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Structure of Furanodiene and Isofuranogermacrene (Curzerene)[1]

Hiroshi Hikino, Kunio Agatsuma, Chohachi Konno,
and Tsunematsu Takemoto

Pharmaceutical Institute, Tohoku University[2]

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Two new furan-containing sesquiterpenoids, furanodiene and isofuranogermacrene (curzerene), have been isolated from zedoary, *Curcuma zedoaria* (Zingiberaceae), and shown by spectroscopic and chemical studies to have the structures I and II, respectively.

Zedoary, *Curcuma zedoaria* Roscoe (Zingiberaceae), is a perennial herb indigenous to and cultivated in tropical Asia. The crude drug prepared from its rhizome has been used as an aromatic stomachic since olden times. We have been undertaking investigation of the constituents of the crude drug and hitherto isolated a number of new sesquiterpenoids, curcumol,[3] curcumenol,[4] isocurcumenol,[5] procurcumenol,[6] curdione,[7] zederone,[8] curcolone,[9] furanodienone, isofuranodienone,[10] curzerenone, epicurzerenone,[11] and pyrocurzerenone.[12] Further survey resulted in the isolation of two other novel sesquiterpenoids for which the names furanodiene and curzerene were proposed.[13,14] Afterwards, we learned of the isolation, from *Lindera strychnifolia* Villar (Lauraceae), by Ishii, *et al.*[15,16] of a sesquiterpenoid called isogermafurene, which was later found to be identical with our curzerene. These workers then proposed to change the term to isofuranogermacrene which we agreed to accept. In preliminary communications, we have reported that furanodiene and isofuranogermacrene (curzerene) possess the structures I and II, respectively.[11,14] The present paper describes the evidence in full detail.

Isofuranogermacrene possesses the molecular formula $C_{15}H_{20}O$ as shown by the presence of the molecular ion peak at *m/e* 216 in the mass spectrum. The nuclear magnetic resonance (NMR) spectrum (CCl_4) indicates the following elements of structure; an α-hydrogen (6.94 ppm) and a β-methyl (1.86 ppm) on a furan ring, a tertiary methyl (1.03 ppm), a vinyl on a quaternary

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[1] This paper constitutes Part XXXV in the series on Sesquiterpenoids. Part XXXIV: H. Hikino, T. Kohama, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1659 (1969).

[2] Location: *Aoba-yama, Sendai.*

[3] H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), 13, 1484 (1965); **14**, 1241 (1966).

[4] H. Hikino, Y. Sakurai, S. Numabe, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 39 (1968).

[5] H. Hikino, K. Agatsuma, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 959 (1969).

[6] H. Hikino, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1605 (1968).

[7] H. Hikino, Y. Sakurai, S. Takahashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1310 (1966); **15**, 1390 (1967).

[8] H. Hikino, S. Takahashi, Y. Sakurai, T. Takemoto, and N.S. Bhacca, *Chem. Pharm. Bull.* (Tokyo), **14**, 550 (1966); **16**, 1081 (1968).

[9] H. Hikino, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1065 (1967); **16**, 827 (1968).

[10] H. Hikino, C. Konno, T. Takemoto, K. Tori, M. Ohtsuru, and I. Horibe, *Chem. Commun.*, **1969**, 662.

[11] H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Letters*, **1968**, 2850.

[12] H. Hikino, K. Agatsuma, C. Konno, and T. Takemoto, *Tetrahedron Letters*, **1968**, 4417.

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

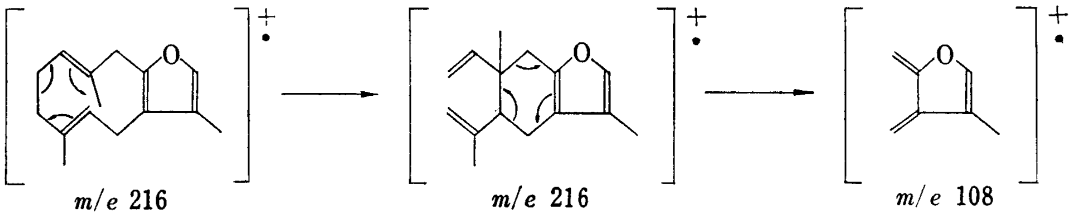
[14] H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Letters*, **1968**, 931.

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

[16] H. Ishii, T. Tozyo, M. Nakamura, and K. Takeda, *Tetrahedron*, **24**, 625 (1968).

carbon (4.88, 4.91, 5.84 ppm), an isopropenyl (1.70, 4.73, 4.77 ppm) and five allylic hydrogens (2.0—2.9 ppm), all the hydrogen atoms being accommodated. This terpenoids is then concluded to have a monocarbocyclic ring fused with the furan nucleus.

In order to clarify the environment of the carbon attached to the α'-position of the furan nucleus, isofuranogermacrene was oxidized with 2,3-dichloro-5,6-dicyano-benzoquinone to yield the conjugated lactone (III) which exhibits in the NMR spectrum a singlet due to a newly formed vinyl hydrogen on the carbon in question, demonstrating that another carbon adjacent to this carbon bears no hydrogen and consequently must carry the tertiary methyl and the vinyl group. From these facts, it is most likely that isofuranogermacrene has structure II, or alternatively the isopropenyl group at C-5 could be at C-6, which possibility was examined as follows. The mass spectrum of isofuranogermacrene shows the base peak at *m/e* 108 which is due to a fragmentation of a retro Diels–Alder reaction type, indicating that both the carbons next to the α'- and β'-positions of the furan ring carry two hydrogens, respectively, and consequently the isopropenyl group is situated at C-5 but not at C-6 (Chart).



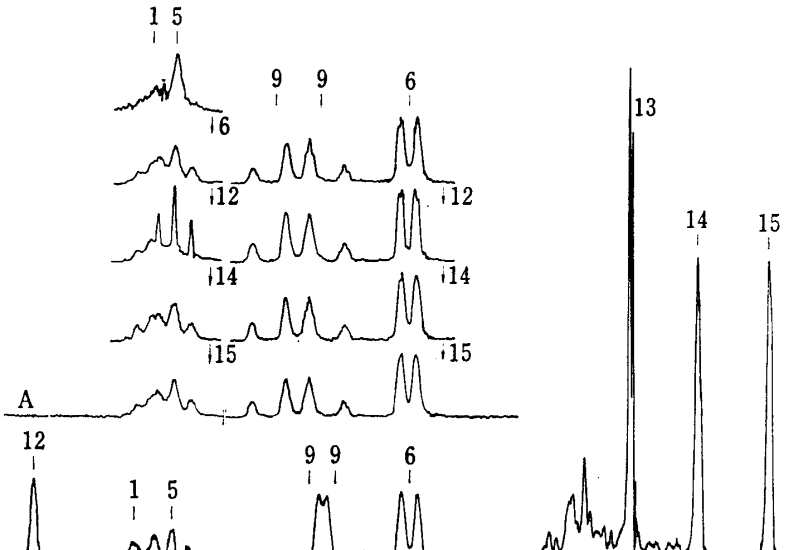
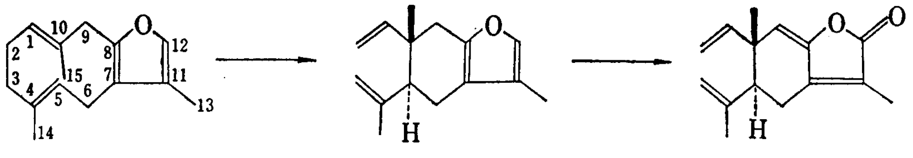


Fig. 1. NMR Spectrum of Furanodiene ($CDCl_3$,100 MHz)

A: that in $CDCl_3$–C_6D_6(1:10) abbreviation: ↓15=irradiation at C(15)H's

This conclusion was further confirmed by the fiinding that pyrolysis of furanodiene (I) resulted in a Cope rearrangement giving isofuranogermacrene, as described below. On the basis of these results isofuranogermacrene is represented by formula II (exclusive of stereochemistry). The configuration will be discussed later.



I II III

Chart 1

Furanodiene has the molecular formula $C_{15}H_{20}O$ as shown by elemental analysis and the presence of the parent peak at *m/e* 216 in the mass spectrum. For the structure elucidation, analysis of the NMR spectrum with the aid of double resonance experiments was particularly instructive (Fig.). The spectrum ($CDCl_3$) exhibits three vinyl methyl signals at 1.28, 1.59 and 1.91 ppm as well as three vinyl hydrogen signals at 4.96, 4.76 and 7.05 ppm. These hydrogens can be classified into the subsequent three functions. The methyl doublet at 1.91 ppm and the slightly multiplying hydrogen quadruplet at 7.05 ppm, spin-coupled each other ($J=1.3$ Hz), indicate the presence of a furan nucleus bearing a β-methyl ($C_{(13)}H_3$) and an α-hydrogen ($C_{(12)}H$). Mutual couplings are also observed between the methyl signals at 1.28 and 1.59 ppm ($C_{(15)}H_3$ and $C_{(14)}H_3$) and the hydrogen signals at 4.96 and 4.76 ppm ($C_{(1)}H$ and $C_{(5)}H$), respectively, a fact which demonstrates the presence of two trisubstituted double bonds. Furthermore, both vinyl hydrogen signals ($C_{(1)}H$ and $C_{(5)}H$) occurring as broad triplets ($J=7$ and 8 Hz, respectively) show the coupling with the adjacent methylene groups ($C_{(2)}H_2$ and $C_{(6)}H_2$), respectively. Two additional signals arising from two methylene groups ($C_{(9)}H_2$ and $C_{(6)}H_2$) appear as a broad quadruplet in an AB type at 3.44 and 3.52 ppm ($J=17$ Hz) and as a broad doublet at 3.08 ppm. The signal for the former methylene ($C_{(9)}H_2$) is long-range coupled with the α-hydrogen ($C_{(12)}H$) of the furan, the vinylic methyl ($C_{(15)}H_3$), and the latter methylene ($C_{(6)}H_2$). This finding reveals that the methylene ($C_{(9)}H_2$) is situated at the α'-position of the furan ring and also attached to the carbon (C-10) bearing the vinyl methyl. The latter methylene signal ($C_{(6)}H_2$) has the appearance of a broadened doublet, the large splitting ($J=8$ Hz) resulting from the coupling to the vinyl hydrogen ($C_{(5)}H$) and the small splittings from the couplings to the vinyl methyl ($C_{(14)}H_3$) and the allylic methylene ($C_{(9)}H_2$). The above NMR evidence leads to the conclusion that furanodiene is represented by formula I except for the geometries of the two trisubstituted ethylenic linkages which were examined by determination of the intramolecular nuclear Overhauser effect.[17] Thus, saturation of either of the C-14 and C-15 methyl signals resulted in the C-5 or C-1 hydrogen signal decoupled, respectively, but the integrated area of each hydrogen signal was unchanged as compared with the case when the irradiation frequency was offset from the methyl signals, indicating that both triply substituted double bonds (C-1:C-10 and C-4:C-5) are *trans*.

In the mass spectrum of furanodiene, the fragmentation pattern is essentially identical with that of isofuranogermacrene except for differences in the relative intensities. In particular, the base peak also appears at *m/e* 108 formed by the sequence depicted in the Chart. These data further support furanodiene to have the structure I.

The structure of furanodiene thus deduced was confirmed chemically by the following observation. Pyrolysis of furanodiene at 310—330° for 7 min resulted in a Cope rearrangement giving a product which was identified as isofuranogermacrene.

After the deduction of the *trans*-configurations of the two double bonds of furanodiene, mechanistic considerations of the Cope rearrangement from furanodiene to isofuranogermacrene demonstrate the *trans* ring junction of isofuranogermacrene.[18] However, since the present isofuranogermacrene shows no optical activity, it is concluded to be the racemic mixture. Although the isofuranogermacrene has been isolated from the extract of zedoary, doubt may naturally be raised whether it exists *per se* in Nature. We are in the opinion at present that the isofuranogermacrene is a natural product, since heat sufficient to cause the Cope rearrangement was not used at any stage of the isolation procedure.

8,12-Oxid-germacra-*trans*-1,*trans*-4,7,11-tetraene (I), which is presently designated as furanodiene, has been one of the missing links in the sesquiterpenoid biosynthesis. Provided that the furan ring is constructed before the modification of the other part of the molecule, furanodiene is the common precursor of all mono-, bi- and tri-carbocyclic sesquiterpenoids pos-

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[17] F.A.L. Anet and A.J.R. Bourne, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).

[18] *cf.*, R. Hoffmann and R.B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4389 (1965).

sessing furan rings, except for the furopelargones[19] which apparently follow the different biogenetic pathway. In fact, the zedoary rhizome, for instance, contains a number of its descendants; *i.e.*, zederone, curcolone, furanodienone, isofuranodienone, curzerenone, epicurzerenone, and pyrocurzerenone.

Experimental[20]

Isolation of Furanodiene and Isofuranogermacrene——The crude drug "Ga-jutsu," the dried rhizomes of *Curcuma zedoaria* Roscoe, was extracted with MeOH. The light petroleum soluble fraction was chromatographed over alumina. Light petroleum eluate was subjected to rechromatography over silica gel.

Elution with light petroleum and distillation under reduced pressure gave isofuranogermacrene (II) as a colorless oil. $[\alpha]_D$ $\pm 0°$ ($c=10.0$, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.90; H, 9.46. Mass Spectrum *m/e* (relative intensity): 216 (57, parent peak), 201 (13), 159 (9), 148 (33), 145 (13), 108 (100), 93 (17), 91 (30), 79 (32), 77 (31), 65 (20), 55 (30), 53 (33), 51 (15), 41 (56), 39 (57). UV λ_{max}^{EtOH} nm ($\log \varepsilon$): 210 (3.80). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3100, 1640, 988, 910, 892 (vinyl, vinylidene), 1565, 1106 (furan). NMR (CCl_4): 3H s at 1.03 ($C_{(15)}\underline{H}_3$), 3H broad s at 1.70 ($C_{(14)}\underline{H}_3$), 3H d at 1.86 ($J=1.5$, $C_{(13)}\underline{H}_3$), 5H m at 2.0—2.9 ($C_{(5)}\underline{H}$, $C_{(6)}\underline{H}_2$, $C_{(9)}\underline{H}_2$), two 1H q's at 4.73, 4.77 ($J=1$, $C_{(3)}\underline{H}_2$), 1H dd at 4.88 ($J=11, 1$, $C_{(2)}\underline{H}$), 1H dd at 4.91 ($J=18, 1$, $C_{(2)}\underline{H}$), 1H dd at 5.84 ($J=11, 18$, $C_{(1)}\underline{H}$), 1H broad peak at 6.94 ($C_{(12)}\underline{H}$). Vanillin–HCl reaction: positive (purple).

Succesive elution with the same solvent and crystallization from light petroleum yielded furanodiene (I) as colorless needles, mp 45—46°. $[\alpha]_D$ $\pm 0°$ ($c=10.0$, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.46; H, 9.37. Mass Spectrum *m/e* (relative intensity): 216 (52, parent peak), 201 (19), 159 (26), 148 (6), 145 (27), 108 (100), 93 (28), 91 (33), 79 (24), 77 (27), 65 (14), 55 (11), 53 (16), 41 (27), 39 (23). IR ν_{max}^{KBr} cm^{-1}: 1542, 1089 (furan). NMR: see Fig. Vanillin–HCl reaction: positive (purple).

Oxidation of Isofuranogermacrene with 2,3-Dichloro-5,6-dicyano-benzoquinone—Isofuranogermacrene (225 mg) in dioxan (4 ml) was treated with DDQ (880 mg) at 55—60° for 10 min. After isolation with ether in the usual way, the product (300 mg) was chromatographed over alumina (7 g). Elution with light petroleum–benzene (1:1) and crystallization from light petroleum gave the lactone (III) as colorless prisms, mp 70.5—71°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3100, 1004, 919, 897 (vinyl, vinylidene), 1777 (γ-enollactone). NMR (CCl_4): 3H s at 1.14 ($C_{(15)}\underline{H}_3$), 3H s at 1.70 ($C_{(14)}\underline{H}_3$), 3H d at 1.83 ($J=1$, $C_{(13)}\underline{H}_3$), 1H s at 5.34 ($C_{(9)}\underline{H}$).

Pyrolysis of Furanodiene——Furanodiene (110 mg) was heated under N_2 at 310—330° for 7 min. The product (110 mg) which gave one spot on TLC was distilled under reduced pressure to afford isofuranogermacrene (II) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3100, 1640, 988, 914, 893 (vinyl, vinylidene). Identification with the natural isofuranogermacrene was carried out in the usual criteria (TLC, IR and NMR).

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19) G. Lukas, J.C.N. Ma, J.A. McCloskey, and R.E. Wolff, *Tetrahedron*, **20**, 1789 (1964).

20) Melting points are uncorrected. NMR spectra were recorded at 60 MHz unless otherwise indicated. Chemical shifts are expressed in ppm downfield from internal Me_4Si and coupling constants (J) in Hz. Abbreviations: s=singlet, d=doublet, q=quadruplet, m=multiplet, and dd=doublet of doublets.