X-Ray Crystal Structure and Absolute Configuration of the Fungal Phenalenone Herqueinone

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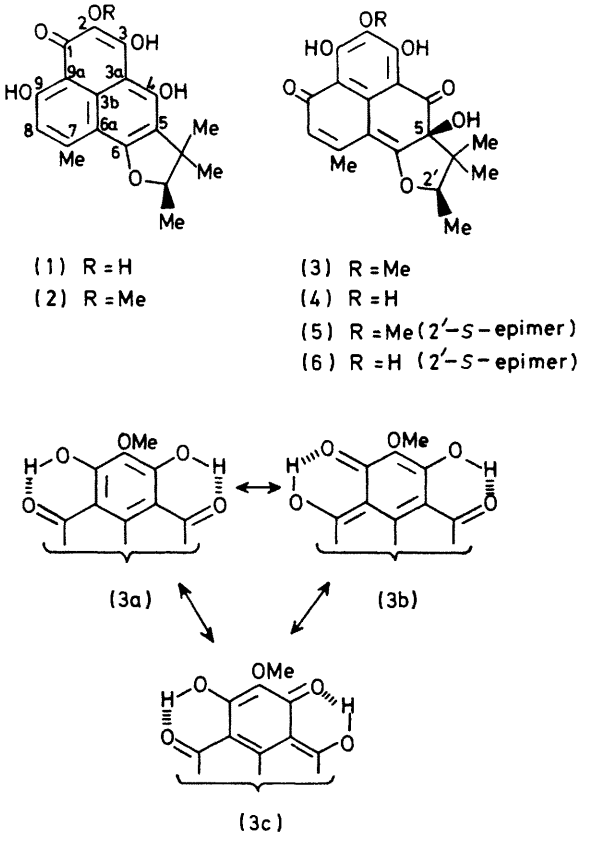
Summary The relative and absolute configurations of the two chiral centres of herqueinone (**3**) have been determined by *X*-ray crystallographic analysis; a biosynthetic mechanism is proposed for the formation of the centre at C(2′) the stereospecificity of which is predetermined by the configuration of an intermediate containing an inverted isoprene unit at a transitory C(5) chiral centre.

PHENALENONES and related products have been shown to occur in a small number of fungi and plants as two biosynthetically distinct groups of predominantly acetate–polymalonate and shikimate origin respectively.[1] The fungal products atrovenetin (**1**) and deoxyherqueinone (**2**) possess a fully conjugated phenalenone nucleus, in contrast with their co-metabolites herqueinone (**3**) and norherqueinone (**4**) in which the conjugation is interrupted by a tertiary hydroxy group at C(5).† The absolute configuration at this centre has now been determined by an *X*-ray crystallographic analysis of herqueinone (crystallised from $CHCl_3$ as fine orange laths, $C_{20}H_{20}O_7.CHCl_3$, m.p. 224—225 °C), which also confirmed the previous structural assignment including the absolute configuration at the side chain secondary methyl carbon C(2′).[3]

Crystal data: orthorhombic, space-group $P2_12_12_1$, a = 6·927(1), b = 10·354(1), c = 30·625(2) Å, Z = 4. 1324 reflections were measured on a diffractometer ($\theta \leqslant 50°$) using Cu-K_α radiation and of these 158 were considered to be unobserved. The structure (Figure) was solved by direct methods after some difficulty due to thermal motion of both the herqueinone and $CHCl_3$ molecules, which seriously limited the amount of observable data. This structure has



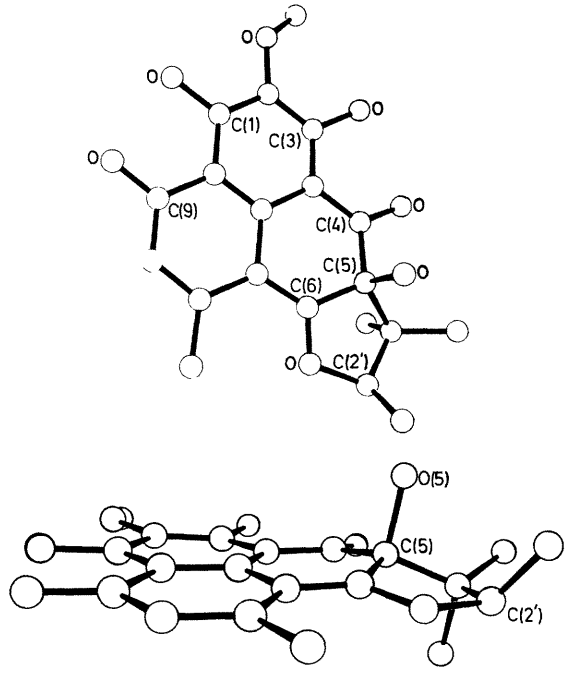


FIGURE. Perspective views of herqueinone (**3**).

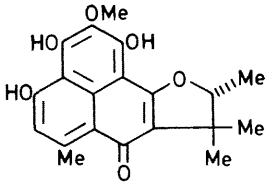
† The phenalenone numbering system used throughout is based on the initial sequence of carbon atoms in the recently established mode of folding of the single chain heptaketide precursor (**9**) (ref. 2); this also corresponds to that widely adopted for the numbering of plant phenalenones.

been refined anisotropically to give a current $R = 0{\cdot}12$ and the absolute configuration determined from the anomalous scattering due to the three chlorine and seven oxygen atoms ($R^{+} = 0{\cdot}121$, *cf* $R^{-} = 0{\cdot}126$) ‡

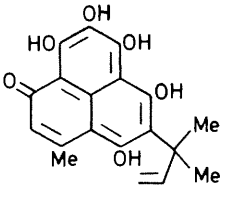
Symmetry-related molecules are linked by an intermolecular hydrogen bond (2·72 Å) between the oxygen atoms at C(5) and C(9) Of the three possible structural forms (**3a**), (**3b**), and (**3c**), the data most closely approximate to (**3a**) However, the C(4)–O and C(9)–O bonds (1·31 and 1·34 Å, respectively) are appreciably longer than those normally associated with C=O (*ca* 1·2 Å) which is indicative of partial C–OH character, as in (**3b**) and (**3c**) In addition to the observed intermolecular hydrogen bond, the proximity of the *peri* oxygen atoms at C(1) and C(9) (2·43 Å) and also at C(3) and C(4) (2·48 Å) is indicative of intramolecular hydrogen bonding between these pairs of atoms, which is consistent with earlier interpretations of i r data [4]

This structure determination confirms the previous assignments of the position of the methoxy substituent and the orientation of the heterocyclic ring,[4] also the (*R*)-configuration[3] of the secondary methyl carbon C(2′), which is common to its biosynthetic precursors[5] atrovenetin (**1**) and deoxyherqueinone (**2**) as well as the shunt metabolite norherqueinone (**4**) The determination of the absolute configuration of the tertiary hydroxy group at C(5) now completes the structural definition of herqueinone (**3a**) and norherqueinone (**4**) as the (5*S*),(2′*R*)-diastereomers and consequently isoherqueinone (**5**) and isonorherqueinone (**6**) as their respective (5*S*),(2′*S*)-epimers, all of which have been isolated from *Penicillium herquei* [4]

The natural occurrence of these C(2′)-epimers and possibly also the enantiomeric (*S*)-atrovenetin[4,6] raises the question of the relative roles of enzyme-catalysed and spontaneous reactions in the terminal biosynthetic steps leading to this series of co-metabolites, an uncertainty which is compounded by the subsequent isolation of the structural isomer herqueichrysin (**7**) [6,7] It has been suggested that an



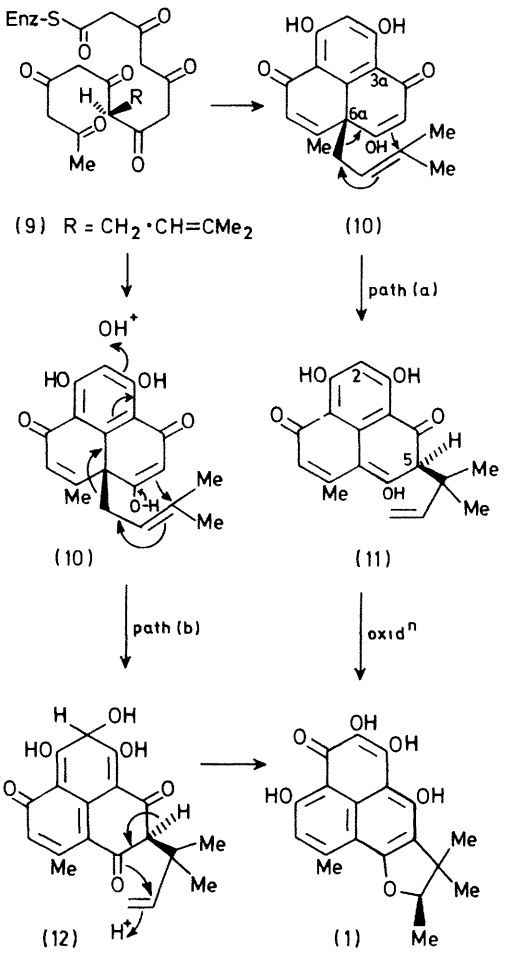
(7)



(8)

achiral *seco*-structure such as (**8**) may serve as a common precursor of all of these isomeric prenylated phenalenones [2,6] The absence of a chiral centre in this hypothetical intermediate would require its stereospecific enzymic cyclisation to (*R*)-atrovenetin, which is the predominant isomer produced by *Penicillium atrovenetum*

An alternative explanation (*cf* the Scheme), which would also account for the presence of the less common 3,3-dimethylallyl substituent, is based on the intermediate formation of a phenalenone derivative (**10**) carrying a dimethylallyl substituent at a chiral bridgehead carbon, *i e* C(3a) or C(6a) This could undergo a Cope-type sigmatropic rearrangement to form a chiral intermediate (**11**) (analogous to the known Claisen-type rearrangement of chorismate to prephenate), with subsequent oxidation leading to (*R*)-atrovenetin (**1**) [path(a)] Alternatively, a concerted oxidative rearrangement [path(b)] could lead directly from (**10**) to (**12**), followed by cyclisation to (*R*)-atrovenetin prior to loss of chirality at C(5) through enolisation, *i e* (**12**)→(**8**) If such a scheme is valid, it could explain the origin of the predominant (*R*)-enantiomer of atrovenetin (and the corresponding series of phenalenones), since this would allow its spontaneous derivation from enzymically derived chiral intermediates such as (**11**) or (**12**) in contrast with the corresponding cyclisation of the achiral intermediate (**8**) which would non-selectively generate a racemic mixture of the (*R*)- and (*S*)-enantiomers



SCHEME

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW Any request should be accompanied by the full literature citation for this communication

Since the C(2′) chiral centre of (**3**) is present in its known precursors (**1**) and (**2**),[5] it is consequently formed prior to the C(5)-centre in herqueinone, norherqueinone, and presumably also their epimeric co-metabolites (**5**) and (**6**). The common (5*S*)-configuration of these naturally occurring pairs of epimers appears to require the unique stereospecific enzyme-catalysed oxidative insertion of a tertiary hydroxy-group at this centre, irrespective of the chirality at C(2′) of their respective precursors.

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