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Warburgin, a New Sesquiterpenoid of the Eremophilane Group

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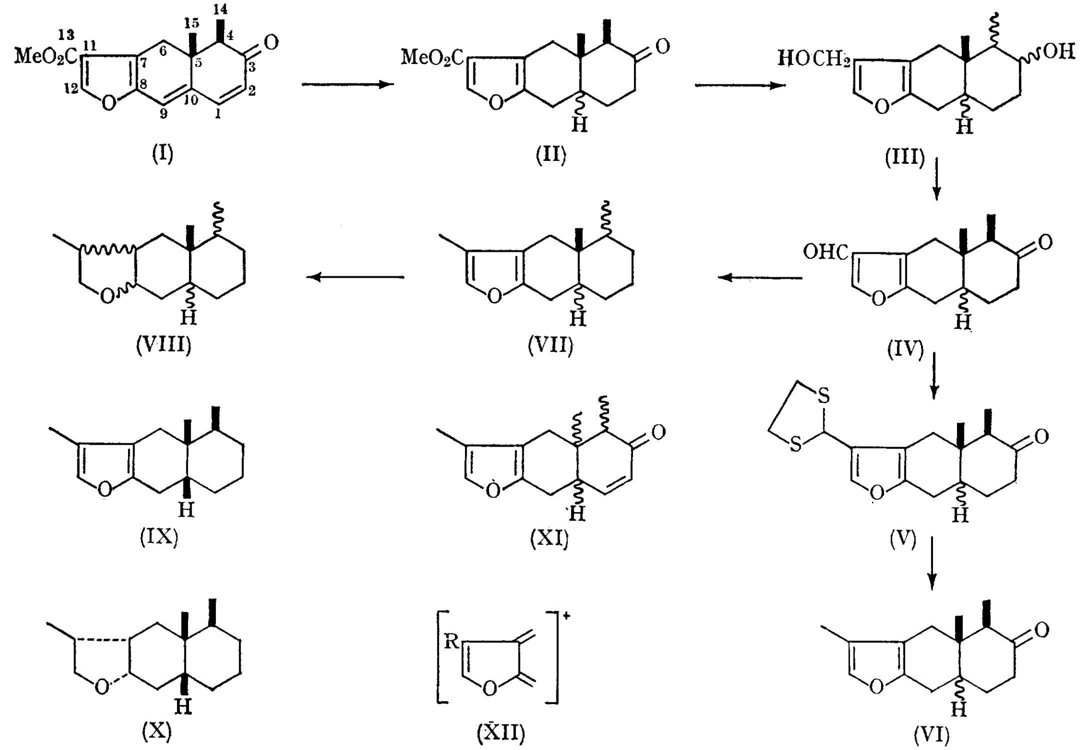
EXTRACTION of the heartwood of *Warburgia ugandensis* Sprague (*Canellaceae*) has afforded a number of new sesquiterpenoids, including a characteristic yellow crystalline keto-ester for which we propose the name warburgin. Its structure and probable absolute configuration as (I) are indicated by the following evidence.

Warburgin, $C_{16}H_{16}O_4$ (analysis and mass spectrum) sublimed *in vacuo* as prisms, unstable towards air and light, m.p. 159—161°; $[\alpha]_D + 120°$ ($CHCl_3$); ν_{max} (CCl_4) 3156 (weak: $\nu_{C\text{-}H}$, furan α-CH), 1734 ($\nu_{C=O}$ of ester), 1679 ($\nu_{C=O}$ of conjugated ketone), 1566 (furan) cm.$^{-1}$;λ_{max} (EtOH) 370 mμ (ε, 20,000). In the 60 Mc./sec. n.m.r. spectrum ($CDCl_3$), signals were observed at τ 9·17 (3H at C-15); 8·76 (doublet, $J = 7$ c./sec.: 3 H at C-14); 7·39 (quartet, $J = 7$ c./sec.: 1 H at C-4); 7·31 (doublet, $J = 17$ c./sec.: 1 H at C-6); 6·72 (doublet, $J = 17$ c./sec.: 1 H at C-6); 6·10 (3 H of OMe); 3·86 (doublet, $J = 9$ c./sec.: 1 H at C-2); 3·29 (1 H at C-9); 2·91 (doublet, $J = 9$ c./sec.: 1 H at C-1); 1·96 (1 H at C-12).

Alkaline hydrolysis of warburgin gave a mixture of two acidic products, treatment of which with diazomethane gave a difficultly-separable mixture of (I) and an unstable isomer (mass spectometry) closely resembling (I) in spectroscopic properties. This product is possibly the 4-epimer of (I) but its identification is not yet complete.

Hydrogenation of warburgin in ethyl acetate with a 10% palladium–charcoal catalyst gave tetrahydrowarburgin (II), $C_{16}H_{20}O_4$ (analysis and mass spectrum), m.p. 172—173°; $[\alpha]_D + 50°$ ($CHCl_3$); ν_{max} (CCl_4) 1730 ($\nu_{C=O}$ of ester), 1721 ($\nu_{C=O}$ of saturated ketone) cm.$^{-1}$; λ_{max} (EtOH) 255 mμ (ε, 2650). The mass spectrum included a base peak at *m/e* 152 resulting from "retro-Diels–Alder" fragmentation [as (XII; R = CO_2Me)]. Analogous peaks were observed in the spectra of the related compounds (III—VII) described below. Lithium aluminium hydride reduction of (II) gave an unstable diol (III), $C_{15}H_{22}O_3$ (mass-spectral molecular ion, *m/e* 250); $[\alpha]_D + 62°$ ($CHCl_3$); ν_{max} (CCl_4) 3624, 3615 cm.$^{-1}$ Oxidation of (III) with chromium trioxide–pyridine yielded the keto-aldehyde (IV) $C_{15}H_{18}O_3$ (analysis and mass spectrum), m.p. 131—135°; $[\alpha]_D + 58°$ ($CHCl_3$); ν_{max} (CCl_4) 2724 ($\nu_{C\text{-}H}$ of aldehyde), 1718 ($\nu_{C=O}$ of ketone), 1690 ($\nu_{C=O}$ of aldehyde) cm.$^{-1}$; λ_{max} (EtOH) 271 mμ (ε, 2600). Wolff–Kishner reduction of (IV) gave a furano-hydrocarbon (VII) isomeric with natural furanoeremophilane (IX) of known absolute configuration.[1] Catalytic hydrogenation of (VII) with platinum oxide in acetic acid afforded two major products (VIII) both different (by g.l.c.) from an authentic sample of tetrahydrofuranoeremophilane (X) of known absolute configuration.[1] Combined gas chromatography–mass spectrometry showed that the two compounds (VIII) were isomeric with (X).

The above chemical and spectroscopic results appeared to require formulation of warburgin as the eremophilane derivative (I) or its 4-epimer. Conversion of (II) into new isomers of furanoeremophilane and tetrahydrofuranoeremophilane suggested a possible *trans*-ring fusion in this compound and its congeners. At this stage, Dr. K. H. Overton



kindly informed us of the (then unpublished) constitution of furanoligularenone (XI) as elucidated by Professor G. Ourisson and his co-workers.[2] The two compounds were correlated as follows. Reduction of the thioacetal (V), characterised by its infrared, n.m.r., and mass spectra, gave the furanoketone (VI), $C_{15}H_{20}O_2$ (mass-spectral molecular ion, 232); m.p. 84—88°; $\nu_{\max}$ (KCl disc) 1711 ($\nu_{C=O}$ of ketone), 1650 and 1563 (weak) cm.$^{-1}$ (furan), identical with a sample of furanoligularanone [the hydrogenation product of (XI)]. The identity was further established by combined gas chromatography–mass spectrometry, and by comparison of the optical rotatory dispersion curves measured in methanol. Compounds (II), (IV), and (VI) all showed negative Cotton-effect curves [*e.g.*, (II): ϕ_{304} −4180°, ϕ_{279} + 5300°, $a = -95$). Provided that the presence of the furan ring does not invalidate the octant rule, absolute configurations at C-4 and C-5 are implied as indicated.[3] The shifts observed for the n.m.r. signals of the 4-methyl group in (II), (IV), and (VI), measured in benzene,[4] are compatible with these configurations. The assignments are probable but are not rigorous. Experiments aimed at confirming the configuration at C-10 in (II)—(VII) are in hand.

Two other sesquiterpenoids, warburgiadione and drimenol, from the same heartwood merit brief mention. Warburgiadione ($C_{15}H_{18}O_2$), a yellow crystalline diketone, m.p. 127—128°, $[\alpha]_D$ + 25° ($CHCl_3$); $\nu_{\max}$(CCl_4) 1686, 1659 cm.$^{-1}$; $\lambda_{\max}$ (EtOH) 292 mμ (ϵ, 21,500), will be the subject of a later Communication. The isolation of drimenol[5] provides an interesting chemotaxonomic link between the *Winteraceae* and *Canellaceae*, confirming their relationship despite the considerable morphological and geographical gap between the families.[6]

Combined gas chromatography–mass spectrometry was carried out with an Atlas CH4 instrument (Houston) modified by Dr. Ryhage, and with an LKB 9000 instrument (Glasgow).

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