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Natural Product Chemistry. Part 121 [1]. Synthesis of Dicoumarinyl Ethers with the Structures Proposed for Fatagarine and Oreojasmine

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Synthesis of the 7,8′-dicoumarinyl ethers: 7-methoxy-7′,8-oxydicoumarin and 6,7-dimethoxy-7′,8-oxydicoumarin, established that the structures of fatagarine and oreojasmine for which these two structures have been proposed, have to be revised. Synthesis of 7-methoxy-5,7′-oxydicoumarin and 8-methoxy-7,7′-oxydicoumarin exclude the possibility of these dicoumarinyl ether structures for fatagarine.

(Keywords: Dicoumarinyl ethers; 6,7-Dimethoxy-7′,8-oxydicoumarin; Fatagarine; 7-Methoxy-5,7′-oxydicoumarin; 7-Methoxy-7′,8-oxydicoumarin; 8-Methoxy-7,7′-oxydicoumarin; Oreojasmine; Ruta oreojasme)

Naturstoffchemie. 121. Mitt.: Synthese von Dicumarinylethern mit den für das Fatagarin und das Oreojasmin vorgeschlagenen Strukturen

Durch die Synthese der 7,8-Dicumarinylether: 7-Methoxy-7′,8-oxydicumarin und 6,7-Dimethoxy-7′,8-oxydicumarin, ließ sich nachweisen, daß die für das Fatagarin und Oreojasmin vorgeschlagenen Strukturen revidiert werden müssen. Die Darstellung des 8-Methoxy-7,7′-oxydicoumarin und 7-Methoxy-5,7′-oxydicumarin schließen die Möglichkeit dieser Strukturen für das Fatagarin aus.

Introduction

Although several dicoumarinyl ethers have been found to occur in nature [3–5], the isolation of fatagarine and oreojasmine from the fruits of *Ruta oreojasme* (Rutaceae) constituted the first report of the natural occurrence of a 7,8′-dicoumarinyl ether [6]. In an attempt to confirm the

structures of these dicoumarinyl ethers, we have synthesized 7-methoxy-7′,8-oxydicoumarin (**1 a**) and 6,7-dimethoxy-7′,8-oxydicoumarin (**1 b**) and have been able to show that the structures proposed for fatagarine and oreojasmine [6] require revision. The physical and spectral data reported for fatagarine [6] were also found to be not in agreement with those of 7-methoxy-5,7′-oxydicoumarin (**2**) or 8-methoxy-7,7′-oxydicoumarin (**3**), which were synthesized as alternative possible structures for fatagarine.

Results and Discussion

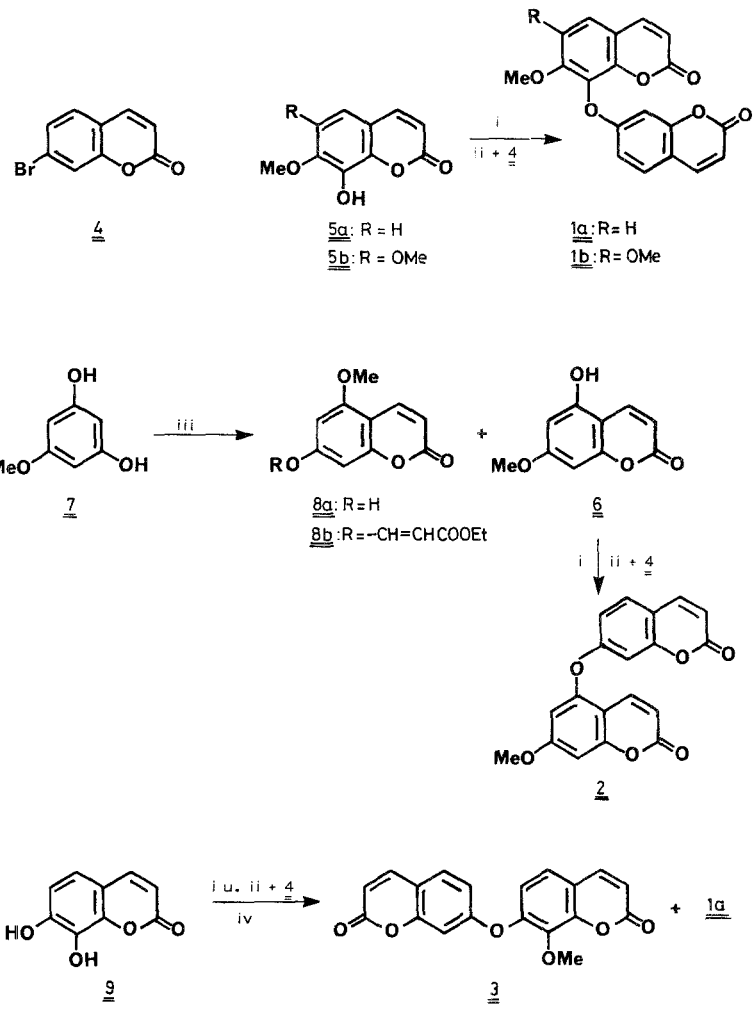
7-Methoxy-7′,8-oxydicoumarin (**1 a**) was synthesized via *Ullmann* condensation [7] of 7-bromocoumarin (**4**) with the sodium salt of 8-hydroxy-7-methoxycoumarin (**5 a**). 7-Bromocoumarin (**4**) and the hydroxycoumarin **5 a** were obtained via *Pechmann* condensation [8] of malic acid with 3-bromophenol and 3-methoxycatechol, respectively. The sodium salt of 8-hydroxy-7-methoxycoumarin (**5 a**) was condensed with bromocoumarin **4** under *Ullmann* conditions [9] to give 7-methoxy-7′,8-oxydicoumarin (**1 a**) in 25% yield. The product, m.p. 264°, differed in its spectral and physical properties from those reported for fatagarine, m.p. 233–234° [6] (Table 1).

6,7-Dimethoxy-7′,8-oxydicoumarin (**1 b**) was prepared in 18% yield in a similar manner via *Ullmann* condensation of 7-bromocoumarin (**4**) with the sodium salt of 6,7-dimethoxy-8-hydroxycoumarin (**5 b**). The product, m.p. 201° differed in its spectral properties from those reported [6] for oreojasmine, m.p. 238–239° (Table 1).

Fatagarine and oreojasmine could therefore not be 7,8′-dicoumarinyl ethers and their structures have to be revised. With a view to propose an alternative structure for fatagarine, the synthesis of the 5,7′-dicoumarinylether, 7-methoxy-5,7′-oxydicoumarin (**2**) and 7,7′-dicoumarinylether, 8-methoxy-7,7′-oxydicoumarin (**3**) were attempted by the *Ullmann* condensation of the sodium salts of 5-hydroxy-7-methoxycoumarin (**6**) and 7,8-dihydroxy-coumarin (**9**), respectively, with 7-bromocoumarin (**4**).

5-Hydroxy-7-methoxycoumarin (**6**) was prepared by the reaction of ethyl propynoate and 5-methoxyresorcinol (**7**) [10]. The major product of the reaction (40%) was 7-hydroxy-5-methoxy-coumarin (**8 a**), the desired hydroxycoumarin **6** (7%) and the ether **8 b** (5%) being formed as minor products. *Ullmann* condensation of the sodium salt of the latter with 7-bromocoumarin (**4**) gave 7-methoxy-5,7′-oxydicoumarin (**2**) in 25% yield. This product, m.p. 196–197°, differed in its spectral properties from those reported for fatagarine [6] (see Table 1).

7,8-Dihydroxycoumarin (daphnetin; **9**) was obtained by *Pechmann* condensation of pyrogallol. *Ullmann* condensation of the sodium salt of



i: NaOMe, MeOH; ii: CuCl, Pyridine, 120° C, 18 h; iii: $CH{\equiv}CCOOEt$, $ZnCl_2$, 100° C, 1 h; iv: Mel, Aceton, K_2CO_3, 60° C, 0.5 h.

daphnetin with 7-bromocoumarin (**4**) gave a mixture of oxydicoumarins. Methylation of this mixture yielded 7-methoxy-7′,8-oxydicoumarin (**1 a**) and 8-methoxy-7,7′-oxydicoumarin (**3**). The latter, m.p. 191–192°, too differed in its spectral properties from those of fatagarin [6] (see Table 1).

The structures of fatagarine and oreojasmine therefore need to be revised as they cannot have the structures **1 a** and **1 b** proposed for them [6].

Table 1. *Chemical shifts (δ_H) (60 MHz) in* $CDCl_3$

Compound	H-3, H-3′ (d, $J = 10$ Hz)	H-4, H-4′ (d, $J = 10$ Hz)	O*Me* (s)	Others			
Fatagarine [4]	6.33	7.47, 7.66	3.88	H-5, H-5′ (d, $J = 8.5$ Hz) 7.37		H-6′, H-8′ (m) 6.75–7.10	
Oxydicoumarin (**1a**)	6.25	7.61, 7.65	3.88	7.38		H-6, H-6′ (dd, $J = 8.5$, 2.5 Hz) 6.93	H-8′ (d, $J = 2.5$ Hz) 6.60
Oxydicoumarin (**2**)	6.23, 6.37	7.72, 7.88	3.87	H-5′ (d, $J = 8.5$ Hz) 7.51	H-6 (d, $J = 2.5$ Hz) 6.42	H-6′, H-8 (m) 7.10–6.85	H-8′ (d, $J = 2.5$ Hz) 6.68
Oxydicoumarin (**3**)	6.33, 6.43	7.71, 7.74	4.00	H-5′ (d, $J = 8.5$ Hz) 7.48	H-5 (d, $J = 8.5$ Hz) 7.29	H-6, H-6′, H-8′ (m) 6.85–7.10	
Oreojasmine [4]	6.34	7.48, 7.67	3.93 3.97	H-5′ (d, $J = 8.5$ Hz) 7.32	H-5, H-6′, H-8′ (m) 6.80–7.10		
Oxydicoumarin (**1b**)	6.25, 6.33	7.67	3.92 3.96	7.43	H-5 (s) 6.88	H-6′ (dd, $J = 8.5$, 2.5 Hz) 6.96	H-8′ (d, $J = 2.5$ Hz) 6.71

Experimental

Melting points (uncorr.): *Kofler*-hot stage microscope; IR (KBr): Pye Unicam SP 3-200; UV (*Me*OH): Carl Zeiss DMR 21; ^{1}H NMR ($CDCl_3$): Varian T 60, Bruker WM 300; ^{13}C NMR ($CDCl_3$): Bruker WM 300; MS (70 eV): MAT 44 S; TLC: Silicagel 60 F_{254} (Merck); Column Chromatography: Silicagel 60 (Merck), grain size 0.063–0.2 mm; 3-Bromphenol (Janssen Chimica), 3-Methoxycatechol (Janssen Chimica), 6,7-Dimethoxy-8-hydroxycoumarin (Carl Roth K.G.) and 5-Methoxyresorcinol (Aldrich Chem. Co.) were used without further purification. Identities of compounds were established by mmp, UV and ^{1}H NMR comparisons, unless otherwise stated.

7-Bromocoumarin (**4**)

A mixture of 3-bromophenol (17.3 g, 0.1 mol), malic acid (13.4 g, 0.1 mol) and conc. H_2SO_4 (45 ml) was heated at 70 °C and then gradually to 120 °C during 4–5 h until the evolution of CO_2 stopped. The cooled reaction mixture was poured on to crushed ice and extracted with ether. Work up followed by chromatography gave 7-bromocoumarin (**4**) (2.12 g, 9.5%), m.p. 123 °C (lit. [8] m.p. 123.5 °C) and 5-bromocoumarin (0.26 g, 1.2%), m.p. 96 °C (lit. [8] m.p. 96 °C).

8-Hydroxy-7-methoxycoumarin (**5 a**)

A mixture of 3-methoxycatechol (3.4 g, 27 mmol), malic acid (2.5 g, 19 mmol) and conc. H_2SO_4 (6.2 ml) was reacted as above. Chromatography followed by crystallisation from *Me*OH/hexane gave 8-hydroxy-7-methoxycoumarin (1.6 g, 30%), m.p. 173–174 °C (lit. [11] m.p. 173–175 °C).

7-Methoxy-7′,8-oxydicoumarin (**1 a**)

7-Bromocoumarin (262 mg, 1.16 mmol) and the sodium salt of 8-hydroxy-7-methoxycoumarin (252 mg, 1.16 mmol) were refluxed in pyridine (2 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, dichloromethane gave two extracts, which on chromatography gave respectively 7-bromocoumarin (170 mg) and on crystallisation from *Me*OH, 7-methoxy-7′,8-oxydicoumarin (35 mg, 25%), m.p. 264 °C.

IR: 1730 (C=O), 1615 (C=C, arom.), 1100, 1110 (C—O), 840 (C—H, arom.). UV (*Me*OH): λ_{max} nm (log ε) = 205 (4.64), 241.5 sh. (3.85), 291 sh. (4.31), 316 (4.47). ^{1}H-NMR: See Table 1. ^{13}C-NMR: δ (ppm) = 56.5 (O—CH_3), 102.4 (C-8′), 108.7 (C-6), 113.2 (C-6′), 113.6, 113.7, 113.9 (C-3,3′,4a,4′a), 125.5 (C-5), 129.0 (C-5′), 129.2 (C-8a), 143.4, 143.5 (C-4, 4′), 147.9 (C-8), 155.2 (C-7), 155.4 (C-8′a), 160.0 (C-7′), 160.8, 161.2 (C-2, 2′). MS: *m*/e (%) = 336 (M^+, 90), 308 (M^+-CO, 20), 293 (308-CH_3, 10), 265 (293-CO, 14), 89 ($C_7H_5^+$, 100). Anal. calc. for $C_{19}H_{12}O_6$: C 67.84, H 3.60. Found: C 67.80, H 3.64%.

6,7-Dimethoxy-7′,8-oxydicoumarin (**1 b**)

The above reaction when repeated using the sodium salt of 6,7-dimethoxy-8-hydroxycoumarin (286 mg, 1.16 mmol) gave recovered 7-bromocoumarin (120 mg) and 6,7-dimethoxy-7′,8-oxydicoumarin as colourless crystals from *Me*OH (41 mg, 18%), m.p. 201 °C.

IR: 1710, 1730 (C=O), 1615 (C=C, arom.), 1140 (C—O), 840 (C—H, arom.). UV (*Me*OH): λ_{max} nm (log ε) = 206 (4.64), 227 sh. (4.37), 248 sh. (3.70), 291 (4.25), 320 (4.27), 340 sh. (4.10). ^{1}H-NMR: See Table 1. ^{13}C-NMR: δ (ppm)

= 56.5, 61.6 (2 × O—CH_3), 103.0 (C-8′), 106.2 (C-6′), 113.0 (C-5), 114.2 (C-4a, 4′a), 114.6 (C-7), 115.8 (C-3, 3′), 129.1 (C-5′), 134.3 (C-6), 142.9, 143.1 (C-4, 4′), 145.9 (C-8a), 150.2 (C-8), 155.5 (C-8′a), 159.7 (C-7′), 160.7 (C-2, 2′). MS: *m*/e (%) = 366 (M^+, 100), 338 (M^+-CO, 8), 89 ($C_7H_5^+$, 26). Anal. calc. for $C_{20}H_{14}O_7$: C 65.56, H 3.85. Found: C 65.47, H 4.01%.

5-Hydroxy-7-methoxycoumarin (**6**)

A stirred mixture of 5-methoxyresorcinol (2.24 g, 16 mmol), ethyl propynoate (2.35 g, 24 mmol) and freshly fused $ZnCl_2$ (2.18 g, 16 mmol) were heated on a steam bath for 1 h. The cooled reaction mixture was acidified (5% aquous. HCl), and filtered. The pale brown residue gave on crystallisation from *Me*OH and from chromatography of the mother liquors, 7-hydroxy-5-methoxycoumarin (1.22 g, 40%), m.p. 251–252 °C (lit. [12] m.p. 244–245 °C). Chromatography of the mother liquors also gave, on crystallisation from ethyl acetate, 5-hydroxy-7-methoxycoumarin (215 mg, 7%), m.p. 238–239 °C (lit. [13] m.p. 224–228 °C) and the less polar ether **7b** (230 mg, 5%), m.p. 158–159 °C.

Less polar ether **7b**: IR: 1720 (C=O), 1650 (C=C), 1620 (C=C, arom.), 1200, 1160 (C—O), 830, 810 (C—H, arom., C=C—H). UV (*Me*OH): λ_{max} nm (log ε) = 203 (4.32), 221 sh. (4.21), 258 (4.08), 316 (4.08). ^{1}H-NMR (60 MHz): δ (ppm) = 8.15 (d, J = 9.6 Hz; 1 H, H-4), 7.05 (d, J = 6.8 Hz; 1 H, C=CH-*o-ph*), 6.67, 6.57 (2 d, J = 2 Hz; 2 H, H-6,7), 6.27 (d, J = 9.6 Hz; 1 H, H-3), 5.34 (d, J = 6.8 Hz; 1 H, C=CH-*oAc*), 4.32 (q, J = 6.6 Hz; 2 H, —CH_2), 1.34 (t, J = 6.6 Hz; 3 H, —CH_3). MS: *m*/e (%) = 290 (M^+, 100), 245 (M^+-OC_2H_5, 38), 217 (245-CO, 90), 189 (217-CO, 42).

7-Methoxy-5,7′-oxydicoumarin (**2**)

7-Bromocoumarin (128 mg, 0.57 mmol), the sodium salt of 5-hydroxy-7-methoxycoumarin (123 mg, 0.57 mmol), and CuCl (12 mg, 0.12 mmol) in pyridine (2 ml) when reacted by the method described above for oxydicoumarins gave recovered 7-bromocoumarin (40 mg) and 7-methoxy-5,7′-oxydicoumarin, colourless crystals from *Me*OH (32 mg, 25%), m.p. 196–197 °C.

IR: 1730 (C=O), 1612 (C=C, arom.), 1125, 1150 (C—O), 840 (C—H, arom.). UV (*Me*OH): λ_{max} nm (log ε) = 207 (4.56), 242 sh. (3.93), 253 sh. (3.82), 291 sh. (4.22), 319 (4.42). ^{1}H-NMR: See Table 1. ^{13}C-NMR: δ (ppm) = 56.1 (O—CH_3), 97.2 (C-6), 102.6 (C-8′), 105.9 (C-4a), 106.5 (C-8), 112.9 (C-6), 115.0, 115.2, 115.3 (C-3, 3′, 4′a), 129.5 (C-5′), 137.7 (C-4), 142.8 (C-4′), 153.1 (C-7′), 155.5 (C-8′a), 156.8 (C-8a), 159.3 (C-7), 160.2 (C-5), 160.6 (C-2′), 163.3 (C-2). MS: *m*/e (%) = 336 (M^+, 100), 308 (M^+-CO, 52), 293 (308-CH_3, 30), 265 (293-CO, 24), 237 (265-CO, 10), 209 (237-CO, 12), 181 (209-CO, 10), 89 ($C_7H_5^+$, 22). Anal. calc. for $C_{19}H_{12}O_6$: C 67.84, H 3.60. Found: C 67.61, H 3.51%.

7,8-Dihydroxycoumarin (Daphnetin) (**9**)

A mixture of pyrogallol (12.6 g, 0.1 mol), malic acid (13.4 g, 0.1 mol) and conc. H_2SO_4 (45 ml) was reacted as earlier. Chromatography followed by crystallisation from methanol gave 7,8-dihydroxycoumarin (3.55 g, 20%) m.p. 255–256 °C (lit. [14] m.p. 253–255 °C).

8-Methoxy-7,7′-oxydicoumarin (**3**)

7-Bromocoumarin (0.562 g, 2.5 mmol), the sodium salt of 7′,8-dihydroxycoumarin (0.502 g, 2.5 mmol), and CuCl (18 mg, 0.18 mmol) in pyridine (5 ml),

when reacted, by the method described above for oxydicoumarins, gave recovered 7-bromocoumarin (0.146 g) and a mixture of hydroxy dicoumarinylethers (0.165 g, 28%). This mixture in dry aceton (10 ml) was refluxed with CH_3I (0.35 g)/anh. K_2CO_3 (0.25 g) for 0.5 h. The product, on chromatographic separation gave 7-methoxy-7′,8-oxydicoumarin (**1 a**) (90 mg, 52%) and 8-methoxy-7,7′-oxydicoumarin (**3**) (60 mg, 35%) as colourless crystals from *Me*OH, m.p. 191–192 °C.

IR: 1 720 (C=O), 1 610 (C=C, arom.), 1 135 (C—O), 850 (C—H, arom.). UV (*Me*OH): λ_{max} nm (log ε) = 209 (4.74), 240 sh. (4.12), 248 sh. (4.03), 294.5 sh. (4.50), 320 (4.59). ^{1}H-NMR: See Table 1. ^{13}C-NMR: δ (ppm) = 61.8 (O—CH_3), 104.9 (C-8′), 113.8 (C-6), 114.6 (C-6, 4a), 115.8 (C-3′), 117.4 (C-4′a), 117.7 (C-3), 122.8 (C-5), 129.2 (C-5′), 139.7 (C-8), 143.0, 143.2 (C-4, 4′), 148.6 (C-8a), 150.0 (C-7), 155.5 (C-8′a), 159.6 (C-7′), 160.4, 160.5 (C-2, 2′). MS: *m*/e (%) = 336 (M^+, 100), 308 (M^+-CO, 10), 305 (M^+-OCH_3, 21), 265 (308-$COCH_3$, 15), 89 ($C_7H_5^+$, 50). Anal. calc. for $C_{19}H_{12}O_6$: C 67.84, H 3.60. Found: C 67.84, H 3.57%.

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