The Structure and Stereochemistry of Hirsutic Acid C, a Novel Fungal Sesquiterpenoid

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A GROUP of metabolites, some with antibiotic properties were isolated from *Stereum hirsutum* and partially characterised by Heatley, Jennings, and Florey.[1] We have re-examined these products[2] and by a necessary combination of chemical and *X*-ray studies now show that the principal metabolite, hirsutic acid C, $C_{15}H_{20}O_4$,[3] m.p. 182°, $[\alpha]_D$ +115°, possesses the constitution and absolute stereochemistry (I; R′ = R″ = H).

Hirsutic acid C formed a methyl ester (I; R′ = Me; R″ = H), m.p. 161—162°, [α] + 119°, showing only end-absorption in the ultraviolet spectrum and ν_{max} ($CHCl_3$) 3660, 3500 (hydroxyl), 1720 (methyl ester), and 885 cm.$^{-1}$ (exocyclic methylene). The latter feature was confirmed by isolation of formaldehyde (as the 2,4-dinitrophenylhydrazone) on ozonolysis and by the uptake of one molecule of hydrogen on catalytic reduction. Oxidation of methyl hirsutate (I; R′ = Me; R″ = H) with manganese dioxide in chloroform afforded an αβ-unsaturated ketone (II), m.p. 103—104°, λ_{max} 231 mμ (ε 5,350) [λ_{calc}[4] 230 mμ], ν_{max} ($CHCl_3$) 1720 (methyl ester), 1727 cm.$^{-1}$ (conjugated cyclopentenone) requiring an allylic relationship between the double bond and a secondary hydroxyl group attached to a five-membered ring. Reduction of methyl hirsutate with lithium aluminium hydride in ether gave the triol (III; R = H), m.p. 117—118°, in which two hydrogen atoms had been added, in addition to reduction of the ester function.

Confirmation of the presence of an epoxide ring and its relationship to the hydroxyl and methylene groups followed from inspection of n.m.r. data. Thus the methylene protons which appear as a pair of doublets centred at τ 4·72 and 5·01 in methyl hirsutate (I; R′ = Me; R″ = H) revert to singlets in the ketone (II) demonstrating long-range

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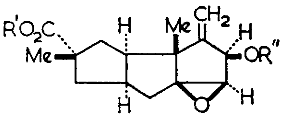
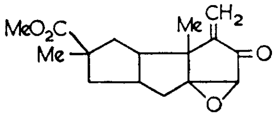
[1] N. G. Heatley, M. A. Jennings, and H. W. Florey, *Brit. J. Exp. Path.*, 1947, **28**, 35.

[2] We warmly thank Dr. N. G. Heatley for a gift of hirsutic acids and for details of the cultivation of *S. hirsutum*.

coupling with the proton (>CH·OH). Acetylation of (III; R = H) reveals that in the product (III; R = Ac) a proton H^1 (τ 6·55) now shows a small coupling (J = 5·8 c./sec.) with H^3 (τ 4·47) absent in the spectrum of (I) and requiring opening an of epoxide in the genesis of (III).


(I)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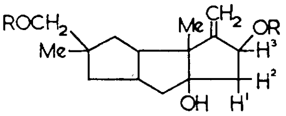
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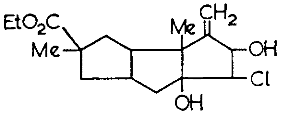
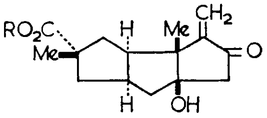

(IV)


(V)

Formation of the chlorohydrin (IV) (from hirsutic acid and ethanolic HCl) confirmed this assignment. The environment of the remaining functional group of methyl hirsutate was shown to be >C·(Me)·CO_2·Me when one of the (tertiary) methyl groups of this ester (τ 8·68) underwent a shift to τ 8·90 on reduction to (III; R = H). Since selenium dehydrogenation of the latter gave products lacking a distinctive chromophore, *X*-ray-diffraction analysis was carried out on *p*-bromophenacyl hirsutate C (I; R′ = *p*-bromophenacyl; R″ = H).

Crystals of the *p*-bromophenacyl ester are orthorhombic, a = 6·49, b = 9·14, c = 35·64 Å, Z = 4, space group $P2_12_12_1$. Structural determination from 800 visual and 1380 counter intensities by Patterson, electron-density, and least-squares methods (final R = 0·136) revealed that an unusual molecular rearrangement had occurred during *X*-irradiation. Thus the completed analysis showed that the irradiated crystals contained an almost equal mixture of two randomly distributed and chemically distinct molecules. One of these, on the basis of the chemical evidence above is the unchanged ester of hirsutic acid C and possesses the structure and, by the anomalous dispersion method, absolute stereochemistry (I; R′ = *p*-bromophenacyl; R″ = H). The rearrangement product, separable from *p*-bromophenacyl hirsutate after preparative *X*-irradiation, is defined as (V; R = *p*-bromophenacyl) and is formed without disruption of the crystal structure and with only minor changes in lattice parameters (to a = 6·56, b = 9·38, c = 35·14 Å). The analogous methyl ester (V; R = Me) can be similarly prepared from methyl hirsutate.

The generality of the radiation-induced rearrangement (I → V) is under investigation as is the possible biosynthetic origin of hirsutic acid C from a double-bond isomer of humulene.[5]

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[3] Satisfactory microanalytical and mass-spectral (Atlas CH-4 and M-V M.S.9. instruments) data were obtained for all compounds cited. N.m.r. spectra were determined at 60 Mc./sec. in deuterochloroform.

[4] A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products" Pergamon, Oxford, 1964, Ch. 2, and refs. cited therein.

[5] J. H. Richards and J. B. Hendrickson, "Biosynthesis of Terpenes, Steroids and Acetogenins," Benjamin, New York, 1964, Ch. 8.