The chemistry of naphthazarin derivatives

4.* A simple preparative synthesis of mompain

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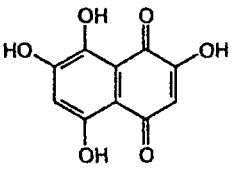
Direct oxidation of naphthazarin with manganese dioxide in conc. H_2SO_4 was found to be a simple and effective method for the synthesis of mompain.

Key words: naphthazarin, 5,8-dihydroxy-1,4-naphthoquinone, mompain, 2,5,7,8-tetrahydroxy-1,4-naphthoquinone, 2,5,6,8-tetrahydroxy-1,4-naphthoquinone, manganese dioxide, oxidation.

Mompain, 2,5,7,8-tetrahydroxy-1,4-naphthoquinone (**1**), is a naturally occurring pigment, which has been isolated for the first time from the microorganism *Helicobasidium mompa*[2] and later from sea urchins of the *Echinothrix* and *Strongylocentrotus* genera.[3] Mompain is a structural fragment of many biologically active compounds occurring in nature,[4] and the number of isolated compounds of this type increases from year to year.[5] For this reason mompain can serve as a convenient intermediate in the synthesis of naturally occurring products.[6] In addition, mompain is known to be used as a dye for keratin fibers.[7] At the same time, published information on simple and convenient methods for the synthesis of this compound is lacking.[8]



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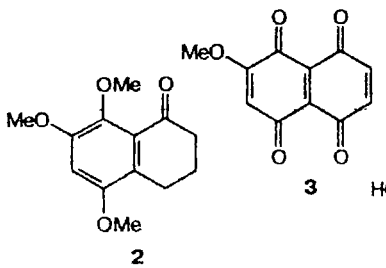
Earlier,[9] mompain was obtained by the method where the key step, *viz.*, oxidation of α-tetralone **2** with atmospheric oxygen in strongly alkaline medium, proceeds only in 16% yield. Recently, the efficiency of this conversion has been increased to 59% by French scientists.[10] However, it should be noted that α-tetralone **2** itself is not easily available because it is synthesized in six steps from substituted γ-phenylpropionic acid.[9]



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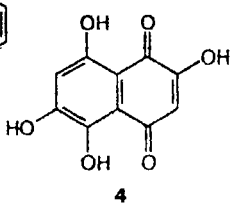

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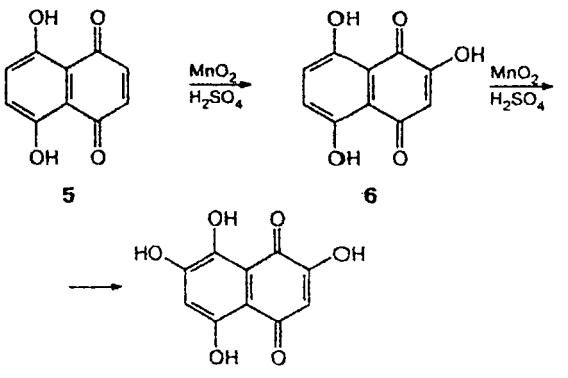
Another route to compound **1** is the modified Thiele reaction, *viz.*, addition of acetic anhydride to biquinone **3**, which finally yields a mixture of mompain (51%) and its isomer, 2,6-dihydroxynaphthazarin (**4**, 10%).[11] Later,[12] product **1** was also synthesized by 1,4-addition of water to biquinone **3**. The latter, in turn, can be obtained in several steps from available compounds.[11]

While synthesizing islandoquinone, a naturally occurring compound,[13] we developed a simple preparative method for the synthesis of mompain from commercially available naphthazarin (**5**). It was found that direct oxidation of substrate **5** with manganese(IV) dioxide in conc. H_2SO_4 proceeds regioselectively to give compound **1** in 50% yield (Scheme 1), 2,6-dihydroxynaphthazarin being formed only in trace amounts (2%). Note that the MnO_2—H_2SO_4(conc.) system had been used earlier[14] for conversion of naphthazarin to naphthopurpurin (**6**), but the use of this reagent for further oxidation of substrate **5** had not been reported. Oxidation of naphthazarin proceeds through intermedi-

Scheme 1



5 **6** **1**

* For Part 3, see Ref. 1.

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ate hydroxynaphthazarin **6** to give product **1** in satisfactory yields only in quite a narrow temperature range, which requires thorough control of the reaction temperature.

Unlike the MnO_2—H_2SO_4(conc.) system, oxidation of naphthazarin with sulfuric acid at elevated temperatures is not regioselective. Under these conditions, a mixture of mompain (24%) and 2,6-dihydroxynaphthazarin (34%) is formed. In the presence of boric acid, the reaction time is significantly reduced, and the yield of compound **1** (32%) somewhat increases with respect to its isomer **4** (25%). Despite the fact that oxidation of naphthazarin with conc. H_2SO_4 at elevated temperatures is not very selective, this method is simple enough to be a good alternative to current methods for the preparation of 2,6-dihydroxynaphthazarin, which can be a useful intermediate in the synthesis of naturally occurring compounds containing such structural fragments.[4]

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in acetone-d_6 with Me_4Si as the internal standard. The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC (Merck Kieselgel 60F-254 plates were preliminarily treated with 0.05 *M* tartaric acid in MeOH and dried at ~50 °C for 2—3 h; a 1 : 1 hexane—acetone mixture was used as the eluent).

2,5,7,8-Tetrahydroxy-1,4-naphthoquinone (mompain, 1). Commercial powdered MnO_2 (~5 g, 55 mmol) was added portionwise at 50—55 °C for 2 h to a vigorously stirred solution of naphthazarine (**5**) (1.05 g, 5.5 mmol) in 40 mL of conc. H_2SO_4. The course of the reaction was monitored by TLC. The reaction being completed, the reaction mixture was poured into 100 mL of a saturated solution of NaCl. The reaction products were extracted with AcOEt (300 mL), and the extract was washed with a saturated solution of NaCl (30 mL), dried with anhydrous Na_2SO_4, and concentrated. The residue was chromatographed on a column with silica gel (the H^+ form).* A gradient benzene—acetone mixture (10 : 1 → 2 : 1, 800 mL) was used for elution of products. 2,5,6,8-Tetrahydroxy-1,4-naphthoquinone (**4**), R_f 0.51, yield 25 mg (2%), m.p. 283—286 °C (sublim.) (Ref. 15: m.p. 270—285 °C (sublim.)). ^1H NMR, δ: 6.45 (s, 2 H, H(3), H(7)); 9.98 (br.s, 2 H, 2×β-OH); 12.84 (br.s, 2 H, 2×α-OH). Mompain (**1**) (main product), R_f 0.47, yield 620 mg (50.6%), m.p. 268—272 °C (sublim.) (Ref. 15: m.p. 265—275 °C (sublim.)). ^1H NMR, δ: 6.46 (s, 2 H, H(3), H(6)); 9.94 (br.s, 2 H, 2×β-OH); 12.07 (br.s, 1 H, α-OH); 13.14 (s, 1 H, α-OH).

Oxidation of naphthazarine (5) with conc. H_2SO_4. A solution of naphthazarin (1.05 g, 5.5 mmol) in 40 mL of conc. H_2SO_4 was stirred at 220 °C for 4 h. The reaction mixture was cooled, poured into 100 mL of a saturated solution of NaCl, and treated as described above to give 2,6-dihydroxynaphthazarin (**4**) (418 mg, 34%) and mompain (**1**) (295 mg, 24%).

Oxidation of naphthazarin (5) with the H_2SO_4(conc.)—H_3BO_3 system. A solution of naphthazarin (1.05 g, 5.5 mmol) and H_3BO_3 (0.4 g, 6.45 mmol) in 40 mL of conc. H_2SO_4 was stirred at 220 °C for 1 h. After cooling, the reaction mixture was treated as described above to give 2,6-dihydroxynaphthazarin (**4**) (308 mg, 25%) and mompain (**1**) (394 mg, 32%).

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* The H^+ form was prepared by addition of 1 to 2 mL of conc. HCl to silica gel (500 mL). The resulting suspension was shaken for 10—15 min and left overnight. If silica gel was used for chromatography, it was regenerated with HNO_3—HCl mixture (1 : 3) and washed with water until pH 3 of the moist adsorbent applied to indicator paper.

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