Studies on Aloe, 12. Furoaloesone, a New 5-Methylchromone from Cape Aloe

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J. Nat. Prod., **1993**, 56 (7), 1089-1094• DOI: 10.1021/np50097a012 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 7, pp. 1089-1094, July 1993

STUDIES ON ALOE, 12.[1] FUROALOESONE, A NEW 5-METHYLCHROMONE FROM CAPE ALOE

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ABSTRACT.—Furoaloesone [**5**], a new 5-methylchromone, was isolated from a commercial sample of Cape aloe. Its structure was determined by spectroscopic methods and total synthesis.

5-Methylchromones appear to be secondary metabolites (polyketides) typical of plants of the genus *Aloe* (Liliaceae) (1–7). In particular, the drug known as Cape aloe, which is the dried exudate of *Aloe ferox* Miller and, occasionally, of its hybrids with *Aloe africana* Miller and *Aloe spicata* Baker (8), has been shown to contain a number of 8-*C*-glucosylated 5-methylchromones. Aloesin [**1**] (9) and aloeresin A [**2**] (10) represent major constituents, along with smaller amounts of the corresponding aglycone, aloesone [**3**] (11).

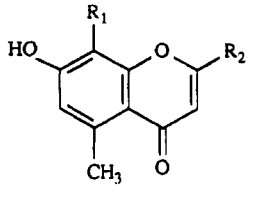
We report here the isolation of two non-glycosylated 5-methylchromones from a commercial sample of Cape aloe, i.e., 7-hydroxy-2,5-dimethylchromone [**4**], previously found in *Polygonum cuspidatum* (12), rhubarb (*Rhei rhizoma*) (13), and *Talaromyces flavus* (14), and a new compound we named furoaloesone [**5**]

RESULTS AND DISCUSSION

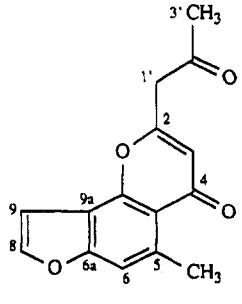
Compounds **4** and **5** were obtained in 0.08 and 0.04% yield, respectively, when an Me_2CO extract of Cape aloe was resolved according to the separation procedure described in the Experimental section.

The structure of furoaloesone [**5**], 2-acetonyl-5-methyl-4*H*-furo[2,3-*h*][1]benzopyran-4-one, was inferred from spectral data and confirmed by synthesis. Compound **4** was identified by comparison of its spectral properties with those reported in the literature (15).

Compound **5**, $C_{15}H_{12}O_4$ by hrms (found 256.0718, calcd for $C_{15}H_{12}O_4$, 256.0735) exhibited uv, ir, and ^1H- and ^{13}C-nmr spectra (Table 1) characteristic of 2-acetonyl-7-



1 R_1=β-D-glucosyl, R_2=CH_2COMe
2 R_1=2′-*O*-*p*-coumaroyl-β-D-glucosyl, R_2=CH_2COMe
3 R_1=H, R_2=CH_2COMe
4 R_1=H, R_2=Me



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[1]For Part 11, see G. Speranza, P. Manitto, P. Cassarà, and D. Monti, *Phytochemistry*, 1993, **33**, 175 (1993).

TABLE 1. ^{1}H- (300 MHz) and ^{13}C-nmr (75.47 MHz) Spectral Data of Furoaloesone [**5**].[a]

Proton	Carbon	ppm
	C-1a	158.67
	C-2	162.64
H-3 ..... 6.24 (s)	C-3	114.73
	C-4	182.01
	C-4a	118.39
	C-5	138.27
H-6 ..... 7.30 (s)	C-6	112.87
	C-6a	153.81
H-8 ..... 7.81 (d, 2.0)	C-8	146.96
H-9 ..... 7.07 (d, 2.0)	C-9	104.94
	C-9a	116.55
5-Me ..... 2.83 (s)	5-Me	23.68
H-1′ ..... [b]	C-1′	[b]
	C-2′	204.15
H-3′ ..... 2.31 (s)	C-3′	30.02

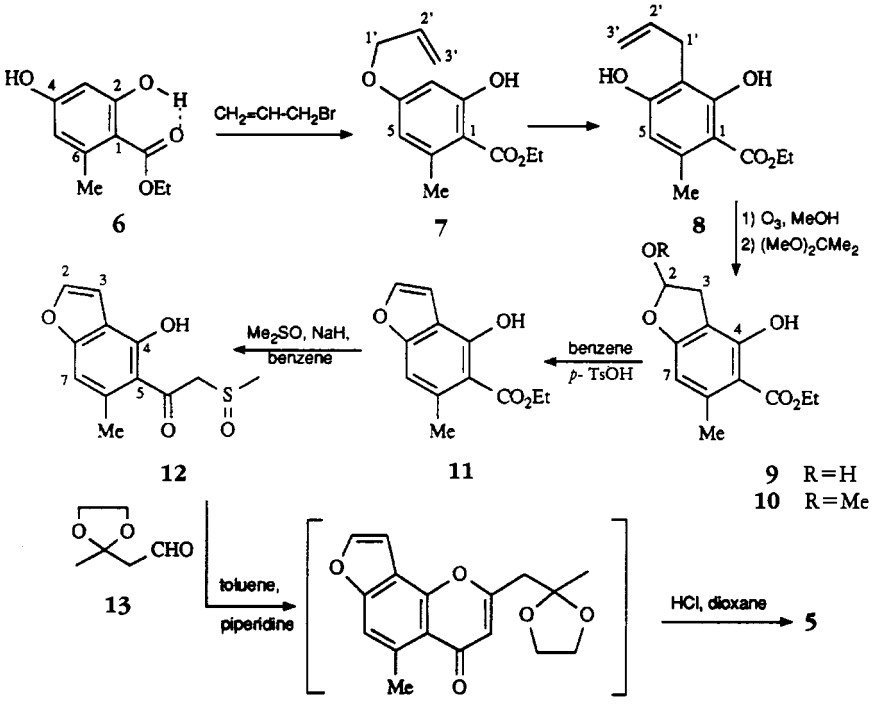
[a]Splitting patterns and J values (Hz) are given in parentheses. Signal assignments were based on DEPT and HETCOR experiments. Spectra were recorded in CD_3OD at 25°.

[b]Lacking due to rapid deuterium exchange. In $CDCl_3$ ^{1}H singlet is at 3.74 ppm.

alkoxy-5-methylchromones (2,3,5). In particular: (i) intense peaks at *m/z* 214 (98%) $[M-C_2H_2O]^+$ and at *m/z* 175 (50%) $[M-C_5H_5O]^+$ in the eims could be interpreted as due to a loss of a ketene fragment from the acetonyl side chain and to a retro-Diels-Alder fragmentation of the pyrone ring (16); (ii) downfield shift of the 5-Me singlet in the ^{1}H-nmr spectrum with respect to frequencies characteristic of benzene-linked Me groups (as a consequence of magnetic anisotropy induced by the chromone carbonyl group) (2–7); (iii) rapid deuterium exchange of the methylene protons at C-1′ (Table 1); and (iv) a sharp singlet in the range δ 6.00–6.30 ppm of the ^{1}H-nmr spectrum corresponding to the H-3 of the pyrone ring (2–7). In addition to this olefinic signal, a couple of doublets at 7.07 and 7.81 ppm (J=2.0 Hz) and only one aromatic proton singlet were observed. They were indicative of the presence of a furan ring fused through its *b* bond to an aloesone-like moiety in 6,7 or 7,8 position (cf. **3**). The first alternative was ruled out on the basis of an nOe experiment which showed an interaction between the 5-Me group and the aromatic proton at δ 7.30 (4.2 and 18.7% intensity enhancement of the former and the latter, respectively, when the other one was irradiated).

The remaining ambiguity, concerning the furan ring orientation with respect to the chromone nucleus, was definitely solved in favor of the [2,3-*b*]possibility (as in **5**) by performing the total synthesis of furoaloesone (Scheme 1).

Ethyl orsellinate [**6**] was converted into its 4-*O*-allyl ether [**7**] by reaction with allyl bromide. It is well known that the reactivity of the OH group in the 2 position in salicyclic acid esters is strongly reduced by an intramolecular hydrogen bond (15). Claisen rearrangement of the ether **7** afforded the 3-allyl derivative **8** as the only isomeric product. Such a regioselectivity is also reported for 7-allyloxychromones (17). The location of the allyl group at the 3 position in compound **8**, as an alternative to the 5-allyl substitution, was confirmed by unequivocal nuclear Overhauser enhancements, i.e., at H-5 (6.8%) upon irradiation of 6-Me and at 6-Me (1.8%) upon irradiation of H-5. The aldehyde arising from the ozonolysis of **8**, when isolated in small amount and examined by ^{1}H nmr, was found to be in equilibrium with its intramolecular hemiacetal **9** (as



SCHEME 1

expected for a ring-chain tautomerism) (18). This mixture was transformed into the methyl acetal **10**, which gave rise to the benzofuran **11** in high yield by MeOH elimination. The last step of the synthesis, i.e., the construction of the γ-pyrone ring (bearing the acetonyl side chain), was then performed via the sulfoxide **12**, according to a procedure which was previously developed to prepare aloesone [**3**] (15). The synthetic furoaloesone [**5**], obtained in 4% overall yield from ethyl orsellinate [**6**], was shown to be identical in all respects with the compound isolated from Cape aloe. Thus, structure **5** was unequivocally proven for the natural furoaloesone.

A number of furochromones have been found in nature (19). Some have been recognized as therapeutically relevant (20,21). For example, khellin from *Amni visnaga* (22) was used in the past as a spasmolytic or a vasodilator, and, at present, it is under investigation for the photochemotherapy of vitiligo (23,24).

Furoaloesone [**5**] represents the first example of a naturally occurring 5-methylfurochromone. From a biogenetic point of view, structure **5** is consistent with the presence of other 2-acetonyl-7-hydroxy-5-methylchromones in Cape aloe (1,2,4,5,7). However, the origin of the furan nucleus is a matter of speculation. The mevalonate origin of the two non-benzenoid α and β carbons of the benzofuran system in furanocoumarins (25) and in other plant metabolites (26) is well documented; they correspond to C-2′ and C-1′, respectively, of the prenyl side chain adjacent to a phenolic function. In spite of this, no prenylated polyketide compounds have been so far isolated from Cape aloe; moreover, *Aloe* species do not seem to use isoprene units to build up secondary metabolites (1). The hypothetical route outlined in Figure 1 appears to be mechanistically plausible, and it is supported by the large abundance of two 8-glucosylated chromones such as aloesin [**1**] and aloeresin A [**2**] in aloe (1).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's are uncorrected. Eims were recorded on a VG 7070 EQ

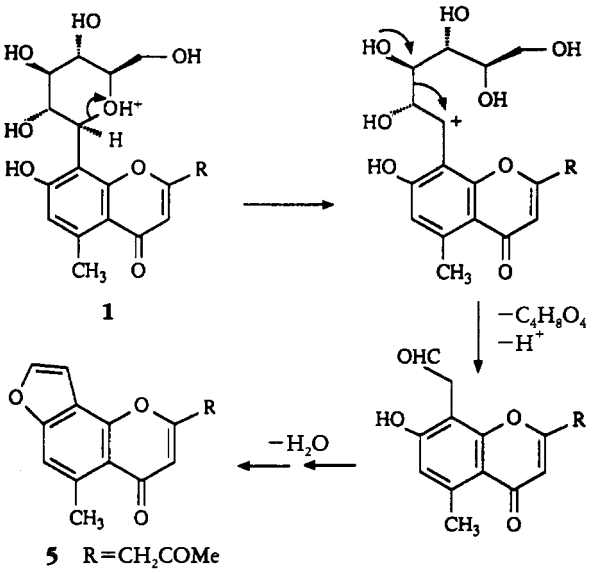


FIGURE 1. Possible origin of the furan ring in furoaloesone [**5**].

mass spectrometer operating at 70 eV and uv spectra on a Perkin Elmer 554 instrument. ^{1}H-(300.135 MHz) and ^{13}C-nmr (75.47 MHz) spectra were recorded on a Bruker AC 300 spectrometer. The ^{1}H and ^{13}C chemical shifts were referenced to the solvent signal (3.30 and 49.00 ppm, 7.25 and 77.00 ppm for CD_3OD and $CDCl_3$, respectively). Tlc was performed on Si gel F_{254} precoated aluminum sheets (0.2 mm layer, Merck); spots were visualized under uv light or by spraying with 0.5% Fast Blue B salt, followed by heating to 140°. Si gel 40–63 μm (Merck) was used for flash chromatography. Dccc was carried out on a Buchi Model 670 equipped with 300 standard glass tubes (40 cm×2.7 cm i.d.). Semi-preparative hplc was performed on a Perkin-Elmer Series 3B liquid chromatograph connected to a variable wave length uv detector (Perkin-Elmer LC 85 spectrophotometric detector) using a LiChrosorb RP8 column, 250×10 mm, flow rate 4 ml/min, detector λ 340 nm.

PLANT MATERIAL.—Commercial Cape aloe used in this investigation was purchased from Pan-African Corporation (Cape Town, South Africa), and a voucher specimen is preserved in our laboratories.

ISOLATION OF FUROALOESONE [**5**].—Powdered Cape aloe (4 kg) was extracted with Me_2CO (4 liters) for 3 h at 40° under vigorous mechanical stirring. $CHCl_3$ (4 liters) and hexane (1.5 liters) were added to the Me_2CO extract, and the resulting mixture was allowed to stand at room temperature overnight. Filtration of insoluble material and removal of the solvent gave a brown syrup (34 g) that was fractioned by flash chromatography using gradient elution [$CHCl_3$-EtOAc (95:5→5:95)]. When examined by tlc analysis [EtOAc-HOAc (99:1)], a number of fractions were found to contain two compounds appearing as orange spots after spraying with Fast Blue B (R_f 0.45 and 0.39). These fractions were combined (2.3 g) and subjected to dccc twice [$CHCl_3$-MeOH-H_2O (4:4:3), ascending mode, 60 ml/h, and then hexane-$MeNO_2$-EtOAc-MeOH (8:2:2.5:3), descending mode, 30 ml/h]. Final purification of the less polar compound by semi-preparative hplc (eluent MeCN/H_2O, linear gradient from 25 to 90% MeCN in 20 min) afforded **5** as an amorphous solid (150 mg): mp 140–143°; ir ν max (KBr) cm^{-1} 3143, 3120, 1719, 1666, 1636, 1617, 1587, 1524, 1398, 1318, 861, 761; uv λ max (MeOH) nm (log ε) 215 (4.37), 222 (4.36), 240 (4.47), 256 sh (4.21), 308 (3.88); ^{1}H and ^{13}C nmr see Table 1; eims *m/z* (rel. int.) $[M]^+$ 256 (100), 214 (98), 185 (34), 175 (50), 128 (15), 81 (24).

Isolation of the more polar compound (300 mg) was performed by a semi-preparative hplc using MeOH/H_2O as eluent (linear gradient from 35 to 100% MeOH in 15 min). It was shown to be identical in spectroscopic properties with a synthetic sample of **4** (15): mp 254–256° [lit. (15) 255–257°].

ETHYL 4-*O*-ALLYLORSELLINATE [**7**].—A stirred mixture of ethyl orsellinate [**6**] (4.3 g, 21.9 mmol), allyl bromide (2.1 ml, 24.3 mmol), anhydrous K_2CO_3 (3.1 g, 22.5 mmol), and dry Me_2CO (300 ml) was refluxed under N_2 for 20 h. Most of the Me_2CO was removed by evaporation under reduced pressure, and the remaining solution was poured into H_2O and extracted with Et_2O (2×100 ml). The combined Et_2O extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography [hexane-EtOAc (9:0.4)] to give **7** (4.4 g, 85%) as colorless amorphous powder: pure in tlc [hexane-EtOAc (9:1)], R_f 0.54;

ir ν max (KBr) cm^{-1} 1650, 1615, 1575, 1450, 995, 930; uv λ max (MeOH) nm (log ε) 258 (4.16), 298 (3.72); ^{1}H nmr ($CDCl_3$) δ 1.41 (3H, t, J=7.5 Hz, *Me*CH_2), 2.51 (3H, s, 6-Me), 4.39 (2H, q, J=7.5 Hz, Me*CH_2*), 4.46 (2H, br d, J=5.0, H-1′), 5.25–5.45 (2H, m, H-3′), 5.90–6.08 (1H, m, H-2′), 6.28 and 6.30 (2×1H, br s, H-3 and H-5), 11.82 (1H, s, 2-OH); eims *m/z* (rel. int.) $[M]^+$ 236 (55), 208 (21), 190 (97), 175 (43), 162 (100).

ETHYL 3-ALLYLORSELLINATE [**8**].—Compound **7** (4 *g*, 16.9 mmol) was placed in a heavy-walled glass tube, sealed under vacuum, and heated at 210–215° for 7 h. Purification by flash chromatography using hexane-EtOAc (10:1) as eluent yielded 1.4 g (35% yield) of **8**, pure in tlc [hexane-EtOAc (8:2)], R_f 0.46; ir ν max (KBr) cm^{-1} 3440, 1640, 1610, 1600, 1420, 1000, 920; uv λ max (MeOH) nm (log ε) 265 (4.24), 300 (3.73); ^{1}H nmr ($CDCl_3$) δ 1.41 (3H, t, J=7.5 Hz, *Me*CH_2), 2.48 (3H, s, 6-Me), 3.45 (2H, br d, J=6.0, H-1′), 4.40 (2H, q, J=7.5 Hz, Me*CH_2*), 5.06–5.18 (2H, m, H-3′), 5.41 (1H, br s, 4-OH), 5.91–6.06 (1H, m, H-2′), 6.22 (1H, s, H-5), 12.16 (1H, s, 2-OH); ^{13}C nmr ($CDCl_3$) δ 14.22 (*Me*CH_2), 24.27 (6-Me), 27.06 (C-1′), 61.27 (*CH_2*Me), 105.47 and 109.91 (C-1 and C-3), 111.11 (C-5), 115.71 (C-3′), 135.87 (C-2′), 141.31 (C-6), 158.73 and 162.75 (C-2 and C-4), 172.10 (*C*OOEt); eims *m/z* (rel. int.) $[M]^+$ 236 (62), 190 (78), 175 (75), 162 (100).

ETHYL 2,3-DIHYDRO-4-HYDROXY-2-METHOXY-6-METHYL-5-BENZOFURANCARBOXYLATE [**10**].—A solution of compound **8** (1.5 g, 6.3 mmol) in MeOH (50 ml) was cooled at −73° and treated with a stream of O_3 until the blue color persisted. After the reaction was purged of the excess of O_3 with a stream of N_2, Me_2S (1 ml) was added. The solution was allowed to reach room temperature and stirred overnight. The solvent was then removed under reduced pressure and the residue dissolved in hexane-H_2O (1:1). The organic layer (200 ml) was washed with H_2O, dried over Na_2SO_4, and evaporated to give a residue which was converted into the title compound without further purification.

The above residue was added to 2,2-dimethoxypropane (50 ml) containing a catalytic amount of *p*-TsOH. After heating under reflux for 2 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. Usual workup and flash chromatography eluting with hexane-EtOAc (10:2.5) yielded **10** (690 mg, 43% yield), pure in tlc (eluent as above), R_f 0.67; ir ν max (KBr) cm^{-1} 1650, 1590; ^{1}H nmr ($CDCl_3$) δ 1.41 (3H, t, J=7.5 Hz, *Me*CH_2), 2.53 (3H, s, 6-Me), 3.01 (1H, dd, J_{AB}=16.5 Hz, J_{AX}=2.25 Hz, H_A-3), 3.26 (1H, dd, J_{AB}=16.5 Hz, J_{BX}=6.75 Hz, H_B-3), 3.52 (3H, s, 2-OMe), 4.39 (2H, q, J=7.5 Hz, Me*CH_2*), 5.72 (1H, dd, J_{AX}=2.25 Hz, J_{BX}=6.75 Hz, H_X-2), 6.29 (1H, s, H-7), 11.85 (1H, s, 4-OH); eims *m/z* (rel. int.) $[M]^+$ 252 (48), 206 (96), 175 (100), 163 (33), 147 (12).

In a separate experiment the reaction mixture arising from the ozonization of **8** (200 mg) was chromatographed on Si gel [hexane-EtOAc (11:5)] giving a white solid product (15 mg): pure in tlc (eluent as above) R_f 0.31; eims *m/z* (rel. int.) $[M]^+$ 238 (22), 210 (24), 193 (21), 162 (70), 163 (100), 136 (40). When examined in ^{1}H nmr ($CDCl_3$, room temperature) it was found to be a mixture (4.5:1) of the hemiacetal **9** [1.39 (3H, t, J=7.5 Hz, *Me*CH_2), 2.52 (3H, s, 6-Me), 3.02 (1H, dd, J_{AB}=15.5 Hz, J_{AX}=3.0 Hz, H_A-3), 3.32 (1H, dd, J_{AB}=16.5 Hz, J_{BX}=6.5 Hz, H_B-3), 4.38 (2H, q, J=7.5 Hz, Me*CH_2*), 6.14 (1H, dd, J_{AX}=2.25 Hz, J_{BX}=6.75 Hz, H_X-2), 6.28 (1H, s, H-7), 11.89 (1H, s, 4-OH)] and its corresponding aldehyde isomer [1.39 (3H, t, J=7.5 Hz, *Me*CH_2), 2.49 (3H, s, *Me*-Ar), 3.77 (2H, d, J=1.5 Hz, *CH_2*CHO), 4.38 (2H, q, J=7.5 Hz, Me*CH_2*), 6.24 (1H, s, Ar-*H*), 9.71 (1H, t, J=1.5 Hz, -*C*HO), 12.19 (1H, s, O*H*)].

ETHYL 4-HYDROXY-6-METHYL-5-BENZOFURANCARBOXYLATE [**11**].—A solution of compound **10** (400 mg, 1.6 mmol) and a catalytic amount of *p*-TsOH in dry C_6H_6 (150 ml) was refluxed for 30 min. After cooling, the reaction was washed with saturated $NaHCO_3$ and H_2O. Evaporation of the solvent and flash chromatography [hexane-EtOAc (10:0.5)] gave pure **11** (200 mg, 57%): tlc (eluent as above) R_f 0.61; ir ν max (KBr) cm^{-1} 3150, 3120, 1650, 1585, 1430, 1400, 1330, 815, 775; uv λ max (MeOH) nm (log ε) 232 (4.29), 256 (3.57), 312 (2.94); ^{1}H nmr ($CDCl_3$) δ 1.45 (3H, t, J=7.5 Hz, *Me*CH_2), 2.64 (3H, s, 6-Me), 4.45 (2H, q, J=7.5 Hz, Me*CH_2*), 6.88 (1H, s, H-7), 6.91 (1H, d, J=2.2 Hz, H-3), 7.48 (1H, d, J=2.2 Hz, H-2), 12.26 (1H, s, 4-OH); eims *m/z* (rel. int.) $[M]^+$ 220 (33), 175 (32), 174 (100), 145 (12), 110 (14).

4-HYDROXY-6-METHYL-5-BENZOFURANYL (METHYL SULFINYL)METHYL KETONE [**12**].—A mixture of dry DMSO (1.2 ml) and NaH (80% in oil, 80 mg) in dry C_6H_6 (20 ml) was heated under N_2 for 2 h at 80°. The solution was cooled to 35° and treated dropwise with **11** (140 mg, 0.63 mmol) in dry C_6H_6 (5 ml). The reaction mixture was then stirred 1 h, diluted with Et_2O (20 ml), and washed with a saturated solution of NH_4Cl, and the two layers were separated. The aqueous layer was extracted with Et_2O (2×50 ml), and the organic extracts were combined and dried over Na_2SO_4. After removal of the solvent in vacuo, the residual solid was crystallized from hexane, giving pure **12** (130 mg, 82% yield): mp 155–156°; ir ν max (KBr) cm^{-1} 3150, 3130, 1640, 1585, 1460, 1310, 875, 860; uv λ max (MeOH) nm (log ε) 204 (4.30), 240 (4.20), 276 sh (3.48), 316 (2.97); ^{1}H nmr ($CDCl_3$) δ 2.61 (3H, s, 6-Me), 2.87 (3H, s, *Me*-SO), 4.46 and 4.74 (2×1H, 2×d, J=21.2 Hz, CO*CH_2*SO), 6.91 (1H, s, H-7), 7.01 (1H, d, J=2.2, H-3), 7.49 (1H, d, J=2.2 Hz, H-2), 12.08 (1H,s, 4-OH); eims *m/z* (rel. int.) $[M]^+$ 252 (36), 234 (27), 188 (100), 187 (56), 175 (50), 174 (36), 159 (15), 130 (25), 118 (8).

FUROALOESONE [**5**].—3,3-Ethylendioxybutanal [**13**] (15) (52 mg, 0.4 mmol) in 5 ml of toluene was slowly added to a warm solution (40°) of **12** (50 mg, 0.2 mmol) in toluene (40 ml) containing catalytic amounts of piperidine, and the resulting mixture was refluxed for 4 h. After cooling and distillation of the solvent, the crude product was dissolved in dioxane-H_2O (1:3) (30 ml), and 0.1 N HCl (5 ml) was added. The reaction was allowed to heat at 60° for 3 h, treated with $NaHCO_3$, extracted with Et_2O (3×40 ml), dried over Na_2SO_4, and concentrated in vacuo. The concentrate was purified by flash chromatography [EtOAc-hexane (8:2)] to give 35 mg (69% yield) of a product (mp 141–142°) which was found to be identical with a sample of natural furoaloesone [**5**] by chromatographic and spectroscopic comparisons.

ACKNOWLEDGMENTS

We thank CNR (Progetto Finalizzato Chimica Fine II) and MURST for financial support.

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Received 24 November 1992