Selective Syntheses of 2-Alkylamino- and 2-Alkoxy-6,7-dichloro-5,8-dihydroxy-1,4-naphthoquinones

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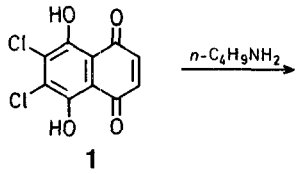
Syntheses of 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) derivatives have been of interest for the preparation of natural quinone antibiotics, as exemplified by Fredericamycin[1], which has a 2-methoxynaphthazarin nucleus as the biologically active moiety. Aminonaphthazarins as dyes also have been of interested because of their functional properties in color chemistry[2,3].

It is known that the reaction of 2,3-dichloronaphthazarin (**1**) with aniline gives exclusively 2-anilino-3-chloronaphthazarin in 70% yield[4]. However, we found that the reaction of **1** with excess butylamine under atmospheric oxygen gave predominantly 2-butylamino-6,7-dichloronaphthazarin (**2a**) together with 2-butylamino-3-chloronaphthazarin (**3a**) in low yield.



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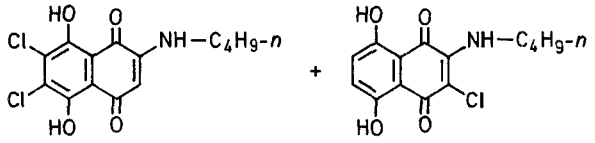
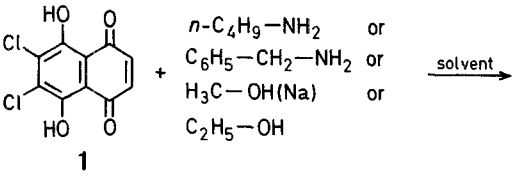


2a **3a**

It is generally known that the chlorine atoms on the quinonoid ring are very reactive whereas the hydrogen atoms on the benzenoid ring are less reactive toward nucleophiles, and that reactions of 2,3-dichloronaphthoquinone with amines or other nucleophiles give exclusively substitution products at the 2- and/or 3-positions[5]. We have now found a novel and selective syntheses of **2** by the reaction of **1** with primary alkylamines under the conditions given in Table 1. Alkylamination at the 2- and 6-positions of **1** were competing reactions and a typical solvent effect was observed. Ethanol, a protic polar solvent, was the best for the selective and high yield synthesis of **2** (run 4). The reaction of **1** with other primary alkylamines such as benzylamine gave **2b** in 76% yield together with **3b** in trace amounts (run 5). However, no reaction occurred between **1** and secondary or tertiary alkylamines.



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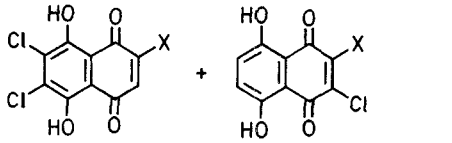


2a X = NH—C4H9-n **3a** X = NH—C4H9-n
b X = NH—CH2—C6H5 **b** X = NH—CH2—C6H5
c X = OCH3 **c** X = OCH3
d X = OC2H5 **d** X = OC2H5

Table 1. Reactions of **1** with Alkylamines or Alcohols

Run	Nucleophile	Solvent	Temp.	Time	Products (Yield[a] [%])	Selectivity **2**/**3** or **4**/**5**
1	n-C_4H_9—NH_2	CH_2Cl_2	10°C	2 h	**2a** (39) + **3a** (14)	2.9
2	n-C_4H_9—NH_2	C_6H_6	20°C	16 h	**2a** (47) + **3a** (14)	3.5
3	n-C_4H_9—NH_2	CH_3CN	20°C	2 h	**2a** (53) + **3a** (8)	6.5
4	n-C_4H_9—NH_2	C_2H_5OH	20°C	2 h	**2a** (76) + **3a** (1)	76
5	C_6H_5—CH_2—NH_2	C_2H_5OH	20°C	2 h	**2b** (76) + **3b** (trace)	< 76
6	H_2N—$CH(CH_3)$—CH_2—NH_2	C_2H_5OH	0°C	2 h	**4a** (55) + **5a** (0.8)	68
7	1,2-di-H_2N—C_6H_{10}-c	C_2H_5OH	0°C	2 h	**4b** (43) + **5b** (trace)	< 43
8[b]	CH_3ONa	CH_3OH/DMSO	20°C	2 h	**2c** (0) + **3c** (63)	0
9	CH_3OH	$CH_3OH/(C_2H_5)_3N$	30°C	3 h	**2c** (36) + **3c** (33)	1.1
10	C_2H_5OH	$C_2H_5OH/(C_2H_5)_3N$	30°C	2 h	**2d** (14) + **3d** (24)	0.6

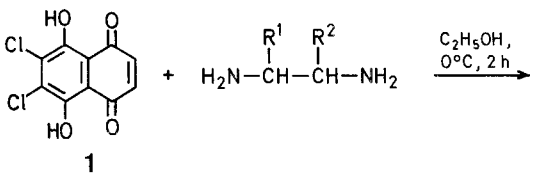
[a] Yield of product isolated by chromatography, based on **1**.
[b] No reaction in the absence of DMSO; **1** (1 mmol), CH_3ONa (30 mmol), CH_3OH (30 ml), DMSO (30 ml).

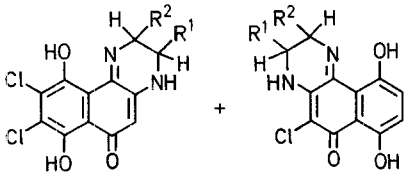
Table 2. Analytical and Spectral Data of Products **2–5**

Products	m.p. [°C] (solvent)	Molecular formula[a]	M.S. *m/e* (rel. int.)[b]	U.V. (Benzene)[c] λ_{max}[nm] (ε)	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ[ppm]
2a	187–188° (benzene)	$C_{14}H_{13}Cl_2NO_4$ (330.2)	331 (M + 2, 32); 329 (M^+, 47); 286 (100)	485 (sh, 8200); 505 (8500); 530 (sh, 6900)	1.0–1.6 (m, 7H); 3.2 (q, 2H, J = 6 Hz, N—CH_2); 5.6 (s, 1$H_{quinoid}$); 6.0 (br. s, 1H, NH); 12.1 (s, 1H, OH); 13.9 (s, 1H, OH)
3a	127–128° (benzene)	$C_{14}H_{14}ClNO_4$ (295.7)	297 (M + 2, 15); 295 (M^+, 41); 252 (100)	480 (sh, 8400); 495 (8700); 530 (sh, 6900)	0.9–1.7 (m, 7H); 3.80 (q, 2H, J = 6 Hz, N—CH_2); 6.13 (br. s, 1H, NH); 6.96 (d, 1H, J = 10 Hz, $H_{benzenoid}$); 7.11 (d, 1H, J = 10 Hz, $H_{benzenoid}$); 11.58 (s, 1H, OH); 12.78 (s, 1H, OH)
2b	204–205° ($CHCl_3$)	$C_{17}H_{11}Cl_2NO_4$ (364.2)	365 (M + 2, 71); 363 (M^+, 100); 272 (14)	482 (sh, 7500); 505 (8000); 540 (sh, 5600)	4.42 (d, 2H, J = 6 Hz, CH_2); 5.77 (s, 1$H_{quinoid}$); 6.46 (br. s, 1H, NH); 7.36 (s, 5H_{phenyl}); 12.37 (s, 1H, OH); 14.13 (s, 1H, OH)
2c	218–219° (benzene)	$C_{11}H_6Cl_2O_5$ (289.1)	290 (M + 2, 31); 288 (M^+, 43); 189 (100)	482 (sh, 6100); 495 (6500); 523 (sh, 5200)	3.95 (s, 3H, CH_3); 6.25 (s, 1$H_{quinoid}$); 12.70 (s, 1H, OH); 13.22 (s, 1H, OH)
3c	161–162° (benzene)	$C_{11}H_7ClO_5$ (254.6)	256 (M + 2, 26); 254 (M^+, 74); 189 (100)	489 (sh, 5000); 515 (6900); 553 (4400)	4.16 (s, 3H, CH_3); 7.11 (s, 2$H_{benzenoid}$); 12.11 (s, 1H, OH); 12.29 (s, 1H, OH)
2d	206–208° (benzene)	$C_{12}H_8Cl_2O_5$ (303.1)	304 (M + 2, 55); 302 (M^+, 81); 274 (100)	482 (sh, 6300); 495 (6800); 523 (sh, 5400)	1.60 (t, 3H, J = 6 Hz, CH_3); 4.18 (q, 2H, J = 6 Hz, CH_2); 6.25 (s, 1$H_{quinoid}$); 12.81 (s, 1H, OH); 13.30 (s, 1H, OH)
3d	124–126° (benzene)	$C_{12}H_9ClO_5$ (268.7)	270 (M + 2, 40); 268 (M^+, 84); 240 (100)	489 (sh, 5300); 515 (6100); 553 (3900)	1.45 (t, 3H, J = 7 Hz, CH_3); 4.65 (q, 2H, J = 7 Hz, CH_2); 7.20 (s, 2$H_{benzenoid}$); 12.20 (s, 1H, OH); 12.35 (s, 1H, OH)
4a	198–200° ($CHCl_3$)	$C_{13}H_{10}Cl_2N_2O_3$ (313.1)	314 (M + 2, 49); 312 (M^+, 78); 297 (100)	471 (sh, 1600); 508 (sh, 3400); 550 (sh, 8400); 588 (14900); 635 (13800)	1.30 (d, 3H, J = 6 Hz, CH_3); 3.3–4.0 (m, 3H); 5.96 (s, 1$H_{quinoid}$); 8.47 (br. s, 1H, NH); 11.58 (br. s. 1H, OH); 15.54 (s, 1H, OH)[d]
5a	> 320° ($CHCl_3$)	$C_{13}H_{11}ClN_2O_3$ (278.5)	280 (M + 2, 20); 278 (M^+, 52); 263 (100)	444 (sh, 3100); 470 (sh, 3900); 505 (4700); 544 (6300); 585 (8300); 632 (5200)	1.34 (d, 3H, CH_3); 3.27–4.16 (m, 3H); 5.61 (br. s, 1H, NH); 7.03 (s, 2$H_{benzenoid}$); 13.08 (br. s, 1H, OH); 14.01 (s, 1H, OH)
4b	283–285° ($CHCl_3$)	$C_{16}H_{14}Cl_2N_2O_3$ (353.2)	354 (M + 2, 22); 352 (M^+, 36); 316 (100)	472 (sh, 1600); 509 (sh, 3200); 550 (sh, 7900); 591 (14000); 637 (13000)	1.20–2.17 (m, 8H); 3.53–3.93 (m, 2H); 5.05 (br. s, 1H, NH); 6.07 (s, 1$H_{quinoid}$); 11.43 (br. s, 1H, OH); 14.98 (s, 1H, OH)

[a] Satisfactory microanalyses obtained: C ± 0.43, H ± 0.33, N ± 0.26; exception: **2b**, C + 0.5.
[b] Only major fragments listed.
[c] sh = shoulder.
[d] In DMSO-d_6.

On the other hand, the rection of **1** with 1,2-diaminopropane gave predominantly the 5,6-ring-closure product **4a**, 7,10-dihydroxy-3(or 2)-methyl-8,9-dichloro-2(or 3),4-dihydrobenzo[*f*]quinoxalin-6-one, in 55% yield together with the 1,2-ring-closure product **5a**, 7,10-dihydroxy-3(or 2)-methyl-5-chloro-2(or 3),4-dihydrobenzo[*f*]quinoxalin-6-one, in 0.8% yield (run 6). Similar reaction of **1** with 1,2-diaminocyclohexane gave **4b** in 43% and a trace amount of **5b** (run 7).





It is proposed that the initial Michael addition of amine to the 6-position of **1** followed by the intramolecular nucleophilic substitution of the 2′-amino group to the 5-carbonyl group gave the leuco ring-closure product which was oxidized to **4** by atmospheric oxygen. The quinone-quinoneimine tautomerization of compounds **4** and **5** was observed in solution[6].

The reaction of **1** with sodium methoxide gave only 2-methoxy-3-chloronaphthazarin (**3c**) in 63% yield, but not 2-methoxy-6,7-dichloronaphthazarin (**2c**) (run 8). Methanol did not react with **1** even under reflux conditions, but the reaction proceeded in the presence of triethylamine and afforded **2c** in 36% yield together with **3c** in 33% yield, respec

tively (run 9). Similar reaction of **1** with ethanol also gave **2d** and **3d** (run 10). Alkoxylation at the 2- and 6-positions of **1** were competing reactions and the selectivity of reactions was not good as compared to those of alkylamination.

In these reactions, when the alkylamine was added to the solution of **1**, the color changed immediately from red (λ_{max} = 523 nm) to blue (λ_{max} = 600 nm), which showed the formation of dianion of **1**. The formation of the dianion plays an important role for the Michael addition of nucleophiles at the 6-position in preference to the chlorine substitution at the 2-position.

Alkylamination of 1; General Procedure:
To a solution of the amine (30 mmol) in a solvent (10 ml), **1** (260 mg, 1 mmol) in a solvent (20–80 ml) is added dropwise for 30 min under atmospheric oxygen. After the reaction, the mixture is poured into aqueous hydrochloric acid (pH 1) to neutralize the amine, and the separated product is filtered. The filtrate is extracted with benzene (2 × 50 ml) and solvent is removed in vacuo. The products are collected and separated by silica gel (Wako gel C-300) column chromatography using benzene as eluent.

Alkoxylation of 1; General Procedure:
To a solution of **1** (260 mg, 1 mmol) in the alcohol (50 ml), triethylamine (1.4 ml, 10 mmol) in the alcohol (10 ml) is added dropwise for 30 min under atmospheric oxygen. After the reaction, the amine is neutralized with aqueous hydrochloric acid (pH 1) and solvent is removed in vacuo to give the products which are purified as described above.

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