PERGAMON

Phytochemistry 55 (2000) 675–678

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

3,5-Dimethoxy-3-(1,1-dimethylprop-2-enyl)-3,4-dihydropsoralen-4-one: an unusual furanocoumarin derivative from *Halfordia kendack*

Nasim Sultana [a], Brian W. Skelton [b], Peter G. Waterman [c,*], Allan H. White [b]

[a] *Phytochemistry Research Laboratories, Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 7NR, Scotland, UK*
[b] *Crystallography Centre, University of Western Australia, Nedlands, WA 6907, Australia*
[c] *Centre for Phytochemistry, Southern Cross University, PO Box 157, Lismore, NSW 2480, Australia*

Received 6 January 2000; received in revised form 4 April 2000

Abstract

The aerial parts of *Halfordia kendack* (Rutaceae) have yielded a new furanocoumarin derivative which has been identified as 3,5-dimethoxy-3-(1,1-dimethylprop-2-enyl)-3,4-dihydropsoralen-4-one on the basis of spectroscopic and X-ray examination. This new compound, present in high concentration, is probably formed from a 4-*O*-prenylated precursor furanocoumarin via a Claisen rearrangement. No trace of the putative precursor was found in this sample. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *Halfordia kendack*; Rutaceae; Furanocoumarins; 3,5-Dimethoxy-3-(1,1-dimethylprop-2-enyl)-3,4-dihydropsoralen-4-one; NMR; X-ray diffraction

1. Introduction

The small genus *Halfordia* F. Muell. (Rutaceae) is restricted in distribution to the rain forests of Australia, New Guinea and New Caledonia (Richard, 1991). Previous studies on two species, *Halfordia kendack* (Montr.) Guillaumin. and *H. scleroxyla* F. Muell., have led to the isolation of furoquinoline alkaloids typical of the Rutaceae together with more unusual 5-phenyloxazole alkaloids and a series of 3,4-dioxygenated furanocoumarins (Gray, 1983; Mester, 1983). While the Rutaceae are a rich source of coumarins the latter are currently unique in the family because of the presence of C-3 and C-4 oxygenation.

We have now been able to re-examine *H. kendack* from material collected in southern Queensland, Australia. As well as re-isolating the previously reported halfordin (**2**) we were able to obtain, as a major constituent, a new furanocoumarin (**1**) possessing the very unusual 2,4-diketo A-ring. In this paper we report on the structure elucidation of **1.**

2. Results and discussion

Both furanocoumarins were obtained in high yield by vacuum liquid chromatography of the *n*-hexane extract of the aerial parts over silica gel, eluting with increasing amounts of ethyl acetate, followed by gel filtration through Sephadex LH-20. One was readily identified as the previously reported halfordin (**2**) (Hegarty and Lahey, 1956) on the basis of EIMS and NMR spectral data. The latter, reported here for the first time, are listed in Table 1.

Compound **1** fluoresced light blue on TLC under UV light (366 nm). In the IR spectrum, two bands at 1775 and 1695 cm^{-1} indicated two carbonyls. The HR-EIMS suggested an empirical formula $C_{18}H_{18}O_6$ and showed a base peak at M^+-68 for the loss of a C_5H_8 moiety, typical of a prenyl side-chain. The ^1H NMR spectrum (Table 1) revealed the signals for a 1,1-dimethylprop-2-enyl side chain and for adjacent protons of a disubstituted furan ring. The remaining signals were for a single aromatic proton which exhibited a small ^5J coupling to one of the furan protons (Jarvis, 1968) and for two methoxyls, one a typical aromatic methoxyl (δ 4.24) and the other shielded to δ 3.36, suggesting bonding to an sp^3 carbon.

The ^{13}C NMR spectrum (Table 1) exhibited 18 carbon resonances. Their direct bonding to protons was studied by the HC-COBI experiment (Benn and Gunther, 1983)

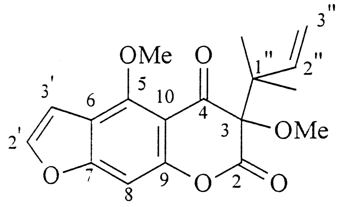
---

* Corresponding author. Tel.: +61-2-6620-3544; fax: +61-2-6621-2236.

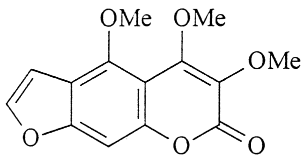
E-mail address: pwaterma@scu.edu.au (P.G. Waterman).

0031-9422/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0031-9422(00)00152-7

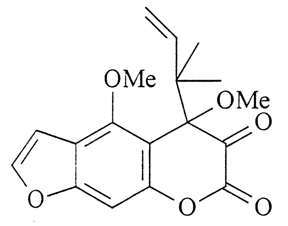
Table 1
^{1}H NMR and ^{13}C NMR spectra[a] of coumarins **1** and **2**



1



2



3

	^{1}H		^{13}C	
C/H	**1**	**2**	**1**	**2**
2	–	–	165.9	160.5
3	–	–	93.3	130.3
4	–	–	187.9	157.2
5	–	–	154.6	150.7
6	–	–	115.6	118.7
7	–	–	159.9	156.5
8	6.90 d (1.0)	7.22 d (1.0)	95.0	96.1
9	–	–	152.7	149.7
10	–	–	110.4	107.0
2′	7.59 d (2.3)	7.59 d (2.3)	145.4	145.5
3′	7.02 dd (2.3, 1.0)	6.93 dd (2.3, 1.0)	106.2	104.6
3-OMe	3.36 s	3.92 s	55.5	60.9
4-OMe	–	4.22 s	–	61.8
5-OMe	4.24 s	4.04 s	61.2	62.7
1″	–	–	46.7	
1″-Me	1.16 s	–	22.4	
1″-Me	1.11 s	–	22.3	
2″	5.70 dd (17.4, 10.8)	–	141.2	
3″	4.94 dd (17.4, 0.8) 4.88 dd (10.8, 0.8)	–	114.9	

[a] Spectra run in $CDCl_3$.

while the HMBC experiment was used to study ^{2}J and ^{3}J heteronuclear interactions (Fig. 1). The latter established the presence of a benzofuran moiety analogous to rings B and C of halfordin (**2**). There remained the signals for the 1,1-dimethylprop-2-enyl side chain, the shielded methoxyl, two carbonyls (one a lactone) and a quaternary sp^3 carbon to which both the methoxyl and prenyl chain were shown to be bonded (Fig. 1). Unfortunately, no heteronuclear coupling were observed to either of the carbonyls in the HMBC experiment leaving open the options for two structures, the 2,3-diketone (**3**) or the 2,4-diketone (**1**).

Differentiation between **1** and **3** was achieved by means of an X-ray diffraction study (Fig. 2) which established the structure as **1**. The results of the single crystal X-ray study are consistent in stoichiometry, stereochemistry and connectivity with the formula for **1**. The aromatic ring and its fused five-membered adjunct and immediate appendages are essentially planar [χ^2 (C_9O_3) 490] with C(2,3,1″) O(2,31,4) deviant by −0.130(4), −0.633(4), −2.231(4), 0.107(5), −0.297(4), 0.247(4) Å, with the lactone/carbonyl planes making dihedral angles of 19.0(1), [C(2)], 38.9(2)° [C(4)] with it. Molecular dimensions of **1** were generally as expected, features of interest noted including:

a. the long C(3)–C(1″) bond (numbering as in Fig. 2);
b. the considerable angular distortions within the aromatic ring;
c. the exocyclic asymmetry at the attachment of the methoxyl group to the aromatic ring, with two methyl hydrogen atoms straddling H(3′) at 2.29(3) and 2.38(3) Å.

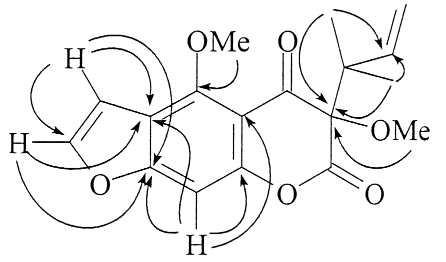


Fig. 1. Selected HMBC correlations in **1**.

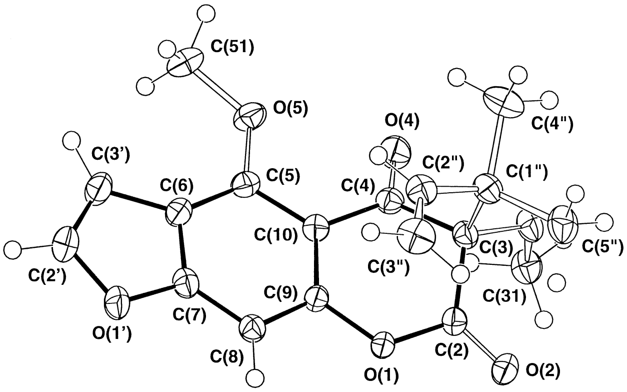


Fig. 2. X-ray diffraction structure for **1**.

It is presumed that **1** is formed by the Claisen re-arrangement (Fig. 3) of the corresponding 4-*O*-(3-methylbut-2-enyl) coumarin (**4**). This proposition is supported by the absence of any optical activity in **1** and by the X-ray structure analysis, which suggests the route of formation is non-enzymatic. Coumarin **4** was not detected in this investigation, but it is interesting to note that the corresponding 4-*O*-(1,1-dimethylprop-2-enyl) derivative has been recorded from *H. kendack* (Macleod, 1970a,b). The extraction and isolation methods employed were not considered likely to give rise to this coumarin and a TLC analysis of an *n*-hexane macerate (no heating) clearly showed its presence in the plant material.

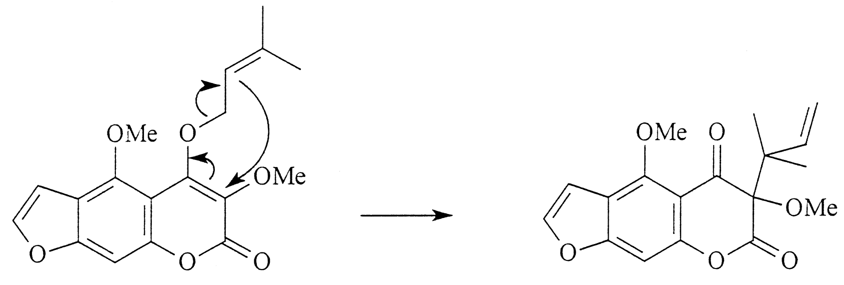
3. Experimental

3.1. General

Melting points are uncorrected. UV spectra were run in methanol and IR spectra as liquid films. HR-EIMS spectra were obtained at 70 eV. NMR spectra were recorded at 400 MHz (^{1}H) and 100.56 MHz (^{13}C) using the solvent as internal standard. Vacuum liquid chromatography (VLC) and column chromatography were performed using Merck (7736) silica gel 60H (15 μm) and Merck (7734) silica gel (0.063–0.2 mm), respectively. Analytical TLC was performed on precoated Merck F254 silica gel plates, spraying with anisaldehyde-sulphuric acid and Dragendorff's reagents. Gel filtration chromatography (GFC) was performed using Sephadex LH-20 (0.25 1.0 mm).

3.2. Plant material

Aerial parts of *H. kendack* were collected in Southern Queensland in March 1992. A voucher specimen (W.J. MacDonald-4775) has been deposited at the Queensland Herbarium, Brisbane (BRI).



4

1

Fig. 3. Probable Claisen re-arrangement of **4** leading to the formation of **1**.

3.3. *Extraction and isolation of coumarins*

The dried, ground, aerial parts (244 g) were sequentially extracted by Soxhlet with *n*-hexane, $CHCl_3$ and MeOH. The *n*-hexane extract (6.82 g) was fractionated by VLC over silica gel with solvents of increasing polarity. The eluate obtained by elution with 15–20% EtOAc in *n*-hexane was subjected to GFC eluting with $CHCl_3$ to give **1** (324 mg). Identical treatment of the VLC eluate obtained with 25% EtOAc in *n*-hexane gave **2** (416 mg).

3.3.1. *3,5-Dimethoxy-3-(1,1-dimethylprop-2-enyl)-3,4-dihydropsoralen-4-one* (***1***)

Needles from *n*-hexane, mp 114-115 °C. $[\alpha]_D$ 0° (*c* 1.00, MeOH). UV λ_{max} (MeOH) nm: 247, 389. IR ν_{max} (liquid film) cm^{-1}: 1775, 1695, 1611, 1544, 1469, 1430, 1348, 1290, 1199, 1170, 1114, 1012, 993, 964, 925, 823, 750, 719. ^1H NMR, ^{13}C NMR (see Table 1). EIMS *m*/*z* (rel. int.): 330 (M^+) (23), 262 (100), 247 (19), 233 (37), 219 (19), 190 (66); found, 330.11036, calcd for M^+ $C_{18}H_{18}O_6$, 330.11034.

3.3.2. *The crystal data for* ***1***

A full sphere of low temperature CCD area detector diffractometer data was measured (T ca. 153 K; ω scans, monochromatic Mo K_α radiation, $\lambda = 0.7107_3$ Å $2\theta_{max} = 58°$), yielding 9420 independent reflections merging to 2053 unique ($R_{int} = 0.020$) after 'empirical' (multiscan) absorption correction ('T'$_{min,max} = 0.85, 0.98$). 1958 with $F > 4\sigma$ (F) were used in the full matrix least squares refinement, refining anisotropic thermal parameter forms for the non-hydrogen atoms and $(x, y, z, U_{iso})_H$. Refinement converged at conventional R on $/F/ = 0.029$, RW [weights: $(\sigma^2(F) + 0.0004F^2)^{-1}) = 0.037$. Neutral atom complex scattering factors were employed within the context of the Xtal 3.4 program system (Hall et al. 1995). Full atomic parameters, molecular non-hydrogen geometries and structure factor amplitudes are deposited.

Crystal data: $C_{18}H_{18}O_6$, $M = 330.3$. Monoclinic, space group *Cc* C_s^4, No. 9), $a = 12.020(2)$, $b = 13.574(2)$, $c = 10.796(2)$ Å, $\beta = 113.647(2)°$, $V = 1614$ Å^3. $Dc(Z = 4) = 1.36_0$ g cm^3; $F(000) = 696$. $\mu_{Mo} = 1.0$ cm^{-1}; specimen: 0.25 × 0.13 × 0.05 mm.

3.3.3. *Halfordin [3,4,5-trimethoxypsoralen]* (***2***)

Needles from *n*-hexane, mp 138–139° (Lit. 136–137 C; Hegarty and Lahey, 1956). UV λ_{max} (MeOH) nm: 248, 263, 306. IR ν_{max} (liquid film) cm^{-1}: 1715, 1614, 1583, 1535, 1465, 1366, 1340, 1268, 1226, 1194, 1148, 1125, 1101, 1069, 1028, 1012, 947, 815, 769, 754, 712. ^1H NMR, ^{13}C NMR (see Table 1). EIMS *m*/*z* (rel. int.): 276 (M^+) (97), 261 (31), 233 (100), 218 (11), 190 (50); found, 276.06187, calcd for M^+ $C_{14}H_{12}O_6$, 276.06339.

Acknowledgements

N.S. thanks the Bangladesh Council of Scientific and Industrial Research (BCSIR) for the award of a scholarship. The collection of the material used in this study by Mr. W.J. Macdonald of the Queensland Herbarium made the study possible.

References

Benn, R., Gunther, H., 1983. Angew. Chem. Int. Ed. Engl. 22, 350–352.

Gray, A.I., 1983. Coumarins and chromones of the Rutales. In: Waterman, P.G., Grundon, M.F. (Eds.), Chemistry and Chemical Taxonomy of the Rutales. Academic Press, London, pp. 97–146.

Hall, S.R., King, G.S.D., Stewart, J.M. (Eds.), 1995. The Xtal 3.4 User's Manual. University of Western Australia, Lamb, Perth.

Hegarty, M.P., Lahey, F.N., 1956. Australian Journal of Chemistry 9, 120–126.

Jarvis, M.W., 1968. Australian Journal of Chemistry 21, 536–541.

Macleod, J.K. 1970a. Tetrahedron Letters, 1319–1322.

Macleod, J.K. 1970b. Tetrahedron Letters, 3611–3614.

Mester, I., 1983. Alkaloids of the Rutales. In: Waterman, P.G., Grundon, M.F. (Eds.), Chemistry and Chemical Taxonomy of the Rutales. Academic Press, London, pp. 31–96.

Richard, P.G, 1991. In: Harden, G.J. (Ed.), Flora of New South Wales, Vol. 2. NSWU Press, Sydney, pp. 271–272.