Synthesis of 5-Amino-8-hydroxy-1,4-naphthoquinone and Derivatives[1]

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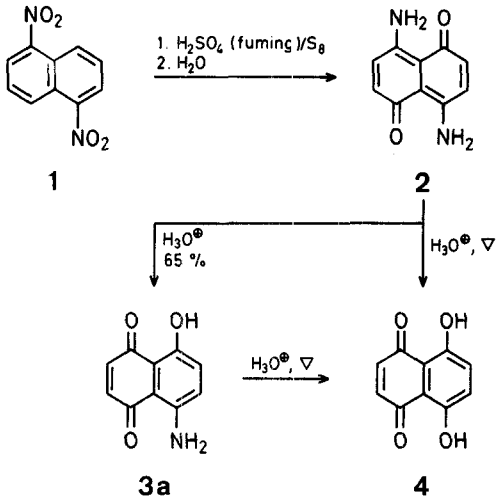
The intermediate **3a** formed during the preparation of naphthazarin **(4)** from 1,5-dinitronaphthalene **(1)** has been isolated and converted to several *O*- and *N*-alkylated (-acylated) derivatives **3b–j**.

Naphthazarin (5,8-dihydroxy-1,4-naphthoquinone; **4**) has proved to be a convenient starting material for the construction of the tetracyclic anthracyclinone[2–5] system, the aglycones of the effective antitumor anthracyclines. Recently, starting from monoacylated derivatives of naphthazarin, cycloaddition reactions were developed which allowed the regiospecific synthesis of (±)-daunomycinone[6].

5-Amino-8-hydroxy-1,4-naphthoquinone **(3a)** and its *N*- and/or *O*-substituted derivatives **3b–j** are similar synthons of potential interest for related synthesis. In fact, the presence of the -NHR instead of the -OH group would facilitate regioselective cycloaddition reactions with unsymmetrically substituted dienes and thus enable subsequent access to other anthracyclinone derivatives of current interest. To our knowledge, however, the preparation of **3a** has not been published, although recently it has been described as a minor component from the reaction of the diaminoquinone **2** with methylamine in the presence of sodium acetate[7].

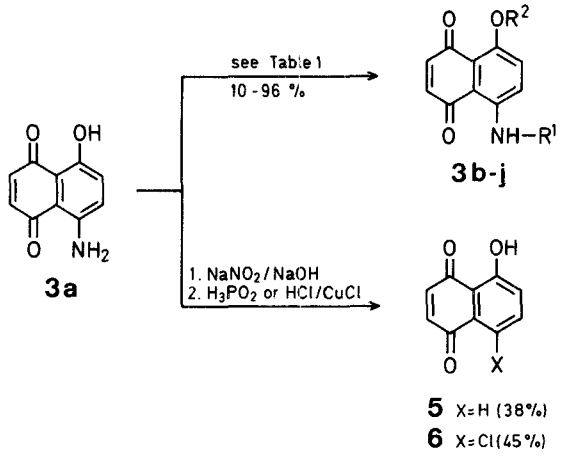
We report here that suitable modifications in the experimental conditions used for the synthesis of naphthazarin **(4)** from 1,5-dinitronaphthalene **(1)** allow the preparation of **3a**, which is obtained as the major component of the reaction. The synthesis of **4** was first achieved[8] by treatment of 1,5-dinitronaphthalene **(1)** with fuming sulphuric acid in the presence of sulphur as a reducing agent. The procedure was later modified[9–11] and has been used on a commercial scale. Although the mechanism of the reaction was not ascertained, formation of **4** was explained[12] by hydrolysis of the isolable violet intermediate **2**, a stable derivative of the unknown 1,5-naphthoquinone. We have now found that, by conducting this hydrolysis step under mild conditions, only partial hydrolysis takes place and, by extraction with chloroform, 5-amino-8-hydroxy-1,4-naphthoquinone **(3a)** is obtained as the main product in 65% yield.



Although the aminohydroxyquinone could exist in different tautomeric forms, **3a** has been considered to be the predominant tautomer on the basis of the ^{1}H-N.M.R. and U.V.-Vis spectral data. We have found no evidence for the presence of 1,5-naphthoquinone tautomers, as reported for the diaminoquinone **2**[13]. The isolation of **3a**, which, in turn, can be hydrolyzed to naphthazarin **(4)**, suggests that the former may also be considered as an intermediate in the first reported[8] synthesis.

We have also studied the conversion of **3a** into its *N*- and/or *O*-substituted derivatives **3b–j**, which could be of interest for regioselective cycloaddition reactions. Mono- and diacylation of **3a** were readily achieved in moderate to good yields by suitable selection of the experimental conditions. Direct methylation of **3a** proved to be more difficult and the yields of pure mono- and dimethylated derivatives **3e, 3f,** and **3g** were low. In contrast, *O*-methylation of the *N*-acylated derivatives **3b** and **3d** afforded **3h** and **3i** in excellent yields (Tables 1 and 2).

Access to derivatives **5** and **6** from **3a** was achieved by diazotization. The diazonium salt was prepared by first dissolving **3a** in alkaline solution, followed by treatment with sodium nitrite and acidification of the ice-cooled mixture. Removal of the amino group by heating of the diazonium salt with hypophosphorous acid led to a new synthesis of juglone **(5)**. Furthermore, 5-chloro-8-hydroxy-1,4-naphthoquinone **(6)** was obtained by the Sandmeyer reaction in the presence of copper(I) chloride.



Quinone **3a** and derivatives **3b–j, 5,** and **6** are potentially useful dienophiles for Diels-Alder reactions. Further studies on the regioselectivity of these cycloadditions are currently in progress and will be reported in due course.

Table 1. *N*- and/or *O*-Alkylated (-Acylated) Derivatives **3b–j** prepared

Substrate	Reagents	Reaction Conditions Solvent/Temperature/Time	Product	R^1	R^2	Yield [%][a]	m.p. [°C] (Solvent)	Molecular Formula[b] or Lit. m.p. [°C]
3a	Ac_2O/NaOAc	Ac_2O/r.t./48 h	**3b**	CO—CH_3	H	80	186° (CH_3OH)	$C_{12}H_9NO_4$ (231.2)
3a	Ac_2O/NaOAc	Ac_2O/reflux/1 h	**3c**	CO—CH_3	CO—CH_3	75	174–175° (C_2H_5OAc/*c*-C_6H_{12})	$C_{14}H_{11}NO_5$ (273.2)
3a	C_6H_5COCl	dioxane/reflux/1 h	**3d**	CO—C_6H_5	H	95	197–199° (C_2H_5OH)	$C_{17}H_{11}NO_4$ (293.4)
3a	JCH_3/NaOCH$_3$	methanol/reflux/6 h	**3e**	CH_3	H	18	161° (PE)	160°[7]
3a	JCH_3/Ag_2O	$CHCl_3$/40 °C/20 h[c]	**3c**	CH_3	H	25	–	–
			3f	H	CH_3	10	195–197° (PE)	196–198°[7]
3a	JCH_3/Ag_2O	$CHCl_3$/40 °C/40 h[d]	**3g**	CH_3	CH_3	35	160–162° (PE)	160–162°[7]
3b	JCH_3/Ag_2O	$CHCl_3$/40 °C/12 h	**3h**	CO—CH_3	CH_3	96	188° (C_2H_5OH)	$C_{13}H_{11}NO_4$ (245.2)
3d	JCH_3/Ag_2O	$CHCl_3$/40 °C/48 h	**3i**	CO—C_6H_5	CH_3	96	185–187° (C_2H_5OH)	$C_{18}H_{13}NO_4$ (307.3)
3d	Ac_2O/NaOAc	Ac_2O/reflux/1 h	**3j**	CO—C_6H_5	CO—CH_3	66	176–179° [$(H_3C)_2CO$/C_6H_{14}]	$C_{19}H_{13}NO_5$ (335.3)

[a] Yield of pure isolated product.
[b] Satisfactory microanalysis obtained: C ±0.29, H ±0.16, N ±0.27.
[c] Isolated by column chromatography on silica gel (chloroform).
[d] Further additions of reagents were made until the monomethylated derivatives **3e** and **3f** disappear. The product was isolated by column chromatography on silica gel (chloroform/ethyl acetate, 4:1).

Table 2. Spectroscopic Data of *N*- and/or *O*-Substituted Derivatives **3b–3j**

Product	I.R. (Nujol) ν [cm^{-1}]	U.V.-Vis (Ethanol) λ_{max} [nm] (log ε)	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	M.S. *m/e* (M^+)
3b	1690 (CONH); 1620 (CO); 1580 (CO)	217 (4.51); 283 (4.05); 496 (3.70)	2.29 (s, 3H, CH_3); 6.94 (s, 2H, $=CH_{quinone}$); 7.31 (d, J = 9 Hz, 1 H_{arom}); 9.07 (d, J = 9 Hz, 1 H_{arom}); 11.99 (br, 1H, NH); 12.75 (s, 1H, OH)	231
3c	1760 ($OCOCH_3$); 1683 (CONH); 1641 (CO); 1600 (CO)	219 (4.20); 262 (4.23); 236sh (2.88); 425 (3.58)	2.29 (s, 3H, N—CO—CH_3); 2.42 (s, 3H, O—CO—CH_3); 6.79, 6.89 (AB system, J = 10.4 Hz, 2H, $=CH_{quinone}$); 7.37 (d, J = 9 Hz, 1 H_{arom}); 9.13 (d, J = 9 Hz, 1 H_{arom}); 12.04 (br, 1H, NH)	273
3d	1675 (CONH); 1620 (CO); 1590 (CO)	221 (4.32); 296 (4.14); 515 (3.68)	6.98 (s, 2H, $=CH_{quinone}$); 7.36 (d, J = 9 Hz, 1 H_{arom}); 7.48–7.65 (m, 3 H_{arom}); 8.0–8.3 (m, 2 H_{arom}); 9.30 (d, J = 9 Hz, 1 H_{arom}); 12.78 (s, 1H, OH); 12.97 (br, 1H, NH)	293
3e	1610 (CO); 1590 (CO)	226 (3.99); 304 (3.64); 560 (3.49); 596 (3.73); 646 (3.68)	3.06 (d, 3H, J = 5.3 Hz, N—CH_3); 6.88 (s, 2H, $=CH_{quinone}$); 7.0 (s, 2 H_{arom}); 10.09 (br, 1H, NH); 13.41 (s, 1H, OH)	203
3f	3390 (NH); 3280 (NH); 1620 (CO)	218 (4.15); 285 (3.78); 566 (3.64)	3.90 (s, 3H, OCH_3); 6.74 (s, 2H, $=CH_{quinone}$); 6.94, 7.19 (AB system, J = 9.0 Hz; 2 H_{arom}); 7.20 (br, 2H, NH_2)	203
3g	1665 (CO); 1635 (CO); 1615 (CO)	222 (4.30); 284 (3.84); 594 (3.66)	3.03 (d, 3H, J = 4.5 Hz, N—CH_3); 3.98 (s, 3H, OCH_3); 6.76, 6.82 (AB system, J = 10.5 Hz, 2H, $=CH_{quinone}$); 7.15, 7.39 (AB system, J = 9 Hz, 2 H_{arom}); 9.68 (br, 1H, NH)	217
3h	1692 (CONH); 1660 (CO); 1640 (CO)	222 (4.25); 278 (4.01); 325 (2.79); 475 (3.53)	2.25 (s, 3H, N—CO—CH_3); 3.95 (s, 3H, OCH_3); 6.77 (s, 2H, $=CH_{quinone}$); 7.32 (d, J = 10.2 Hz, 1 H_{arom}); 9.02 (d, J = 10.2 Hz, 1 H_{arom}); 11.86 (br, 1H, NH)	245
3i	1676 (CONH); 1660 (CO); 1640 (CO)	222 (4.15); 293 (3.98); 490 (3.41)	4.03 (s, 3H, OCH_3); 6.86 (s, 2H, $=CH_{quinone}$); 7.42 (d, J = 9.9 Hz, 1 H_{arom}); 7.45–7.75 (m, 3 H_{arom}); 7.95–8.15 (m, 2 H_{arom}); 9.33 (d, J = 9.9 Hz, 1 H_{arom}); 13.22 (br, 1H, NH)	307
3j	1765 ($OCOCH_3$); 1685 (CONH); 1668 (CO); 1645 (CO)	216 (3.76); 275 (3.68); 430 (2.93)	2.44 (s, 3H, CO—CH_3); 6.82, 6.90 (AB system, J = 10.8 Hz, 2H, $=CH_{quinone}$); 7.44 (d, J = 9.0 Hz, 1 H_{arom}); 7.45–7.70 (m, 3 H_{arom}); 7.95–8.25 (m, 2 H_{arom}); 9.36 (d, J = 9.0 Hz, 1 H_{arom}); 13.11 (br, 1H, NH)	335

5-Amino-8-hydroxy-1,4-naphthoquinone (3a):

To an ice-cooled slurry of 1,5-dinitropnaphthalene (20 g, 0.092 mol) in concentrated sulphuric acid (45 ml) is added dropwise with stirring a mixture of sulphur (7.5 g) and fuming sulphuric acid (60% SO_3; 85 ml). Stirring is continued for 1 h and then the mixture is warmed at 50 °C for 10 min. The mixture is cooled, allowed to stand at room temperature for 18 h, and finally poured on crushed ice. The solution is filtered and extracted with chloroform in a liquid/liquid extractor. The crude quinone is purified by short column chromatography on silica gel (chloroform); yield: 11.3 g (65%); m.p. 267–269 °C (light petroleum); (Lit.[7], m.p. 273–274 °C.

$C_{10}H_7NO_3$ (189.2)	calc.	C 63.48	H 3.73	N 7.40
	found	63.19	3.70	7.23

M.S.: *m/e* (relative intensity) = 189 (100, M^+); 161 (7); 133 (8).

I.R. (Nujol): ν = 3346, 3258, 3154, 1590 cm^{-1}.

U.V.-Vis. (ethanol): λ_{max} = 217 (log ε = 4.39); 296 (3.78); 541 (sh) (3.71); 572 (3.89); 617 nm (3.81).

^{1}H-N.M.R. (DMSO-d_6): δ = 6.95 (s, 2H, $=CH_{quinone}$); 7.19, 7.42 (AB system, J = 9.3 Hz, 2 H_{arom}); 8.36 (br.s, 2H, NH_2); 13.86 ppm (s, 1H, OH).

***N*- and/or *O*-Alkylated (or -Acylated) Derivatives 3b–j; Typical Procedures:**

Method A: A mixture of **3a** (1.5 g, 7.93 mmol), sodium acetate (1.5 g) and acetic anhydride (50 ml) is allowed to stand at room temperature for 48 h. The resulting solution is poured into ice/water to give a red precipitate, which is collected, washed with water, and crystallized from methanol to give **3b**; yield: 1.47 g (80%).

Method B: Silver(I) oxide (2 g) and methyl iodide (15 ml) are added to **3b** (1 g, 4.33 mmol) dissolved in chloroform (300 ml). The resulting mixture is stirred at 30–40 °C for 12 h, then filtered, and the solvent removed in vacuum to afford **3h**; yield: 1.01 g (96%).

5-Hydroxy-1,4-naphthoquinone (5):

Sodium nitrite (200 mg, 2.89 mmol) is added to a magnetically stirred solution of **3a** (200 mg, 1.06 mmol) in sodium hydroxide (350 mg in 50 ml of water) and the mixture is then added over a solution of hypophosphorous acid (20 ml) in ice (50 g). After 15 min, if a positive test for free nitrous acid appears, the mixture is warmed at 40 °C for 2 h and allowed to stand at room temperature for 10 h. The precipitate is collected, washed with water and crystallized from *n*-pentane; yield: 70 mg (38%); m.p. 153 °C (dec); [Lit.[14], m.p. 150–154 °C (dec)].

5-Chloro-8-hydroxy-1,4-naphthoquinone (6):

Sodium nitrite (200 mg, 2.89 mmol) is added to a magnetically stirred solution of **3a** (200 mg, 1.06 mmol) in sodium hydroxide (350 mg in 50 ml of water) and then poured onto a mixture of ice (50 g), water (5 ml), and concentrated hydrochloric acid (5 ml). During the diazotization, a suspension of copper(I) chloride is prepared as follows: crystallized copper(II) sulphate (4.4 g, 17.6 mmol) and sodium chloride (0.95 g, 16.2 mmol) in water (10 ml) are warmed until dissolution is complete. This solution is added with stirring to sodium hydrogen sulphite (1.4 g, 13.5 mmol) in water (25 ml) and the mixture is cooled to 10–15 °C. The white precipitate of copper(I) chloride is rapidly collected, washed, sucked dry, and suspended in a mixture of concentrated hydrochloric acid (2.5 ml) and water (10 ml). The above diazonium salt solution is then added dropwise with stirring to the hot (60 °C) suspension of copper(I) chloride. Stirring at 60 °C is continued for 10 min and then the mixture is heated at 100 °C for 30 min and allowed to stand at room temperature for 24 h. The precipitate is collected to give **6** contaminated with some juglone (**5**). The mother liquors are extracted with chloroform (3 × 20 ml) to provide another portion of the same product. The combined products are recrystallized from benzene/light petroleum; yield: 51 mg (45%); m.p. 198–200 °C (Lit.[15], m.p. 201–202 °C).

M.s.: *m/e* (relative intensity) = 208 (100, M^+); 210 (35.3, M^+ + 2).

I.R. (Nujol): ν = 1665; 1640 cm^{-1}.

U.V.-Vis. (ethanol): λ_{max} = 215 (log ε = 4.28); 253 (4.11); 420 nm (3.58).

^{1}H-N.M.R. ($CDCl_3$): δ = 6.90 (s, 2H, $=CH_{quinone}$); 7.36 (m, $2H_{arom}$); 12.56 ppm (s, 1H, OH).

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