The Constitution of Warburgiadione

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THE isolation of the new sesquiterpenoids, warburgin and warburgiadione, from the heartwood of *Warburgia ugandensis* Sprague (*Canellaceae*) has been reported and structure (II) established for warburgin.[1] The following evidence establishes structure (I) for warburgiadione, $C_{15}H_{18}O_2$ (analysis and mass spectrum), yellow prisms, m.p. 127—128°; $[\alpha]_D$ + 25° ($CHCl_3$); ν_{max} (CCl_4) 1686, 1659 cm.$^{-1}$; λ_{max} (EtOH) 292 mμ (ϵ, 21·5 × 10^3).

The 100 Mc./sec. n.m.r. spectrum (Table) indicated a close structural similarity to warburgin

(II). The presence of an isopropylidene group was recognised from the signals at τ 7·85, and 8·12, that at lower field being assigned to the methyl group (C-12) adjacent to the C-8 carbonyl. The n.m.r. data also afforded stereochemical information, as discussed below.

TABLE

Comparative data from 100 *Mc./sec. n.m.r. spectra*

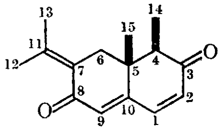
	Warburgiadione (I)		Warburgin (II)	
	τ	peak pattern[a]	τ	peak pattern[a]
1 H at C-1	3·10	d, J = 10·0	3·06	d, J = 10·0
1 H at C-2	3·89	d, J = 10·0	4·02	d, J = 10·0
1 H at C-9	4·03	s	3·45	s
1 H at C-6 (βH)	7·06	d, J_{gem} = 13·6	6·80	d, J_{gem} = 17·0
1 H at C-6 (αH)	7·65	dm, J_{gem} = 13·6	7·42	d, J_{gem} = 17·0
1 H at C-4	7·44	q, J = 6·8	7·47	q, J = 6·5
3 H at C-14	8·85	d, J = 6·8	8·81	d, J = 6·5
3 H at C-15	9·03	s	9·21	s
3 H at C-12	7·85	d, J = 2·0	—	
3 H at C-13	8·12	d, J = 1·4	—	

[a] J = Values in c./sec. Peak patterns denoted: s = singlet; d = doublet; dm = doublet of multiplets; q = quartet.

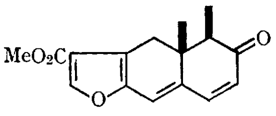
Catalytic hydrogenation of warburgiadione afforded the hexahydro-compound as a colourless oil, ν_{max} 1714 cm.$^{-1}$ (CCl_4), $C_{15}H_{24}O_2$ (mass-spectral molecular ion, 236).

From the above evidence, together with the data in the Table, and an assumed biosynthetic relationship with warburgin, structure (I) is indicated for warburgiadione. This has been confirmed by a partial synthesis from isopetasin (III) obtained by extraction of the rhizomes of *Petasites hybridus* L. (*Compositae*) and chromatography of the oil as described by Aebi and Waaler.[2] Mild alkaline hydrolysis of (III) gave isopetasol (IV). Chromium trioxide–sulphuric acid (Jones) oxidation of (IV) gave isopetasone (V). All physical data for compounds (III), (IV), and (V) proved to be in agreement with those reported by Aebi and Waaler.[2] Conversion of isopetasone (V) into warburgiadione was achieved in 40% yield by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (D.D.Q.) in dioxan (10 hr. at 100° under nitrogen). Mixed m.p., $[\alpha]_D$, i.r., (KCl disc), u.v., mass-spectral and gas-chromatographic data confirmed the identity of the synthetic dione with natural warburgiadione.

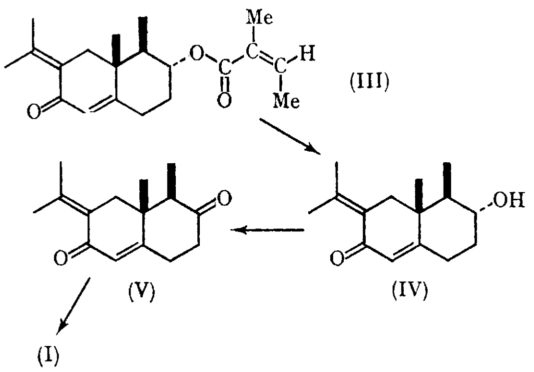
In the 100 Mc./sec. n.m.r. spectrum of (I) (Table) the signals due to the geminal protons at C-6 occur at τ 7·06 and 7·65. The doublet at 7·06 shows no indication of long-range coupling, and is ascribed to a proton in the plane of the C-7 : C-11 double bond.[3] From models the preferred conformation of (I) appears to be that in which the 6β-proton is in this plane. The 6α-proton is then axial and the relative magnitudes of its coupling constants with the protons of C-13 (J = 1·4 c./sec.) and C-12 (J = 2·0 c./sec.) are in accordance with this conformation.[3] These conclusions receive support from the data for warburgin, in which the signals for the C-6-protons appear as doublets at τ 6·80 and 7·42. The higher-field doublet is of lower intensity, suggesting that it corresponds to the 6α-proton coupled to the protons of the 5β angular methyl group.



(I)



(II)



The absolute configuration of isopetasin as (III) has been established.[4] Provided that the transformation of (IV) through (V) to warburgiadione does not involve inversion at C-4 (which would require conversion of an equatorial into an axial methyl) the absolute configuration of warburgiadione is as represented in formula (I).

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[1] C. J. W. Brooks and G. H. Draffan, *Chem. Comm.*, 1966, 393.

[2] A. Aebi and T. Waaler, "Uber die Inhaltstoffe von *Petasites hydridus* (L.) Fl. Wett", Verlag Helbing und Lichtenhahn, Basel, 1958.

[3] S. Sternhell, *Rev. Pure Appl. Chem.* (*Australia*), 1964, **14**, 15.

[4] D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 4337; A. Aebi and C. Djerassi, *Helv. Chim. Acta*, 1959, **42**, 1785.