Tetrahedron Letters No.24, pp. 2855-2858, 1968. Pergamon Press. Printed in Great Britain.

STRUCTURE OF CURZERENONE, EPICURZERENONE, AND ISOFURANOGERMACRENE (CURZERENE)

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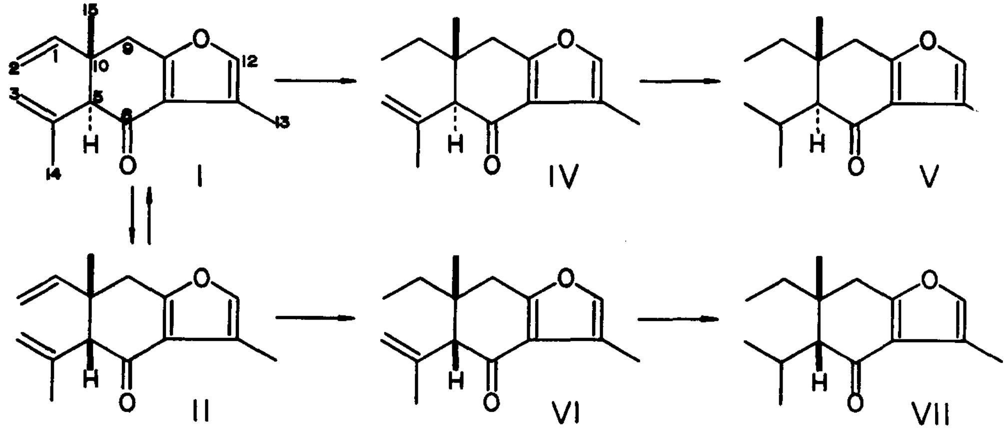
(Received in Japan 14 February 1968; received in UK for publication 18 March 1968)

From the rhizome of zedoary, Curcuma zedoaria Roscoe (Zingiberaceae), three new furan-containing sesquiterpenoids of the elemane type have been isolated. It is shown in the present communication that these sesquiterpenoids now designated as curzerenone, epicurzerenone, and isofuranogermacrene[*1] have structures I, II, and III, respectively.[*2]

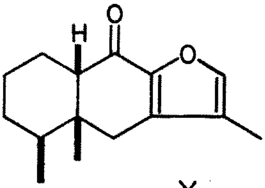
Curzerenone, $C_{15}H_{18}O_2$, $[\alpha]_D$ ±0°, is revealed by its UV, IR, and NMR spectra to contain a carbonyl involved in a β-furoyl system (λ_{max} 272 mμ, ν_{max} 1675 cm^{-1}), an α-hydrogen and a β-methyl on a furan ring, a methylene flanked by quaternary carbons and weakly coupled with the α-hydrogen of the furan, a tertiary methyl, a vinyl on a quaternary carbon, an isopropenyl, and an isolated hydrogen. Partial hydrogenation of curzerenone over Raney-nickel in methanol resulted in the saturation of the vinyl group yielding the dihydro-derivative (IV), which was further hydrogenated with platinum in methanol to furnish the tetrahydro-derivative (V). Curzerenone must thus be represented as in formula I (disregarding the stereochemistry).

Epicurzerenone, $C_{15}H_{18}O_2$, $[\alpha]_D$ ±0°, possesses very similar spectral properties to those of curzerenone. Indeed, the UV, IR, and mass spectra of both substances are practically identical

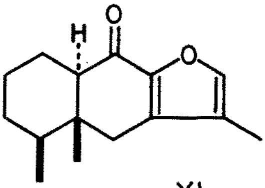


and the NMR spectra differ only slightly. Furthermore, epicurzerenone was also converted into the dihydro-derivative (VI) and the tetrahydro-derivative (VII) by methods similar to those described above. These observations led us to conclude that the substances might be epimeric in the position α to the carbonyl function, i.e., C-5. In confirmation, alkali treatment of curzerenone and epicurzerenone was carried out and, in both cases, the same equilibrium mixture of the same substances was obtained.

Since curzerenone and epicurzerenone show no optical activity, both substances are racemic. Therefore, the remaining problem was to determine the relative configurations at C-5 and C-10 for which the NMR study was informative. In the cis- and trans-furanoeremophil-9-ones (X and XI)[1,2] presently chosen as reference compounds, the C-5 methyl groups are situated at β-positions in the cyclohexenone systems in quasi-equatorial and quasi-axial configurations, respectively. Although the furanoeremophil-9-ones (X and XI) are α-furoyl derivatives while the tetrahydrocurzerenones (V and VII) are β-furoyl derivatives, the C-15 methyl protons of the latter two (V and VII) are predicted to show similar NMR properties to those of the former (X and/or XI). Indeed, the chemical shifts of the C-15 methyl protons of tetrahydrocurzerenone (V) and tetrahydroepicurzerenone (VII) are consistent with that of cis-furanoeremophil-9-one (X) but not with that of the trans-isomer (XI). The solvent-induced shifts for the C-15 methyl protons of both tetrahydro-derivatives (V and VII) on passing from chloroform to benzene solution ($\Delta^{CHCl_3}_{C_6H_6}$) are also compatible with those of cis-furanoeremophil-9-one (X) but not with those of its trans-counterpart (XI). These observations demonstrate the orientation of both the C-10 methyl groups



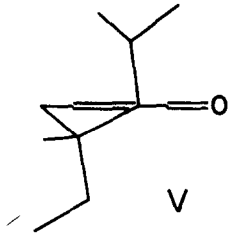
X



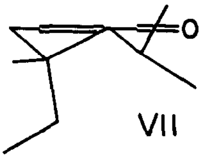
XI

TABLE. NMR data of the methyl protons of the sesquiterpenoids.

Substances	Chemical shifts of C-15 Me (CCl_4, p.p.m. from TMS)	$\Delta^{CHCl_3}_{C_6H_6}$ of C-15 Me (p.p.m.)	$\Delta^{CHCl_3}_{C_6H_6}$ of C-3, 14 Me (p.p.m.)
Tetrahydrocurzerenone (V)	1.00	+0.23	+0.13, -0.03
Tetrahydroepicurzerenone (VII)	1.12	+0.34	-0.03, -0.03
cis-Furanoeremophil-9-one (X)	1.07	+0.26	
trans-Furanoeremophil-9-one (XI)	0.77	+0.18	



V

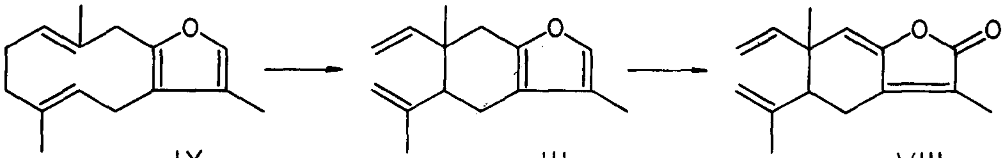


VII

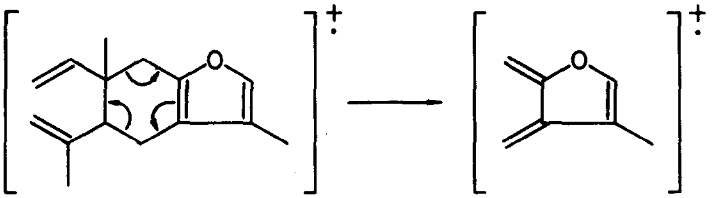
of tetrahydrocurzerenone (V) and tetrahydroepicurzerenone (VII) to be quasi-equatorial, and consequently, the conformations of both substances to be related to the projections V and VII. The solvent shifts ($\Delta^{CHCl_3}_{C_6H_6}$) for the C-3 and 14 methyl protons of tetrahydrocurzerenone (V) are +0.13 and -0.03 p.p.m. (Table), indicating that one methyl is located behind the carbonyl and the other situated in front of the carbonyl (projection V). On the other hand, the solvent shifts ($\Delta^{CHCl_3}_{C_6H_6}$) for the C-3 and 14 methyl protons of tetrahydroepicurzerenone (VII) is both -0.03 p.p.m. (Table), a fact which demonstrates the two methyls to be oriented in front of the carbonyl (projection VII). These observations permitted the relative configurations V and VII to be written for tetrahydrocurzerenone and tetrahydroepicurzerenone, and the stereostructures I and II for curzerenone and epicurzerenone follow.

Although epicurzerenone has been obtained from the extract of zedoary, it may be an artifact formed from curzerenone during the process of isolation, rather than a natural product present in plant.

Isofuranogermacrene, $C_{15}H_{20}O$, $[\alpha]_D$ ±0°, has the NMR spectrum closely resembling the spectra of the curzerenones. Its empirical formula contains one less oxygen than that of curzerenone, which is accounted for by its UV and IR spectra that exhibit the absence of a conjugated carbonyl system. The NMR spectrum indicates the following elements of structure: an α-hydrogen and a β-methyl on a furan ring, a tertiary methyl, a vinyl on a quaternary carbon, an isopropenyl, and five allylic hydrogens. On oxidation with 2,3-dichloro-5,6-dicyano-benzoquinone,[3] isofuranogermacrene yielded the conjugated lactone (VIII), m.p. 70.5~71°, which exhibits in the NMR spectrum a signal due to a newly formed vinyl hydrogen on C-9 as a singlet, demonstrating the quaternary nature of the adjacent carbon (C-10). From these facts, isofuranogermacrene must have structure



IX III VIII



m/e 216 m/e 108

III, or alternatively the isopropenyl group at C-5 could be at C-6, which possibility was examined as follows. The mass spectrum of isofuranogermacrene showed the expected molecular ion peak at m/e 216. The base peak appeared at m/e 108 due to a fragmentation of a retro Diels-Alder reaction type, indicating that the isopropenyl group is not situated at C-6 but at C-5. This conclusion was further confirmed by the finding that pyrolysis of furanodiene (IX), another constituent of zedoary, resulted in a Cope rearrangement giving isofuranogermacrene (curzerene).4) On the basis of these results isofuranogermacrene (curzerene) is represented by formula III.

We are in the opinion at present that isofuranogermacrene is a natural product, since heat *sufficient to cause the Cope rearrangement was not used at any stage of the isolation.*

We are greatly indebted to Dr. L. Novotný, Czechoslovak Academy of Science, for generous gift of the furanoeremophil-9-ones. Thanks are also due to Research Laboratory, Yoshitomi Pharmaceutical Co., Ltd., for determinations of the mass spectra.

FOOTNOTES AND REFERENCES

*I This sesquiterpenoid was originally announced by us under the name curzerene.4,5) We later learned of the isolation, from *Lindera strychnifolia* (Lauraceae), of a sesquiterpenoid called isogermafurene,6) which was later found to be identical with our curzerene. We were recently informed7) that they changed the term to isofuranogermacrene which we agreed to accept.

*2 Formulas (I ~ VII) are expressed by ones of the enantiomeric pairs.

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2) L. Novotný, private communication.

3) K. Takeda, M. Ikuta, M. Miyawaki, and K. Tori, *Tetrahedron*, **22**, 1159 (1966).

4) H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Letters*, **1968**, 931.

5) H. Hikino, K. Agatsuma, and T. Takemoto, *Abstract of the 6th Annual Meeting of the Tohoku Branch of the Pharmaceutical Society of Japan*, Sendai, p. 6, 1 Oct., 1967.

6) H. Ishii, T. Tozyo, M. Nakamura, and K. Takeda, *Abstract of the 11th Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics*, Matsuyama, p. 168, 20 Oct., 1967.

7) H. Minato, private communication.