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AUTO-OXIDATION PRODUCTS OF GLECHOMAFURAN

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The oxidative transformation of furanoeremophilanes to eremophilanolides has been studied by chemical and photochemical reactions (1-6). Although spectral data were not given, the auto-oxidation of glechomafuran to a lactone was first observed by Stahl (7). During a recent investigation of the relative configuration of glechomafuran (8), we observed its facile oxidation. When dissolved in $CHCl_3$ and left at room temperature exposed to air and daylight, the auto-oxidation of glechomafuran started within 2 h. It was observed by tlc that at the end of 22 days, no glechomafuran was left in the $CHCl_3$ solution. Upon evaporation, a resinous mixture was obtained. Silica gel column chromatographic separation of this mixture yielded five glechomanolides. The first compound (**1**) obtained from the column had the structure given by Stahl (7), but with a 70° higher melting point.

Compound **1** had mp 212-215° [lit. (7), 145-147°], and molecular formula $C_{15}H_{20}O_4$ as determined by ms (M^+ 264, 7%). The ir showed a γ-lactone peak at 1745 cm^{-1}, with no hydroxyl peak present. The ^{1}H-nmr spectrum exhibited signals for methyl singlets at δ 1.14 (H-14), 1.28 (H-15) and a methyl triplet at 1.87 (J=1.5 Hz, H-13). A one proton multiplet at δ 5.12 (H-8) indicated the lactone proton. The structure of **1** was determined by spin-decoupling experiments as well as by inspecting a Dreiding model. When the signal at δ 5.12 (H-8) was irradiated, the double doublets at δ 2.74 (H-9) and 1.96 (H-9′) collapsed the doublets (J=14 Hz for each), and the triplet at δ 1.87 (H-13) collapsed to a doublet (J=1.5 Hz). Irradiation of the signal at δ 3.02 (H-6) collapsed the double doublets at δ 2.65 (H-6′) and at δ 3.18 (H-5) to doublets, while irradiation of the signal at δ 3.18 (H-5) collapsed the signals of H-6 and H-6′ to doublets (J=14 Hz for each), showing interrelation between these protons. The stereochemistry at C-8 followed from the observed coupling constants between H-8 and H-9, H-9′ and a study of a Dreiding model. The ^{13}C-nmr spectrum of **1** was in agreement with the assigned structure (Table 1).

Compound **2** was established as the 8-hydroxyl derivative of **1** by comparing its spectra and Rf value to that of an authentic sample which was previously isolated from *Smyrnium cordifolium* (9).

Compound **3** was amorphous with a molecular ion peak at *m/z* 308, indicating a molecular formula $C_{17}H_{24}O_5$. The ir spectrum exhibited a γ-lactone peak at 1760 cm^{-1}, and no hydroxyl peak was present. The ^{1}H-nmr spectrum showed the signals of three methyl singlets at δ 1.17 (H-15), 1.40 (H-14), and 2.05 (H-13). A methyl triplet at δ 1.27 (J=7 Hz) together with the methylene quartet at δ 4.20 indicated the presence of an ethoxyl group. The lack of lactone proton signal and the presence of an isolated methylene group at C-9 (δ 3.15, d, J=14 Hz, H-9 and 2.39, d, J=14 Hz, H-9′) showed that compound **3** was the ethoxyl derivative of **2**, which apparently formed during elution from the column.

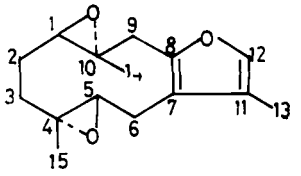
Compound **4** had mp 188-190°, with the molecular formula $C_{15}H_{22}O_5$ on the basis of ms (M^+ 282, 1%). The ir spectrum exhibited peaks of a γ-lactone at 1760 cm^{-1}, and a hydroxyl at 3450 cm^{-1}. The structure of **4** was established by spin-decoupling experiments and by inspection of a Dreiding model. The ^{1}H-nmr spectrum showed the signals of two methyl singlets at δ 1.35 (H-15), 1.45 (H-14), and a methyl triplet at

TABLE 1. ^{13}C nmr of Compounds **1**, **4** and **5** ($CDCl_3$, TMS)

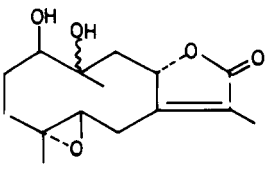
Atom No.	Compound		
	1	**4**	**5**
C-1	59.1 d	60.1 d	204.1 s
C-2	28.5 t	25.0 t	25.0 t
C-3	23.2 t	23.8 t	22.3 t
C-4	57.8 s	56.8 s	57.3 s
C-5	58.2 d	66.9 d	53.4 d
C-6	36.6 t	34.5 t	29.9 t
C-7	128.5 s	127.9 s	129.0 s
C-8	80.9 d	80.5 d	61.3 s
C-9	39.9 t	43.4 t	34.8 t
C-10	59.9 s	60.1 s	59.7 s
C-11	156.4 s	157.8 s	148.1 s
C-12	172.8 s	172.2 s	166.1 s
C-13	9.6 q	8.2 q	13.1 q
C-14	17.8 q	17.2 q	14.8 q
C-15	16.3 q	16.2 q	16.5 q
C-16	—	—	60.5 t
C-17	—	—	13.6 q

δ 1.92 (J=1.5 Hz, H-13). The signal for the lactone proton was at δ 4.98 as a broad doublet. Because a hydroxyl signal was observed in its ir spectrum, apparently one of the epoxy groups opened up, either at C-1 or at C-4. Irradiation experiments suggested it to be the one at C-1. Irradiation of the signal at δ 1.92 (H-13) sharpened the broad doublet at δ 4.98 (H-8) in a well-divided double doublet (J=4 Hz and 11 Hz), while irradiation of the signal at δ 4.98 collapsed the triplet at δ 1.92 to a doublet (J=1.5 Hz) and the double doublets at δ 2.94 (H-9), and 1.20 (H-9′) into doublets (J=14 Hz for each). Irradiation of the signal at δ 2.70 (H-6) collapsed the double doublets at δ 2.35 (H-6′) and the broad doublet at δ 3.02 (H-5) into narrow doublets. The stereochemistry at C-10 was not established. ^{13}C-nmr (Table 1) is in agreement with the suggested structure.

Compound **5** was amorphous, with molecular formula $C_{17}H_{24}O_6$ on the basis of elemental analysis. No molecular ion peak was present in the mass spectrum, but the peak at *m/z* 306 corresponds to $(M-H_2O)^+$. The ir spectrum showed the presence of a γ-lactone at 1760 cm^{-1}, carbonyl at 1720 cm^{-1}, and hydroxy at 3400 cm^{-1}. The struc-



Glechomafuran



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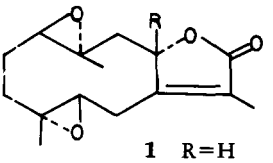
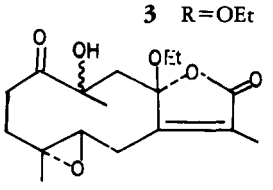


1 R=H
2 R=OH
3 R=OEt



5

ture of **5** was established by spin-decoupling experiments and by studying Dreiding models. The ^{1}H-nmr spectrum showed the presence of three methyl signals as singlets at δ 1.22 (H-15), 1.44 (H-14), and 2.05 (H-13). No lactone proton was observed, but a two proton multiplet at δ 4.20 and a methyl triplet at δ 1.30 (J=7 Hz) indicated the presence of an ethoxyl group. Irradiation of the signal at δ 1.30 collapsed the signal of the multiplet at δ 4.20 to a distorted AB quartet. Irradiation of the signal at δ 3.18 (H-5) collapsed the broad doublet at δ 2.85 (H-6) and the double doublet at δ 2.70 (H-6′) to doublets (J=13 Hz for each), while irradiation of the signal at δ 2.85 (H-6) collapsed the signals for H-5 and H-6′ into narrow doublets. ^{13}C nmr of **5** exhibited four methyl signals at 13.1, 13.6, 14.8, and 16.5 ppm together with an extra methylene signal at 60.5 ppm, which confirmed the presence of an ethoxyl group (Table 1). In addition to the lactone carbonyl signal at 166.1 ppm, there was a signal at 204.1 ppm confirming the presence of the keto group, which could be either at C-1 or at C-5. Because only one isolated methylene group was observed in the ^{1}H-nmr spectrum of **5** and because the lactone proton was missing, the isolated methylene should be at C-9. This analysis indicated that the alternative structure which needed two isolated methylene groups was not possible.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Spectra were recorded with the following instruments: uv, Varian Techtron model 635; ir, Perkin-Elmer 577; ^{1}H nmr FT-NT 200 MHz and Bruker 400 MHz (for **2** and **3**); ^{13}C nmr, Bruker WH-90; ms, DuPont 490 and Varian MAT 711 (for **1, 2, 3**).

OXIDATION OF GLECHOMAFURAN.—Crystalline glechomafuran (5 g) was dissolved in $CHCl_3$ and left at room temperature in an open flask. More $CHCl_3$ was added to the flask from time to time. In order to follow the oxidation, the solution was monitored by tlc every 5 min. Oxidation started after 2 h, and the solution was checked by tlc at longer intervals. Within 22 days, all glechomafuran disappeared, leaving a resinous mixture that was separated on a silica gel column (2×60 cm), eluted with a gradient of $CHCl_3$ to $CHCl_3$-EtOH (90:10). The combined

TABLE 2. ^{1}H nmr of Compounds **1-5** ($CDCl_3$, TMS)[a]

Atom No.	Compound				
	1	**2**	**3**	**4**	**5**
H-1	2.85 dd	2.80 br d	2.85 dd	2.75 dd	—
H-2	2.10 m	1.95 m	2.37	2.12	2.15 m
H-2′	1.45 m	1.48 m	1.45 ddd	1.30 m	1.50 ddd
H-3	2.25 m	2.15 br d	2.22 dt	2.15 br d	2.22 dt
H-3′	1.35 m	1.30 m	1.30 m	1.30 ddd	1.35 m
H-5	3.18 dd	3.07 dd	2.40 br d	3.02 br d	3.18 br d
H-6	3.02 dd	2.70 dd	2.95 br d	2.70 dd	2.85 br d
H-6′	2.65 dd	2.55 dd	2.68 dd	2.35 dd	2.70 dd
H-8	5.12 m	—	—	4.98 br d	—
H-9	2.74 dd	3.02 d	3.15 d	2.94 dd	2.94 d
H-9′	1.96 dd	2.82 d	2.39 d	1.22 dd	2.40 d
H-13	1.87 t	1.91 s	2.05 s	1.92 t	2.05 s
H-14	1.14 s	1.49 s	1.40 s	1.45 s	1.44 s
H-15	1.28 s	1.32 s	1.17 s	1.35 s	1.22 s
H-16	—	—	4.20 q	—	4.20 m
H-17	—	—	1.27 t	—	1.30 t

[a]J (Hz)-**1**: 1,2=15; 1,2′=4; 5,6=5; 5,6′=10; 6,6′=14; 9,9′=14; 8,9=5; 8,9′=14.5. **2**: 1,2=15; 5,6=5; 5,6′=10; 6,6′=15; 9,9′=15. **3**: 1,2=14; 1,2′=4; 5,6=6; 6,6′=14; 9,9′=14. **4**: 1,2=14; 1,2′=4; 5,6=10; 6,6′=14; 8,9=4.5; 8,9′=13; 9,9′=14. **5**: 5,6=3; 5,6′=10; 6,6′=13; 9,9′=15; 16,17=7.

fractions were purified on preparative tlc plates and crystallized from EtOH when possible.

Compound **1**.—Yield 237 mg; uv λ max (MeOH) 220 nm (log ε 4.2); ir ν max (KBr) 2940, 2800, 2730, 1745, 1450, 1375, 1100, 1000, 940, 890, 760 cm^{-1}; ^1H nmr given in Table 2; ^{13}C nmr given in Table 1; ms *m/z* (rel. int.) 264 $(M)^+$ (7), 221 $(M\text{-}CO\text{-}CH_3)^+$ (28), 124 (100), 107 $(C_7H_7O)^+$ (78), 95 $(C_6H_7O)^+$ (80).

Compound **2**.—Yield 6 mg; uv λ max (MeOH) 220 nm (log ε 4.2); ir ν max (KBr) 3450, 2975, 2835, 1755, 1680, 1630, 1450, 1380, 1275, 1200, 1170, 1090, 1050, 980, 800, 750 cm^{-1}; ^1H nmr given in Table 2; ms *m/z* (rel. int.) 280 $(M)^+$ (2), 262 $(M\text{-}H_2O)^+$ (14), 220 $(262\text{-}CO\text{-}CH_2)^+$ (32), 205 $(220\text{-}CH_3)^+$ (45).

Compound **3**.—Yield 5 mg; uv λ max (MeOH) 218 nm (log ε 4.3); ir ν max (KBr) 2980, 2840, 1760, 1680, 1640, 1455, 1390, 1280, 1240, 1170, 1090, 980, 810, 740 cm^{-1}; ^1H nmr given in Table 2; ms *m/z* (rel. int.) 308 $(M)^+$ (1), 279 $(M\text{-}C_2H_5)^+$ (3), 265 $(M\text{-}CO\text{-}CH_3)^+$ (38), 220 $(265\text{-}OC_2H_5)^+$ (22), 205 $(220\text{-}CH_3)^+$ (40), 183 $(M\text{-}C_7H_9O_2)^+$ (100), 155 $(183\text{-}CO)^+$ (70), 126 $(C_7H_{12}O_2)^+$ (70).

Compound **4**.—Yield 40 mg; uv λ max (MeOH) 216 nm (log ε 4.2); ir ν max (KBr) 3450, 2980, 1760, 1620, 1455, 1390, 1280, 1240, 1110, 1080, 1020, 950, 900, 820, 750 cm^{-1}; ^1H nmr given in Table 2; ^{13}C nmr given in Table 1; ms *m/z* (rel. int.) 282 $(M)^+$ (1), 264 $(M\text{-}H_2O)^+$ (5), 246 $(M\text{-}2\times H_2O)^+$ (4), 221 $(264\text{-}CO\text{-}CH_3)^+$ (80), 203 $(221\text{-}H_2O)^+$ (17), 125 (100), 107 $(C_7H_7O)^+$ (80), 95 $(C_6H_7O)^+$ (80).

Compound **5**.—Yield 20 mg; uv λ max (MeOH) 220 nm (log ε 4.3); ir ν max (KBr) 3400, 2930, 2850, 1760, 1720, 1680, 1625, 1450, 1390, 1280, 1240, 1170, 1100, 1090, 895, 810, 750 cm^{-1}; ^1H nmr given in Table 2; ^{13}C nmr given in Table 1; ms *m/z* (rel. int.) 306 $(M\text{-}H_2O)^+$ (5), 279 $(M\text{-}OC_2H_5)^+$ (10), 264 $(M\text{-}OC_2H_5\text{-}CH_3)^+$ (32), 192 $(220\text{-}CO)^+$ (70), 183 $(M\text{-}C_7H_9O_3)^+$ (95), 155 $(183\text{-}CO)^+$ (95), 126 $(C_7H_{10}O)^+$ (90), 107 $(C_7H_7O)^+$ (90); (Found: C, 63.02; H, 7.49. $C_{17}H_{24}O_6$ requires: C, 62.96; H, 7.40%).

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