INVESTIGATION OF QUINONES

XXV.* NUCLEOPHILIC ADDITION OF HYDROGEN CHLORIDE AND AMINES TO NAPHTHO[2,3-a]PHENAZINE-8,13-DIONE

M. V. Gorelik and T. F. Bezrukova

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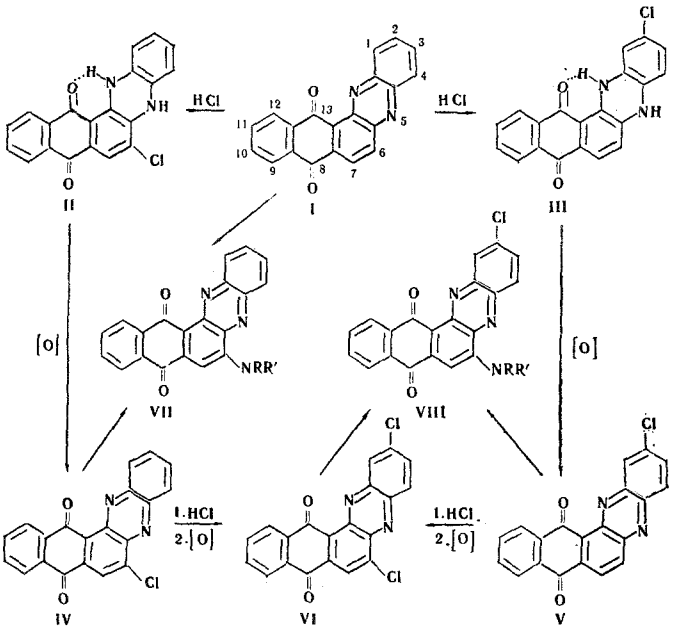
The reaction of naphtho[2,3-a]phenazine-8,13-dione (I) with hydrogen chloride leads, depending on the solvent, to 2- or 6-chlorodihydroazines, which are converted to 2,6-dichloro derivatives after oxidation and retreatment with hydrogen chloride; the corresponding 6-amino-substituted naphthophenazinediones are formed by reaction with amines. The direction of nucleophilic attack in these reactions is caused by the coordinated electron-acceptor effect of the peri-oriented oxygen atoms of the quinone grouping and the heterocyclic nitrogen and by intensified protonation with the closing of an intramolecular hydrogen bond.

We have previously [1] shown that the addition of benzenesulfinic acid to naphtho[2,3-a]phenazine-8,-13-dione (I) and its derivatives proceeds at one of the three reaction centers – the carbon atom in the 2 or 6 position and the oxygen atom in the 8 position. This paper is devoted to reactions with nucleophilic agents such as hydrogen chloride and amines.



* See [7] for communication XXIV.

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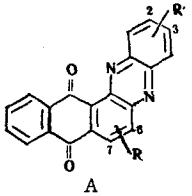
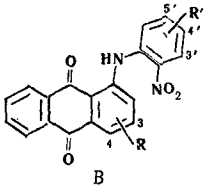
TABLE 1



A



B

Formula	Compound No.	R′	R	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Found, % Cl	Calc., % C	Calc., % H	Calc., % N	Calc., % Cl	Yield, %
	V	2-Cl	H	259,5—261,5		69,49 69,68	2,62 2,52	8,20 8,06	10,19 9,97					85*
A	IV	H	6-Cl	277—279 (dec.)	$C_{20}H_9N_2O_2Cl$	69,47 69,63	2,57 2,70	8,12 8,27	9,82 9,94	69,68	2,63	8,12	10,28	90*
	—	H	7-Cl	261—263		—	—	7,82 7,78	10,08 10,24					—
	VI	2-Cl	6-Cl	308—312 (dec.)	$C_{20}H_8N_2O_2Cl_2$	63,41 63,41	2,05 2,19	7,20 7,26	18,83 18,94	63,39	2,13	7,38	18,69	88*
	—	5′-Cl	H	300—302 (dec.)		—	—	7,18 7,37	9,68 9,41					86
B	—	H	3-Cl	223,5—224,5	$C_{20}H_{11}N_2O_2Cl$	63,57 63,82	2,88 2,80	7,14 7,17	9,70 9,74	63,42	2,93	7,39	9,36	69

	—	H	4-Cl	243,5—244,5		—	—	7,58 7,70	9,34 9,18					—
	—	5′-Cl	3-Cl	261—262,5	$C_{20}H_{10}N_2O_2Cl_2$	58,00 58,30	2,46 2,44	6,70 6,77	17,15 16,98	58,13	2,44	6,78	17,16	70
	VIIa	H	6-NHC_6H_{11}	213,5—215	$C_{26}H_{21}N_3O_2$	76,48 76,68	5,41 5,50	10,32 10,19	—	76,63	5,19	10,31	—	76
	VIIb	H	6-Piperidino	210,5—211,5	$C_{25}H_{19}N_3O_2$	76,28 76,62	4,78 4,87	10,74 10,77	—	76,32	4,87	10,68	—	70
A	VIIc	H	6-NHC_6H_5	235—236,5	$C_{26}H_{15}N_3O_2$	—	—	10,26 10,17	—	—	—	10,47	—	70,5
	VIId	H	6-$N(CH_3)C_6H_5$	229—230	$C_{27}H_{17}N_3O_2$	—	—	10,20 10,40	—	—	—	10,11	—	84,5
	VIIIa	2-Cl	6-Piperidino	217—218,5	$C_{25}H_{18}N_3O_2Cl$	—	—	9,71 9,77	7,90 7,99	—	—	9,82	8,28	78,5
	VIIIb	2-Cl	6-NHC_6H_5	260—262 (dec.)	$C_{26}H_{14}N_3O_2Cl$	—	—	9,82 9,88	7,81 7,81	—	—	9,64	8,13	86,5

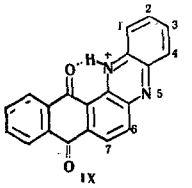
* Obtained by cyclization of the corresponding B compound.

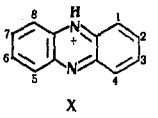
The 6-chloro derivative IV and a small amount of 2,6-dichloro derivative VI are formed when hydrogen chloride is bubbled into a solution of naphthophenazinedione I in acetic acid or dioxane under nitrogen with subsequent oxidation by nitric acid; 2-chloro derivative V, which also contains 2,6-dichloro derivative VI, is formed when hydrogen chloride is bubbled into a solution of I in dimethylformamide and on refluxing in hydrochloric acid. When the experiments are carried out in the presence of air oxygen, the yield of 2,6-dichloro derivative VI increases to 40-45%, which is explained by the oxidation of dihydroazines II and III to the corresponding azines, which in turn add a molecule of HCl. In fact, both 2- and 6-chloronaphthophenazinedione are converted to 2,6-dichloro derivatives on treatment with hydrogen chloride.

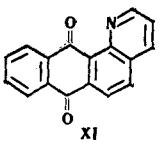
The structures of the reaction products were established after chromatographic separation by comparison with compounds synthesized by the cyclization of the corresponding chloro-substituted 1-(2-nitrophenylamino)anthraquinones (see Table 1). This method was used to synthesize 2-, 3-, 6-, and 7-monochloro- and 2,6-dichloronaphthophenazinediones. The compounds were identified from their chromatographic behavior, melting points, and IR spectra. The absence of 2-chloro derivative V in experiments carried out in dioxane and in acetic acid, of 6-chloro derivative IV in experiments carried out in water and dimethylformamide, and of 3- and 7-chloro derivatives in both cases was attested to by paper chromatographic data and by the IR spectra of the monochloro derivative fraction isolated by chromatography. The presence of each of the isomers can be detected on the background of the others with a sensitivity of 3-5% from the characteristic bands, especially in the region of the out-of-plane deformation vibrations of the C–H bonds.

Naphthophenazinedione I and its chloro derivatives react readily with primary and secondary amines. In stronger bases such as piperidine and cyclohexylamine, quinone I reacts even at room temperature and in the absence of an acid catalyst. The reaction proceeds with aromatic amines only in the presence of proton acids. Naphthophenazinedione I and its 6-chloro derivative (IV) are converted to the same amino compound (VII) on treatment with piperidine and heating with a mixture of aniline and aniline hydrochloride in dioxane, while 2-chloro derivative V and 2,6-dichloro derivative VI are converted to aminochloro derivative VIII. Consequently, the amine residue enters the 6 position of the naphthophenazinedione molecule under the indicated conditions. The absence of an NH vibrational band in the IR spectra of the piperidino and N-methyl-N-phenylamino derivatives is evidence that aminocompounds VII and VIII exist in the azine form rather than in the dihydroazine form.

The direction of nucleophilic attack of the protonated anthraquinonepyrazine (I) molecule to the 2 and 6 positions indicates the addition of a proton to the nitrogen atom in the α position of the anthraquinone ring (IX). It is known [2, 3] that the 2(7) position is the most active with respect to nucleophilic attack in the phenazinium cation (X). Nucleophilic attack at the 3 and 7 positions should therefore have been expected in the case of protonation of the nitrogen atom in the 5 position of I.


IX


X


XI

The protonation of the nitrogen atom in the peri position relative to the CO group is energetically more favorable as a consequence of the closing of an intramolecular hydrogen bond (IX). The formation of the latter with the participation of the unshared pair of the carbonyl oxygen atom intensifies its electron-acceptor effect, thereby promoting nucleophilic attack to a greater degree in the 6 position and to a lesser extent in the 4 position.

Thus the capacity of anthraquinonepyrazine I for nucleophilic addition reactions is a consequence of the coordinated effect of the heterocyclic nitrogen atom and the peri-oriented carbonyl oxygen atom. Protonation, which is accompanied by the formation of an intramolecular hydrogen bond, intensifies this effect. The same factors are responsible for nucleophilic addition to anthraquinonepyridine (X) [4, 5].

The role of the solvent, which is a decisive one that directs the reaction to either the 2 position or the 6 position of naphthophenazinedione I, requires additional study. It is possible that it consists in reinforcing or weakening the intramolecular hydrogen bond in cation IX as a function of whether the attack at the 6 position is facilitated to a greater or lesser extent.

The activating effect of proton acids in nucleophilic additions to condensed anthraquinone derivatives that contain a nitrogen atom in the α position of the six-membered aromatic heterocycle is a special variety of acid catalysis in which the addition of a proton, owing to closing of an intramolecular hydrogen bond, leads to reinforcement of the electron-acceptor effect of not just one but of two heteroatoms simultaneously. This sort of acid catalysis should also occur in other cases when closing of an intramolecular hydrogen bond is possible with the participation of two heteroatoms, each of which is conjugated with the reaction center.

EXPERIMENTAL

Reaction of Naphtho[2,3-a]phenazine-8,13-dione (I) with Hydrogen Chloride. A suspension of 3.1 g (0.01 mole) of quinone I in 60 ml of hydrochloric acid was refluxed for 3 h and diluted with water. The blue precipitate of dihydroazines was removed by filtration and stirred for 1 h with 2 ml of 58% nitric acid in 40 ml of acetic acid. The mixture was filtered, dissolved in dioxane, and passed through a layer of anhydrous aluminum oxide to give 2.37 g of a mixture of azines. For reaction in an organic solvent, dry hydrogen chloride was bubbled through a solution of 0.01 mole of quinone I in 200 ml of dioxane or in 150 ml of acetic acid at 100° or in 120 ml of dimethylformamide at 45-50° for 4-5 h. The mixture was cooled and diluted with water, and the product was removed by filtration, oxidized, and purified as described above to give 2.7-2.8 g of a mixture of azines.

A chloroform solution of the mixture was chromatographed on aluminum oxide with separation of 2,6-dichloro derivative VI as the first zone, the monochloro derivative as the second zone, and starting quinone I as the third zone. In experiments carried out under nitrogen, 79% of the 2-chloro derivative (V), 3% of the 2,6-dichloro derivative, (VI) and 2% of the starting compound (based on the amount of quinone I used in the reaction) were isolated when dimethylformamide was the solvent while 70% of the 6-chloro derivative (IV), 9% of the 2,6-dichloro derivative (VI), and 8% of the starting quinone were isolated from the reaction mixture when the solvent was dioxane. The yield of the 2,6-dichloro derivative (VI) increased to 40-45% when the experiments were carried out in dioxane in the presence of air oxygen. About 50% of the starting quinone I was isolated along with chloro derivatives V and VI in experiments carried out in water. The absence of the 2-chloro derivative (V) in experiments carried out in acetic acid and dioxane was indicated by the absence, in the IR spectra of the monochloro derivative fraction, of bands characteristic for V at 785 (medium), 790 (weak), 849 (strong), 1019 (weak), and 1438 (strong) cm^{-1}, while the absence of the 6-chloro derivative (IV) in experiments carried out in water and dimethylformamide was indicated by the absence in the IR spectra of bands at 762 (strong) 1035 (weak), and 1260 (strong) cm^{-1}. In both cases, the IR spectra did not contain bands characteristic for the 3-chloro derivative at 1205 (medium), 1295 (strong), and 1465 (medium) cm^{-1} and for the 7-chloro derivative at 1045 (medium), 1080 (strong), and 1500 (weak) cm^{-1}. Compounds IV, V, and VI were identified from the R_f values from paper chromatography, IR spectra, and melting points of mixed samples on comparison with azines synthesized by an alternative route (see Table 1). The R_f values from chromatography of a mixture of the azines on Whatman No. 1 paper in an α-bromonaphthalene–85% acetic acid system were as follows (substituent position and R_f value with respect to the R_f value of unsubstituted quinone I given): 7-Cl 0.71; 2-Cl, 0.62; 3-Cl 0.58; 6-Cl 0.47; 2,6-dichloro 0.24.

2-Chloro-, 6-Chloro-, 7-Chloro-, and 2,6-Dichloronaphtho[2,3-a]phenazine-8,13-diones. A mixture of 2 g of the appropriate chloro derivative of 1-(2-nitrophenylamino)anthraquinone, 10 g of crystalline sodium sulfide, and 50 ml of alcohol was refluxed for 1 h and diluted with water. A blue dihydroazine (1.5-1.6 g) separated and was oxidized as indicated above in the description of the reaction of naphthophenazinedione I with HCl to give 85-90% of an azine (see Table 1); the 3-chloro derivative was synthesized according to the method in [6].

3-Chloro-2'-nitro-, 4-Chloro-2'-nitro-, 5'-Chloro-2'-nitro-, and 3,5'-Dichloro-2'-nitrophenylaminoanthraquinones. A mixture of 1.25 g of 1-chloroanthraquinone, 1 g of 5-chloro-2-nitroaniline, 0.7 g of potassium carbonate, 0.1 g of cupric acetate, and 0.05 g of copper powder was stirred for 3 h at 200-210° in 7 ml of nitrobenzene. When the mixture was cooled, 1.68 g (86%) of 5'-chloro-2'-nitrophenylaminoanthraquinone separated. 3-Chloro- and 3,5'-dichloro derivatives of nitrophenylaminoanthraquinone, respectively, were similarly obtained from 1-bromo-3-chloroanthraquinone and 2-nitroaniline and from 1-bromo-3-chloroanthraquinone and 5-chloro-2-nitroaniline.

A 2.5 g sample of 1-amino-4-chloroanthraquinone was added at 140° to a mixture of 10 g of o-nitrochlorobenzene, 0.1 g of cupric acetate, and 0.05 g of copper powder, and the mixture was heated rapidly to

210° and maintained at this temperature for 5 min. It was then cooled and diluted with methanol. The precipitate was separated and chromatographed on anhydrous aluminum oxide to give 4-chloro-2'-nitrophenylaminoanthraquinone. Recrystallization from chlorobenzene or acetic acid gave orange-red or red needles.

6-Amino Derivatives of Naphtho[2,3-a]phenazine-8,13-dione (see Table 1). A solution of 0.001 mole of azine I, IV, V or VI in 5 ml of piperidine or cyclohexylamine was refluxed for 2-3 min, and the precipitate that formed when the mixture was cooled was separated, dissolved in chloroform, and chromatographed; the violet zone of the amino derivative was eluted. No amino compound formed when axine I was heated in aniline at 150° for 3 h.

A solution of 0.001 mole of azine in 20 ml of dioxane was refluxed for 2-3 min with 3 ml of aniline or N-methylaniline and 3 ml of 4% hydrochloric acid. The dioxane solution was passed through aluminum oxide, and the violet zone of the amino derivative was eluted by chloroform. Azine I did not change in the absence of acid.

The amino derivatives are shiny, dark-violet needles (from chlorobenzene), or filaments (from chloroform) that are soluble in benzene and chloroform and insoluble in water. Compounds VIIb, c, obtained from azine I, were identical to the compound obtained from azine IV, according to their melting points and IR spectra; VIIIa, b, obtained from azine V and from azine VI, were also identical.

The IR spectra of KBr pellets were recorded with a UR-10 spectrophotometer.

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