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HALFORDIN AND ISOHALFORDIN - REVISED STRUCTURES

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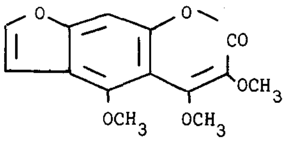
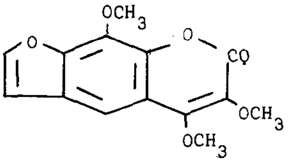
The two furano coumarins halfordin and isohalfordin isolated from Halfordia scleroxyla by Hegarty and Lahey(1) were given structures based on the examination of degradation products. While the evidence appeared to point to their being 3-methoxy coumarins the decision between isomeric pairs of coumarins was not reached. Dr. C. S. Barnes kindly pointed out to us that the N.M.R. spectrum of halfordin was not consistent with either of the proposed structures.

We have further examined the N.M.R. spectra of halfordin and isohalfordin and their respective products of ozonolysis and now propose structure (I) for halfordin and structure (II) for isohalfordin.



I



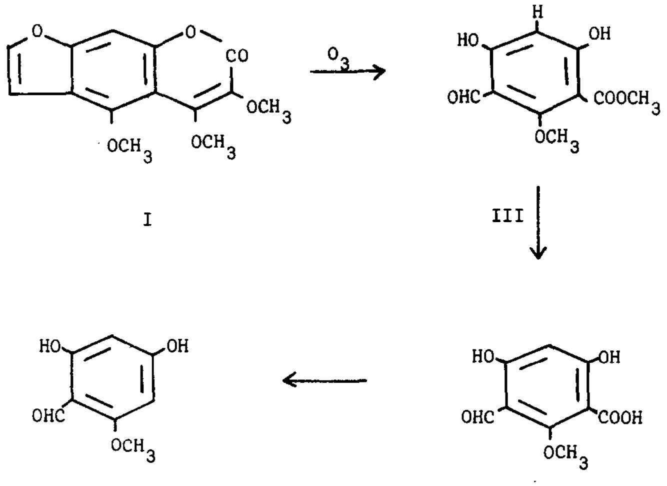
II

The N.M.R. spectrum of halfordin shows three methoxyl signals at 4.23, 4.05 and 3.93τ; α and β furan protons at 2.37 and 3.05τ (J = 2.5 cps) and the remaining proton as a doublet at 2.75τ coupled with the β-furan proton (J 1.1 cps). This long range splitting is also present in the N.M.R. spectrum of the linear furanocoumarin psoralene but not in that of xanthotoxin (8-methoxypsoralene) showing that the 8-proton but not the 5-proton is split by the β-furan proton.

On the basis of formula (I) for halfordin the $C_{10}H_{10}O_6$ phenolic aldehyde m.p. 119-20°C formed on ozonolysis would have structure (III). Its N.M.R. spectrum showed two methoxyl signals at 6.00 and 5.92τ; two phenolic protons at low field values (-2.36 and -2.54τ); an aldehydic proton at -0.23τ. The remaining signal (at 3.59τ) could be assigned only to an aromatic proton. Using the table of substituent effects on chemical shifts of benzene protons compiled by Corio and Dailey(2) the calculated position of the aromatic proton in structure (III) is 3.27τ in reasonable agreement with the observed value. The presence of this aromatic proton supports the view that halfordin contains a 3,4-dimethoxyfuranoquinoline system and eliminates a 3-methoxyfuranoquinoline structure with a hydrogen in position 4 which might equally well explain the N.M.R. spectral data given above for the original coumarin. Such a structure, however, would have no unsubstituted positions on the aromatic ring and the derived phenolic aldehyde would have no aromatic proton.

When the methyl ester group in (III) was hydrolysed it gave an acid $C_9H_8O_6$ (IV) m.p. 172-3° (decomp.) which on decarboxylation gave a product (V) m.p. 202-3°C. This m.p. agrees with that recorded in the literature for 2,4-dihydroxy-6-methoxybenzaldehyde.

The only other structure that could have accommodated the spectral data is (VI). Ozonolysis of this would have yielded the methyl ester of 2,4-dihydroxy-6-methoxy*iso*phthalaldehydic acid (VII), recorded m.p. 184°C and on hydrolysis, the corresponding acid m.p. 185° (decomp.)(3). The evidence therefore strongly supports formula (I) for halfordin.

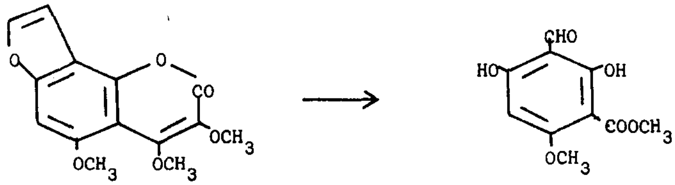


I

III

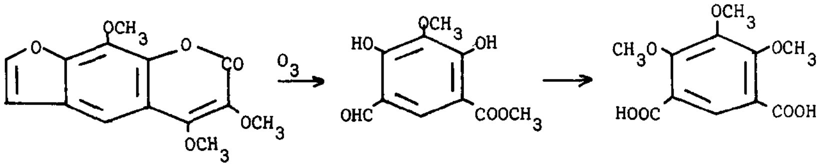
V

IV



VI

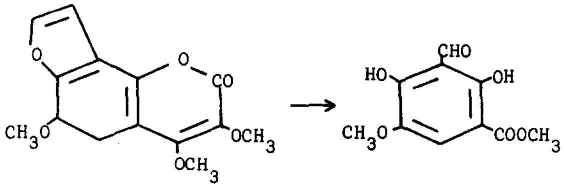
VII



II

VIII

IX



X

XI

The N.M.R. spectrum of isohalfordin showed three methoxyl signals at 5.63, 5.7 and 6.03τ; an AB pattern corresponding to the α and β furan protons (J 2.5 cps) with origins at 2.24 and 3.12τ respectively; and the uncoupled 5-proton at 2.32τ. On ozonolysis we obtained a compound $C_{10}H_{10}O_6$ (VIII) m.p. 142-3° (recorded as 114-5° by Hegarty and Lahey(1)) the N.M.R. spectrum of which showed two phenolic protons at -1.7 and -1.8τ; one aldehydic proton at -0.03τ; two methoxyl signals at 5.98 and 5.94τ and an aromatic proton at 1.9τ. The calculated value 2.04τ for the chemical shift of the aromatic proton in (VIII) based on the Corio and Dailey substituent effects, is in good agreement with this. The calculated value for the position of the aromatic proton in (XI), the ozonolysis product from the alternative angular structure (X) is 2.4τ.

This product of ozonolysis of isohalfordin gave, on methylation and oxidation, a compound m.p. 193-4° (1) which was considered to be tetramethoxyisophthalic acid. We now suggest that this compound is 4,5,6-trimethoxyisophthalic acid (IX) recorded in the literature as melting at 191°C. The analytical figures quoted in the first paper(1) are not inconsistent with the values calculated for (IX), but unfortunately sufficient material was not available at that time to carry out methoxyl estimations. The chemical and spectroscopic evidence thus supports structure (II) for isohalfordin and the biogenetic relationship between halfordin (I) and isohalfordin is thus the same as that found in other pairs of naturally occurring furanoquinolines e.g. imperatorin(4) and isoimperatorin(5).

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