A Convenient Synthesis of Naphthazarin and Naphthopurpurin

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(Z. Naturforsch. 33b, 1473-1475 [1977]; eingegangen am 10. August 1977)

Naphthazarin, Naphthopurpurin

A high yielding synthesis of naphthazarin or naphthopurpurin can be achieved by SnCl₂ reduction of 2,3-dichloronaphthazarin followed by oxidation in the absence or presence of KO₂. The spectral properties of these compounds are discussed.

The naphthazarin moiety (1) is an integral feature of a number of pharmacologically active compounds, e.g. shikonin¹, and arnebin² as well as being a portion of the tetracyclic antitumor antibiotics granaticin (1) (litomycin)², funiculosin⁴, daunomycin⁵, adriamycin⁶, nogalomycin⁷, the nanaomycins⁸, actinorhodin⁹, kalafungin¹⁰, the granaticins¹² and of bikaverin¹³. We wish to report a convenient and efficient synthesis of naphthazarin (1) and its hydroxy analogue naphthopurpurin (2) utilising 2,3-dichloronaphthazarin (3) as starting material.

Condensation of 1,4-dimethoxybenzene with dichloromaleic anhydride has been described by HUOT and BRASSARD¹⁴ to give up to 97% of 2,3-dichloronaphthazarin (3), we find reduction of this quinone with SnCl₂ gives dihydronaphthazarin (4) in 73% yield which upon brief treatment with alkali gave naphthazarin (1) in 93% yield. The overall yield from the dichloroquinone (3) being 68%.

Treatment of naphthazarin (1) with KO₂ in dry DMSO gave a rapid and quantitative conversion to naphthopurpurin (2). Alternatively 2 can be produced directly from 4 by treatment with KO₂, giving an overall yield of 67%. The addition of a crown ether assists in the solubilising of KO₂ for these oxidations¹⁵.

The structures assigned to all the compounds described in this paper have been based on an analysis of their respective NMR and mass spectral data.

In the case of naphthazarin considerable controversy exists as to the location of the hydrogen bonded phenolic groups¹⁶. X-ray studies have suggested a 1,5-quinonoid structure (5) but the IR data have been interpreted against this formulation¹⁷. Our examination of the proton chemical shift values for naphthazarin shows no temperature dependence (to —40 °C) which indicates the symmetrical nature of the molecule. This can best be represented by 6 which possesses an unusually long hydrogen bond (as has been reported by Musso and Seeber¹⁹).

2,3-Dichloronaphthazarin (3) shows a chemical shift value for its ring protons as a singlet at δ 7.27 indicating that the two chlorine substituents are localised on the quinoid ring. This is confirmed by the production of ion 7 at m/e 223 through loss of chlorine from the parent ion, subsequent loss of CO gives 8 at m/e 195. Similar breakdowns of 2-substituted naphthoquinones have been reported²¹.

### Table. ¹H NMR and IR data.

<table>
<thead>
<tr>
<th>Compound</th>
<th>¹H NMR data (CDCl₃)</th>
<th>IR data (Nujol)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OH</td>
<td>H-2</td>
</tr>
<tr>
<td>3</td>
<td>12.28</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11.30</td>
<td>3.05</td>
</tr>
<tr>
<td>1</td>
<td>12.33</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12.81, 7.45d</td>
<td>7.30d</td>
</tr>
<tr>
<td></td>
<td>11.55</td>
<td></td>
</tr>
</tbody>
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Dihydronaphthazarin (4) also shows a benzenoid proton chemical shift at δ 7.25 together with the dihydroquinone protons resonating as a singlet at δ 3.5. The mass spectrum shows loss of water, CO and HCO giving ions at m/e 174, 137, 136 followed by loss of ethene as indicated by the scheme.

Naphthopurpurin (2) shows two benzenoid protons as doublets centred at δ 7.45 and 7.30 J = 10 Hz thus indicating the disymmetry introduced into the molecule by the ‘extra’ hydroxy group and confirming that the β-hydroxy group is located on the quinonoid ring, the quinonoid hydrogen H-4 resonates at δ 6.47 and the non-bonded hydroxy group at H-3 is not seen. The mass spectrum indicated loss of CO to give ion 9 at m/e 178 followed by loss of either CO or CH₂CO to give 10 and 11 respectively, with subsequent loss of CO to give m/e 108 (12).

Experimental Section

2,3-Dichloronaphthazarin (3)

This compound was prepared in 97% yield from dichloromaleic anhydride and 1,4-dimethoxybenzene according to the method described by HVOR and BRASSARD14, crystallisation from petrol-ether (b.p. 80–100 °C) gave the quinone m.p. 198–199 °C. m/e 260(50%), 258(100), 225(11), 223(50), 197(2), 195(7), 185(2).

2,3-Dihydronaphthazarin (4)

A mixture of 0.6 g of 2,3-dichloronaphthazarin 3.6 g, SnCl₂, and 150 ml of 4 M HCl was refluxed for 0.5 h. The green solution was filtered directly, cooled and extracted with CHC₃, the extract being washed with water, dried (MgSO₄), and evaporated to give a green solid (637 mg) which crystallised from ethanol giving 324 mg (73%) of (4) as light green prisms, m.p. 148–151 °C, m/e 193(5%), 192(100), 174(6), 164(4), 163(8), 137(7), 136(12), 121(3), 108(25).

Naphthazarin (1)

0.2 g of dihydronaphthazarin (4) in 100 ml of 5 M NaOH was heated for about 15 min until a deep blue colour formed whence acidification with dil. HCl, extraction with CHC₃ (2 × 50 ml) and isolation of the product in the usual way gave crude naphthazarin (1); 196 mg, purification of this crude product was best achieved by direct elution from a silica gel column using CHC₃ giving 184 mg of naphthazarin (93%), m.p. 230–240 °C (sublim.)32, m/e 191(5), 190(100), 189(18), 152(8), 151(8), 136(2), 134(6), 108(11).

Naphthopurpurin (2)

A mixture of 0.2 g of naphthazarin (1), 225 mg of KO₂ and 10 mg of 18 crown —Δ₅ in 10 ml of DMSO was left at r.t. for 16 h, on pouring this mixture into dil. HCl followed by extraction with ethyl acetate (2 × 50 ml) and isolation of the product in the usual way, 198 mg of crude naphthopurpurin was obtained. Crystallisation from benzene gave violet platelets of 4 (91% yield), m.p. 200–210 °C (sublimation)34, m/e 207(5), 206(100), 178(9), 150(4), 137(3), 136(25), 108(5).

Oxidation of dihydronaphthazarin (4) directly to naphthopurpurin was achieved by reacting 200 mg of 4 in 10 ml of DMSO with 225 mg of KO₂ and 10 mg of 18 crown-6 for 16 h at r.t., isolation of the product in the usual way gave 198 mg of crude naphthopurpurin, recrystallising from benzene to give m.p. 200–210 °C (sublimation) (92% yield).

We thank the Science Research Council for a grant (J. P.).

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