

SYNTHESIS OF NATURALLY OCCURRING 2,5-DIALKYLCHROMONES. PART 1.
SYNTHESIS OF ALOESONE AND ALOESOL

Paola Gramatica^a, M. Pia Gianotti^a, Giovanna Speranza^b, and
Paolo Manitto^{a*}

(a) Dipartimento di Chimica Organica e Industriale and Centro
di Studio per le Sostanze Organiche Naturali del CNR, Universi-
tà di Milano, Via Venezian 21 - 20133 Milano, Italy

(b) Centro Studi M. Branca, Via E. Porro 1 - 20158 Milano, Italy

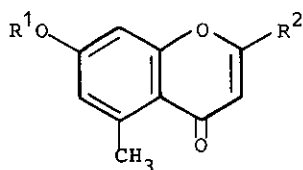
Abstract - A number of 2-alkyl-7-alkoxy (or hydroxy)-5-methyl-
chromones, including naturally occurring aloesone and aloesol,
were synthesized starting from ethyl orsellinate via β -keto-
sulfoxides as intermediates.

In connection with our studies on the constituents of aloe¹, the dried latex of
the leaves of Aloe spp.², we needed substantial amounts of 2-acetonil-7-hydroxy-
5-methylchromone (1a). This compound, commonly known as aloesone, has been
reported to be present in a few species of Aloe³. It might be a biosynthetic
precursor of the C-glucosylchromones occurring in Aloe spp.^{1,4}, but no experiments
have so far been reported on the in vivo C-glucosylation of the chromone nucleus⁵.
In addition, other 5-methylchromones, e.g. 1b and (S)-1c, have recently been
found in Polygonum cuspidatum⁶ and in rhubarb⁷. Thus, a convenient synthesis of
1a and related compounds appeared to be desirable in order: i) to use them as
reference standards in routine analyses of commercial samples, ii) to evaluate
their physiological properties⁸, and iii) to prepare properly labelled samples
for precursor-incorporation experiments.

This paper deals with a general procedure to obtain 2-alkyl-7-alkoxy (or hydroxy)-
5-methylchromones (1) and particularly describes the first total synthesis of
aloesone (1a) and (R,S)-aloesol (1c).

Ethyl orsellinate (4) was prepared according to Sonn's method⁹, i.e. via Claisen
condensation between ethyl acetoacetate and methyl crotonate followed by bromina-
tion of 2 to 3 and reductive dehalogenation of the aromatic ring (Scheme 1).
4 was then selectively protected at the 4-hydroxyl function by treatment with
methyl iodide or β -methoxyethoxymethyl (MEM) chloride¹⁰, taking advantage of the
presence of a strong intramolecular hydrogen bond between the ethoxycarbonyl
group and the hydroxyl function in ortho-position.

The construction of the γ -pyrone ring to complete the chromone nucleus was
achieved using β -ketosulfoxides 6a,b as key intermediates¹¹. They were prepared
by condensation of the (4-OH)-protected ethyl orsellinate, i.e. 5a,b, with sodium
methylsulfinylmethide^{11,12}.



<u>1</u>	R ¹	R ²
<u>a</u>	H	
<u>b</u>	H	CH ₃
<u>c</u>	H	
<u>d</u>	CH ₃	CH ₃
<u>e</u>	CH ₃ O(CH ₂) ₂ OCH ₂ -	CH ₃
<u>f</u>	CH ₃	
<u>g</u>	CH ₃ O(CH ₂) ₂ OCH ₂ -	
<u>h</u>	CH ₃	

When 6a,b were allowed to react with acetaldehyde in toluene under reflux (in the presence of catalytic amounts of piperidine)¹¹, 2-methylchromones, i.e. 1d¹³ and 1e, were obtained in good yields. 1e was then converted into 1b^{6,7,13a-c,14} by treatment with anhydrous zinc chloride in methylene chloride¹⁰. Analogously, the reaction of 6a,b with 3,3'-ethyldioxybutanal [8, R² = -CH₂-C(OCH₂CH₂O)Me] gave compounds 1f,g which afforded 7-O-methylaloesone (1h)^{13d} and aloesone (1a)³ after heating with HCl in dioxane¹⁵. It is worth of note that the MEM ether cleavage in 1g occurred in one step with the removal of the ethyldioxy protecting group. Finally, aloesol (1c)⁷ was synthesized by selective reduction of the side-chain carbonyl group of 1a with NaBH₄ in methanol at room temperature. It must be pointed out that aloesone (1a) and (R,S)-aloesol (1c), specifically labelled with isotopic carbon at 3-position, are readily obtainable by the above route using commercially available ¹³C- or ¹⁴C-DMSO.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^1H -nmr spectra were obtained with a Bruker WP80 SY; chemical shifts are reported in δ from internal tetramethylsilane. ^{13}C -nmr were recorded on a Varian XL-100 spectrometer operating at 25.2 MHz. Ms spectra were recorded on a Varian MAT 112 mass spectrometer. Tlc were carried out on silica gel Merck 60 F₂₅₄ plates; flash chromatography was performed on silica gel Merck 60 (230-400 mesh).

4-Ethoxycarbonyl-5-methylcyclohexa-1,3-dione (2). Prepared by Claisen condensation between ethyl acetoacetate and methyl crotonate in EtONa: mp 88-89°C (lit.¹⁶ 89-90°C); ir (nujol) 1730, 1600 cm^{-1} ; ^1H -nmr (CDCl_3): δ 5.6 (1H, broad s, 4-OH), 10.1 (1H, s, 2-OH) (indicating the existence of 2 in the bis-enolic tautomeric form). Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_4$: C, 60.59; H, 7.12. Found: C, 60.48; H, 7.13.

Ethyl 3,5-Dibromo-orsellinate (3). Bromine (9.3 ml, 0.16 mol) in glacial acetic acid (50 ml) was slowly added to a solution of 2 (10 g, 0.05 mol) in glacial acetic acid (50 ml) and the mixture stirred for 1 h. After standing overnight at room temperature, the product was collected by filtration. Additional product was precipitated from mother liquors by water addition (100 ml). Both precipitates were washed with water and dried to afford 3 (15.5 g, 87.5% yield), which was pure in tlc (hexane:ethyl acetate 7:3) and used for the next step without further purification: mp 143-145°C (lit.⁹ 143-144°C); ir (KBr) 3400, 1600 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.3 (3H, t, $J=8$ Hz, OCH_2CH_3), 2.5 (3H, s, Ar- CH_3), 4.4 (2H, q, $J=8$ Hz, OCH_2CH_3), 6.5 (1H, broad s, 4-OH), 12.1 (1H, s, 2-OH). Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_4\text{Br}_2$: C, 33.93; H, 2.85. Found: C, 34.08; H, 2.85.

Ethyl Orsellinate (4). 3 (4 g, 11.3 mmol) dissolved in 2N NaOH (60 ml) at 0°C was hydrogenated over 10% Pd/C (745 mg) at room temperature and atmospheric pressure for 15 h. The catalyst was removed by filtration over celite, the filtrate flowing into ice-cold conc. HCl (25 ml, pH=4-5). The precipitate was collected by filtration and dried giving pure 4 (2g, 88% yield): mp 131-132°C (lit.⁹ 132°C); ir (nujol): 3350, 1640 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.4 (3H, t, $J=8$ Hz, OCH_2CH_3), 2.6 (3H, s, Ar- CH_3), 4.5 (2H, q, $J=8$ Hz, OCH_2CH_3), 6.4 (3H, broad s, 2H arom and OH), 12.1 (1H, s, OH); ^{13}C -nmr (CDCl_3): δ 14 ($\text{CH}_3\text{CH}_2\text{O}$), 24 (CH_3 -Ar), 62 (CH_2O), 101 (C_3), 112 (C_5), 145 (C_6), 163 (C_2), 166 (C_4), 174 (CO_2Et). Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4$: C, 61.22; H, 6.16. Found: C, 61.19; H, 6.25.

Ethyl 2-Hydroxy-4-methoxy-6-methylbenzoate (5a). Methyl iodide (0.5 ml, 7.9 mmol) was slowly added to 4 (1 g, 5.1 mmol) in dry acetone (10 ml) containing dry potassium carbonate (1.1 g, 7.9 mmol). The reaction mixture was refluxed under nitrogen for 3 h, potassium carbonate filtered off and the solvent distilled to give 5a (1.05 g, 98% yield) pure in tlc (hexane:AcOEt 8:2): mp 73-74°C (lit.¹⁷ 72-75°C); ir (KBr): 1640, 1320, 1260 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.4 (3H, t, $J=8$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.5 (3H, s, Ar- CH_3), 3.8 (3H, s, Ar- OCH_3), 4.4 (2H, q, $J=8$ Hz, CO_2CH_2), 6.3 (2H, m, arom), 11.8 (1H, s, OH). Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.84; H, 6.71. Found: C, 62.75; H, 6.73.

Ethyl 2-Hydroxy-4-[(β -methoxyethoxy)methoxy]-6-methylbenzoate (5b). A suspension of 4 (500 mg, 2.55 mmol) in dry methylene chloride (8 ml) was treated with methoxyethoxymethyl chloride (freshly distilled) (0.8 ml, 6.45 mmol) and with dry triethylamine (0.8 ml)¹⁰. The mixture was stirred under nitrogen at room temperature for 48 h. After washing with water, the crude product was purified by flash-chromatography (CHCl₃:AcOEt 9:1 as eluent) to afford pure 5b (60% yield): ir (KBr): 1650, 1250, 1110, 1060 cm⁻¹; ¹H-nmr (CDCl₃) δ 1.4 (3H, t, J=8 Hz, CO₂CH₂CH₃), 2.5 (3H, s, Ar-CH₃), 3.4 (3H, s, OCH₃), 3.5-3.9 (4H, m, OCH₂CH₂O), 4.4 (2H, q, J=8 Hz, CO₂CH₂CH₃), 5.2 (2H, s, OCH₂O), 6.4 (2H, m, arom), 11.7 (1H, s, OH). Anal. Calcd for C₁₄H₂₀O₆: C, 59.14; H, 7.09. Found: C, 58.79; H, 6.91.

2'-Hydroxy-4'-methoxy-6'-methyl-2-(methylsulfinyl)acetophenone (6a). A mixture of dry dimethylsulfoxide (9 ml) and sodium hydride (70% in oil, 0.85 g, 25 mmol) in dry benzene (20 ml) was stirred at 80°C for 1 h, then cooled to 35°C and treated dropwise with 5a (1 g, 5 mmol) in dry benzene (10 ml). The exothermic (45-50°C) reaction was allowed to cool for 1 h. The benzene was removed *in vacuo*, the residue was treated with water (20 ml), then glacial acetic acid was slowly added to precipitate the product in 85% yield: mp 146-148°C; ir (nujol): 1630, 1010 cm⁻¹; ¹H-nmr (CDCl₃): δ 2.5 (3H, s, Ar-CH₃), 2.8 (3H, s, CH₃SO), 3.9 (3H, s, OCH₃), 4.3-4.6 (2H, 2d, J=16 Hz, COCH₂SO), 6.3 (2H, s, arom), 11.4 (1H, s, OH). Anal. Calcd for C₁₁H₁₄O₄S: C, 54.52; H, 5.82. Found: C, 54.16; H, 5.91.

2'-Hydroxy-4'-[(β -methoxyethoxy)methoxy]-6'-methyl-2-(methylsulfinyl)acetophenone (6b). Prepared as 6a starting from 5b (86% yield): mp 106-107°C; ir (nujol): 1640, 1280, 1100, 1090 cm⁻¹; ¹H-nmr (CDCl₃): δ 2.4 (3H, s, Ar-CH₃), 2.9 (3H, s, CH₃SO), 3.3 (3H, s, OCH₃), 3.5-3.9 (4H, s, OCH₂CH₂O), 4.3-4.7 (2H, 2d, J=15 Hz, COCH₂SO), 5.2 (2H, s, OCH₂O), 6.4 (2H, m, arom), 11.2 (1H, s, OH). Anal. Calcd for C₁₄H₂₀O₆S: C, 53.15; H, 6.37. Found: C, 53.47; H, 6.29.

2,5-Dimethyl-7-methoxychromone (1d). Acetaldehyde (2 ml, 35 mmol) was slowly added to a warm solution of 6a (600 mg, 2.5 mmol) in toluene containing catalytic amounts of piperidine (2 drops) and the mixture refluxed for 5 h. After distillation of the solvent the crude product was purified by flash-chromatography (benzene:AcOEt 6:4) to afford pure 1d (450 mg, 89% yield): mp 115-117°C (lit.^{13a,c} 116-117°C); ir (nujol): 1650, 1600, 1280 cm⁻¹; ¹H-nmr (CDCl₃): δ 2.3 (3H, s, 2-CH₃), 2.9 (3H, s, Ar-CH₃), 3.9 (3H, s, OCH₃), 6.0 (1H, s, 3-H), 6.7 (2H, s, arom); ms (dis) m/z (I%): 204 (M⁺, 100), 176 (59), 175 (86), 164 (59), 161 (31), 136 (14), 121 (13). Anal. Calcd for C₁₂H₁₂O₃: C, 70.57; H, 5.92. Found: C, 70.33; H, 5.91.

2,5-Dimethyl-7-[(β -methoxyethoxy)methoxy]-chromone (1e). Prepared as 1d starting from 6b (80% yield): mp 77-79°C; ir (nujol): 1640, 1600, 1280, 1140 cm⁻¹; ¹H-nmr (CDCl₃): δ 2.3 (3H, s, 2-CH₃), 2.8 (3H, s, Ar-CH₃), 3.3 (3H, s, OCH₃), 3.5-3.9 (4H, m, OCH₂CH₂O), 5.3 (2H, s, OCH₂O), 6.0 (1H, s, H-3), 6.7-6.9 (2H, m, arom); ms (dis) m/z (I%): 278 (M⁺, 100), 203 (21), 190 (24), 173 (9), 162 (13), 161 (18), 134 (28), 106 (5). Anal. Calcd for C₁₅H₁₈O₅: C, 64.74; H, 6.52. Found: C, 64.59; H, 6.51.

2,5-Dimethyl-7-hydroxychromone (1b). 1e (149 mg, 0.54 mmol) in dry methylene chloride (10 ml) was slowly added to a suspension of ZnBr_2 (3 g, 13.4 mmol) in dry methylene chloride (10 ml). The mixture was stirred under nitrogen at room temperature for 4 days. After filtering off the solid, the solvent was washed with NaHCO_3 , with brine, then dried (MgSO_4) and evaporated under vacuum to give 1b (66 mg, 65% yield): mp 255-257°C (lit.^{14c} 243-248°C, lit.^{13b} 257-260°C); ir (nujol): 3340, 1650 cm^{-1} ; $^1\text{H-nmr}$ (DMSO-d_6): δ 2.3 (3H, s, 2- CH_3), 2.7 (3H, s, Ar- CH_3), 5.9 (1H, s, 3-H), 6.6 (2H, s, arom), 11.5 (1H, broad s, OH); ms (dis) m/z (I%): 190 (M^+ , 100), 175 (2), 162 (13), 161 (20), 150 (11), 122 (13), 94 (5). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_3$: C, 69.46; H, 5.30. Found: C, 69.37; H, 5.42.

3,3-Ethylendioxybutanal (8, $\text{R}^2 = \text{CH}_2\text{-C}(\text{OCH}_2\text{CH}_2\text{O})\text{-CH}_3$). Ethyl 3,3-ethylendioxybutanoate (1g, 5.75 mmol) (prepared as in ref. 18) was treated with LiAlH_4 (3 mmol) in dry ether for 24 h at refluxing temperature to give the corresponding alcohol (75% yield): ir (nujol): 3410, 1300, 1000 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3): δ 1.4 (3H, s, CH_3), 1.9 (2H, t, $\text{J}=6$ Hz, 2- CH_2), 2.7 (1H, s, OH), 3.8 (2H, t, $\text{J}=6$ Hz, 1- CH_2), 4.0 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$). Anal. Calcd for $\text{C}_6\text{H}_{12}\text{O}_3$: C, 54.52; H, 9.15. Found: C, 54.63; H, 9.17.

3,3-Ethylendioxybutanol (2.5 g, 18.9 mmol) was slowly added to a stirred ice-cooled suspension of pyridinium chlorochromate (15 g, 69 mmol) in dry methylene chloride (100 ml). After stirring under nitrogen for 2 h at 25°C, the suspension was filtered on celite. The resulting solution was washed with NaHCO_3 , then with brine, dried with MgSO_4 and evaporated to afford the pure title compound in 70% yield: ir (nujol): 1720, 1300-1000 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3): δ 1.4 (3H, s, CH_3), 2.8 (2H, d, $\text{J}=2$ Hz, CH_2), 4.0 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 9.8 (1H, t, $\text{J}=2$ Hz, CHO). Anal. Calcd for $\text{C}_6\text{H}_{10}\text{O}_3$: C, 55.38; H, 7.69. Found: C, 55.67; H, 7.46.

2-(2',2'-Ethylendioxypropyl)-5-methyl-7-methoxychromone (1f). Prepared as 1d starting from 6a and 3,3-ethylendioxybutanal (68% yield): ir (CHCl_3): 1650, 1600, 1240, 1160-1080 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3): δ 1.4 (3H, s, CO- CH_3), 2.8 (3H, s, Ar- CH_3), 2.9 (2H, s, CO- CH_2), 3.9 (3H, s, OCH_3), 4.0 (4H, s, ethylendioxy group), 6.1 (1H, s, 3-H), 6.7 (2H, s, arom); ms (dis) m/z (I%): 290 (M^+ , 19), 275 (5), 245 (17), 217 (21), 204 (92), 190 (22), 175 (100), 165 (77), 115 (82), 113 (79). Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_5$: C, 66.29; H, 6.24. Found: C, 66.12; H, 6.33.

2-(2',2'-Ethylendioxypropyl)-5-methyl-7-[(β -methoxyethoxy)methoxy]-chromone (1g). Prepared as 1d starting from 6b and 3,3-ethylendioxybutanal (65% yield): ir (nujol): 1650, 1600, 1270, 1160, 1080 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3): δ 1.45 (3H, s, CO- CH_3), 2.8 (3H, s, Ar- CH_3), 2.9 (2H, s, CO- CH_2), 3.4 (3H, s, OCH_3), 3.5-3.9 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.0 (4H, s, ethylendioxy group), 5.3 (2H, s, OCH_2O), 6.1 (1H, s, 3-H), 6.8-6.9 (2H, m, arom); ms (dis) m/z (I%): 364 (M^+ , 91), 349 (12), 289 (26), 278 (100), 202 (23), 190 (25), 161 (29), 151 (47), 149 (53). Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_7$: C, 62.62; H, 6.64. Found: C, 62.75; H, 6.82.

Aloesone (1a). 0.2N HCl (5 ml) was slowly added to a solution of 1g (60 mg, 0.16 mmol) in dioxane (3 ml). The mixture was heated at 80°C under stirring for 6 h, neutralized with NaHCO_3 (10%) and extracted with chloroform. The organic phase, when dried (MgSO_4) and evaporated, gave pure 1a (37 mg, 95% yield): mp 151-152°C (lit.³ 150-152°C); ir (nujol): 3335, 1715, 1660 cm^{-1} ; $^1\text{H-nmr}$ (DMSO-d_6): δ 2.3

(3H, s, CO-CH₃), 2.7 (3H, s, Ar-CH₃), 3.8 (2H, s, CO-CH₂), 6.1 (1H, s, 3-H), 6.7 (2H, s, arom), 11.1 (1H, broad s, OH); ms (dis) m/z (I%): 232 (M⁺, 73), 190 (20), 189 (100), 176 (23), 167 (23), 161 (20), 151 (50), 149 (63). Anal. Calcd for C₁₃H₁₂O₄: C, 67.23; H, 5.21. Found: C, 67.42; H, 5.34.

5-Methyl-7-methoxy-2-(2-oxopropyl)chromone (1h). Prepared as 1a starting from 1f (95% yield): mp 82-84°C; ir (CHCl₃): 1720, 1640, 1600, 1260 cm⁻¹; ¹H-nmr (CDCl₃): δ 2.3 (3H, s, CO-CH₃), 2.8 (3H, s, Ar-CH₃), 3.9 (5H, s, OCH₃ and CO-CH₂), 6.1 (1H, s, 3-H), 6.7 (2H, s, arom); ms (dis) m/z (I%): 246 (M⁺, 61), 204 (100), 190 (22), 175 (15), 165 (49), 149 (18), 104 (24), 103 (22). Anal. Calcd for C₁₄H₁₄O₄: C, 68.28; H, 5.73. Found: C, 68.03; H, 5.82.

Aloesol (1c). NaBH₄ (50 mg, 1.3 mmol) were added to a solution of aloesone (1a) (60 mg, 0.26 mmol) in methanol (10 ml). After 10 min. at room temperature under stirring the reaction mixture was diluted with water (10 ml), acidified with dil. HCl to pH 4-5 and extracted with ether. The organic phase was dried on MgSO₄ and evaporated under vacuum giving a residue which was crystallised from AcOH-MeOH: 1c (40 mg), mp 186-187°C; uv, ms (dis), ¹H- and ¹³C-nmr spectra were identical with those reported in lit. for natural (S)-aloesol⁷.

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