Studies in Terpenoids. Part 42.[1] Synthesis of 3-(2-Hydroxyisopropyl)-5,8-dimethyl-1,2-naphthoquinone (Emmotin-H)

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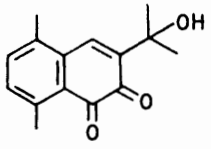
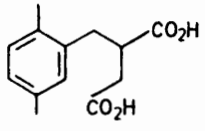
Emmotin-H, a naturally occurring sesquiterpenoid 1,2-naphthoquinone pigment (1) has been synthesised in a four step sequence starting from the known 5,8-dimethyl-4-oxotetralin-2-carboxylic acid (3a). Selenium dioxide oxidation of its methyl ester (3b) gives 3-methoxycarbonyl-5,8-dimethyl-1,2-naphthoquinone (4) which on reductive acetylation affords the corresponding diacetoxynaphthalene ester (5). Its reaction with excess of methylmagnesium iodide is accompanied by aerial oxidation during work-up and furnishes emmotin-H (1).

On the basis of spectral data and chemical correlation with compounds having closely related carbon skeletons, Gottlieb *et al.*[2] proposed the structure 3-(2-hydroxyisopropyl)-5,8-dimethyl-1,2-naphthoquinone (1) for emmotin-H, a sesquiterpenoid occurring in the trunk wood of *Emmotum nitens* (Icacinaceae). In continuation of our work on the total synthesis of naturally occurring naphthoquinone sesquiterpenoids,[3] emmotin-H has now been synthesised for the first time and its structure (1) as proposed by Gottlieb *et al.* has been confirmed.

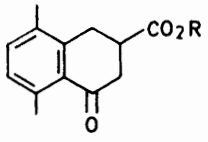
The starting material for the synthesis is the known[4] 2,5-dimethylbenzylsuccinic acid (2). Intramolecular Friedel–Crafts acylation of the anhydride of (2) was



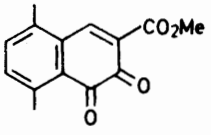
(1)



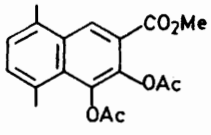
(2)



(3)
a; R = H
b; R = Me



(4)



(5)

reported[4] to give a mixture of isomeric oxotetralin- and oxoindane-carboxylic acids in the ratio 2 : 1, from which the required acid (3a) was separated by fractional crystallization. In the present work intramolecular cyclodehydration by polyphosphoric acid (PPA) of 2,5-dimethylbenzylsuccinic acid (2), without going through the anhydride as reported,[4] proved to be a more convenient method of obtaining the acid (3a) directly in 63% yield.

Oxidation of the ester (3b) with selenium dioxide, as reported for a similar tetralone substrate in the synthesis of mansonone-G[3c] gave 3-methoxycarbonyl-5,8-dimethyl-1,2-naphthoquinone (4). Reductive acetylation afforded 1,2-diacetoxy-3-methoxycarbonyl-5,8-dimethylnaphthalene (5) in quantitative yield. A Grignard reaction with a large excess of methylmagnesium iodide on the ester (5) gave emmotin-H (1), apparently by aerial oxidation during work-up of the resulting naphthalene-1,2-diol. Analytical data and spectra (i.r. and n.m.r.) of synthetic emmotin-H agreed with those of the naturally occurring sample.

EXPERIMENTAL

General details and instruments used have been reported.[5]

Methyl 5,8-dimethyl-4-oxotetralin-2-carboxylate (3b).—2,5-Dimethylbenzylsuccinic acid (2) [6.5 g; 2,5-dimethylbenzyl chloride required in the preparation of (2) was obtained in the present work in much better yield (69%) by a known older procedure[6] in preference to that adopted by the Japanese workers[4]] was stirred with PPA, prepared from P_2O_5 (25 g) and H_3PO_4 (15.5 ml), at 100 °C for 3 h. The black pasty mixture was poured onto crushed ice (75 g). The product was extracted with ether (3 × 300 ml). The combined organic extract was washed with water (2 × 100 ml), dried, and evaporated, when a crystalline mass was left. The keto-acid (3) (3.8 g, 63%) on two crystallisations from benzene melted at 137° (lit.,[4] 135—137°), and gave an n.m.r. spectrum with features as reported.[4]

Esterification of the foregoing acid (3a) (2.5 g) by boiling with dry methanol (10 ml) and concentrated sulphuric acid (0.5 ml) for 3.5 h followed by the usual work-up gave the *methyl ester* (3b) (2.25 g), m.p. 64—65° (benzene–hexane); $\nu_{max.}$ (Nujol) 1 730 (ester C=O) and 1 665 cm^{-1} (ketone C=O); $\delta(CCl_4)$ 2.33 (3 H, s, ArMe), 2.57 (3 H, s, ArMe *peri* to C=O), 2.91 (5 H, m, $2CH_2$ and $\geqslant$CH), 3.7 (3 H, s, CO_2Me), 6.91 (1 H, d, *J* 8 Hz, ArH), and 7.13 (1 H, d, *J* 8 Hz, ArH) (Found: C, 72.75; H, 7.0. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.7%).

3-Methoxycarbonyl-5,8-dimethyl-1,2-naphthoquinone (4).—A mixture of the keto ester (3b), (0.5 g) and selenium dioxide (1.5 g) in dry ethanol (4.5 ml) was refluxed for 5 h. The orange solution was filtered off and the filtrate was diluted with ether (50 ml). The ethereal solution was washed with aqueous NaOH (5%, 25 ml) and then with water. Evaporation of the solvent and filtration of the residual red solid through a column (SiO_2–$CHCl_3$) followed by crystallisation from benzene–hexane gave the quinone

ester (4) as orange needles (245 mg), m.p. 150—152° (turns black at 110°); $\nu_{max.}$ (Nujol) 1 710 and 1 680 cm^{-1} (ester and quinone C=O); $\delta(CDCl_3)$ 2.6 (3 H, s, ArMe), 2.7 (3 H, s, ArMe *peri* to C=O), 3.95 (3 H, s, CO_2Me), 7.4 (2 H, d, *J* 7 Hz ArH), 9.1 (1 H, s, CH=C–C=O) (Found: C, 69.4; H, 5.5. $C_{14}H_{12}O_4$ requires C, 68.85; H, 4.95%).

1,2-*Diacetoxy*-3-*methoxycarbonyl*-5,8-*dimethylnaphthalene* (5).—A mixture of the quinone ester (4) (200 mg) zinc dust (1.7 g), and acetic anhydride (60 ml) was refluxed for 4.5 h. The zinc dust was filtered and the acetic anhydride was distilled off under reduced pressure to give the diacetate (5) as a yellow crystalline *solid*, m.p. 180—182.5° (benzene–hexane); $\lambda_{max.}$ (EtOH) 220 (log ε 4.83), 250 (5.08), 285 (4.10), 295 (4.16), and 305 nm (4.07); $\nu_{max.}$ (KBr) 1 787 (OAc) and 1 730 cm^{-1} (CO_2Me); $\delta(CDCl_3)$ 2.38, 2.40 (6 H, 2s, ArMe or $OCOCH_3$), 2.70, 2.72 (6 H, 2s, $OCOCH_3$ or $ArCH_3$), 3.94 (3 H, s, CO_2*Me*), 7.25 (2 H, s, 6- and 7-H), and 8.68 (1 H, s, 4-H) (Found: C, 65.45; H, 5.8. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.4%).

3-(2-*Hydroxyisopropyl*)-5,8-*dimethyl*-1,2-*naphthoquinone* (*Emmotin-H*) (1).—To a suspension of Grignard reagent prepared from methyl iodide (5.5 ml) and magnesium (1.5 g) in dry ether (75 ml) was added dropwise with stirring a solution of the ester (5) (100 mg) in dry ether (50 ml). The mixture was refluxed for 2 h, left overnight, and decomposed with cold saturated NH_4Cl solution (50 ml). The ether layer was separated and the aqueous layer was extracted with ether (50 ml). Removal of the solvent from the combined organic phase gave emmotin-H (1) (55 mg) as red crystals (hexane–ether), m.p. 177—179° (lit.,[2] 178—180°); $\lambda_{max.}$ (EtOH) 225 (log ε 4.23), 255 (4.32) and 400 nm (3.14); $\nu_{max.}$ (KBr) 3 480 (OH), 1 688, 1 656 (quinone C=O), and 1 624 cm^{-1} (aromatic); $\delta(CDCl_3)$ 1.6 (6 H, s, CMe_2), 2.55 (3 H, s, ArMe), 2.70 (3 H, s, ArMe *peri* to C=O), 7.23 (1 H, d, *J* 7 Hz, ArH), 7.47 (1 H, d, *J* 7 Hz, ArH), and 8.0 (1 H, s, 4-H) (Found: C, 73.45; H, 7.0. Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.6%). The quinoxaline derivative when prepared from (1) in the usual way with *o*-phenylenediamine was obtained as a yellow crystalline solid, m.p. 189—190° (hexane) (lit.,[2] 190—192°).

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