The Synthesis of Aloesaponarins I and II

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The largest group of naturally occurring anthraquinones derive structurally from emodin (1,3,8-trihydroxy-6-methylanthraquinone), while some insect pigments are found with the less usual substitution pattern of deoxyerythrolaccin (1,3,6-trihydroxy-8-methylanthraquinone)[1,2]. Whereas more simple analogues of the former, lacking the β-hydroxy group, e.g., chrysophanol, islandicin, etc., are widely distributed in plants and microorganisms, the corresponding 1,6-dihydroxy-8-methylanthraquinones have not been isolated until recently[3] and, somewhat surprisingly, were found in a higher plant, *Aloe saponaria Haw.* This communication records the first syntheses of the prototype of this group, aloesaponarin II (**4**) as well as of its naturally occurring methoxycarbonyl derivative, aloesaponarin I (**6**), thus confirming the proposed structures of these important metabolites.

The syntheses were envisaged in terms of a regiospecific cycloaddition to 3-chlorojuglone (**1**) of the appropriate vinylogues of ketene acetals, the 4-methoxy-2-trimethylsiloxypentadienes **2a, b** and **3a, b,** prepared earlier[4]. The required 3-chlorojuglone (**1**) was obtained by the peracetic acid oxidation of commercial 1,5-dihydroxynaphthalene[5], followed by chlorination and regioselective dehydrohalogenation[6], while the readily accessible 2-methoxy-2-penten-4-one and its 3-methoxycarbonyl derivative were converted into the corresponding trimethylsilyl enol ethers[4] (**2, 3**) by the method of Danishefsky and Kitahara[7].

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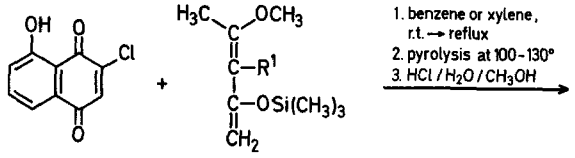
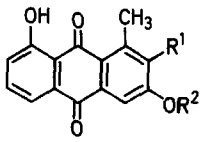
Condensations of the quinone **1** with the dienes **2a, b** and **3a, b** were conducted both in refluxing benzene followed by pyrolysis of the adduct at 120–130° and in xylene at 100°. Acidic hydrolysis of the crude product completed the one-pot synthesis and gave mixtures of the natural pigment **4** or **6** and of its monomethyl ether **5** or **7**, which were separated by dry-column chromatography. The diene **2a, b** gave better overall yields (93–97 %) than the more substituted **3a, b** (69–84 %). The monomethyl ether in all cases and under various conditions always constituted the major product and was 2 to 3 times more abundant than the dihydroxylated substance. As noted earlier[8], the methyl ethers probably arise by addition of eliminated methanol to an intermediate enol ether.



1 **2a,b** R^1 = H **3a,b** R^1 = $-COOCH_3$



4 $R^1 = R^2 = H$
5 $R^1 = H$, $R^2 = CH_3$
6 $R^1 = -COOCH_3$, $R^2 = H$
7 $R^1 = -COOCH_3$, $R^2 = CH_3$

Three of the four compounds obtained (**4, 6, 7**; the natural products and a derivative) have been described[3]. Their published physical and spectral characteristics were found to be essentially concordant with those of the synthetic materials and absolute identity could be established in the case of aloesaponarin I by direct comparison with an authentic sample (a published I.R. band at 1740 cm^{-1} did not appear in the spectra of either the synthetic or the natural products).

Aloesaponarin II (4) and its 6-Methyl Ether (5):

Method A: A solution of the 4-methoxy-2-trimethylsiloxy-1,3-pentadiene[4] (**2a, b**; 744 mg, 4.00 mmol) in dry benzene (10 ml) is added over 10 min to a stirred suspension of 3-chlorojuglone[6] (**1**; 348 mg, 1.67 mmol) in dry benzene (10 ml). The mixture is stirred at room temperature for 1.5 h, refluxed for 1.5 h, evaporated to dryness, and the residue pyrolysed at 120° for 30 min. The crude material is hydrolyzed by refluxing for 10 min in a mixture of methanol (10 ml) and 2 % aqueous hydrochloric acid (10 ml), diluted with water (50 ml), extracted with ethyl acetate (3 × 100 ml), and separated by dry-column chromatography (silica gel, benzene). A first zone consists of *1-hydroxy-6-methoxy-8-methylanthraquinone (aloesaponarin II 6-methyl ether*, **5**); yield: 289 mg (65 %); m.p. 179–180° (acetone).

$C_{16}H_{12}O_4$	calc.	C 71.63	H 4.51
(268.3)	found	71.70	4.54

M.S.: $m/e = 268$ (M^+).

I.R. (KBr): $\nu_{max} = 3420, 1662, 1624, 1594$ cm^{-1}.

U.V. (dioxane): $\lambda_{max} = 267$ ($\log\varepsilon = 4.41$); 290 sh (3.94); 410 nm (3.78).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): $\delta = 2.74$ (s, 3H, 8-CH_3); 3.93 (s, 3H, 6-OCH_3); 6.94 (d, 1H, $J = 2.5$ Hz, 7-H); 7.23 (dd, 1H, $J = 8.0$, 2.0 Hz, 2-H); 7.56 (dd, 1H, $J = 8.0$, 8.0 Hz, 3-H); 7.59 (d, 1H, $J = 2.5$ Hz, 5-H); 7.71 (dd, 1H, $J = 8.0$, 2.0 Hz, 4-H); 12.98 ppm (s, 1H, 1-OH).

Elution of the column with benzene/ethyl acetate (10:1) gives *1,6-dihydroxy-8-methylanthraquinone (aloesaponarin II*, **4**); yield: 134 mg (32 %); m.p. 269–270° (dec, methanol) (Ref. [3], m.p. 250–254°, dec).

$C_{15}H_{10}O_4$	calc.	C 70.86	H 3.96
(254.2)	found	70.56	3.74

M.S.: $m/e = 254$ (M^+).

I.R. (KBr): $\nu_{max} = 3300$ br, 1661, 1630, 1603 cm^{-1}.

U.V. (methanol): $\lambda_{max} = 217$ ($\log\varepsilon = 4.15$); 269 sh (4.09); 278 (4.11); 390 sh (3.55); 400 (3.59); 430 (sh) nm (3.53).

^{1}H-N.M.R. (90 MHz, DMSO-d_6): $\delta = 2.60$ (s, 3H, 8-CH_3); 6.92 (d, 1H, $J = 2.5$ Hz, 7-H); 7.24 (dd, 1H, $J = 8.0$, 2.0 Hz, 2-H); 7.35 (d, 1H, $J = 2.5$ Hz, 5-H); 7.52 (dd, 1H, $J = 8.0$, 2.0 Hz, 4-H); 7.66 (dd, 1H, $J = 8.0$, 8.0 Hz, 3-H); 12.94 ppm (br s, ~2H, 1,6-OH).

Method B: When the foregoing reaction is carried out in dry xylene with stirring for 1 h at room temperature and then for 24 h at 100°, the pyrolysis step can be eliminated. The mixture is evaporated, hydrolyzed, and worked up as in Method A; yield of **5**: 331 mg (74 %); yield of **4**: 98 mg (23 %).

Aloesaponarin I (6) and its 3-Methyl Ether (7):

Method A: The condensation of 3-chlorojuglone (**1**; 348 mg, 1.67 mmol) with the 4-methoxy-3-methoxycarbonyl-2-trimethylsiloxy-1,3-pentadiene[4] (**3a, b**; 977 mg, 4.00 mmol) is conducted according to method A above, except that the initial refluxing is extended to 24 h when an additional portion of the diene (4.00 mmol) is added and refluxing continued for 48 h. The pyrolysis is carried out at 130° for 1 h after which the usual procedure gives *8-hydroxy-3-methoxy-2-methoxycarbonyl-1-methylanthraquinone (aloesaponarin I 3-methyl ether*, **7**); yield: 299 mg (55 %); m.p. 210–212° (acetone) (Ref. [3], m.p. 213–216°).

$C_{18}H_{14}O_6$	calc.	C 66.25	H 4.32
(326.3)	found	66.34	4.28

M.S.: $m/e = 326$ (M^+).

I.R. (KBr): $\nu_{max} = 3400, 1722, 1668, 1631$ cm^{-1}.

U.V. (dioxane): $\lambda_{max} = 268$ ($\log\varepsilon = 4.37$); 291 sh (3.88); 410 nm (3.69).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): $\delta = 2.71$ (s, 3-H, 1-CH_3); 4.00, 4.03 (2s, 2 × 3H, 2-$COOCH_3$, 3-OCH_3); 7.27 (dd, 1H, $J = 8.0$, 2.0 Hz, 7-H); 7.60 (dd, 1H, $J = 8.0$, 8.0 Hz, 6-H); 7.71 (s, 1H, 4-H); 7.74 (dd, 1H, $J = 8.0$, 2.0 Hz, 5H); 12.86 ppm (s, 1H, 8-OH).

Elution of the column with benzene/ethyl acetate (10:1) gives *3,8-dihydroxy-2-methoxycarbonyl-1-methylanthraquinone (aloesaponarin I*, **6**); yield: 105 mg (20 %); m.p. 206.5–207.0° (methanol) (Ref. [3], m.p. 199–203°, dec); mixture m.p. 205–206°.

$C_{17}H_{12}O_6$	calc.	C 65.38	H 3.88
(312.3)	found	65.68	4.00

M.S.: $m/e = 312$ (M^+).

I.R. (KBr): $\nu_{max} = 3370, 1721, 1681, 1668, 1635$ cm^{-1}.

U.V. (methanol): $\lambda_{max} = 218$ ($\log\varepsilon = 4.26$); 275 (4.20); 308 (3.27); 410 (3.51); 425 nm (3.44).

^{1}H-N.M.R. (90 MHz, DMSO-d_6): $\delta = 2.56$ (s, 3H, 1-CH_3); 3.91 (s, 3H, 2-$COOCH_3$); 7.17–7.78 (m, 4H, 4, 5, 6, 7-H); 12.76 ppm (br s, ~2H, 3,8-OH).

Method B: The reaction is carried out according to Method B above, using 2.5 times the given scale and heating at 100° for 48 h; yield of **7**: 655 mg (48 %); yield of **6**: 465 mg (36 %).

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