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THE STRUCTURE OF CANESCIN

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Canescin, $C_{15}H_{14}O_7$, m.p. 200-202°, $[\alpha]_D^{23}$ +17.8°, is an antibiotic from Penicillium canescens[1] and Aspergillus malignus. It contains 1 CMe and 1 OMe and has $\lambda_{max.}$ 247, 278, 290, 327 mμ (log. ε 4.68, 3.84, 3.65, 3.77), $\nu_{max.}$ 1680, 1775 cm.$^{-1}$. The last band corresponds to a γ-lactone since it vanishes with alkali and is regenerated by acid. Diazomethane in ether gives a mono-methyl-and in methanol a dimethyl-derivative. In both the spectra are virtually unchanged, except that the latter no longer contains OH or hydrogen-bonded carbonyl, the band at $\nu_{max.}$ 1680 being replaced by one at 1740 cm.$^{-1}$.

Canescin, or its mono-methyl- but not di-methyl derivative gives, with potassium carbonate and methyl iodide in acetone, a trimethyl derivative, $C_{18}H_{20}O_7$, m.p. 123-124°, $[\alpha]_D$ -113°, lacking the γ-lactone, the 1770 cm.$^{-1}$ band being replaced by a broad one at 1735 cm.$^{-1}$ and a sharp one at 1660 cm.$^{-1}$. The

ultraviolet spectrum shows increased conjugation, and two new olefinic protons show in the n.m.r. spectrum as doublets (J = 6 c.p.s.) at τ 5.73 and 3.20. Hydrogenation to a dihydro-derivative restores the original ultraviolet spectrum of the dimethyl-derivative. An elimination reaction must occur, presumably involving the missing γ-lactone, since [^{14}MeO] canescin, produced biosynthetically, retains its full label in the trimethyl-derivative, which has therefore not lost a mole of methanol.

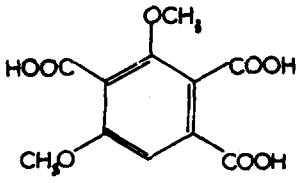
Oxidation of the trimethyl-derivative with permanganate gives (I), identified by direct comparison of the anhydride-acid and the trimethyl ester with authentic samples made from 4-carbethoxy-3,5-dimethoxyphthalic acid, kindly supplied by Dr.J.F.W.McOmie. Canescin therefore contains the fragment (II).

Further information can be obtained by pyrolysis of canescin under nitrogen. The products are carbon dioxide, methanol, and pyrocanescin, $C_{13}H_{10}O_4$, m.p. 143-144° $[\alpha]_D$ 0°, the ultraviolet spectrum of which indicates a considerable change in chromophore. A blue ferric test, a band at $\nu_{max.}$ 1685 cm.$^{-1}$, with the fact that on methylation it gives a mono-methyl derivative $\nu_{max.}$ 1735 cm.$^{-1}$ with a negative ferric test, indicate the continued presence of the original hydrogen-bonded OH and carbonyl, but loss of the γ-lactone. That these are in a hydrogen-bonded enol ζ-lactone in pyrocanescin is supported by alkaline hydrolysis of methyl pyrocanescin. The acid product after methylation gives a keto-ester $C_{15}H_{16}O_5$, $\nu_{max.}$ 1715, 1735 cm.$^{-1}$; the former band is absent in the

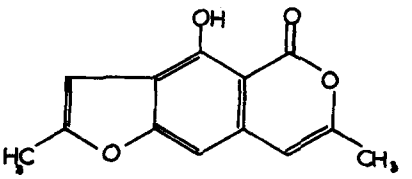
2,4-dinitrophenylhydrazone, $\lambda_{max.}$ 360 mμ (EtOH). Hydrolysis has therefore generated a carboxyl group and an unconjugated carbonyl, the latter in MeCO according to n.m.r. spectra, which also suggest the presence of an α-Me furan ring. A probable structure, supported by n.m.r. evidence, for pyrocanescin can be deduced as (III), on the basis of this evidence and of the oxidation evidence above.

The sum of evidence is in favour of the presence of the same type of isocoumarin structure in canescin itself and was further supported when it was realised that there is a close correspondence in the ultraviolet spectrum of reticulol (6,8-dihydroxy-7-methoxy-3-methylisocoumarin)[2] ($\lambda_{max.}$ 245, 278, 330 mμ, log ε 4.68, 3.86, 3.76) and canescin. On the basis of this evidence and the presence of (II), canescin must have a 6,8-dihydroxy-3-methylisocoumarin structure with a group $C_5H_6O_3$ in the 7-position, containing a γ-lactone, OMe and an asymmetric centre. The trimethyl-derivative of canescin has the original nucleus, and the side-chain group has been altered to one containing a disubstituted double bond conjugated with the ring, an OMe, an active centre and a CO_2Me. It must therefore be (IV), a conclusion supported by ozonolysis and permanganate oxidation of its dihydroderivative to succinic acid and the monomethyl ester of 2-methoxyglutaric acid, identified by gas-liquid chromatography (of ester) and thin-layer chromatography (of acids). Canescin must therefore be (V). This formulation is supported by the n.m.r. spectra of canescin and its derivatives and by further reactions which will be discussed

elsewhere with the mechanisms of those noted here. Biosynthetic experiments indicate that the isocoumarin ring is derived, as expected, by the polyketide route. The origin of the side-chain is under investigation.



(I)



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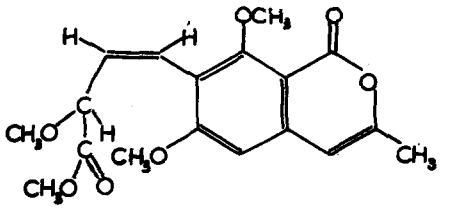

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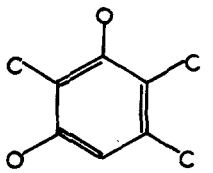
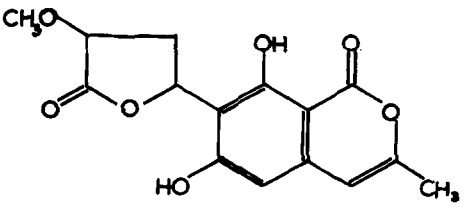


(II)



(V)

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