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NOVEL TETRAHYDROFUROBENZOFURANOXANTHONES FROM *PSOROSPERMUM FEBRIFUGUM*

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Abstract: Two novel tetrahydrofurobenzofuranoxanthones, 1 and 2, were isolated from *Psorospermum febrifugum*. The structures and relative configurations were determined by MS, ^1H NMR, ^{13}C NMR spectroscopy and NOE experiments.

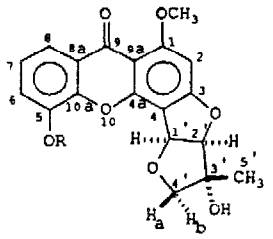
As a part of our investigation for antitumor agents from *Psorospermum febrifugum* Spach. (Guttiferae), the antitumor active psorospermin 5 and several active furanoxanthone analogs have been reported (1,2). In this paper, we report the isolation and structure elucidation of two novel xanthone analogs, 1 and 2, containing a new fused tetrahydrofurobenzofuran ring system. The compounds were isolated from the chloroform fraction of the ethanolic extract of the root bark of *Psorospermum febrifugum* by repeated chromatography on silica gel columns. The IR and UV spectra of 1 and 2 showed the similar presence of a xanthone carbonyl absorption at 1640 cm^{-1} and of polyoxygenated xanthone nucleus absorptions at 247 and 312 nm, respectively.

Compound 1 was isolated as white crystals with mp. 266-268°C (decomp.) and $[\alpha]_D$= -83° (c= 0.15, MeOH). The molecular formula of the compound was determined as $C_{19}H_{16}O_7$ by high resolution EI mass spectrometry (M^+ obsd. 356.091, cald. 356.090). The 470 MHz ^1H NMR spectrum (Table 1) showed the characteristic signals (1, 2) for the xanthone nucleus of the psorospermin group accounting for $C_{14}H_8O_4$. The ^1H NMR signals of the remaining isoprenoid unit ($C_5H_8O_3$) were assigned as a fused tetrahydrofurobenzofuran ring based on the following data. The doublet at 6.01 ppm (1'-H), typical for a benzylic methine proton directly bonded to an oxygenated carbon, was coupled to the doublet at 4.93 ppm (2'-H) with J= 5.6 Hz. These oxygenated methine carbons were also revealed by the 50 MHz ^{13}C NMR signals (Table 1) as two doublets at 79.3 ppm (C-1') and 90.2 ppm (C-2'), respectively (1). The proton signals at 3.67 and 3.17 ppm which appeared as two doublets (J= 9.6 Hz) were assigned to the methylene protons attached to the oxygenated carbon appearing as a triplet at 74.7 (C-4') in the ^{13}C NMR spectrum. The tertiary methyl group at 1.33 ppm and hydroxyl group at 5.38 ppm were bonded to the quaternary C-3' which appeared as a broad singlet at 77.9 ppm in the ^{13}C NMR spectrum.

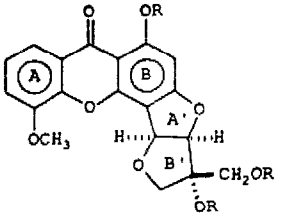
The placement of this fused ring at the 3,4 position of the B-ring of the xanthone nucleus was comfirmed by the intensity enhancement of the 2-H (39%) upon irradiation of 1-OCH_3 protons. Comparison of the 2'-H chemical shift at 4.93 of 1 with that of the

sterigmatocystin analog 6 at 6.75 ppm (3) suggested that **1** should differ in the oxygen arrangement from 6 in the side-chain ring. Finally, the fragment ion in eims at m/z 282 due to two-bond cleavage of the side-chain ring (Fig.1) confirmed the proposed structure of 1.

The relative configurations at C-1', C-2', and C-3' were established by homonuclear NOE experiments from the acetate derivative 3 (4). Intensity enhancement of the 1'-H (13%) upon irradiation of the 2'-H suggested their *syn* relationship. Irradiation of the 3'-CH_3 enhancing 16% of the 2'-H, 6% of the 4'-H_b, and 5% of the 4'-H_a intensity, but no intensity enhancement for the 1'-H suggested that the 3'-CH_3 should be *anti* to the 1'-H and in a pseudoequatorial relationship to the 2'-H.



1 R= H
3 R= Ac



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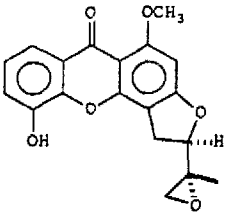
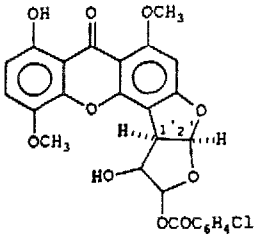
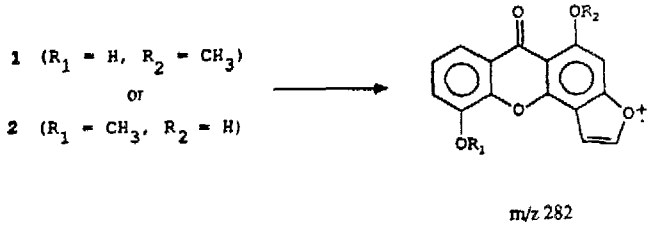
4 R= Ac



5 Psorospermin



6



1 (R_1 = H, R_2 = CH_3)
or
2 (R_1 = CH_3, R_2 = H)

m/z 282

Figure 1 Fragmentation pattern of **1** and **2**

Compound 2 was isolated as white fine crystals with mp. 216-217°C and $[\alpha]_D$= -75° (c= 0.06, MeOH). The molecular formula of 2 was established as $C_{19}H_{16}O_8$ (M^+ obs. 372.085, cald. 372.085) by high resolution EIMS. The structure of 2 was closely related to 1 based on the UV, IR, MS, and NMR spectral data. The EIMS of 2 also yielded the fragment ion at m/z 282 indicating the typical xanthone moiety. However, the 470 MHz ^1H NMR data (Table 1) of 2 showed the presence of a chelated phenolic proton at 13.22 which was assigned to the 1-OH (instead of 1-OCH_3 in 1) and was confirmed by a downfield shift of the C-2 proton upon acetylation (5). In addition, the ^1H NMR and ^{13}C NMR data of 2 also exhibited the typical signals for the fused bis-furan system. However, the presence of a proton triplet at 4.82 ppm (exchangeable with D_2O) and an AB spin system of two double doublets at 3.68 and 3.55 ppm (collapsed to two doublets upon addition of D_2O) indicated the presence of a CH_2OH group which must reside at C-3'. This evidence was supported by a triplet at 62.0 ppm in the fully coupled ^{13}C NMR spectrum. Therefore, the structure of this compound was proposed as 2. Compound 2 was determined to have the same relative configurations as 1 by NOE experiments of the acetate derivative 4. Irradiation of the 3'-CH_2 increased the intensities of the 2'-H (6%) and 4'-H_b (9%) and irradiation of the 1'-H increased the intensity of the 2'-H (22%).

Table 1 470 MHz ^1H and 50 MHz ^{13}C NMR Data of 1 and 2[a].

	1		2	
C#-H	δC	δH(J)	δC	δH(J)
C1	164.0,bs	-	148.1,bs	-
C2-H	94.2,bd	6.59,s	93.2,d	6.37,s
C3	165.8,bs	-	167.6,bs	-
C4	104.8,d	-	103.3,d	-
C4a	154.8,s	-	153.1,s	-
C5	146.0,d	-	164.9,d	-
C6-H	115.2,dd	7.21,dd (1.1,7.6)	115.8,dd	7.53,dd (1.3,8.0)
C7-H	123.9,d	7.17,t(7.6)	124.6,d	7.41,t(8.0)
C8-H	119.4,dd	7.47,dd (1.1,7.6)	117.3,dd	7.68,dd (1.3,8.0)
C8a	123.7,d	-	120.6,d	-
C9	173.4,d	-	180.0,d	-
C9a	106.4,d	-	103.9,d	-
C10a	143.4,dd	-	145.0,t	-
C1'-H	79.3,bd	6.01,d(5.6)	78.8,d	5.92,d(5.6)
C2'-H	90.2,d	4.93,d(5.6)	93.1,d	5.02,d(5.6)
C3'	77.9,bs	-	81.9,bs	-
C4'-Ha	74.7,bt	3.17,d(9.6)	72.5,t	3.27,d(9.8)
C4'-Hb		3.67,d(9.6)		3.71,d(9.8)
C5'-H	18.9,q	1.33,s	62.0,t	3.68,dd & 3.55,dd (4.0,11.5)[b]
1-OH	-	-	-	13.22,bs[c]
5-OH	-	10.30,b[c]	-	-
1-OCH_3	56.5,q	3.86,s	-	-
5-OCH_3	-	-	56.5,q	3.97,s
3'-OH	-	5.38,bs[c]	-	5.41,s[c]
5'-OH	-	-	-	4.82,bt(4.0)[c]

a) recorded in DMSO-d_6 (δ in ppm, J in Hz). b) collapsed to doublets (J= 11.5 Hz) upon addition with D_2O. c) exchangeable with D_2O.

Biogenetically, the fused side-chain ring is probably derived from the quinone methide of the 1-hydroxybenzofuranxanthone via intramolecular nucleophilic attack by the 4'-OH of the hydroxyisopropyl side chain. Compound 1 showed borderline cytotoxicity in the colon carcinoma cell line (HT-29) at ED_{50}= 8 μg/ml, but 2 was inactive (6).

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REFERENCES

1. Habib, A.M., Ho, D.K., Masuda, S., McCloud, T., Reddy, K.S., Abou-shoer, M., McKenzie, A., Byrn, S.R., Chang, C.-j., and Cassady, J.M., J. Org. Chem., 52, 412 (1987).

2. Abou-shoer, M., Boettner, F.E., Chang, C.-j., and Cassady, J.M., Phytochemistry, 27, 2795 (1988).

3. Essery, J.M., O'Herron, F.A., McGregor, D.N., and Bradner, W.T., J. Med. Chem., 19, 1339 (1976).

4. ^1H NMR (200 MHz, DMSO-d_6) δ in ppm, 1.32 (3H, s, 5'-CH_3), 2.42 (3H, s, 5-OAc), 3.15 (1H, d, J= 9.6, 4'-Ha), 3.68 (1H, d, J= 9.6, 4'-Hb), 3.88 (3H, s, 1-OCH_3), 4.95 (1H, d, J= 5.9, 2'-H), 5.35 (1H, br s, 3'-OH), 5.92 (1H, d, J= 5.9, 1'-H), 7.41 (1H, t, J= 8.0, 7-H), 7.61 (1H, dd, J= 1.6, 8.0, 6-H), 7.94 (1H, dd, J= 1.6, 8.0, 8-H); CIMS m/z, 399 (MH^+); IR (KBr) 3400, 1780, 1640, 1600 cm^{-1}.

5. ^1H NMR (200 MHz, DMSO-d_6) δ in ppm, 2.07 (3H, s, 5'-OAc), 2.11 (3H, s, 3'-OAc), 2.37 (3H, s, 1-OAc), 3.59 (1H, d, J=10.8, 4'-Ha), 3.95 (3H, s 5-OCH_3), 4.32 (1H, d, J= 10.8, 4'-Hb), 4.63 (1H, d, J= 11.5, 5'-Ha), 4.70 (1H, d, J=11.5, 5'-Hb), 5.61 (1H, d, J= 6.0, 2'-H), 6.06 (1H, d, J= 6.0, 1'-H), 6.92 (1H, s, 2-H), 7.37 (1H, t, J= 7.8, 7-H), 7.49 (1H, dd, J= 1.5, 7.8, 6-H), 7.62 (1H, dd, J= 1.5, 7.8, 8-H); CIMS m/z, 499 (MH^+); IR (KBr), 1770, 1750, 1660, 1630, 1590 cm^{-1}.

6. Alley, M.C., Scudiero, D.C., Monks, A., Hursey, M.L., Czerwinski, M.J., Fine, D.L., Abbott B.J., Mayo, J.C., Shoemaker, R.H., and Boyd, M.R., Cancer Res., 48, 589 (1988).

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