Journal of Natural Products
Vol. 52, No. 6, pp. 1379-1382, Nov-Dec 1989

SYNTHESIS OF DICOUMARINYLETHERS WITH STRUCTURES POSSIBLE FOR OREOJASMIN: COUMARINS OF *RUTA OREOJASME* FRUITS[1,2]

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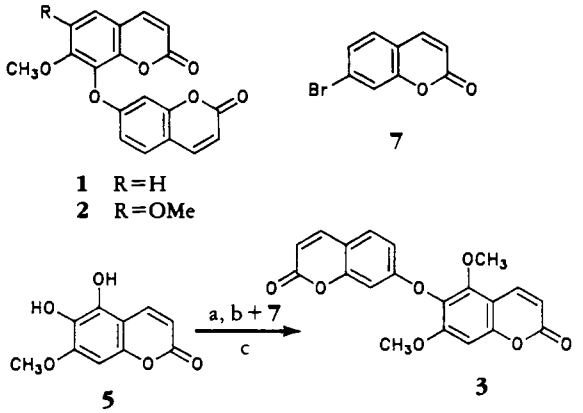
ABSTRACT.—The structures of fatagarin [**1**] and oreojasmin [**2**], dicoumarinyl ethers isolated from the fruits of *Ruta oreojasme*, have been shown to require revision. The synthesis of 5,7-dimethoxy-7′,6-oxydicoumarin [**3**] and 6,7-dimethoxy-7′,5-oxydicoumarin [**4**], which are possible structures for oreojasmin, ruled out these structures for it. Gc-ms analysis of extracts of *R. oreojasme* fruits did not show the presence of dicoumarinyl ethers.

Ruta oreojasme Webb. (Rutaceae) is endemic to the Canary Islands. Apart from the simple coumarins, furanocoumarins, and pyranocoumarins isolated from various parts of the plant (1–3), two new dicoumarinyl ethers, fatagarin [**1**] and oreojasmin [**2**], have been reported from the fruits (4). In pursuing our studies on the constituents of Rutaceae, we earlier synthesized compounds with the structures proposed for fatagarin and oreojasmin (5) and showed that these two structures required revision. In an attempt to revise the structure of oreojasmin, we have now synthesized 5,7-dimethoxy-7′,6-oxydicoumarin [**3**] and 6,7-dimethoxy-7′,5-oxydicoumarin [**4**], which are two possible structures for it. A gc-ms analysis of the fruits of *R. oreojasme* has also been carried out.

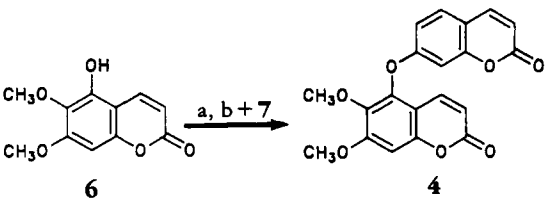
Because the acid hydrolysis of oreojasmin [**2**] yielded 7-hydroxycoumarin and 6,7-dimethoxycoumarin (4), the synthesis of 6,7-dimethoxy-7′,5-oxydicoumarin [**4**] was attempted. This is an alternative structure to the 6,7-dimethoxy-7′,8-oxydicoumarin structure proposed for oreojasmin. The sodium salt of 5,6-



SCHEME 1. (a) NaOMe, MeOH (b) CuCl, pyridine, 120°, 18 h (c) MeI, Me_2CO, K_2CO_3, 60°, 0.5 h.

[1]Part 128 in the series "Natural Product Chemistry." For part 127, see J. Reisch and M. Iding, *Monatsh. Chem.*, **120**, 363 (1989). This note is part of the Ph.D. Thesis of Anura Wickramasinghe, Münster/Peradeniya, Sri Lanka.

[2]In memory of the late Prof. Michael F. Grundon, The University of Ulster, Coleraine, Northern Ireland.



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SCHEME 2. (a) NaOMe, MeOH (b) CuCl, pyridine, 120°, 18 h.

dihydroxy-7-methoxycoumarin [**5**] (6) was condensed with 7-bromocoumarin [**7**] under Ullmann conditions (7) and subsequently methylated. Although the formation of a mixture of 6,7-dimethoxy-7′,5-oxydicoumarin [**4**] and 5,7-dimethoxy-7′,6-oxydicoumarin [**3**] was expected, the only product obtained (in 20% yield) was shown by nOe experiments to be the latter.

When 6,7-dimethoxy-5-hydroxycoumarin [**6**] (8) was condensed with 7-bromocoumarin [**7**] under the same Ullmann conditions, it gave 6,7-dimethoxy-7′,5-oxydicoumarin [**4**] in 18.5% yield. Both dicoumarinyl ethers **3**, mp 201–202°, and **4**, mp 204–205°, differed in their spectral characteristics from those reported (4) for oreojasmin, mp 238–239° (Table 1).

A mixture of synthetic dicoumarinyl ethers was subjected to gc-ms analysis to select optimum conditions for their separation, and these conditions were used for the analysis of the CH_2Cl_2-soluble fraction of the MeOH extract of *R. oreojasme* fruits. Although gc-ms analysis (Table 2) showed the presence of eight coumarins, which were identified as 5,7-dimethoxycoumarin, xanthotoxin, bergapten, isopimpinellin, pimpinellin, oxypeucedanin, pabularinone, and gosferol, it gave no indication that any dicoumarinyl ethers were present. Isopimpinellin was the major constituent. Because the composition of the constituents of the analyzed fruit sample is dependent on the season of collection, this analysis does not confirm the absence of dicoumarinylethers in *R. oreojasme*. However, the nonavailability of authentic fatagarin and oreojasmin

TABLE 1. ^{1}H-nmr Data of Oreojasmin [**2**] and Synthetic Dicoumarinylethers **3** and **4**.

Proton	Compound		
	2[a]	Oxydicoumarin **3**	Oxydicoumarin **4**
H-3, -3′	6.34	6.30	6.26
(d, J = 10 Hz)			6.32
H-4, -4′	7.48	7.67	7.67
(d, J = 10 Hz)	7.67	7.96	7.71
OMe	3.93	3.84	3.75
	3.97	3.97	3.99
H-5′	7.32	7.43	7.44
(d, J = 8.5 Hz)			
H-6′		6.88	
		(dd, J = 8.5, 2.4 Hz)	
H-8′	multiplet	6.77	multiplet
	6.80–7.10	(d, J = 2.4 Hz)	6.82–6.88
H-8		6.72	
		(s)	

[a]Data for oreojasmin [**2**] are taken from González *et al.* (4).

TABLE 2. Gc-ms Analysis of the CH_2Cl_2 Extract of *Ruta oreojasme* Fruits.

Constituent	Gc retention time (min:sec)	(100%) *m/z*	*m/z*
5,7-Dimethoxycoumarin	28:27	206	206
Xanthotoxin	29:25	216	216
Bergapten	29:54	216	216
Isopimpinellin	32:42	231	246
Pimpinellin	34:28	59	246
Oxypeucedanin	36:16	59	286
Pabularinone	36:41	43	286
Gosferol	37:56	202	286

prevents us from carrying out further experiments in order to elucidate their structures.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Ir spectra were recorded for KBr discs on a Pye-Unicam SP 3-200 and uv spectra in MeOH solutions on a Carl Zeiss DMR 21 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were measured at Varian Gemini 200 MHz in $CDCl_3$ solutions using TMS as internal standard. Mass spectral analyses were carried out at 70 eV on a MAT 44 S spectrometer.

Gc-ms analyses were recorded on a Varian MAT CH 7A, 70 eV mass spectrometer connected to a Shimadzu GC-8AX gas chromatograph fitted with a quartz capillary column (50 m, 0.32 mm i.d.) coated with HP-1. Temperature programming was from 70° to 300° at 6°/min, injector temperature 300°, split valve 1:10. Merck Si gel 60 F_{254} coated on aluminum sheets and glass plates was used for analytical and preparative (2 mm) chromatography.

The dried, ground plant material (5 g) was extracted with 95% MeOH for three successive 24-h periods at 20°, and the concentrated extract was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was concentrated to give the CH_2Cl_2 extract (53 mg).

5,7-DIMETHOXY-7′,6-OXYDICOUMARIN [**3**].—7-Bromocoumarin [**7**] (225 mg, 1 mmol) and the sodium salt of 5,6-dihydroxy-7-methoxycoumarin [**5**] (231 mg, 1 mmol) were refluxed in pyridine (5 ml) with CuCl (18 mg, 0.18 mmol) for 18 h under N_2. Acidification (2 N HCl) followed by extraction with hexane and then with CH_2Cl_2 gave two extracts. On chromatographic separation, the hexane extract gave back 7-bromocoumarin (95 mg).

The CH_2Cl_2 extract was concentrated in vacuo and refluxed in dry Me_2CO (10 ml) with MeI (300 mg) and anhydrous K_2CO_3 (250 mg) for 0.5 h. The product on chromatographic separation gave 5,7-dimethoxy-7′,6-oxydicoumarin [**3**] (43 mg, 20%) (Scheme 1) as colorless crystals from MeOH: mp 201–202°; found C 65.58, H 3.88, $C_{20}H_{14}O_7$ requires C 65.56, H 3.85%; ir ν max cm^{-1} 1730 (C=O), 1600 (C=C, arom.), 1250, 1120 (C=O), 1100, 840 (C-H, arom.); uv λ max nm (log ϵ) 207 (4.64), 228 sh (4.30), 252 sh (3.84), 294 sh (4.31), 321 (4.51); ^{1}H nmr see Table 1; ^{13}C nmr δ (ppm) 56.8, 62.2 (2 OMe), 96.2 (C-8′), 103.4 (C-6′), 107.7 (C-4a), 112.7 (C-4′a), 112.6 113.5, and 114.5 (C-8, -3′, -3), 129.5 (C-5′), 131.5 (C-6), 138.9 (C-4), 143.5 (C-4′), 150.0 (C-7), 153.7 (C-5), 156.2 and 156.9 (C-8a, -8′a), 161.1, 161.2, and 161.4 (C-2, -2′, -7′); ms *m/z* (%) $[M]^+$ 366 (85), $[M-CO]^+$ 338 (10), 221 (26), 193 (26), $[C_7H_5]^+$ 89 (100).

6,7-DIMETHOXY-7′,5-OXYDICOUMARIN [**4**].—7-Bromocoumarin [**7**] (270 mg, 1.2 mmol), the sodium salt of 6,7-dimethoxy-5-hydroxycoumarin [**6**] (147 mg, 0.6 mmol), and CuCl (12 mg, 0.12 mmol) in pyridine (2 ml), when reacted by the above method, gave recovered 7-bromocoumarin (190 mg) and 6,7-dimethoxy-7′,5-oxydicoumarin [**4**] (24 mg, 18.5%) (Scheme 2) as colorless crystals from MeOH: mp 204–205°; found C 65.44, H 3.92, $C_{20}H_{14}O_7$ requires C 65.56, H 3.85%, ir ν max cm^{-1} 1725 (C=O), 1610 (C=C, arom.), 1450, 1260, 1130 (C-O), 830 (C-H, arom.); uv λ max nm (log ϵ) 207 (4.67), 225 sh (4.45), 291 sh (4.33), 320 (4.52); ^{1}H nmr see Table 1; ^{13}C nmr δ (ppm) 56.7 and 61.5 (2-OMe), 98.5 (C-8′), 104.0 (C-8), 107.6 (C-4a), 112.7, 114.3, and 114.9 (C-3, -3′, -6′), 114.7 (C-4′a), 129.6 (C-5′), 138.0 (C-4′), 138.1 (C-6), 143.2 (C-7), 143.3 (C-4), 152.1 (C-5), 156.1 and 157.7 (C-8a, -8′a), 160.9 and 161.4 (C-2, -2′, -7′); ms *m/z* (%) $[M]^+$ 366 (100), $[M-Me]^+$ 351 (35), $[M-Me-CO]^+$ 323 (28), $[C_7H_5]^+$ 89 (95).

ANALYSIS OF FRUIT EXTRACT.—The CH_2Cl_2 extract of *R. oreojasme* fruits was subjected to gc-ms analysis. The results are shown in Table 2.

The spectra of the compounds were compared with those of authentic specimens and with published data (9,10).

ACKNOWLEDGMENTS

We thank the Deutschen Forschungsgemeinschaft for financial support and the Deutschen Akademischen Austauschdienst for the award of a fellowship to A.W. We thank the vice-consul of FRG in Santa Cruz de Tenerife, Canary Islands, Spain, and Mrs. Christine Jordan, Santa Cruz de Tenerife for authentic material of *R. oreojasme.* We are grateful to Prof. Dr. A.G. Gonzáles, Centro de productos naturales organicos "Antonio Gonzáles," Instituto Universitario de Quimica Organica, Universidad de la Laguna, Tenerife, Spain for his valuable information.

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Received 25 July 1989