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α-CUBEBENE AND β-CUBEBENE. SYNTHETIC PROOF OF GROSS STRUCTURE.

Edward Piers, Ronald W. Britton and William de Waal

Department of Chemistry, University of British Columbia,

Vancouver 8, B.C., Canada

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The cadinane-type sesquiterpenes α-cubebene and β-cubebene, isolated from commercial oil of cubeb (Piper cubeba L.), have been assigned the interesting structures I and II, respectively (1). Furthermore, subsequent (2) direct correlation of α-cubebene (I) with the sesquiterpenes cubenol and epi-cubenol (3) allowed the assignment of stereochemistry (as depicted by I and II) to the cubebenes. We report here preliminary synthetic work which fully corroborates the gross structural proposals for these latter compounds.

Condensation of a mixture of (±)-menthone and (±)-isomenthone (III)* with ethyl formate in the presence of sodium methoxide in benzene gave, in 88% yield, the hydroxymethylene derivatives IV, b.p. 71-73°/0.2 mm. The corresponding n-butylthiomethylene compounds V (b.p. 138-142°/0.2 mm), formed in 98% yield from IV by standard procedure (4) gave, upon reduction with sodium borohydride in methanol, followed by hydrolysis (5) of the resulting crude alcohols VI with dilute hydrochloric acid in acetone, a good yield of the α,β-unsaturated aldehydes VII, b.p. 66-68°/0.35 mm; IR(film): 5.96, 6.15 μ; NMR ($CDCl_3$): τ 0.60 (singlet, -CHO), 3.35 (unresolved multiplet, olefinic H). Reduction of VII with sodium borohydride in methanol afforded alcohols VIII [90%; b.p. 77-78°/0.25 mm; NMR ($CDCl_3$): τ 4.44 (broad multiplet, olefinic H), 5.97 (broad multiplet, -$C\underline{H}_2OH$)] which, upon reaction with phosphorus tribromide in benzene-pyridine, gave the allylic bromides IX [65%; b.p. 75°/0.2 mm; NMR ($CDCl_3$): τ 4.27 (broad multiplet, olefinic H), 5.78-6.22 (multiplet, -CH_2Br)].

When the mixture of bromides (IX) was reacted with carbethoxymethylenetriphenylphosphorane (6) in hot ethyl acetate and the resulting crude product was hydrolyzed with 10% potassium

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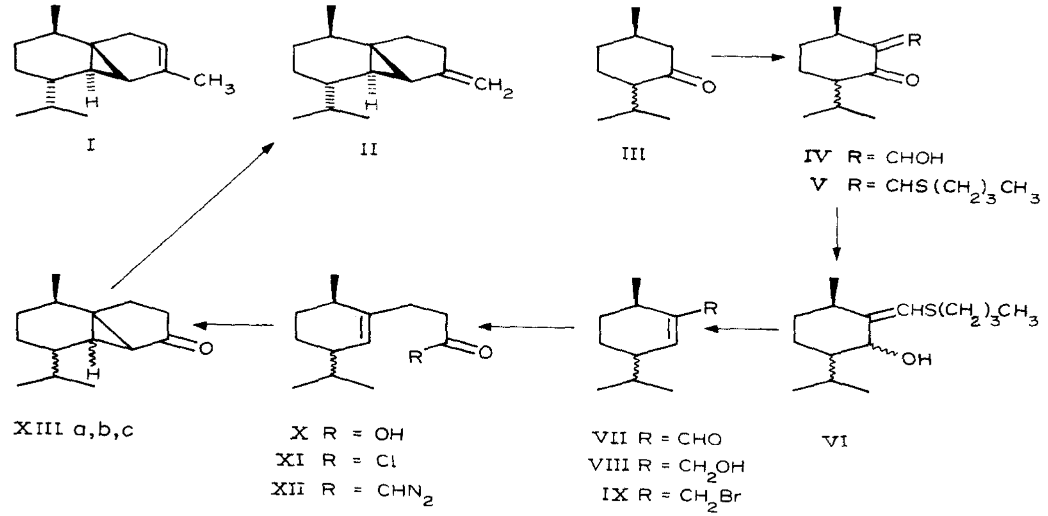
* Compounds III-V and VII-XII represent racemic diastereoisomeric pairs. Analytical and spectral data of these mixtures were, in each case, in full accord with the assigned structures.



hydroxide in 1:1 methanol-water (7), the carboxylic acids X [b.p. 118-124°/0.2 mm; NMR ($CDCl_3$): τ 4.70 (broad multiplet, olefinic H)] were produced in 86% yield. Reaction of the sodium salt of the latter with oxalyl chloride in benzene gave the acid chlorides XI [IR(film): 5.58 μ] which were converted, by reaction with diazomethane in alcohol-free ether, into the corresponding diazoketones XII [IR(film): 4.78, 6.10 μ].

When the mixture of olefinic diazoketones (XII) was refluxed in cyclohexane in the presence of cupric sulfate (8) for 1.5 hours, a remarkably clean and high-yielding intramolecular cyclization occurred, producing *three* isomeric ketones (XIII a, b, c) in a ratio (g.l.c. analysis) of 2:3:5, respectively. The minor isomer (XIIIa) [colorless oil; UV: λ_{max}^{MeOH} 206 mμ (ε=6,150); IR (film): 5.85 μ; NMR ($CDCl_3$): τ 9.00, 9.04, 9.08 (doublets, J = 6.5 Hz, three secondary methyls)] was isolated by preparative g.l.c and gave, upon treatment with methylenetriphenylphosphorane in dimethyl sulfoxide (9), a quantitative yield of (±)-β-cubebene (II) as a clear colorless oil, b.p. 100°/0.2 mm; n_D^{20} 1.4975; UV: λ_{max}^{MeOH} 209 mμ (ε=9,850); IR(film): 6.09, 11.63 μ;NMR ($CDCl_3$): τ 5.28, 5.47 (unresolved multiplets, $=CH_2$), 9.04, 9.06, 9.10 (doublets, J = 6.5 Hz, three secondary methyls).

Although we were not able to secure an authentic sample of natural β-cubebene, correlation of our synthetic product [(±)-II] with the natural series was achieved as follows. Catalytic hydrogenation (platinum oxide, ethanol) (1) of (±)-β-cubebene (II) gave a mixture of two dihydro derivatives in a ratio of 45:55. These epimers were separated by preparative g.l.c. and the minor product was shown to be identical (infrared, g.l.c. retention time on three different columns) with dihydro α-cubebene (1), obtained by catalytic hydrogenation (platinum oxide, ethanol) of an authentic sample of α-cubebene (I).**

It should be noted that ketones XIIIb and XIIIc, upon reaction with methylenetriphenylphosphorane in dimethyl sulfoxide, gave isomers of (±)-β-cubebene. Catalytic hydrogenation of these isomers was highly stereoselective and, in each case, only one dihydro derivative was produced. These dihydro compounds were shown to be different from dihydro α-cubebene.

We are currently engaged in determining the stereochemistry of our synthetic intermediates with the aim of confirming the stereochemical proposal (2) for α- and β-cubebene. The results will be reported in the detailed paper.

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REFERENCES

1. Y. Ohta, T. Sakai, and Y. Hirose, Tetrahedron Letters, 6365 (1966).
2. Y. Ohta, K. Ohara, and Y. Hirose, Tetrahedron Letters, 4181 (1968).
3. Y. Ohta and Y. Hirose, Tetrahedron Letters, 2073 (1967).
4. R.E. Ireland and J.A. Marshall, J. Org. Chem. **27**, 1615 (1962).
5. See R.E. Ireland and J.A. Marshall, J. Org. Chem. **27**, 1620 (1962).
6. See S. Trippett, Advances in Organic Chemistry: Methods and Results, p. 83. Interscience Publishers, Inc., New York (1960).
7. H.J. Bestmann and H. Schulz, Chem. Ber., **95**, 2921 (1962).
8. M.M. Fawzi and C.D. Gutsche, J. Org. Chem. **31**, 1390 (1966), and references therein.
9. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc. **87**, 1345 (1965), and references therein.

** It is important to note that correlation of natural β-cubebene (II) with α-cubebene (I) had already been accomplished (ref. 1) by comparison of their respective dihydro derivatives and by direct conversion of II into I *via* partial isomeriation of the former on a polypropylene capillary column at 150°.