The Constitution of Fusicoccin

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IN preliminary experiments[1,2] the functional groups of fusicoccin were characterised and the parent aglycone, $C_{21}H_{34}O_5$, obtained by degradation. We present chemical evidence to support the constitutions (I) for fusicoccin and (IIa) for the aglycone. The constitution and stereochemistry of the latter have been established by *X*-ray crystallography.[3]

The aglycone (IIa) forms a tetra-acetate (IIb), m.p. 111—112° $[\alpha]_D$ −69° (all $[\alpha]_D$ in $CHCl_3$ at *c* 1—2, unless stated otherwise), a tetrabenzoate (IIc), m.p. 159—160°, $[\alpha]_D$ −75°, and an acetonide (IId), m.p. 149—150°, $[\alpha]_D$ +32°. (All new compounds have been adequately characterised by microanalytical and/or mass spectral data.) The

aglycone contains, therefore, four hydroxy-groups and one methoxy-group.[1,2] The following evidence demonstrates the presence of two olefinic linkages so that the aglycone is tricyclic. Only one vinyl proton and one tertiary methyl group (n.m.r. spectrum) are present.

With sodium periodate (1 mole uptake) the aglycone gave an unstable $\alpha\beta$-unsaturated dialdehyde (III), ν_{max} 1710 and 1660 cm.$^{-1}$ (all ν_{max} for solutions in $CHCl_3$), and λ_{max} 238 mμ (ϵ 4000; all data for solutions in cyclohexane). There must, therefore, be an α-glycol system alongside a double bond.

Spin-decoupling experiments (Varian HA 100 spectrometer; $CDCl_3$ solutions) on the tetra-acetate (IIb) and the tetrabenzoate (IIc) demonstrated the following (isolated) spin systems:

(a) C:C·CH^1(OBz)·CH^2(OBz)·CH^{3}Me·C

[H^1, τ 4·04; H$_2$, τ 4·23; H^3, τ 7·80; Me, τ 8·80; $J_{H^1H^2}$ 10·5 (all coupling constants in c./sec.); $J_{H^2H^3}$ 5·1; J_{MeH^3} 7]

(b) –C(–)–CH^4(OBz)–CH$_2^{5,6}$–C(–)=C(–)–

(H^4, τ 4·72; H^5, τ 7·17; H^6, τ 7·47; $J_{H^4H^5}$ 6; $J_{H^4H^6}$ 3·9; $J_{H^5H^6}$ 16·8)

(c) MeCH^7(–)–CH$_2^{8,9}$–OAc

(H^7, τ 6·50; H^8, τ 5·99; H^9, τ 6·16; Me, τ 8·89; J_{MeH^7} 6·5; $J_{H^7H^9}$ 7·5; $J_{H^7H^8}$ 6·8; $J_{H^8H^9}$ 10·8).

Decoupling of the vinyl proton (τ 4·51) showed it to be coupled to two separate single (allylic) protons (τ 7·00, J 1·6 and τ 7·36, J 1·6). These allylic protons were not coupled to each other and therefore the presence of

(d) –C(–)–CH=C(–CH)–CH

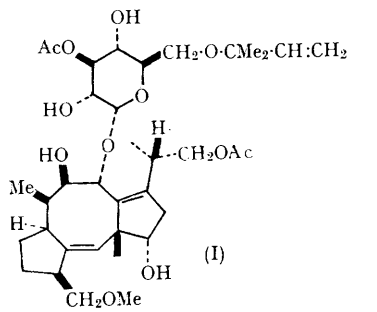
was inferred.

The above results show that the α-glycol group [see (a)] and a secondary hydroxy-group [see (b)] must be related to a second, tetrasubstituted double bond.

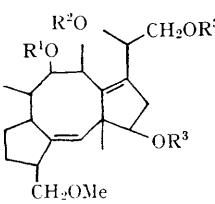
Protection of the primary hydroxy-function [see (c)] of the acetonide (IId) as the trityl ether (IVa), m.p. 152—153°, $[\alpha]_D$ +38°, followed by oxidation with dimethyl sulphoxide–acetic anhydride, gave the $\beta\gamma$-unsaturated ketone (IVb), m.p. 171—172°, $[\alpha]_D$ −105°, ν_{max} 1745 cm.$^{-1}$, λ_{max} 300 mμ (ϵ 130). The n.m.r. spectrum showed the system

(e) –C=C(–)–CH$_2^{5,6}$–C(–)=O with H^5 at τ 7·17; H$_6$ at τ 7·49 and $J_{H^5H^6}$ 24.[5]

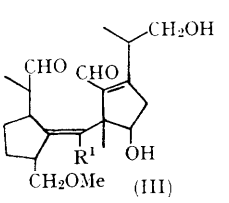
Following a helpful suggestion by Mr. S. Neidle, we treated the aglycone with the usual mercuribromination reagents to give the derivative (Va),



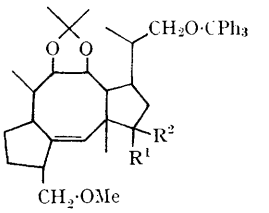
(I)



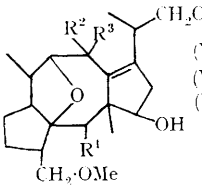
(IIa) R^1=R^2=R^3=H
(IIb) R^1=R^2=R^3=Ac
(IIc) R^1=R^2=R^3=COPh
(IId) R^1,R^2=CMe$_2$,R^3=H



(III)



(IVa) R^1=H, R^2=OH
(IVb) R^1,R^2=O



(Va) R^1=HgBr, R^2=H, R^3=OH
(Vb) R^1=R^2=H, R^3=OH
(Vc) R^1=H, R^2,R^3=O

m.p. 163—165°, $[\alpha]_D$ +20° (in EtOH), which was used in the *X*-ray work.[3] Reduction of (Va) with sodium borohydride[6] gave (Vb), m.p. 152—154°, $[\alpha]_D$ +37°, isomeric with the aglycone (IIa). This new derivative (Vb) had lost the α-glycol system and an oxygen bridge had been formed. That it

was not the allylic hydroxy-group that was involved in the cyclisation was shown by the ready manganese dioxide oxidation of (Vb) to the ketone (Vc), m.p. 158—159°, $[\alpha]_D$ +11° (in EtOH), existing predominantly in the hemiacetal form with the primary hydroxy-group.

All these results, as well as further data which space considerations do not permit us to present here, are in accord with the constitution (IIa) for the aglycone.[3]

With regard to the complete structure of fusicoccin, the glucose moiety must be attached to one of the α-glycol hydroxy-groups of the aglycone, since the latter is inert to periodate oxidation until the glycosidic linkage is cleaved. Now, fusicoccin itself could be converted *via* mercuribromination (derivative, m.p. 112—118°) and reduction to a cyclic isomer. Removal of the glucose residue as for fusicoccin itself[2] yielded the same isomeric aglycone (Vb) as obtained earlier from the aglycone (IIa). The glucose residue is therefore, attached to the allylic hydroxy-group of the α-glycol grouping of (IIa). The acetoxy-group in the aglycone part of the molecule is primary, since a trityl derivative cannot be prepared, and on the basis of n.m.r. evidence. The complete structure of fusicoccin is, therefore, given by (I).

After Professor Rogers[3] had informed us of the *X*-ray results on compound (Va), and whilst preparing the drafts of this manuscript, we received at Imperial College the important article by A. Ballio and his colleagues[7] in which the full structure, including absolute configuration, of fusicoccin is also given. The results of the two sets of investigations are in complete accord.

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