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REACTION OF 6-HYDROXY-2,3-DICHLORO-7-ETHYLNAPHTHAZARIN WITH KF—MeOH—Al_2O_3. SYNTHESIS OF CRISTAZARIN, A METABOLITE OF THE LICHEN *Cladonia cristatella*

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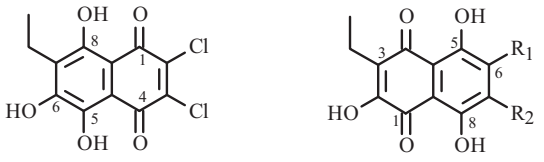
The reaction of 2-hydroxy-6-methoxy-7-chloro-3-ethylnaphthazarin with methanol activated by fluoride anion on the surface of Al_2O_3 at 120°C gave echinochrome dimethyl ether, a metabolite of the sea urchin Scaphechinus mirabilis. *Its isomer 2-hydroxy-7-methoxy-6-chloro-3-ethylnaphthazarin was converted under the same conditions into cristazarin, a metabolite of the lichen* Cladonia cristatella.

Keywords: 2,5,8-trihydroxy-6,7-dimethoxy-3-ethyl-1,4-naphthoquinone, echinchrome dimethyl ether, 2,5,8-trihydroxy-7-methoxy-3-ethyl-1,4-naphthoquinone, cristazarin, sea urchin *Scaphechinus mirabilis*, lichen *Cladonia cristatella.*

The system KF–MeOH–Al_2O_3 is a highly efficient reagent for nucleophilic substitution of Cl by methoxy in chlorinated naphthazarins (5,8-dihydroxy-1,4-naphthoquinones) [1] and anthraquinones [2]. This reaction is a key step in the synthesis of several natural polyhydroxylated naphthazarins, which exhibit biological activity [3, 4] or act as drug substances [5, 6].

We investigated the possibility of using this reagent for conversion of hydroxydichloronaphthazarin (**1**) into echinochrome dimethyl ether (**2**). The C-6 hydroxyl in **1** is in basic medium a powerful inhibitor of nucleophilic substitution. Only a mixture of monosubstitution products **3** and **4** was formed under the conditions described earlier for this reaction (90–95°C) [1]. Therefore, the **1**→**2** conversion required a significant increase of the temperature.



1 **2 - 6**

2: $R_1 = R_2 = OCH_3$
3: $R_1 = OCH_3$, R_2 = Cl; **4:** R_1 = Cl, $R_2 = OCH_3$
5: R_1 = H, $R_2 = OCH_3$; **6:** $R_1 = OCH_3$, R_2 = H

1 → **2** + **3** + **5** + **6**
3 → **2** + **6**
4 → **5** + **2**

It was found that intermediates **3** and **4** were completely converted at 120°C. Substitution products **2** (9%) and **3** (42%) and unexpected products of reductive dehalogenation **5** (39%) and **6** (2%) were isolated from the reaction mixture. Naphthazarin (**4**), an isomer of **3**, was found only in trace quantities in the reaction mixture.

A study of the nucleophilic substitution of the Cl atoms by methoxyls in **3** and **4** using KF–MeOH–Al_2O_3 at 120°C found that the chemical properties of these methoxychloronaphthazarins differed greatly. Thus, **3** gave product **2** (echinochrome dimethyl ether, a metabolite of the sea urchin *Scaphechinus mirabilis* [7]) in high yield (75%) and product **6** (16%). Its isomer **4** under the same conditions gave the reductive dehalogenation product **5** in high yield (69%). The yield of **2** was only 5%.

The formation of methyl ethers **5** and **6** under these reaction conditions was possibly due to the involvement of redox-active metal cations (e.g., Fe^{2+}) that could occupy the surface of the Al_2O_3. However, simple addition of anhydrous $FeSO_4$ did not noticeably increase the yield of **5**. It is possible that dopants within the Cr–Ni alloy of which the autoclave was constructed were involved in the reduction. It is surprising that isomers **3** and **4** have such similar structures and behave differently under

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the reaction conditions. Additional studies are required in order to explain the reasons and mechanism for such different behavior of these substrates in the Cl nucleophilic substitution reaction using KF–MeOH–Al_2O_3 and the reductive dehalogenation of **4**, which occurred simultaneously under the same conditions.

Compound **5** turned out to be completely identical to cristazarin, a naphthazarin that was isolated comparatively recently from culture of the lichen *Cladonia cristatella* [8] and was synthesized earlier [9]. However, the observed conversion **1**→**5** is the simplest route to this rare product.

EXPERIMENTAL

Melting points were determined on a Boetius heating stage and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Bruker Vector 22 spectrophotometer. NMR spectra were recorded in $CDCl_3$ with Me_4Si internal standard on Bruker Avance DPX-300 (300.13 MHz for ^1H and 75 MHz for ^{13}C) and Bruker Avance DPX-500 (500.13 and 125 MHz, respectively) spectrometers. Mass spectra (EI) were taken in an LKB-9000S instrument with direct sample introduction with ionizing-electron energy 18 eV. The course of reactions and purity of products were monitored by TLC on 60F-254 plates (Merck) impregnated with alcoholic tartaric acid (0.05 M) [10] using hexane:acetone (2:1). Yields of products were not optimized. Starting materials **1** [4], **3** [11], and **4** [9] were synthesized by the literature methods.

Reaction of Chloronaphthazarins 1, 3, and 4 with KF–MeOH–Al_2O_3. A mixture of well dried substrate (1 mmol), anhydrous KF (6 mmol), neutral anhydrous Al_2O_3 (1.2 g), and anhydrous MeOH (24 mL)* was stirred in an autoclave at 120 ± 5°C for 12 h, cooled, filtered, washed with a small quantity of acetone, and acidified with HCl (10%, 3 × 1 mL). The combined filtrate was concentrated at reduced pressure, diluted with H_2O (10 mL), and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The dry solid was chromatographed over a column of silica gel (L40/100 μ) with elution by hexane:acetone.

The following compounds were isolated from the reaction mixture obtained from 2-hydroxy-6,7-dichloro-3-ethylnaphthazarin (**1**) and KF–MeOH–Al_2O_3.

2,5,8-Trihydroxy-6-methoxy-7-chloro-3-ethyl-1,4-naphthoquinone (3), 125 mg (42%), mp 132–137°C (lit. [9] 137–139°C). PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.17 (3H, t, J = 7.5, CH_3), 2.68 (2H, q, J = 7.5, CH_2), 4.20 (3H, s, OCH_3), 7.37 (1H, br.s, *β*-OH), 12.23 (1H, s, *α*-OH), 13.48 (1H, s, *α*-OH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 12.5 (C-10), 16.3 (C-9), 61.8 (C-11), 106.3 (C-4a), 109.5 (C-8a), 122.7 (C-7), 126.8 (C-3), 153.6 (C-2), 154.5 (C-8), 155.8 (C-6), 157.5 (C-5), 178.3 (C-1), 186.4 (C-4).

2,5,8-Trihydroxy-7-methoxy-3-ethyl-1,4-naphthoquinone (cristazarin) (5), 103 mg (39%), mp 228–230°C (lit. [8] 154–157°C; [9] 230–232°C). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.16 (3H, t, J = 7.6, CH_3), 2.64 (2H, q, J = 7.6, CH_2), 3.96 (3H, s, OCH_3), 6.57 (1H, s, H-6), 7.13 (1H, br.s, *β*-OH), 12.04 (1H, s, *α*-OH), 13.34 (1H, s, *α*-OH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 12.6 (C-10), 16.4 (C-9), 56.6 (C-11), 104.1 (C-4a), 108.4 (C-6), 110.2 (C-8a), 128.0 (C-3), 152.6 (C-2), 154.1 (C-7), 156.6 (C-8), 163.0 (C-5), 178.4 (C-1), 183.3 (C-4). Mass spectrum (EI, 18 eV, *m*/*z*, I_{rel}, %): 266 (9) $[M + 2]^+$, 265 (83) $[M + 1]^+$, 264 (100) $[M]^+$, 249 (20), 235 (18), 221 (11).

2,5,8-Trihydroxy-6,7-dimethoxy-3-ethyl-1,4-naphthoquinone (2), 27 mg (9%), mp 152–154°C (lit. [7] 153–154°C). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.15 (3H, t, J = 7.5, CH_3), 2.63 (2H, q, J = 7.5, CH_2), 4.05 (3H, s, OCH_3), 4.15 (3H, s, OCH_3), 7.25 (1H, s, *β*-OH), 12.15 (1H, s, *α*-OH), 13.49 (1H, s, *α*-OH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): 12.6 (C-10), 16.3 (C-9), 61.59 (C-11), 61.63 (C-12), 106.5 (C-4a), 106.6 (C-8a), 126.6 (C-2), 146.1 (C-6), 150.2 (C-7), 153.3 (C-3), 158.8 (C-8), 159.5 (C-5), 175.2 (C-4), 183.2 (C-1). Mass spectrum (EI, 18 eV, *m*/*z*, I_{rel}, %): 296 (7) $[M + 2]^+$, 295 (25) $[M + 1]^+$, 294 (100) $[M]^+$, 279 (35), 251 (16), 233 (14).

2,5,8-Trihydroxy-6-methoxy-3-ethyl-1,4-naphthoquinone (6), 4 mg (2%), mp 196–199°C (lit. [9] 198–201°C). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.15 (3H, t, J = 7.6, CH_3), 2.62 (2H, q, J = 7.6, CH_2), 3.99 (3H, s, OCH_3), 6.50 (1H, s, H-7), 7.46 (1H, br.s, *β*-OH), 12.09 (1H, s, *α*-OH), 13.60 (1H, s, *α*-OH). Mass spectrum (EI, 18 eV, *m*/*z*, I_{rel}, %): 265 (17) $[M + 1]^+$, 264 (100) $[M]^+$, 250 (9), 249 (22).

The following compounds were isolated from the reaction mixture obtained from 2-hydroxy-6-methoxy-7-chloro-3-ethylnaphthazarin (**3**) and KF–MeOH–Al_2O_3.

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* Anhydrous starting reagents were prepared as before [1].

2,5,8-Trihydroxy-6,7-dimethoxy-3-ethyl-1,4-naphthoquinone (2), 225 mg (75%); **2,5,8-trihydroxy-6-methoxy-3-ethyl-1,4-naphthoquinone (6)**, 32 mg (16%).

The following compounds were isolated from the reaction mixture obtained from 2-hydroxy-7-methoxy-6-chloro-3-ethylnaphthazarin (**4**) and KF–MeOH–Al_2O_3.

2,5,8-Trihydroxy-7-methoxy-3-ethyl-1,4-naphthoquinone (cristazarin) (5), 186 mg (69%); **2,5,8-trihydroxy-6,7-dimethoxy-3-ethyl-1,4-naphthoquinone (2)**, 15 mg (5%).

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