The Structure of Viridin

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VIRIDIN, $C_{20}H_{16}O_6$, $[\alpha]_D^{19} - 224°$, a mould metabolite with remarkably high fungistatic activity, was first described in 1945.[1] From the results of nuclear magnetic resonance spectroscopy and hitherto unpublished chemical degradations we suggest structure (I; R = H) for the antibiotic.

Viridin contains one methoxyl group (Zeisel; $\tau = 6{\cdot}25$) and one alcoholic hydroxyl group (ν_{max} 3390 cm.$^{-1}$). The acetate, $C_{22}H_{18}O_7$ (λ_{max} 300 mμ; log ϵ 4·1 ν_{max} OH absent, 1745, 1710, and 1675 cm.$^{-1}$) formed in acidic media, was further acetylated in pyridine–acetic anhydride to a diacetate, $C_{24}H_{20}O_8$ (λ_{max} 317 mμ; log ϵ 4·0) formulated as an enol acetate by reason of the bathochromic shift in its ultraviolet spectrum compared with that of the monoacetate and of the appearance in the infrared spectrum of a new band at 1648 cm.$^{-1}$ attributed to an ethylenic bond. This spectrum, which showed carbonyl bands at 1702 (indanone) and 1673 cm.$^{-1}$ in addition to ester carbonyl absorption, suggested that viridin contained at least three carbonyl groups and experimental proof of the presence of three such groups has been obtained by stepwise reductive removal from acetylviridin of all three groups in the sequence (I; R = Ac) → (II; R = Ac; X = Y = O) → (II; R = Ac; X = O; Y = H_2) → (II; R = H; X = H, OH; Y = H_2). The ultraviolet spectrum (λ_{max} 269, 278 mμ, log ϵ 2·90, 2·92) of the ultimate product, a diol, $C_{20}H_{26}O_4$ (no C=O absorption) was typically benzenoid and the presence of a benzene ring was confirmed by oxidation of viridin with nitric acid to benzene-1,2,3,4-tetracarboxylic acid. Whereas the carbonyl group (ν_{max} 1734 cm.$^{-1}$) in the ketone (II; R = Ac; X = O; Y = H_2) is isolated from the aromatic ring, the second such group (ν_{max} 1699 cm.$^{-1}$) in the diketone (II; R = Ac; X = Y = O) (ν_{max} 216, 257, 309 mμ; log ϵ 4·34, 4·01, 3·53) is conjugated with it and contained in a six-membered ring. Hydrolysis of (II; R = Ac; X = O; Y = H_2) gave an $\alpha\beta$-unsaturated ketone (III) (λ_{max} 270 mμ, log ϵ 4·00), the ketonic group (ν_{max} 1688 cm.$^{-1}$) of which is contained in a six-membered ring; hydrogenation of (III) yielded a saturated ketone, $C_{20}H_{24}O_3$, (ν_{max} 1730 cm.$^{-1}$). In the formation of the diketone (II; R = Ac; X = Y = O) by catalytic hydrogenation, two double bonds and one carbonyl group were reduced. The sixth oxygen atom in viridin is presumed to be present in an ether linkage and on this basis the molecule is pentacyclic.

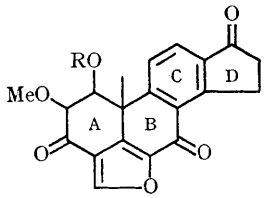
Oxidation of viridin with chromic oxide gave a keto-ester (VI; R = CO·CO_2·Me), three keto-acids, $C_{17}H_{12}O_6$ (VI; R = CO_2H), $C_{12}H_{10}O_4$ (V; R = OH), and $C_{11}H_8O_5$ (IV), and a keto-lactone $C_{12}H_{10}O_3$ (V; R = H) further oxidation of which with potassium permanganate gave the keto-acid (V; R = OH) and, finally, benzene-1,2,3,4-tetracarboxylic acid.

The structure of the dibasic acid (IV) was established by synthesis. The keto-lactone (V; R = H) was then prepared by cyclisation of β-(3-methyl-7-phthalidyl)propionic acid, which had been obtained by peracetic acid oxidation of 1-acetyl-7-hydroxynaphthalene and catalytic reduction of the product.

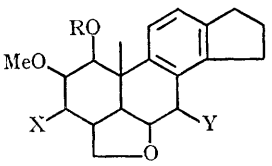
Oxidation of viridin with hydrogen peroxide in acetic acid gave the keto-acid (VI; R = CO_2H) and a naphtholic carboxylic acid, $C_{17}H_{12}O_5$ (VII; R = CO_2H; R′ = OH; X = O) (λ_{max} 228, 278, 325, 340, 399 mμ; log ϵ 4·37, 4·72, 3·73, 3·76, 3·93). The nature of the ring system in this compound was proved by a multi-stage synthesis of a transformation product (VIII; R = H) starting from 2-hydroxy-6-methylbenzaldehyde. The location of the carboxyl group in (VIII; R = CO_2H) and hence in (VII; R = CO_2H; R′ = OH; X = O) was indicated by spectral evidence and by the behaviour of (VIII; R = NH_2) on heating, which gave (VII; R = R′ = H; X = H_2). The position

[1] P. W. Brian and J. C. McGowan, *Nature*, 1945, **156**, 144.

of the phenolic hydroxyl group in (VII; R = CO_2H; R′ = OH; X = O) must correspond with that of the conjugated carbonyl group in the diketone (II; R = Ac; X = Y = O).



(I)



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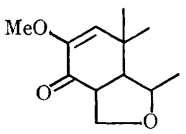

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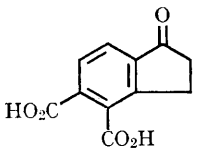

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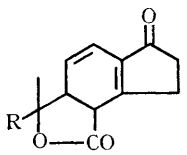
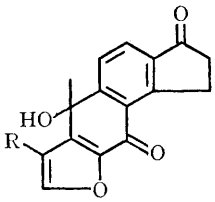
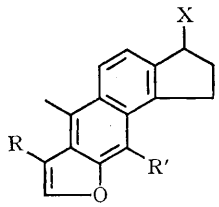


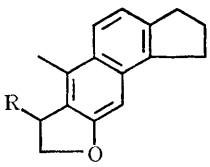
(V)



(VI)



(VII)



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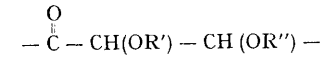

(IX)

R ≠ H,

R′R″ = Me,H

Viridin is unstable in neutral or alkaline media, and even on weakly acid alumina is converted into an epimer, β-viridin $[\alpha]_D^{19}$ − 23°; the asymmetric centre concerned is adjacent to the carbonyl group involved in enol acetate formation since acetylation of β-viridin gave diacetylviridin.

The manner in which the structure of viridin is derived from that of the tetracyclic oxidation product (VII; R = CO_2H; R′ = OH; X = O) by the addition of a C_2 fragment carrying the methoxyl and hydroxyl substituents in such a way as to block the aromatisation of ring B and form a six-membered ring containing the centres of asymmetry, was indicated by the nuclear magnetic resonance spectrum of viridin itself. This showed, in addition to A_2B_2 and AB systems at τ = 6·2, 7·1 and 1·2, 1·9; J, 8 c./sec. respectively attributed to protons on rings D and C and a one-proton singlet at τ = 1·55 (O—CH=), a tertiary methyl group at τ = 8·3, and a second AB system at τ = 5·55, 6·05; J, 5 c./sec. indicative of the partial structure (IX). The latter can be accommodated in one way only giving (I; R = H), the arrangement (IX; R′ = Me; R″ = H) having been assigned after consideration of the structure of the oxidation product $C_{19}H_{14}O_7$ (VI; R = CO·CO_2Me) (λ_{max} 306 mμ, log ε 4·10): this retained the chromophore of viridin, contained an ester grouping (ν_{max} 1745 cm.$^{-1}$; τ = 5·85) and a new hydroxyl group (ν_{max} 3410 cm.$^{-1}$), considered to be tertiary from its behaviour on attempted acetylation. The ester (VI; R = CO·CO_2Me) was oxidised by hot chromic acid to the keto-acid $C_{17}H_{12}O_6$, the spectral properties of which were likewise consistent with the structure (VI; R = CO_2H). The coupling constant (10 c./sec.) associated with the protons of the system (IX) in acetyl-β-viridin, showed that these are diaxial and therefore *trans*, and the oxygen substituents di-equatorial. The methoxyl group in viridin therefore has the axial orientation.

Structure (I; R = H) accounts satisfactorily for all the known chemistry of viridin and represents a notable addition to the family of antibiotics based on the steroid nucleus.

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