keto alcohol Va. Its acetate Vb was hydrogenated to VIa which was then converted to the cyanohydrin acetate VIb by an exchange reaction (16). The dehydration of VIb furnished the acetoxy unsaturated nitrile VIIa as a major product which on alkaline hydrolysis gave the hydroxy unsaturated acid VIIb. Oxidation (Jones' reagent) gave the keto acid IIa (17), m.p. 65-66° (as regenerated from its S-benzylthiuronium salt, m.p. 162°). It gave an IR spectrum (CCl_4) almost superimposable with that of the natural todomatuic acid (Ia) (18).



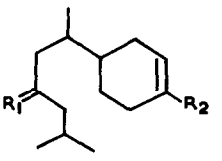
IV. a, R = O
b, R =



V. a, R = H
b, R = Ac



VI. a, R_1 =  ; R_2 = O
b, R_1 =  ; R_2 = 
c, R_1 =  ; R_2 = O
d, R_1 =  ; R_2 = 
e, R_1 = O; R_2 = 

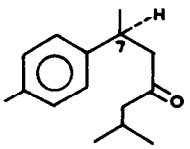


VII. a, R_1 = 
R_2 = CN
b, R_1 = 
R_2 = CO_2H
c, R_1 = O
R_2 = CN

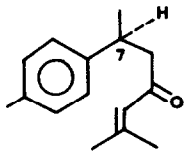
Several attempts to resolve the methyl ester IIb by TLC(11) including $AgNO_3$-SiO_2 (19), GLC (11) and IDCC (20) gave no evidence for its separation into its diastereomeric components. The structure of the synthetic keto acid IIa was correlated with that of the natural todomatuic acid (Ia) by conversion of IIa into desoxo- and the anilide of <u>trans</u> (±)-dihydro-desoxo-todomatuic acids, both of which gave completely superimposable IR spectra (CCl_4) with the corresponding samples derived from the natural acid (8,18).

The synthesis of <u>ar</u>-todomatuic acid arose from a consideration that the occurrence, in nature in different sources or often in the same source, of perhydro terpenoids and the corresponding aromatised compounds is quite widespread (21).

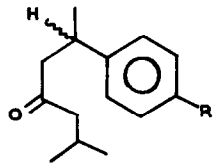
Conjugate addition of CH_3MgI to the styrylisobutyl ketone (22) furnished 2-phenyl-6-methylheptan-4-one (VIIIa). Chloromethylation of VIIIa gave the chloromethyl ketone VIIIb which was converted by standard procedures to the keto acid VIIId and (±)-<u>ar</u>- juvabione VIIIe <u>via</u> the aldehyde VIIIc. Dehydrogenation of the keto acid IIa to give the <u>ar</u>-keto acid VIIId provided mutually confirmatory support to both the structures.



X.



IX.



VIII. a, R = H
b, R = CH_2Cl
c, R = CHO
d, R = CO_2H
e, R = CO_2Me

Alternatively (+)-ar-turmerone (IX) of known absolute configuration (23) at C-7 appeared to be an attractive starting material for the preparation of optically active ar-todomatuic acid (IIIa) and ar-juvabione (IIIb).

Aromatisation of the sesquiterpene ketone fraction from Curcuma longa L. consisting chiefly of turmerone and ar-turmerone, by the hydrogen transfer technique of Kindler and Lahrs (24) gave (+)-ar-turmerone (IX) (25). On oxidation (26,27) by a modified procedure (CrO_3-AcOH-H_2O), (+)-ar-dihydroturmerone (X) gave ar-todomatuic acid (IIIa) contaminated with terephthalic acid. Extensive purification of the esterified material by successive chromatographic separations gave pure (+)-ar-juvabione (IIIb) (12). Since the C-7 centre in ar-turmerone was established as S (23), the same stereochemistry follows for the (+)-ar-juvabione prepared by us. However, since the naturally occurring todomatuic acid (Ia) (8) and juvabione (Ib) (9) possess R chirality at C-7, they are expected to give on aromatisation the corresponding levorotatory ar-compounds.

Acknowledgements. We thank Prof. D.K. Banerjee of this department for his interest in this work and encouragement. We also gratefully acknowledge the generous help of Prof. F. Sorm (11,12), Dr. Sukh Dev (11) and Dr. S. Isoe (18).

References and Footnotes

1) Part III of this series: L.R. Subramanian and G.S. Krishna Rao, Tetrahedron, In Press.

2) Part of this work under the title "Studies in the synthesis of (±)-Todomatuic Acid and its Analogues" was presented and published in an Abstract form at the symposium on "Recent Advances in the Chemistry of Terpenoids" held at the National Chemical Laboratory, Poona (India) in June 1965.

3) (a) Part of Ph.D. thesis (1967), Indian Institute of Science, Bangalore; (b) Present address: Forest Research Laboratory, Bangalore.

4) The title of the Japanese work came to our notice from Current Contents, 10(No.26), 42 (1967). The original journal is not yet received in our Library.

5) K. Mori and M. Matsui, Tetrahedron Letters, 2515 (1967).

6) R. Tuchihashi and T. Hanzawa, Chem. Abst., 37, 258 (1943).

7) T. Momose, Chem. Abst., 44, 9383 (1950).

8) M. Nakazaki and S. Isoe, Bull. Chem. Soc. Japan, 36, 1198 (1963).

9) W.S. Bowers, H.M. Fales, M.J. Thompson and E.C. Uebel, Science, 154, 1020 (1966).

10) V. Cerny, L. Dolejs, L. Labler, F. Sorm and K. Slama, Tetrahedron Letters, 1053 (1967).

11) The methyl ester IIb gave a single peak on GLC (on two columns - diethyleneglycol polysuccinate and silicon). It showed an identical R_F value on TLC and gave a superimposable IR spectrum as the natural juvabione (Ib). The NMR data of IIb showed good agreement as reported for Ib (9). Our synthetic keto ester IIb exhibited medium (as expected of a dl-specimen) juvenile hormone activity against Pyrrhocoris apterus L. and Dysdercus intermedius at 10 micrograms/1 bug dosage. We are grateful to Dr. Sukh Dev for the GLC and the NMR of IIb and to Prof. F. Sorm who kindly took the comparison IR spectra of IIb and Ib, examined their TLC behaviour and evaluated for us the physiological activity of IIb.

12) The aromatic analogue (+)-IIIb of juvabione exhibited identical physiological effects as IIb. We sincerely thank Prof. F. Sorm for the IR spectrum of our sample and its physiological evaluation. (We sent our samples IIb and (+)-IIIb to Prof.Sorm on May 6, 1967).

13) J.C. Bardham and D.N. Mukherji, J. Chem. Soc., 4629 (1956).

14) H.O. House, W.S. Respess and G.M. Whitesides, J. Org. Chem., 31, 3128 (1966).

15) For all new compounds reported acceptable elemental analyses and spectral evidence were obtained.

16) H.J. Ringold, J. Am. Chem. Soc., 82, 961 (1960).

17) The following route also was investigated for the synthesis of the keto acid IIa. The alkaline hydrolysis of the keto unsaturated

Va —— VIc —— VId —— VIe —— VIIc

nitrile VIIc gave a solid bicyclic non-ketonic diene acid which is under investigation. Its acid hydrolysis however, furnished the required keto acid IIa.

18) Our grateful thanks are due to Dr. S. Isoe for kindly sending us the authentic samples.

19) A.S. Gupta and Sukh Dev, J. Chromatog., 12, 189 (1963).

20) V.K. Bhalla, U.R. Nayak and Sukh Dev, J. Chromatog., 26, 54 (1967).

21) W. Sandermann in Comparative Biochemistry ed. M. Florkin and H.S. Mason, Vol. III, Chapters 10 and 11, Academic Press, New York (1962); H. Erdtman and T. Norin in the Chemistry of Organic Natural Products, Ed. L. Zechmeister, Vol.24, Springer-Verlag, Wien (1966); Sukh Dev, J. Sci. Industr. Res. India, 25, 494 (1966).

22) R.P. Mariella and R.R. Raube, J. Am. Chem. Soc., 74, 521 (1952).

23) V.K. Honwad and A.S. Rao, Tetrahedron, 20, 2921 (1964).

24) K. Kindler and K. Luhrs, Ann., 685, 36 (1965); K. Kindler and K. Luhrs, Chem. Ber., 99, 227 (1966).

25) We thank Dr. A.S. Rao for the IR spectrum of ar-turmerone and an authentic sample of its 2,4-dinitrophenylhydrazone.

26) C. Enzell and H. Erdtman, Tetrahedron, 4, 361 (1958).

27) K.B. Wiberg in Oxidations in Organic Chemistry, Ed. K.B. Wiberg, Part A, Academic Press, New York (1965).