September, 1981] © *1981 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***54***, *2735—2738 (1981)* 2735

A Novel Ring-closure Reaction between 1,4-Dihydroxyanthraquinone and Diamines Promoted by Copper Ions

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(Received November 17, 1980)

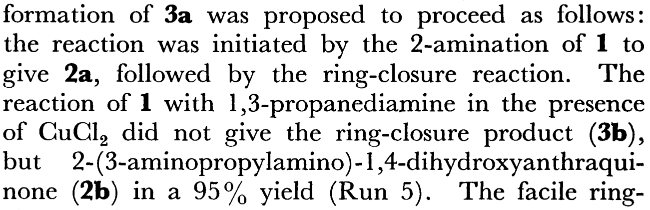
The reaction of 1,4-dihydroxyanthraquinone(DHAQ, **1**) with various diamines were carried out in the presence of $CuCl_2$. Primary 1,2-ethylenediamines or 1,2-cyclohexanediamine afforded the ring-closure products, 6-hydroxy-1,2,3,4-tetrahydronaphtho[2,3-*f*]quinoxaline-7,12-dione derivatives, in good yields of 70—98%. On the other hand, in the cases of *N*-alkylethylenediamines or 2-(alkylamino)ethanols, the major products were the 2-aminated 1,4-dihydroxyanthraquinones. The direct 2-amination of **1** was greatly inhibited when an alkyl group was introduced to the amino group because of its steric requirement. The role of copper ions, the effect of a steric requirement of the *N*-alkyl substituent of amines, and the effect of the chain length of alkanediamines in the reaction of **1** with amines were studied. It was proposed that the reaction was initiated by the direct 2-amination of **1** *via* the copper complex, followed by the intramolecular nucleophilic substitution of the 2-amino group on the 2-alkylamino substituent to give the ring-closure product.

Aminoanthraquinone derivatives are very important compound as dyes or dye intermediates. A large number of papers and patents have been reported on substitution reactions introducing amino groups into the anthraquinone nucleus,[1] but little is known about the direct amination of the anthraquinone nucleus. The direct amination of anthraquinone or aminoanthraquinones with hydroxylamine catalyzed by iron sulfate or vanadium pentaoxide has been described, but it produces random substitution products.[2] Hida *et al.*[3] recently reported the direct amination of anthraquinone catalyzed by a rhodium complex to give α-aminoanthraquinones. Recently, the present authors reported[4,5] the metal-promoted direct alkylamination of α-substituted anthraquinones, in which the amination products were obtained in good yields under mild conditions. On the other hand, in the reaction of DHAQ (**1**) with ethylenediamine (ETDA) in the presence of copper ions, a ring-closure product, 6-hydroxy-1,2,3,4-tetrahydronaphtho[2,3-*f*]quinoxaline-7,12-dione (**3a**), was obtained in a quantitative yield at the ambient temperature.[6] Such a metal-promoted direct amination of α-substituted anthraquinones is a useful method for preparing some aminoanthraquinone derivatives.

In this paper, we whish to report on the reaction of **1** with diamines in detail and propose a possible mechanism of this novel ring-closure reaction.

Results and Discussion

In our previous paper,[6] it was reported that the reaction of DHAQ (**1**) with ethylenediamine (ETDA) in the presence of $CuCl_2$ afforded the ring-closure products, 6-hydroxy-1,2,3,4-tetrahydronaphtho[2,3-*f*]-quinoxaline-7,12-dione (**3a**), in a 98% yield at the ambient temperature (Run 1). Without copper ions under atmospheric oxygen, **3a** was obtained in a 47% yield, together with a 15% yield of leucoquinizarin (1,4-dihydro-9,10-dihydroxyanthracene-1,4-dione) and a 9% recovery of **1** (Run 2). The reaction of **1** with ETDA in the presence of CuCl under the conditions without oxygen gave **3a** in a 96.6% yield, together with the deposition of metal copper in a 44.1% yield (Run 3). On the other hand, the reaction of ETDA with quinizarinquinone (1,4,9,10-tetrahydroanthracene-1,4,9,10-tetrone, **4**), which has previously been prepared by the oxidation of **1** with lead tetraacetate,[7] gave **3a** in a 90.7% yield, along with a 1.2% yield of **1** (Run 4). These results suggested that the role of copper ions is the same as in our previous cases of the quantitative 2-butylamination of **1**,[4] that is; the copper ions oxidize **1** to quinizarinquinone (**4**) *via* the copper complex,[8] and the copper ions are reduced to metal copper. Thus, the formation of **3a** was proposed to proceed as follows: the reaction was initiated by the 2-amination of **1** to give **2a**, followed by the ring-closure reaction. The reaction of **1** with 1,3-propanediamine in the presence of $CuCl_2$ did not give the ring-closure product (**3b**), but 2-(3-aminopropylamino)-1,4-dihydroxyanthraquinone (**2b**) in a 95% yield (Run 5). The facile ring-closure of **1** with ETDA, but not with 1,3-propanediamine, was proposed to result from the fact that the spontaneous formation of the six-membered ring in **3a** was much more favorable in entropy than that of the seven-membered ring in **3b**. The six-membered ring could be formed by the intramolecular nucleophilic substitution of the 2-aminoethylamino group to the 1-hydroxyl group of **2a**, as is shown in Scheme 1. The reaction of **1** with 1,2-propanediamine (Run 6) or 1,2-cyclohexanediamine (Run 7) gave **3c** or **3d** in a yield of 89.5% or 68.9% respectively, but none of the corresponding **2c** or **2d** was obtained. These results suggested that the ring-closure reaction was not inhibited by the alkyl substituents at the 1 and/or 2-position of ETDA. On the

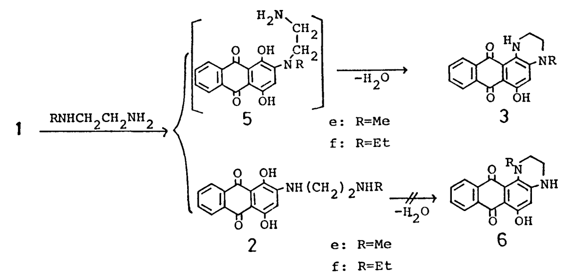


Scheme 1.

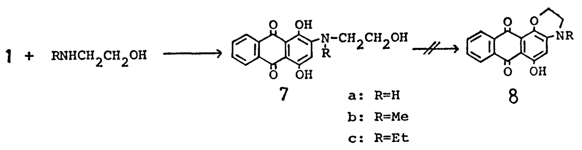
TABLE 1. THE REACTION OF **1** WITH VARIOUS DIAMINES[a)]

Run	Diamines	Copper salt	Yield/%		
			1 (Recovered)	**2**	**3**
1	$NH_2(CH_2)_2NH_2$ $n=2$	$CuCl_2$	0	0	98.0
2[b)]	$NH_2(CH_2)_2NH_2$ $n=2$	None	9	0	47.0
3[c)]	$NH_2(CH_2)_2NH_2$ $n=2$	CuCl	0	0	96.6
4[d)]	$NH_2(CH_2)_2NH_2$ $n=2$	None	1.2	0	90.7[e)]
5	$NH_2(CH_2)_3NH_2$ $n=3$	$CuCl_2$	0	95.0	0
6	$NH_2CH(CH_3)CH_2NH_2$ $n=2$	$CuCl_2$	7.6	0	89.5
7	$NH_2CH(CH_2)_4CHNH_2$ $n=2$	$CuCl_2$	28.2	0	68.9
8[f)]	$NH_2(CH_2)_2NHMe$ $n=2$	$CuCl_2$	0	31.4	31.1
9	$NH_2(CH_2)_2NHEt$ $n=2$	$CuCl_2$	0	93.3	3.6

a) Reactant **1**(2.5 mmol) and diamine(12 ml) were stirred with or without copper salts(5.0 mmol) in pyridine (6 ml) at 30 °C for 6 h. Unless otherwise noted, the reaction was carried out under atmospheric oxygen. b) Leucoquinizarin was obtained in a 15% yield. c) Reaction was carried out under reduced pressure without oxygen. Metal copper was obtained in a 44.1% yield. d) Quinizarinquinone (**4**) was used as the reactant instead of **1**. e) The instability of **4** as a reactant caused a decrease in the yield of **3a**, and a 1.2% yield of **1**, which is the reduced product of **4**, was obtained. f) A complex mixture of compounds(246 mg) was obtained, but these compounds were not identified.

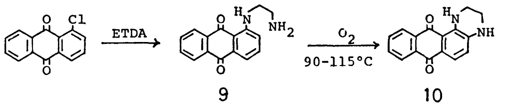


Scheme 2.



Yield(%)	Recovered(%)
7a (62.6)	1 (29.5)
7b (7.9)	1 (7.9)
7c (Trace)	1 (96.6)

Scheme 3.



Scheme 4.[9)]

other hand, the *N*-alkyl substituent of ETDA markedly inhibited both the 2-amination and the ring-closure reaction. The reaction of **1** with *N*-methylethylenediamine gave **3e** in a 31% yield, together with **2e** in a 31% yield (Run 8). The yield of **3e** was greatly decreased in comparison with that of **3a** (Run 1). The reactions of **1** with various diamines are summarized in Table 1. As is shown in Scheme 2, the formation of **5e** and **2e** should compete on the 2-amination of **1** with *N*-methylethylenediamine. On the other hand, the formation of **5e** was much more unfavorable than that of **2e** because of the steric hindrance of the *N*-methyl group; the **5e** intermediate could be easily cyclized to give **3e**, and no **5e** was obtained. On the other hand, **2e** could not give the ring-closure product (**6e**) because of the steric hindrance of the *N*-methyl group. Another example of the steric hindrance was observed in the reaction of **1** with *N*-ethylethylenediamine (Run 9). The ring-closure product (**3f**) *via* **5f** was obtained only in a 3.6% yield, while **2f** was obtained in a 93.3% yield. The competitive 2-amination of **1** with *N*-ethylethylenediamine was obviously much more likely to give **2f** than **5f**, and only a small amount of **3f** was obtained. Compound **2f** could not be converted to **6f** because of the steric hindrance under these conditions, just as in the case of **2e**. Under the more severe conditions of 95—100 °C for 96 h, **2f** afforded **3a**, the deethylation product of **6f**, in a 19.7% yield, along with a 61% recovery of **2f**, but no **6f** was obtained. A similar steric hindrance of the *N*-alkyl group of amines in the 2-amination of **1** was also observed in the case of the reaction of **1** with 2-(alkylamino)ethanols (Scheme 3). The yield of **7** was markedly decreased with the increase in the size of *N*-alkyl substituents, and none of the ring-closure product (**8**) was obtained.

From these results, together with our previous results obtained from the reactions of **1** with various amines,[4)] another possibility of ring-closure reaction (shown in Scheme 4) was excluded; it had been reported in the case of the reaction of 1-chloroanthraquinone with ETDA under atmospheric oxygen at 90—115 °C.[9)] In this reaction, α-amination took place first, followed by direct β-amination at a higher temperature.

On the basis of the experimental results described above, together with previous results,[4)] the mechanism of this ring-closure reaction of **1** with ETDA was

$$\mathbf{1} + \text{ETDA(excess)} \longrightarrow \text{Dianion} \tag{1}$$

$$\left.\begin{array}{l} \text{Dianion} + \text{CuCl}_2(\text{CuCl}_2\!:\!\mathbf{1}=2\!:\!1) \longrightarrow \\ \qquad 2\!:\!1 \text{ Copper(II) complex[I]} \\ \text{Dianion} + \text{CuCl}_2(\text{CuCl}_2\!:\!\mathbf{1}=1\!:\!1) \longrightarrow \\ \qquad 1\!:\!1 \text{ Copper(II) complex[II]} \\ \text{Dianion} + \text{CuCl}(\text{CuCl}\!:\!\mathbf{1}=2\!:\!1) \longrightarrow \\ \qquad 2\!:\!1 \text{ Copper(I) complex[III]} \end{array}\right\} \tag{2}$$

$$\text{Copper complex}^{8)} \left\{\begin{array}{l} \text{[I]} \longrightarrow \mathbf{4} + 2\text{Cu}^+ \\ \text{[II]} \longrightarrow \mathbf{4} + \text{Cu}^0 \\ \text{[III]} \longrightarrow \mathbf{4} + 2\text{Cu}^0 \end{array}\right\} \tag{3}$$

$$\mathbf{1} + \text{O}_2 \longrightarrow \mathbf{4} \text{ (without copper salt)} \tag{4}$$

$$\mathbf{1} \longrightarrow \mathbf{4} + \text{Leucoquinizarin (without copper salt and/or O}_2\text{)} \tag{5}$$

$$\mathbf{4} + \text{ETDA} \longrightarrow \mathbf{2a} \tag{6}$$

$$\mathbf{2a} \xrightarrow[-\text{H}_2\text{O}]{} \mathbf{3a} \tag{7}$$

Scheme 5.

proposed to be as is shown in Scheme 5. The formation of dianion was proved by the color change of the reaction mixture from orange to violet (λ_{max} 566, 606 nm) after the addition of excess amines (Eq. 1). The formation of the copper complex (Eq. 2) and the redox system of the copper complex (Eq. 3) have previously been reported in the cases of the reactions of **1** with amines in our previous paper;[4)] the deposition of metal copper, the effect of the atmosphere (with or without O_2), the effect of the molar ratio of copper salts, and the effect of the kind of copper salt were there discussed in detail. Without copper salts, atmospheric oxygen oxidized **1** to **4** (Eq. 4), and/or **1** spontaneously disproportionated to **4** and leucoquinizarin (Eq. 5), and 47% of **3a** was obtained, together with 15% of leucoquinizarin (Run 2). Similar results (48% yield) were obtained in the 2-amination of **1** with butylamine under the same conditions.[4)] When the reaction was carried out without either O_2 or copper salts, none of the oxidizing agent was present, **1** spontaneously disproportionated to **4** and leucoquinizarin (Eq. 5), and the yield of the 2-aminated product was reduced from 48.1% to 13.1%.[4)] Without copper salt, leucoquinizarin was also obtained in a 15% yield (Run 2). The Michael-type addition of ETDA to **1** give rise to **2a** (Eq. 6). The intramolecular substitution of the 2-aminoethylamino group with the 1-hydroxyl group of **2a** gives rise to the ring-closure product **3a** (Eq. 7).

Experimental

The melting points are uncorrected. The visible spectra were measured using a Hitachi EPS-3T spectrophotometer. The ^{1}H-NMR spectra were recorded on a Hitachi Perkin Elmer Model R-20 spectrometer, with TMS as the internal standard. The elemental analyses were recorded on a Yanaco CHN recorder, MT-2. Column chromatography was carried out on silica gel (Wakogel C-300), using benzene as the eluent. The structural assignment of the products were done by means of their NMR, Mass spectra, and elemental analyses.

Materials. 1,4-Dihydroxyanthraquinone(**1**) was supplied by the Mitsubishi Chemical Industry, Inc., and was purified by column chromatography, using benzene as an eluent, followed by recrystallization from benzene. The metal salts, amines, and solvents were of a reagent grade and were used without further purification.

*Reaction of **1** with Various Diamines.* A typical example of the reaction is shown below: *N*-ethylethylenediamine (12 ml, 135 mmol) was added into a mixture of **1** (0.6 g, 2.5 mmol), pyridine (6 ml), and CuCl_2 (0.63 g, 5.0 mmol), after which the mixture was stirred under atmospheric oxygen for 5 h at room temperature and then poured into a solution of concd HCl (40 ml) and water (100 ml). The separated products were filtered, washed with water, dried, and extracted with benzene. The extract was concentrated and separated by column chromatography, using benzene as the eluent, to give **3f** (28 mg, 3.6%), which was then recrystallized from 1-butanol. The residue was washed with benzene several times to give the HCl salt of **2f** (845 mg, 93.3%).

The reactions of **1** with other diamines were carried out in the same way.

In the reaction of **1** with 1,2-cyclohexanediamine(Run 7), two isomeric compounds of **3d** were obtained; they were identified on the basis of their ^{1}H-NMR spectra. Similar compounds had previously been reported by Koeliker *et al.*[9)] in the reaction of 1-chloroanthraquinone with 1,2-cyclohexanediamine.

*Reaction of **1** with 2-(Alkylamino)ethanols.* A typical example of the reaction is shown below: 2-aminoethanol (12 ml, 200 mmol) was added to a mixture of **1** (0.6 g, 2.5 mmol), pyridine (6 ml), and CuCl_2 (0.673 g, 5.0 mmol), after which the mixture was stirred under atmospheric oxygen at room temperature for 5 h. The mixture was then poured into water and the separated products were filtered, washed with water, and dried. The residue was boiled in an aqueous solution of oxalic acid and filtered, washed with water, dried, and chromatographed using a mixture of benzene–methanol (95:5) as the eluent to give **1** (177 mg 29.5%) and **7d** (468 mg 62.2%).

The reactions of **1** with other 2-(alkylamino)ethanol were carried out in the same way.

Characterization and Identification of Products. Compounds **2b** and **3a** were already reported in our previous paper.[6)]

3c: Mp 227—229 °C (1-butanol); UV, λ_{max} (benzene) (ε) 585 (18800), 543 (18000), 509^{s} nm (9400); ^{1}H-NMR (DMSO-d_6): δ 1.25 (3H d) 6.02 (1H s), 7.52—8.15 (4H, m), 7.86 (1H, broad), 10.34 (1H, broad), 15.20 (1H, s); MS, *m/e* (rel intensity): 294 (M^+, 46), 293 (3), 279 (58), 262 (100).

*4-N-Benzoyl Derivative of **3c***: Mp 179—180 °C (methanol); UV, λ_{max} (benzene) (ε) 596 (14900), 552 (15200), 521^{s} nm (9200); Found: C, 72.37; H, 4.64; N, 6.87%. Calcd for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_4$: C, 72.35; H, 4.55; N, 7.03%; ^{1}H-NMR (CDCl_3): δ 1.35 (3H, dd), 3.32—4.34 (3H, m), 6.47 (1H, s), 7.35 (5H, m), 7.64 (2H, m), 8.18 (2H, m), 10.52 (1H, broad), 13.43 (1H, s).

3d: Mp 181—181.5 °C (benzene); UV, λ_{max} (benzene) (ε) 586 (18300), 544 (17500), 510^{s} nm (9000); Found: C, 71.75; H, 5.51; N, 8.18%. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3$: C, 71.84; H, 5.43; N, 8.38%; ^{1}H-NMR (CDCl_3): δ 1.10—2.20 (8H, m), 3.00 (1H, broad), 3.60 (1H, broad), 4.84 (1H, broad), 6.04 (1H, s), 7.54 (2H, m), 8.14 (2H, m), 10.24 (1H, broad), 14.84 (1H, s); MS, *m/e* (rel intensity): 334 (M^+, 100), 333 (10).

2e: UV, λ_{max} (methanol) 532^{s}, 502 nm.

2′-N-Benzoyl Derivative of ***2e***: Mp 207—208 °C (methanol); UV, λ_{max} (benzene) (ε) 514 (11700), 545^s nm (8900); Found: C, 69.51; H, 5.02; N, 7.05%. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73%; ^{1}H-NMR ($CDCl_3$): δ 3.02 (3H, s), 3.29—4.03 (4H, m), 6.03 (1H, s), 7.32 (5H, s), 7.63 (2H, m), 8.08 (1H, broad), 8.15 (2H, m), 13.73 (1H, s), 14.03 (1H, s); IR (KBr), ν_{CO} 1610 cm^{-1}; MS, *m/e* (rel intensity): 416 (M$^+$, 9), 281 (100), 268 (88), 239 (45).

3e: Mp 213—214 °C (1-butanol); UV, λ_{max} (benzene) (ε) 584 (23100), 543 (21900), 508^s nm (11100); Found: C, 69.14; H, 4.94; N, 9.32%. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52%; ^{1}H-NMR ($CDCl_3$): δ 2.98 (3H, s), 3.40 (4H, m), 5.84 (1H, s), 7.54 (2H, m), 8.10 (2H, m), 10.65 (1H, broad), 14.95 (1H, s); MS, *m/e* (rel intensity): 294 (M$^+$, 100), 293 (90), 279 (16), 262 (92).

2f: UV, λ_{max} (methanol) 542^s, 512 nm.

2′-N-Benzoyl Derivative of ***2f***: Mp 209—210 °C (methanol); UV, λ_{max} (benzene) (ε) 513 (12900), 545^s nm (9700); Found: C, 70.23; H, 5.32; N, 6.73. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51%; ^{1}H-NMR ($CDCl_3$): δ 1.14 (3H, t), 3.06—3.92 (6H, m), 6.02 (1H, s), 7.28 (5H, m), 7.63 (2H, m), 8.01 (1H, s), 8.24 (2H, m), 13.53 (1H, broad), 13.83 (1H, s); IR (KBr): ν_{CO} 1615 cm^{-1}; MS, *m/e* (rel intensity): 430 (M$^+$, 27), 281 (100), 268 (58), 239 (66).

3f: Mp 190—190.5 °C; UV λ_{max} (benzene) (ε) 588 (25000), 546 (23400), 511^s nm (11800); Found: C, 69.78; H, 5.19; N, 8.83%. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.28; N, 9.09%; ^{1}H-NMR ($CDCl_3$): δ 1.22 (3H, t), 3.13—3.65) (6H, m), 6.01 (1H, s), 7.55 (2H, m), 8.15 (2H, m), 10.72 (1H, broad), 14.97 (1H, s); MS, *m/e* (rel intensity): 308 (M$^+$, 100), 307 (56), 293 (30), 279 (16).

7a: Mp 263—264 °C (1-butanol); UV, λ_{max} (benzene) (ε) 544^s (9000), 512 nm (11700); Found: C, 64.08; H, 4.28; N, 4.45%. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68%; MS, *m/e* (rel intensity): 299 (M$^+$, 38), 281 (13), 268 (100).

7b: Mp 138.5—140 °C (1-butanol); UV, λ_{max} (benzene) (ε) 532 nm (11200); Found: C, 64.71; H, 4.91; N, 4.36%. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47%; MS, *m/e* (rel intensity): 313 (M$^+$, 20), 295 (54), 282 (100).

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

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