## INVESTIGATION OF HETEROCYCLIC QUINONES XVII.\* OXIDATIVE AMINATION OF 6-HYDROXYQUINAZOLINE

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Representatives of a new class of heterocyclic quinones – quinazoline-5,6-quinones – were obtained by the oxidative amination of 6-hydroxyquinazoline, 2-phenyl-6-hydroxyquinazoline, and 4-piperidino-6-hydroxyquinazoline. 6-Hydroxyquinazolines that are not substituted in the 2 position are aminated in this position during oxidation. A possible mechanism for the amination is proposed.

In investigating the range of application of oxidative amination for the synthesis of heterocyclic quinones, we studied the possibility of using this method to obtain a new class of compounds – quinazoline-5,6-quinones. Unsubstituted 6-hydroxyquinazoline (Ia) [2] was used as the starting compound, since, in this case, we have previously observed an interesting transformation – amination of the pyrimidine ring [3]. The oxidation of Ia with oxygen in the presence of copper acetate and secondary amines (piperidine, dimethylamine, and morpholine) leads to quinazoline-5,6-quinones that contain two secondary amine residues; about 2 g-mole of oxygen is absorbed in the process. In conformity with the stepwise scheme of the oxidation of other phenols under these conditions [4, 5], one secondary amine residue is attached to  $C_{(8)}$ . We have assumed that the second residue is attached to  $C_{(2)}$  or  $C_{(4)}$ . The PMR spectrum of the quinone in the presence of piperidine (IIa, see Fig. 1) does not make it possible to unambiguously determine the position of the second piperidine residue.

Bearing in mind the ease of nucleophilic attack at  $C_{(4)}$  in quinazoline [6], it might have been expected that the secondary amine is added at this position. However, the oxidation of 2-phenyl-6-hydroxyquinazoline (Ib) proceeds with the absorption of 1.5 g-mole of oxygen and leads to 2-phenyl-8-piperidinoquinazoline-5.6-quinone (IId). This sort of trend speaks in favor of substitution at  $C_{(2)}$  during the oxidation of Ia.



Fig. 1. PMR spectra of quinones IIa and IIe in CDCl<sub>3</sub>.



A definitive proof of the structure of the quinones obtained by the oxidation of 6-hydroxyquinazoline might be the independent synthesis of one of the possible isomers. With this end in mind, we oxidized 4-piperidino-6-hydroxyquinazoline (Ic), which was obtained via a number of steps from 2-nitro-5-methoxybenzoic acid. In the oxidation of Ic, the reaction does not cease after the absorption of 1.5 g-mole of oxygen; subsequent slow oxygen absorption is observed.

\* See [1] for communication XVI.

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• 1971 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011, No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00. Thin-layer chromatography on silicic acid demonstrates that two quinones in a ratio of  $\sim 3:1$  are contained in the reaction mass after the absorption of 1.5 g-mole of  $O_2$ . The quinone that was obtained in larger amounts was isolated by means of preparative thin-layer chromatography on silicic acid and was identified as 4,8-dipiperidinoquinazoline-5,6-quinone (IIe) on the basis of the results of elementary analysis and the IR and PMR spectra. A comparison of the properties of quinones IIa and IIe and of their phenazines (IIIa and IIIe) shows that they are not identical. The 2,8-dipiperidinoquinazoline-5,6-quinone structure can consequently be assigned unambiguously to quinone IIa. The PMR spectra of the quinones confirm their structure: in addition to the signals of the piperidine protons, each of the spectra also contains two singlets with  $\delta$  6.20 and 9.07 ppm for IIa and  $\delta$  5.91 and 8.50 ppm for IIe. The singlets with  $\delta$  6.20 and 5.91 ppm correspond to the vicinal H-7 protons (compare with  $\delta$  6.29 ppm for IId and 5.7 ppm for 2-phenyl-4-piperidinobenzothiazole-6,7-quinone [7]), while the singlets at 9.07 and 8.50 ppm correspond to the H-4 and H-2 protons, respectively. It should be noted that the signal of the H-4 proton is found at weaker field than the signal of the H-2 proton, as observed also in the PMR spectra of quinazolines [8] (Fig. 1). The second quinone that was formed during the oxidation of Ic could not be isolated in pure form. To establish its structure, the mixture of the two quinones from the reaction mass was converted to a mixture of the more stable phenazines by the action of o-phenylenediamine. The mixture of phenazines was separated into two pure compounds with mp 201-202° and 176-177° by means of chromatography on silicic acid and aluminum oxide. The PMR spectrum of the first phenazine (IIIe) contains, in addition to signals corresponding to the protons of two piperidine residues and multiplets with  $\delta$  7.65 and 8.10 ppm (which correspond to the 8-, 9-, 10-, and 11-H protons of the phenazine ring), two singlets at 7.37 (6-H) and 8.67 ppm (3-H). The PMR spectrum of the second phenazine demonstrates the presence of three piperidine residues, 8-, 9-, 10-, and 11-H protons, and the absence of the 3-H signal. On the basis of this and the results of elementary analysis, the 1,3,5-tripiperidinopyrimido[5,4-a]phenazine structure (IIIf) was assigned to the second phenazine, and the 2.4.8-tripiperidinoquinazoline-5,6-quinone structure (IIf) was assigned to the corresponding quinone.

Quinone IIe was completely converted to IIf under the conditions of the oxidation reaction. (The reaction was monitored by thin-layer chromatography on silicic acid.) However, a large excess of piperidine is required for the reaction to proceed at an adequate rate. In this case, nucleophilic attack at the second position is hindered because of the electron-donor effect of the piperidine residue attached to  $C_{(4)}$ . A similar effect of a substituted amino group on covalent hydration has been previously observed [9].

The results make it possible to assume a possible amination mechanism involving the 2 position. Intermediate quinone V, in which, owing to the acceptor properties of the  $C_{(5)} = O$  carbonyl, the electron density of  $C_{(2)}$  is reduced more markedly than that on  $C_{(4)}$ , is apparently formed in the oxidation of 6-hydrox-yquinazoline. 1,6-Addition of a secondary amine to quinone V therefore occurs readily. The system is then stabilized through aromatization to VI, which is further oxidized to IIa-c under the reaction conditions.



Quinones IIa-IIf are red or dark-red substances that are stable on storage in the dark. Their phenazines are the first representatives of the previously undescribed heterocyclic pyrimido[5,4-a]phenazine system. Depending on the substituents, the color of the phenazines changes from yellow to orange. There are intense carbonyl group bands in the IR spectra of quinones II at 1600-1700 cm<sup>-1</sup>.



o-Quinones II can be converted to 6-hydroxy- and 6-methoxyquinazoline-5,8-quinones. Thus saponification of IIa with alkali gives 2-piperidino-6-hydroxyquinazoline-5,8-quinone (IVa), while the action of methyl alcohol, in the presence of sulfuric acid, on IId gives 2-phenyl-6-methoxyquinazoline-5,8-quinone (IVb), which is saponified to 2-phenyl-6-hydroxyquinazoline-5,8-quinone (IVc). It should be noted that the alkaline hydrolysis of IId does not proceed satisfactorily: the starting material is recovered under mild

Com- pound	mp, °C (crys- tallization solvent)	IR spec- trum, vC=O' cm <sup>-1</sup>	UV spec- trum, $\lambda_{max}$ , nm (log $\varepsilon$ )	Empirical formula	Found, %			Calc., %			0/0
					с	н	N	с	н	N	Yield.
lla	206—208 (benzene)	1668 1625	246 (4,32) 293 (3,90) 342 (4,18) 390 (4,22)	C <sub>18</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub>	66,6	6,8	17,4	66,2	6,8	17,2	88
Шb	184—185 (ethyl acetate – hexane)	1668 1606	242 (4,31) 281 (3,84) 338 (4,20) 388 (4,20)	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	58,5	5,8	22,8	58,5	5,7	22,8	21*
IIc	204—206 (dioxane)	1670 1637	242 (4,31) 332 (4,20) 348 (4,33)	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub>	58,3	5,5	17,2	58,2	5,5	17,0	55
ΙId	179—181 (chloroform – hexane)	1693 1618	230 (4,20) 280 (4,31) 324 (4,31)	$C_{19}H_{17}N_3O_2$	71,7	5,5	13,2	71,5	5,4	13,2	84
IIIa	241-243 (benzene)	-	—	$C_{24}H_{26}N_6$	72,5	6,7	21,1	72,3	6,6	21,1	-
IIIc	221-222 (alcohol)			C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sub>2</sub>	65,8	5,3	21,0	65,8	5,5	20,9	-
Шd	225-226 (acetone - water)	-		$C_{25}H_{21}N_5$	76,5	5,6	17,7	76,7	5,4	17,9	

TABLE 1. Compounds Synthesized

\* An additional amount of quinone IIb can be obtained from the filtrate.

conditions, and resinification occurs when the mixture is heated. Like other hydroxyquinones, IVa and IVc are rather strong acids and dissolve readily in aqueous sodium bicarbonate.

## EXPERIMENTAL

The UV spectra of alcohol solutions were recorded with a Unicam-SP-800. The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrometer. The PMR spectra of deuterochloroform solutions were recorded with a JNM-4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The reaction was monitored and the purity of the quinones was determined by thin-layer chromatography on silicic acid in a chloroform-methanol (20:1) system.

Oxidation of 6-Hydroxyquinazoline (Ia). A suspension of 0.58 g (4 mmole) of Ia in a mixture of 6 ml of methanol, 20 mmole of amine, and 0.016 g of copper acetate was stirred under oxygen until oxygen absorption ceased (from 2 to 4 h, depending on the basicity of the amine; the reaction proceeds more rapidly with piperidine and more slowly with morpholine). The precipitate was removed by filtration, washed with methanol and ether, and dried. The yields and physical constants of quinones IIa-c are presented in Table 1.

Oxidation of 2-Phenyl-6-hydroxyquinazoline (Ib). This compound was oxidized under conditions similar to those used for Ia. PMR spectrum in  $CDCl_3$ ,  $\delta$ , ppm: 1.90 (singlet,  $\beta$ , $\gamma$ -CH<sub>2</sub>), 3.93 (singlet,  $\alpha$ -CH<sub>2</sub>), 6.29 (singlet, H<sub>7</sub>), 7.59 and 8.48 (multiplets, C<sub>6</sub>H<sub>5</sub>), 9.40 (singlet, 4-H). See Table 1 for the yield and physical constants of IId.

<u>Pyrimido[5,4-a]phenazines (IIIa,c,d).</u> A 0.13-g (1.2 mmole) sample of o-phenylenediamine was added at  $60-70^{\circ}$  to 1 mmole of quinone II in a mixture of 3 ml of alcohol and 1 ml of acetic acid (in acetic acid for IId), and the mixture was refluxed for 10 min. It was then cooled, and the precipitate was separated and recrystallized. See Table 1 for the physical constants.

 $\frac{2-\text{Piperidino-6-hydroxyquinazoline-5,8-quinone (IVa).} \text{ A solution of 0.5 g (12.5 mmole) of NaOH in 5 ml of water was added to a suspension of 0.2 g (0.76 mmole) of IIa in 5 ml of alcohol, and the mixture was stirred at 20° for 1.5 h and then acidified to pH 5 with 4 N HCl. The precipitate was separated, washed with water, and dried to give 0.09 g (57%) of a product with mp 174-176° [from alcohol-water (2:3)]. Found: C 60.4; H 5.3; N 16.4%. C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>. Calculated C 60.2; H 5.1; N 16.2%. IR spectrum, cm<sup>-1</sup>: 1630, 1667 (C = O), 3340 (OH). UV spectrum, <math>\lambda_{\text{max}}$ , nm (log  $\varepsilon$ ): 241 (4.30), 315 (4.12). 338 (4.47).

2-Phenyl-6-methoxyquinazoline-5,8-quinone (IVb). A 1.0-g (3.14 mmole) sample of 2-phenyl-8piperidinoquinazoline-5,6-quinone (IId) was heated for 10 min in 10 ml of methanol containing 0.5 ml of concentrated  $H_2SO_4$ . The mixture was cooled, and the precipitate was removed by filtration, washed with 10 ml of methanol and 10 ml of ether, and dried to give 0.66 g (78%) of a product with mp 208-209° (from benzene). Found: C 70.8; H 4.3; N 9.7%.  $C_{15}H_{10}N_2O_3 \cdot \frac{1}{2}C_6H_6$ . Calculated: C 70.8; H 4.3; N 9.2%. IR spectrum, cm<sup>-1</sup>: 1675, 1684 (C=O). UV spectrum,  $\lambda_{max}$ , nm (log  $\epsilon$ ): 254 (4.14), 298 (4.22).

<u>2-Phenyl-6-hydroxyquinazoline-5,8-quinone (IVc)</u>. A suspension of 0.37 g (1.28 mmole) of IVb in a solution of 0.064 g (1.6 mmole) of sodium hydroxide in 8 ml of water was stirred for 20 min at 50°, and the mixture was cooled and acidified to pH 5 with 4 N HC1. The precipitate was removed by filtration, washed with water, and dried to give 0.25 g (75%) of a product with mp 227-229° (from dioxane). Found: C 66.5; H 3.3; N 10.9%.  $C_{14}H_8N_2O_3$ . Calculated: C 66.6; H 3.2; N 11.1%. IR spectrum, cm<sup>-1</sup>: 1648, 1680 (C = O), 3200 (OH). UV spectrum,  $\lambda_{max}$ , nm (log  $\epsilon$ ): 244 (4.17, 315 (4.47), 275 (4.01).

<u>2-Nitro-5-methoxybenzoic Acid.</u> A mixture of 12 g (72 mmole) of 2-nitro-5-methoxytoluene and 27.5 g (173 mmole) of potassium permanganate in 2 liters of water was refluxed with stirring until the solution was decolorized. Another 5.5 g (35 mmole) of potassium permanganate was added, and the mixture was again refluxed until the solution was decolorized. Steam distillation of the mixture gave 6.1 g of unchanged 2-nitro-5-methoxytoluene. The precipitated manganese dioxide was removed by filtration and washed with hot water. The filtrate and wash waters were evaporated to 200 ml, cooled, and acidified with concentrated hydrochloric acid. The precipitate was removed by filtration and dried to give 5.4 g (58%) of a product with mp 131-133° (mp 133° [10]).

4-Chloro-6-methoxyquinazoline. This compound was obtained from 2-nitro-5-methoxybenzoic acid by the method in [11].

<u>4-Piperidino-6-methoxyquinazoline</u>. A mixture of 1.4 g (7.25 mmole) of 4-chloro-6-methoxyquinazoline, 15 ml of alcohol, and 3.6 ml (36 mmole) of piperidine was refluxed for 2 h, diluted with 40 ml of water, and cooled. The resulting precipitate was removed by filtration to give 1.3 g (81%) of a product with mp 141-142° (from alcohol). Found: C 69.3; H 7.2; N 17.5%.  $C_{14}H_{17}N_{3}O$ . Calculated: C 69.1; H 7.0; N 17.3%.

<u>4-Piperidino-6-hydroxyquinazoline (Ic)</u>. A suspension of 1 g (4.1 mmole) of 4-piperidino-6-methoxyquinazoline and 1.1 g (8.2 mmole) of aluminum chloride in 23 ml of xylene was stirred and refluxed for 5 h and cooled. The xylene was decanted, and the solid residue was washed with ether, pulverized, and treated with 10 ml of 2 N HCl. The mixture was then made alkaline with ammonia to pH 8 and extracted with three 50-ml portions of ethyl acetate. The extract was dried with sodium sulfate and vacuum-evaporated to give 0.6 g (63%) of a product with mp 196-197° [from ethyl acetate-hexane (3:2)]. Found: C 68.3; H 6.6; N 18.3%. C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O. Calculated: C 68.1; H 6.6; N 18.3%.

Oxidation of 4-Piperidino-6-hydroxyquinazoline (Ic). A 0.34-g (1.5 mmole) sample of Ic was added to a solution of 0.01 g of copper acetate in a mixture of 4 ml of methanol and 0.6 ml (6 mmole) of piperidine and the mixture was stirred under oxygen for 5 h. One hour after stirring commenced, a precipitate formed and later partially redissolved. The reaction mass was diluted with 30 ml of chloroform, and the mixture was neutralized with 80% acetic acid. The chloroform solution was washed with two 10-ml portions of water, dried with sodium sulfate and vacuum-evaporated. The residue (0.3 g) was a mixture of two quinones according to thin-layer chromatography. Preparative thin-layer chromatography on silicic acid in a chloroform-methanol (20:1) system of 0.15 g of the mixture gave 0.08 g (33%) of IIe with  $R_f$  0.9 and mp 142-144° [from benzene-hexane (1:1)]. Found: C 65.9; H 7.1; N 17.5%.  $C_{18}H_{22}N_4O_2$ . Calculated: C 66.2; H 6.8; N 17.2%. IR spectrum, cm<sup>-1</sup>: 1630, 1667 (C=O). UV spectrum,  $\lambda_{max}$ , nm (log  $\varepsilon$ ): 267 (4.19), 275 (4.17), 296 (4.20).

1,5-Dipiperidinopyrimido[5,4-a]phenazine (IIIe). This compound was obtained in the same way as IIIa,c,d from IIe and had mp 201-202° [from acetone-water (1:1)]. Found: N 21.2%.  $C_{24}H_{26}N_5$ . Calculated: N 21.1%.

Pyrimido[5,4-a]phenazines (IIIe and IIIf). A 0.4-g sample of o-phenylenediamine was added to a hot solution of 0.56 g of the mixture of quinones obtained in the oxidation of Ic in 5 ml of alcohol and 3 ml of acetic acid, and the mixture was refluxed for 0.5 h and cooled. It was then diluted with 50 ml of water, and the precipitate was separated and dried. Chromatography on silicic acid (benzene) gave 0.12 g of IIIe with mp 201-202° and  $R_f$  0.85. This product was identical to the IIIe obtained from IIe. Rechromatography with benzene on activity II aluminum oxide of the fractions that did not contain IIIe gave 0.035 g of IIIf with mp 176-177° and  $R_f$  0.65. Found: C 72.3; H 7.1; N 20.7%.  $C_{29}H_{35}N_7$ . Calculated: C 72.3; H 7.3; N 20.4%.

Conversion of Quinone IIe to Quinone IIf. A solution of 0.021 g (0.064 mmole) of IIe in 1 ml of methanol was added to a mixture of 2 ml of methanol, 0.4 ml (4 mmole) of piperidine, and 0.005 g of copper acetate, and the mixture was stirred under oxygen. In 45 min, IIe (Rf 0.9) was completely converted to IIf (Rf 0.6) according to thin-layer chromatography. The reaction mass was diluted with 10 ml of chloroform, and the mixture was washed with 1.1 ml of 4N HCl and 10 ml of water, dried with sodium sulfate, and evaporated. The residue (0.02 g) was dissolved in a mixture of 1 ml of alcohol and 1 ml of acetic acid containing 0.01 g of o-phenylenediamine, and the mixture was refluxed for 10 min and vacuum-evaporated to dryness to give IIIf with Rf 0.65.

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