INVESTIGATION OF HETEROCYCLIC QUINONES

XVIII.* SYNTHESIS AND STRUCTURE OF 4-HYDROXYQUINAZOLINE QUINONES

Yu. S. Tsizin, N. B. Karpova,
and I. E. Shumakovich

UDC 547.856.07

Amino derivatives of 4-hydroxyquinazoline quinones were obtained by the oxidative amination of 6-hydroxy-4-quinazolone and 2-phenyl-6-hydroxy-4-quinazolone. The IR spectra established that 2,8-dipiperidino(dimorpholino)-4-hydroxyquinazoline 5,6-quinone exists in the hydroxy form, while 2-phenyl-4-hydroxy-8-piperidinoquinazoline 5,6-quinone can exist in both the oxo and hydroxy forms.

The use of oxidative amination for the synthesis of a new class of heterocyclic quinones – quinazoline quinones – was described in a previous communication [1]. It was shown that 2,8-diaminoquinazoline 5,6-quinones are formed in the oxidation of 2-unsubstituted 6-hydroxyquinazolines with oxygen in the presence of Cu^{+2}-secondary amine complexes. The present paper is devoted to a study of the oxidative amination of 6-hydroxy-4-quinazolones and to the elucidation of the possibility of amination in the 2 position in the absence of substituents.

It is known that 4-quinazolones exist in the oxo form [2]. However, in analogy with the oxidation of 6-hydroxy-4-quinolones [3], it can be expected that o-quinones in which the oxo form will be stabilized by a chelate hydrogen bond will be obtained from I and II. The oxidation of I and II proceeds only with an equivalent amount of copper acetate, which is explained by tying up of copper ions by the quinone formed (see [3]). The reaction rate depends on the basicity of the amine. Thus the oxidation of I in the presence of morpholine proceeds much more slowly and gives lower yields. To decompose the stable copper complex and isolate the free quinones, it is necessary to acidify the reaction mixture with a strong acid (for example, hydrochloric acid). In the oxidation of I and II in the presence of piperidine, 4 and 3 g-equivalents of oxygen, respectively, are absorbed, which speaks in favor of the amination of I in the 2 position [1]. In fact, 2,8-dipiperidino-4-hydroxyquinazoline 5,6-quinone (IIIa) and 2,8-dimorpholino-4-hydroxyquinazoline 5,6-quinone (IIIb) are obtained from I, while 2-phenyl-4-hydroxy-8-piperidinoquinazoline 5,6-quinone (IIIc) is obtained from II.

The o-quinoid structure of IIIa-c was confirmed by their conversion to substituted pyrimido[5,4-a]-phenazines (V). Quinones III have acidic properties: they are quite soluble in water in the presence of piperidine or morpholine, while IIIa and IIIb are soluble in aqueous sodium bicarbonate solution. Mild alkaline hydrolysis of quinones III gives pyrimidine-ring-substituted 6-hydroxyquinazoline 5,8-quinones (VI).

There is no doubt that, in accordance with our proposed scheme [1], the first step in the oxidative amination of 6-hydroxy-4-quinazolones is the formation of 8-amino-4-quinazolone 5,6-quinone. Amination in the 2 position in the case of 6-hydroxyquinazolines is explained by the effect of the $C_5=O$ carbonyl group. Hindrance to nucleophilic attack in the 2 position of quinazoline 5,6-quinones under the influence of a electron-donor substituent in the 4 position has been noted. This effect is not observed in the amination of 8-amino-4-quinazolone 5,6-quinone, since the latter exists as a chelate copper complex in the reaction medium and does not contain a free hydroxyl group in the 4 position. The chelate ring of VIII has a pseudo aromatic character, which leads to a coordinated electron-acceptor effect of the oxygen atoms attached to

---

*See [1] for communication XVII.

E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 836-840, June, 1972. Original article submitted April 27, 1971.

TABLE 1. Absorption Frequencies of Quinones III and VII

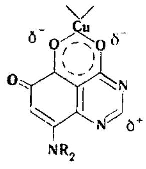
Com-pound	Mineral oil (1600-1700 cm^{-1})‡	Chloroform (1500-1700 cm^{-1})	Dioxane (1500-1700 cm^{-1})
VIIa	1668 m 1626 s	1678w 1620 m, 1589 s, 1556s, 1520 sh	1646 s, b 1593 s, 1567 s
IIIa	1628s, 1605 s	1620s, b. 1556 s, 1520 sh, w	1632s, b 1552 s, b
IIIa*	—	1620 s, b 1563s, 1520 sh, w	—
IIIb	1628 s, 1600 m	1622 s, b 1555 sh, 1545 s, 1515 w	—
VIIc†	1687 m, 1612 s	1697 m, 1617 s, 1582 s, 1557 s	1646 s, b 1580sh, 1562 s, 1540 s
VIIc†	—	1697 m, 1617s, 1580 s, 1559 s	—
IIIc	1710s, 1645 m, 1612 m	1710 w, 1660 m, 1616 s, 1593 m, 1565 m,	1636 s, b 1590 m, 1565 s, 1538 s
IIIc†	—	1720 w, 1660 m, 1610s, 1585 m, 1573 m	—
IIIc*	—	1715s, 1665 s, 1600 s, b	—

*Spectrum of a solution in chloroform – 20% ethanol with a 1.0-mm-thick cuvette.

†Spectrum of a solution in chloroform – triethylamine with 1.0-mm-thick cuvette.

‡Abbreviations: m is medium, s is strong, w is weak, sh is shoulder, and b is broad.

C_4 and C_5 and creates an electron deficit in the 2 position. This sort of assumption of the effect of the chelate complex is in agreement with the

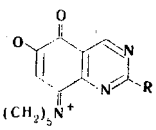


VIII

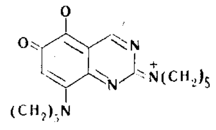
information on the reactivities of other chelate complexes [4]. Nucleophilic attack of the amine is hindered in the oxidation of II probably because of delocalization of the partial positive charge on C_2 owing to the presence of a phenyl group.

It seemed of interest to establish whether 4-hydroxyquinazoline quinones exist in the hydroxy form (III) or in the oxo form (IV). For this, we made a comparative study of the carbonyl absorption in the IR spectra of quinones III and previously obtained quinones (VII) [1], which do not contain substituents in the 4 position (see Table 1).

Quinones VIIa and VIIc each have two maxima at 1600-1700 cm^{-1}, in both the solid state and in chloroform solutions. The low-frequency maxima can be assigned to C_6=O, since it can be expected that they are shifted due to the contribution of structure A. The high-frequency maximum of VIIa is shifted by 19 cm^{-1} as compared with VIIc, which indicates transfer of the mesomeric effect through the pyrimidine ring and an appreciable contribution of structure B to the first compound.



A



B

In comparison with the spectra of VIIa, the spectra of quinones IIIa and IIIb display a pronounced shift of the high-frequency bands of the carbonyl absorption to the long-wave region, and only one broad band centered at ~1620 cm^{-1} is observed in the spectrum of a chloroform solution. This reduction in the frequency is explained by the formation of a chelate hydrogen bond.

A different pattern is noted for IIIc. The spectra of a mineral-oil suspension and of a chloroform solution differ markedly (Table 1 and Fig. 1), which indicates a change in the structure of the compound. If it is assumed that the quinone exists in oxo form IVc in the solid state but primarily in the hydroxy form IIIc in chloroform solution, the strong absorption at 1710 cm^{-1} in mineral oil can be assigned to C_4=O. The ex-

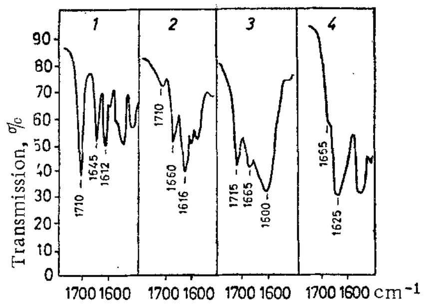
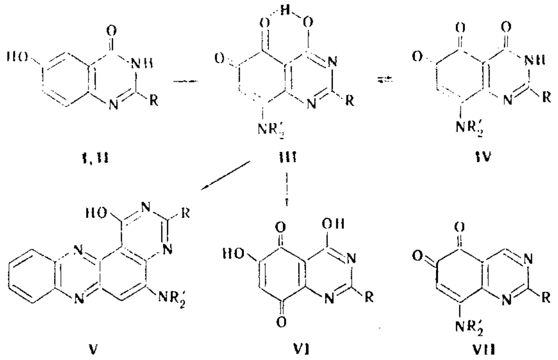


Fig. 1. IR spectra of 2-phenyl-4-hydroxy-8-piperidinoquinazole 5,6-quinone (IIIc): 1) in mineral oil; 2) in chloroform; 3) in chloroform–20% alcohol; 4) copper complex (IX) in mineral oil.

istence of an equilibrium that is shifted to favor the hydroxy form in chloroform is confirmed by the fact that the spectrum of IIIc, like that of VIIc, does not change substantially when triethylamine is added to the solution. However, in chloroform containing 20% ethanol, IIIc, in contrast to IIIa, displays a strong band at 1715 cm^{-1}, since a proton-donor solvent (alcohol) shifts the equilibrium to favor oxo form IVc. The weak absorption in the region of the stretching vibrations of the OH and NH groups does not make it possible to make the assignments of the bands in this region for IIIa-c in the solid state and in solutions.

A shift in the frequencies of the carbonyl absorption to the short-wave region is usually noted on passing from chloroform solutions to dioxane solutions [3, 5]. The IR spectrum of quinone IIIa in dioxane is subject to this principle, while one broad band, which is anomalously shifted to the long-wave region, is observed for the remaining quinones in dioxane.



I R=H; II R=C_6H_5; III-VII a R=NR'_2=$N(CH_2)_5$; b R=NR'_2=$N(CH_2CH_2)_2O$; c R=C_6H_5, NR'_2=$N(CH_2)_5$

The reaction of copper acetate with quinone IIIc gave its copper complex (IX). The carbonyl band at ~1710 cm^{-1} that is related to C_4=O is absent in the IR spectrum of this compound in mineral oil.

Thus it has been established that quinone IIIc, in contrast to IIIa and IIIb, exists in the oxo form in the solid state. This is apparently explained by the lower strength of the intramolecular hydrogen bond in IIIc. It is known that the strength of a hydrogen bond is proportional to the basicity of the carbonyl group [6]. The spectral data are evidence in favor of an appreciable contribution of form B for 2-aminoquinazoline 5,6-quinones, and the negative charge on the oxygen attached to C_5 is greater in IIIa and IIIb than in IIIc; this also explains the great strength of the intramolecular hydrogen bond of these quinones.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrophotometer. The data presented in Table 1 relative to the spectra of solutions were obtained with chloroform solutions (c 0.01 mole/liter, cuvette thickness 0.6 mm) and dioxane solutions (c 0.005 mole/liter, cuvette thickness 0.6 mm).

6-Hydroxy-4-quinazolone. (I). This compound was obtained in 94% yield by demethylation of 6-methoxy-4-quinazolone with 48% hydrobromic acid and had mp 339-341° (from alcohol) (mp 340-345° [7]). IR spectrum (cm^{-1}): 3555 s (OH), 3275 sh, 3170 s (NH), 1673 s (C=O).

2,8-Dipiperidino-4-hydroxyquinazoline 5,6-Quinone (IIIa). An-0.81 g (5 mmole) sample of I was added to a solution of 0.5 g (2.5 mmole) of cupric acetate in a mixture of 4 ml (40 mmole) of piperidine and 6 ml of methanol, and the suspension was stirred under oxygen. After 3 h, 230 ml of O_2 had been absorbed (the calculated value is 224 ml). The reaction mixture was cooled to 5°, acidified with 12 ml of 4 N hydrochloric acid, and extracted with 50 ml of chloroform. The chloroform extract was washed with three 30-ml aliquots of water, dried with sodium sulfate, and vacuum evaporated to give 1.28 g (75%) of violet crystals that were quite soluble in alcohol and chloroform, Moderately soluble in dioxane and benzene, and insoluble in ether and petroleum ether and melted at 193-194° (from benzene). Found: C 63.1; H 6.5; N 15.8%. $C_{18}H_{22}N_4O_3$. Calculated: C 63.1; H 6.5; N 16.3%.

1-Hydroxy-3,5-dipiperidinopyrimido[5,4-a]phenazine (Va). This compound was obtained as yellow crystals with mp 239-240° (from dioxane) from IIIa and o-phenylenediamine as described in [1]. Found: N 20.3; 20.6%. $C_{24}H_{26}N_6O$. Calculated: N 20.3%.

2,8-Dimorpholino-4-hydroxyquinazoline 5,6-Quinone (IIIb). This compound was obtained by oxidation of 0.81 g (5 mmole) of I in the presence of morpholine as in the preparation of IIIa. After 7 h, 180 ml of O_2 had been absorbed (the calculated value is 224 ml). The dark-red crystals [0.86 g (49%)] had mp 212-214° [from chloroform–heptane (6 : 1)] and were moderately soluble in chloroform and alcohol, slightly soluble in ethyl acetate and benzene, and insoluble in ether and petroleum ether. Found: C 55.7; H 5.1; N 16.2%. $C_{16}H_{18}N_4O_5$. Calculated: C 55.5; H 5.2; N 16.2%.

2-Phenyl-6-hydroxy-4-quinazolone (II). This compound was obtained by demethylation of 2-phenyl-6-methoxy-4-quinazolone with 75% sulfuric acid [8]. IR spectrum (cm^{-1}): 2600-3400 s, b (OH bond), 3180w, (NH), 1660 s (C=O).

2-Phenyl-4-hydroxy-8-piperidinoquinazoline 5,6-Quinone (IIIc). This compound [0.4 g (24%)] was obtained by oxidation of 1.19 g (5 mmole) of II in the presence of piperidine as in the preparation of IIIa. After 3 h, 170 ml of O_2 had been absorbed (the calculated value is 167 ml). The brown crystals with mp 260° (dec., from chloroform–heptane (2 : 1)] were moderately soluble in chloroform, dioxane, benzene, and alcohol, and insoluble in petroleum ether and ether. Found: C 67.9; H 4.9; N 12.6%. $C_{19}H_{17}N_3O_3$. Calculated: C 68.0; H 5.1; N 12.6%. Recrystallization from alcohol gave a substance with mp 261° (dec.). Found: C 66.0; H 5.7; N 11.2%. $C_{19}H_{17}N_3O_3 \cdot C_2H_5OH$. Calculated: C 66.1; H 6.0; N 11.0%.

1-Hydroxy-3-phenyl-5-piperidinopyrimido[5,4-a]phenazine (Vc). This compound was obtained in the same way as Va as orange crystals with mp 258-260° (from benzene). Found: N 17.4%. $C_{25}H_{21}N_5O$. Calculated: N 17.2%.

2-Piperidino-4,6-dihydroxyquinazoline 5,8-Quinone (VIa). A solution of 0.5 g (12.5 mmole) of NaOH in 4 ml of water was added to a suspension of 1.06 g (3.1 mmole) of IIIa in 15 ml of alcohol, and the mixture was stirred at room temperature for 2 h, during which the color of the suspension changed from red to brick-brown. The reaction mixture was cooled to 5° and acidified with 10.0 ml of 2 N hydrochloric acid. After 1 h, the precipitate was removed by filtration, washed with alcohol and ether, and dried to give 0.41 g (48%) of orange crystals with mp 260° (dec., from dioxane) that were moderately soluble in alcohol, dioxane, and water, and insoluble in chloroform, benzene, ether, and petroleum ether. Found: C 56.8; H 5.2; N 15.1%. $C_{15}H_{13}N_3O_4$. Calculated: C 56.7; H 4.8; N 15.2%. IR spectrum (cm^{-1}): 3262 s (OH bond), 1691 s, 1633 sh (C=O).

2-Phenyl-4,6-dihydroxyquinazoline 5,8-Quinone (VIc). This compound was obtained in 47% yield by saponification of IIIc as in the preparation of VIa. The light-yellow crystals decomposed above 240° (from dioxane) and were moderately soluble in methanol and dioxane, and insoluble in chloroform, benzene, ether, and petroleum ether. Found: C 61.0; H 4.3; N 7.8%. $C_{14}H_8N_2O_4 \cdot C_4H_8O_2$. Calculated: C 60.7; H 4.5; N 7.9%. IR spectrum (cm^{-1}): 3100 s, b (OH bond), 1692 s, 1655 w, 1630 m (C=O).

Copper Complex of 2-Phenyl-4-hydroxy-8-piperidinoquinazoline 5,6-Quinone (IX). A solution of 0.4 g (2 mmole) of cupric acetate in 10 ml of alcohol was added to a solution of 0.2 g (0.58 mmole) of IIIc in 20 ml of chloroform, and the mixture was stirred at 20° for 10 min and washed three times with 20-ml portions of water, during which a precipitate formed from the alcohol–chloroform solution. The precipitate was removed by filtration, washed with water, and dried over P_2O_5 to give 0.11 g (51%) of a black substance that did not change on heating up to 350° and was moderately soluble in alcohol and chloroform. Found: C 58.2; H 5.0; Cu 7.7; N 11.4%. $C_{38}H_{32}CuN_6O_6 \cdot 3H_2O$. Calculated: C 58.2; H 4.9; Cu 8.1; N 10.7%. IR spectrum (cm^{-1}): 3470 s, b (H_2O), 1655 sh (H_2O) 1625 s, b (C=O).

LITERATURE CITED

1. Yu. S. Tsizin and N. B. Karpova, Khim. Geterotsikl. Soedin., 1698 (1971).
2. Y. Hagiwara, M. Kurihara, and N. Yoda, Tetrahedron, 25, 783 (1969).
3. M. E. Pudel' and Yu. S. Tsizin, Khim. Geterotsikl. Soedin., 1112 (1970).
4. D. Kendlin, K. Taylor, and D. Thompson, Reactions of Coordination Compounds of the Transition Metals [Russian translation], Mir, Moscow (1970), pp. 67, 72.
5. J. Brand and G. Eglinton, Applications of Spectroscopy in Organic Chemistry[Russian translation], Moscow (1967), p. 143.

6. L. Bellamy, New Data on the IR Spectra of Complex Molecules [Russian translation], Mir, Moscow (1971), p. 279.
7. J. Maillard, M. Benard, M. Vincent, Vo Van Tri, R. Jolly, R. Morin, M. Benharkate, and C. Menillet, Chim. Ther., 2, No. 4, 231 (1967); Chem. Abstr., 69, 36,066 (1968).
8. Yu. S. Tsizin, N. B. Karpova, and O. V. Efimova, Khim. Geterotsikl. Soedin., 418 (1971).