Tetrahedron Letters No. 16, pp. 1319-1322, 1970. Pergamon Press. Printed in Great Britain.

HALFORDININ, A 3,4,5-OXYGENATED FURANOCOUMARIN WITH A NOVEL α,α-DIMETHYLALLYL ETHER SUBSTITUENT

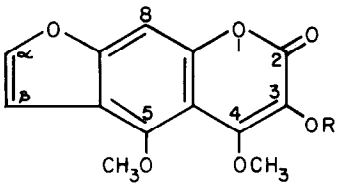
J.K. MacLeod

Research School of Chemistry, Australian National University

P.O. Box 4, Canberra, A.C.T. Australia

(Received in UK 13 February 1970; accepted for publication 5 March 1970)

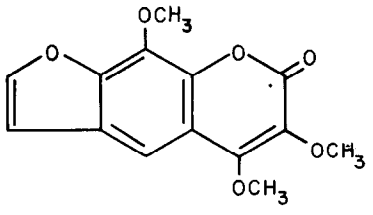
In addition to the 3,4,5- and 3,4,8-trimethoxylated linear furanocoumarins halfordin (I) and isohalfordin[1] (IV), a methanol extract of the bark of Halfordia kendak yielded a small quantity of hand-separated crystals of a compound of m.p. 110° which has been named halfordinin.



I, R=CH_3

II, R=H

III, R = $CH_2 = CH\text{-}C(CH_3)_2-$



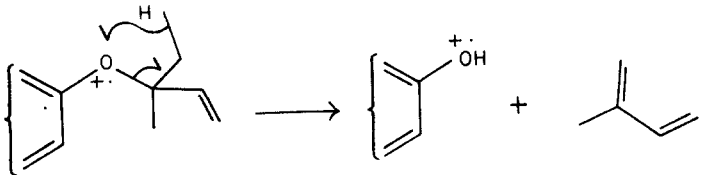
IV

Microanalysis (found: C, 65.5; H, 5.6; OMe, 18.0. $C_{18}H_{18}O_6$ requires: C, 65.5; H, 5.5; OMe, 18.8 for 2 methoxyls) and mass spectrometry (M^+ at m/e 330) established the composition of halfordinin as $C_{18}H_{18}O_6$. Its UV spectrum exhibited absorption maxima at 342, 288 and 247 nm in ethanol solution (log ε: 3.46, 3.81 and 4.48, respectively) while the IR spectrum of the compound showed a broad carbonyl absorption peak at 1775-1765 cm^{-1} (nujol mull).

The PMR spectrum of halfordinin was well-defined, showing a pair of non-equivalent methyl signals at τ values of 8.86 and 9.0; two methoxyl signals at 5.82 and 6.68τ; an AB quartet, identified as α- and β- furan ring protons (J ≈2.5 Hz) with centres at 2.45 and 3.02τ, the β- furan proton being further split (J ≈ 1 Hz) by long-range coupling with an aromatic proton at 3.14τ. The remainder of the spectrum was comprised of a low field three-proton multiplet for which first order analysis as an ABX system gave the following

values: chemical shifts of A, B and X protons = 5.21, 5.07 and 4.24τ respectively; J_{AX} = 17.5 Hz, J_{BX}= 10.5 Hz, J_{AB} = 1.0 Hz. This analysis gives values typical of that of a vinyl group attached to a fully-substituted carbon item.[2]

In the mass spectrum of halfordinin the base peak at m/e 262 ($C_{13}H_{10}O_6$ by high resolution) corresponds to the loss of C_5H_8 from the molecular ion. This was supported by the presence of a "metastable" peak at m/e 208.0 for M^+ at m/e 330 decomposing to the fragmention at m/e 262 in the field-free region of the mass spectrometer. Also present was a peak at m/e 69 (57% relative abundance) which accurate mass measurement showed to have the composition C_5H_9. Combining this information with the PMR spectroscopic evidence it becomes possible to define this C_5 sidechain as an α,α-dimethylallyl ether substituent on an aromatic nucleus which would be expected to undergo a facile loss of C_5H_8 on electron impact, e.g. a → b.



a b C_5H_8

Hydrogenation of halfordinin in ethyl acetate solution over palladium/charcoal (10%) gave a tetrahydro derivative (M^+ at m/e 334), the PMR and mass spectrum of which showed that the unsubstituted furan ring double bond and the terminal vinyl group in the starting compound had been reduced.

Because this compound co-occurs with halfordin (I) and isohalfordin (IV) whose structures have been determined[1], the latter also having recently been synthesised[3], it appeared reasonable to base the structure of halfordinin on a linear furanocoumarin nucleus. PMR evidence had shown that the α- and β- furan ring positions and the 8- position (H_8 at 3.14τ long range coupled to the β- furan proton[4]) were unsubstituted leaving the 3,4 and 5- positions to be occupied by the two methoxyl and one α,α-dimethylallyl ether moieties.

Treatment of halfordinin with conc. HCl under reflux for 20 mins gave norhalfordin (II) identical in all respects (m.p., mixed m.p., U-V, PMR, mass spectra) with the compound obtained by acid-catalysed demethylation of halfordin[5] under the same conditions. This established the position of the α,α-dimethylallyl sidechain as a 3- ether substituent, since earlier evidence[5] had shown that norhalfordin possessed a 3-hydroxyl group. Therefore the

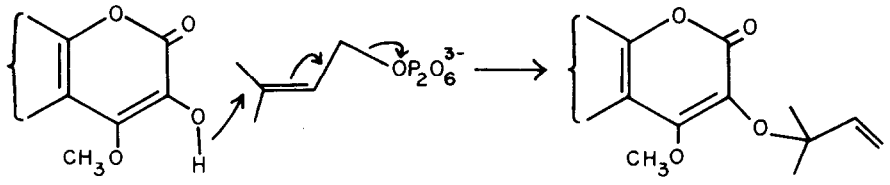
structure of halfordinin is (III). The non-equivalence of the two gem dimethyl groups in the PMR spectrum of halfordinin can readily be explained by examining a molecular model of (III) which shows hindered rotation of the C_5-sidechain about the ether linkage.

A number of interesting biogenetic points arise from the isolation of halfordinin.

Firstly, it is only the third example of a natural coumarin oxygenated in the 3- and 4-positions, the other two being halfordin (I) and isohalfordin (IV), the major components of the bark extracts from Halfordia kendak and Halfordia scleroxyla.

Secondly, although a rapidly increasing number of natural products possessing an α,α-dimethylallyl sidechain are being reported[6], halfordinin provides the first recorded example of a naturally occurring compound with this moiety present as an ether grouping.

Thirdly, the recent rationalisation[6] of the biogenesis of the α,α-dimethylallyl group in terms of a biosynthetic Claisen rearrangement of a γ,γ-dimethylallyl ether substituent cannot apply in the case of halfordinin. It is apparent that the only way the C_5-ether substituent can arise in halfordinin is by direct alkylation of the 3- hydroxy group of the coumarin ring by γ,γ-dimethylallyl pyrophosphate or its biogenetic equivalent at its tertiary centre, viz. (II) → (III).



II III

References

(1) F.N. Lahey and J.K. MacLeod, Tetrahedron Lett., 4, 447 (1968).

(2) H. Pozzi, E. Sanchez and J. Comin, Tetrahedron, 23, 1129 (1967) and references therein.

(3) K. Fukui, M. Nakayama, S. Fujimoto and O. Fukuda, Experientia, 25, 354 (1969).

(4) M.W. Jarvis and A.G. Moritz, Aust. J. Chem., 21, 2445 (1968).

(5) M.P. Hegarty and F.N. Lahey, Aust. J. Chem., 9, 1201 (1956).

(6) T.R. Chamberlain, J.F. Collins and M.F. Grundon, Chem. Commun., 1269 (1969) and references therein.