INVESTIGATION OF HETEROCYCLIC QUINONES

XX.* N-SUBSTITUTED 2-PHENYL-4-AMINOQUINAZOLINEQUINONES

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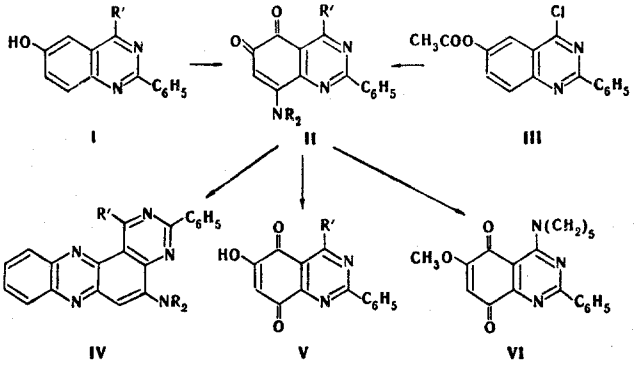
Oxidation of 4-substituted 2-phenyl-6-hydroxyquinazolines with oxygen in the presence of a Cu^{2+}–secondary amine complex gave N-substituted 2-phenyl-4,8-diaminoquinazoline-5,6-quinones, which form diquinazolino[6,5-d:8',7'-b]furan-7,8-quinones on acid hydrolysis.

Within our plan for the further study of oxidative amination, we carried out the oxidation of a series of 2-phenyl-6-hydroxyquinazolines (I) containing, in the 4-position, amino groups with different degrees of substitution. The oxidation of I occurs with a catalytic amount of copper acetate and gives quinones II (Table 1). In contrast to 4-amino-6-hydroxyquinolines [2], the oxidation of Ia is not accompanied by tying up of the copper ions by the reaction product. This is possibly explained by weakening of the chelate properties of aminoquinone IIa as compared with the quinoline analog under the influence of the acceptor-nitrogen atom in the 3 position.

Quinones containing identical secondary amine residues in the 4 and 8 positions, for example, IIc and IIe, can be obtained by oxidation of 2-phenyl-4-chloro-6-acetoxyquinazoline (III) in the presence of an excess of the appropriate amines.



I a R'=NH_2; b R'=n-C_4H_9NH; c R'=$N(CH_3)_2$; d R'=$N(CH_2CH_2)_2O$; e R'=$N(CH_2)_5$

Quinones II are brightly colored substances (from light red to dark-cherry red) that are stable on storage in the dark. The IR spectra of the compounds contain characteristic bands at 1500-1700 cm^{-1}, while the spectra of IIa,b also contain bands of NH stretching vibrations. Their ortho-quinoid structure is confirmed by the formation of phenazine derivatives IV by the action of o-phenylenediamine. Compounds II are readily saponified to the corresponding 6-hydroxyquinazoline-5,8-quinones (V) by mild alkaline hydrolysis; V are also capable of giving phenazine derivatives (IVc) with o-phenylenediamine.

The behavior of quinones II in acidic media was studied in the case of 2-phenyl-4,8-dipiperidinoquinazoline-5,6-quinone (IIe). 2-Phenyl-4-piperidino-6-methoxyquinazoline-5,8-quinone (VI) is obtained when IIe is heated in methanol in the presence of concentrated sulfuric acid (compare with [1]). Hydrolysis of quinone IIe in alcohol–2 N hydrochloric acid (refluxing for 30 min) gives a mixture from which

*See [1] for communication XIX.

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TABLE 1. Quinones II

Comp.	R′	NR_2	mp, °C (crystallization solvent)	IR spectra, cm^{-1}		Empirical formula	Found, %			Calc., %			Yield, %
				3600—3300	1700—1600		C	H	N	C	H	N	
IIa	NH_2	NC_5H_{10}	183—185 (ethyl acetate—hexane)	3434 3314	1654, 1600 vs	$C_{19}H_{18}N_4O_2$	68,5	5,6	16,6	68,3	5,4	16,8	79
IIb	NHC_4H_9	NC_5H_{10}	142—143 (benzene—hexane)	3325	1645 sh, 1630 s 1600 s	$C_{23}H_{26}N_4O_2 \times$ $\times 1/2\ C_6H_6$	72,7	7,0	13,0	72.7	6,8	13,1	65
IIc	$N(CH_3)_2$	$N(CH_3)_2$	182—183 (ethyl acetate—hexane)	—	1655, 1620	$C_{18}H_{18}N_4O_2$	66,9	5,5	17,8	67,0	5,6	17,4	75†
IId	$N(CH_2CH_2)_2O$	NC_5H_{10}	189—190 (alcohol)	—	—	$C_{23}H_{24}N_4O_3$	67,1	5,8	15,6	67,0	5,9	15,5	70
IIe	NC_5H_{10}	NC_5H_{10}	177—179 (acetone—water)	—	1660, 1610	$C_{24}H_{26}N_4O_2$	71,7	6,8	14,1	71,6	6,5	13,9	65* 66†
IVa	NH_2	NC_5H_{10}	263—264 (benzene)	—	—	$C_{25}H_{22}N_6 \cdot C_6H_6$	76,2	6,2	17,6	76,6	5,9	17,5	—
IVb	NC_5H_{10}	NC_5H_{10}	211—212 (benzene)	—	—	$C_{30}H_{30}N_6$	76,1	6,3	17,7	75,9	6,4	17,6	—
IVc	NC_5H_{10}	OH	216—218 (benzene)	—	—	$C_{25}H_{21}N_5O$	—	—	17,3	—	—	17,2	—
Va	NH_2	—	172—174 (alcohol)	3444, 3326	1652 sh, 1602 s	$C_{14}H_9N_3O_3$	62,6	3,8	15,7	62,9	3,4	15,7	94
Vb	$N(CH_3)_2$	—	181—182,5 (alcohol)	3215	1686 sh, 1660	$C_{16}H_{13}N_3O_3$	65,0	4,6	14,3	65,1	4,4	14,2	88
Vc	NC_5H_{10}	—	176—178 (benzene)	3286	1663, 1632	$C_{19}H_{17}N_3O_3 \times$ $\times 1/2\ C_6H_6$	70,4	5,2	11,1	70,6	5,4	11,2	75

* From I.

† From III.

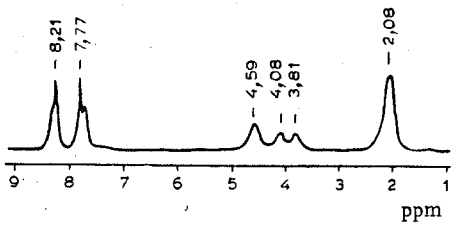


Fig. 1. PMR spectrum of 1,9-dipiperidino-3,11-diphenyl-5-hydroxydiquinazolino[6,5-d: 8',7'-b]furan-7,8-quinone (VII).

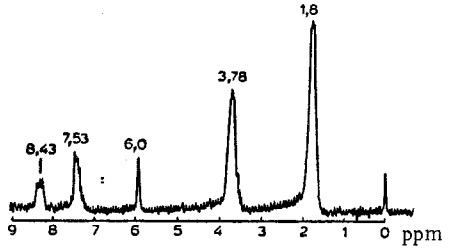


Fig. 2. PMR spectrum of 2-phenyl-4,8-dipiperidinoquinazoline-5,6-quinone (IIe).

quinone Vc (R_f 0.2) was isolated in a yield of about 70% along with a substance with R_f 0.9. A substance with R_f 0.9 was obtained in 20-25% yield by heating IIe for 5 h in dioxane–4 N hydrochloric acid (1 : 1). According to thin-layer chromatography (TLC), acid hydrolysis of quinone Vc under these conditions gives similar results.

The chromatographically purified substance with R_f 0.9 was obtained as violet crystals that decomposed above 270°. The IR spectrum of the compound (in chloroform) contains bands at 3385 (OH), 1689 and 1650 (CO) cm^{-1} (at 3353, 1685, and 1650 cm^{-1} in the spectrum of a mineral oil suspension). Since this compound gives a bright-yellow phenazine derivative (VIII) on reacting with o-phenylenediamine, an ortho-quinoid structure was assigned to it. The presence of a phenolic hydroxyl group is confirmed by the chemical properties of the compound. It is insoluble in aqueous alkali, only slightly soluble in alcohol, but quite soluble in alcoholic KOH and precipitates when the solution is acidified. The action of acetic anhydride gave an acetyl derivative, the IR spectrum of which does not contain absorption at 3300-3600 cm^{-1} but does contain a band at 1770 cm^{-1} (acetyl group).

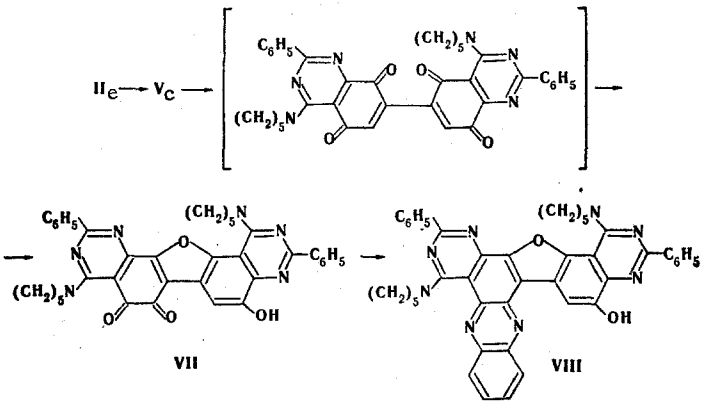
The maximum peak in the mass spectrum of the substance corresponds to the molecular ion (M^+) with m/e 636, while the intense peak with m/e 318 corresponds to the doubly charged molecular ion (M^{2+}). The elementary analysis also corresponds satisfactorily to empirical formula $C_{38}H_{32}N_6O_4$ (mol. wt. 636.72). The relatively weak peak with m/e 619 in the mass spectrum corresponds to detachment of a hydroxyl group from the starting molecular ion. The more intense peaks with m/e 608 and 607 are also formed from the molecular ion as a result of the loss of 28 and 29 mass units (CO and CHO). Elimination of these particles (OH, CO, and CHO) is a characteristic fragmentation process of phenols. The fragment peak with m/e 580 is explained by simultaneous expulsion from M^+ of two CO groups. This process is characteristic for the fragmentation of quinones [3]. The peak with m/e 559 is of only slight intensity and corresponds to detachment of a phenyl ion with m/e 77. The loss of a piperidine radical from M^+ is confirmed by the presence in the spectrum of a metastable M* peak with m/e 481. This process leads to simultaneous formation of fragments with m/e 552 ($M^+ - 84$) and m/e 84. Thus the mass spectrum showed that the substance with R_f 0.9 is a dimerization product, that it contains piperidine and phenyl residues and a phenolic hydroxyl group, and that it has a quinoid structure.

The PMR spectrum of the compound in trifluoroacetic acid is quite simple (Fig. 1). The multiplet at δ 2.08 ppm shows that the β,γ-protons of the two piperidine residues (12H) are almost equivalent; the α protons of one piperidine residue show multiplets at 3.81 (2H) and 4.08 (2H) ppm, while those of the second are at 4.59 (4H) ppm (compare with the PMR spectrum of starting quinone IIe, Fig. 2). The two multiplets at 7.77 and 8.21 ppm with an area ratio of about 6 : 5 correspond to the protons of two phenyl groups and another single aromatic proton. The PMR spectrum of the acetate of this compound in trifluoroacetic acid shows, in addition to the signals of protons of piperidine (12H + 2H + 2H + 4H) and phenyl (6H + 4H) residues, the singlet of a methyl group of an acetate grouping at 2.74 ppm (3H) and an aromatic proton at 8.82 ppm (1H). The signal of the aromatic proton is shifted to weak field because of the presence of an acetoxy group in the o-position.

On the basis of the data presented above, the 1,9-dipiperidino-3,11-diphenyl-5-hydroxydiquinazolino[6,5-d:8',7'-b]furan-7,8-quinone structure (VII) was assigned to the compound. According to TLC, deeply colored products with high R_f values are also formed in the acid hydrolysis of the other quinones (II).

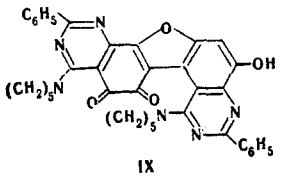
Since quinone IIe is initially converted to Vc on acid hydrolysis, the formation of VII can be depicted as indicated in the scheme on the following page.

It is known that under conditions of acid catalysis 2-hydroxy-1,4-naphthoquinones undergo a reaction of the crotonic condensation type with aldehydes [4, 5]. It is extremely likely that the first step in the formation of VII from Ve is a similar condensation, in which a second molecule of quinone enters into the reaction as the carbonyl component.



VII VIII

The known cases of dimerization of hydroxyquinones lead to different polycyclic systems [6, 7], while the dimerization that we detected is observed here for the first time.



IX

It should be noted that alternative structure IX does not contradict the data obtained in establishing structure VII. We consider it to be less likely, since it should be strained.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrophotometer. The PMR spectra in deuterochloroform (quinone IIe) or in trifluoroacetic acid (VII and its acetate) were recorded with a JNM-4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The mass spectrum was recorded with a Hitachi RMU-6D spectrometer. The reactions were monitored and the purities of the quinones were determined by TLC on silicic acid with a chloroform–methanol (20 : 1) system; benzene–ethyl acetate (1 : 1) was used for phenazine VIII.

Oxidation of N-Substituted 2-Phenyl-4-amino-6-hydroxyquinazolines (Ia-e). A 10-mmole sample of I [8] was introduced into a solution of 0.01 g of copper acetate in a mixture of 15 ml of methanol and 60 mmole of secondary amine, and the mixture was stirred in an oxygen atmosphere until gas absorption ceased. The precipitate was removed by filtration, washed with alcohol and ether, and crystallized (Table 1).

Oxidation of 2-Phenyl-4-chloro-6-acetoxyquinazoline (III). A 3.0-g (10 mmole) sample of III [8] was added to a solution of 1 g (5 mmole) of copper acetate in a mixture of 15 ml of methanol and 6 g (70 mmole) of piperidine [or 3.6 g (78 mmole) of dimethylamine], and the suspension was stirred in an oxygen atmosphere until gas absorption ceased (about 3 h). The mixture was filtered to remove a small amount of solid, and the filtrate was cooled to 5°, acidified with 4 N HCl, and extracted with chloroform (three times with 30 ml aliquots). The chloroform extract was washed with water (three times with 10-ml samples), dried with sodium sulfate, and vacuum evaporated. The residue was then crystallized (Table 1).

3-Phenylpyrimido[5,4-*a*]phenazines (IVa-c). A 0.26-g (2.4 mmole) sample of o-phenylenediamine was added to a hot solution of 2 mmole of quinone IIa (or IIe, Vc) in 5-10 ml of a mixture of alcohol and acetic acid (1 : 1), and the mixture was refluxed for 10 min and allowed to stand for 2 h. The precipitate was then removed by filtration. If no precipitate formed, the mixture was diluted with water and neutralized with ammonia. The precipitate was separated, dried, and crystallized. All of the phenazines were yellow crystalline substances (Table 1).

Alkaline Saponification of Quinones II. A solution of 1.2 g (30 mmole) of sodium hydroxide in 15 ml of water was added to a suspension of 3.75 mmole of quinone IIa (or IIc, IIe) in 30 ml of alcohol, and the mixture was stirred at 20° for 2 h. The starting quinone dissolved initially, and the sodium salt of the hydroxyquinone then precipitated gradually. The suspension was acidified with 10 ml of 4 N HCl, and the

precipitated 6-hydroxyquinazoline-5,8-quinones (Va,c,e) were removed by filtration, washed with water, dried, and crystallized (Table 1).

2-Phenyl-4-piperidino-6-methoxyquinazoline-5,8-quinone (VI). A 1.0-g (2.5 mmole) sample of quinone IIe was refluxed for 40 min in a mixture of 10 ml of methanol and 0.5 ml of concentrated sulfuric acid, during which the red color of the solution changed to orange. The mixture was cooled, treated with 30 ml of chloroform, washed with water to neutrality, dried with sodium sulfate, and vacuum evaporated. The residue was chromatographed with a column filled with silicic acid (3 by 20 cm) with elution with chloroform to give 0.56 g (64%) of orange crystals, with mp 200-201° (from benzene–heptane), that were moderately soluble in alcohol, dioxane, benzene, and chloroform and insoluble in ether and petroleum ether. Found,%: C 68.7; H 5.6; N 12.3. $C_{20}H_{19}N_3O_3$. Calculated,%: C 68.8; H 5.5; N 12.3. IR spectrum: 1670, 1610, 1554, 1530 cm^{-1}.

1,9-Dipiperidino-3,11-diphenyl-5-hydroxydiquinazolino[6,5-d:8',7'-b]furan-7,8-quinone (VII). A 3.6-g (8.8 mmole) sample of quinone IIe was heated at 80-90° for 5 h in a mixture of 26 ml of 4 N HCl and 26 ml of dioxane. The precipitate was removed by filtration, washed successively with water (to pH 7), methanol, and ether; dried, and chromatographed with a column filled with silicic acid (3 by 30 cm) with elution with chloroform–benzene (2 : 3) to give 0.6 g (21%) of violet crystals with mp 336-340° (fluctuates from 270°); the product was only slightly soluble in most organic solvents. Found,%: C 71.3; H 4.9; N 13.4. $C_{38}H_{32}N_6O_4$. Calculated,%: C 71.7; H 5.1; N 13.2.

Acetate of VII. A mixture of 150 mg (0.23 mmole) of quinone VII, 24 ml of pyridine, 10 ml of acetic anhydride, and 6 ml of acetic acid was stirred at 60° for 4 h. Acetic acid (20 ml) was added to the mixture, after which it was vacuum evaporated to 10 ml, and the resulting precipitate was separated, washed with ether, and vacuum dried over P_2O_5 and paraffin at 50° to give 150 mg (94%) of light-violet crystals with mp 219-220°; the product was moderately soluble in chloroform, acetic acid, and dimethylformamide. Found,%: C 70.9; H 5.1; N 12.6. $C_{40}H_{34}N_6O_5$. Calculated,%: C 71.1; H 4.9; N 12.4. IR spectrum: 1770 ($OOCCH_3$), 1685, 1655 (C = O) cm^{-1}. PMR spectrum: signals at δ 2.06 (12H). 2.74 (3H, singlet), 3.80 (2H), 4.14 (2H), 4.60 (4H), 7.80 (6H), 8.20 (4H), 8.82 ppm (1H, singlet).

Phenazine Derivative VIII. A solution of 50 mg (0.078 mmole) of quinone VII in a mixture of 8 ml of dioxane and 8 ml of acetic acid containing 90 mg (0.82 mmole) of o-phenylenediamine was refluxed for 30 min and then vacuum evaporated to dryness. The residue was chromatographed with a column filled with silicic acid (2 by 15 cm) with elution with benzene to give 50 mg of yellow crystals with mp 314-316° (from dioxane). Found,%: C 72.5; H 5.7; N 14.3. $C_{44}H_{36}N_8O_2 \cdot C_4H_8O_2$. Calculated,%: C 72.3; H 5.6; N 14.1.

LITERATURE CITED

1. Yu. S. Tsizin and N. B. Karpova, Khim. Geterotsikl. Soed., 841 (1972).
2. Yu. S. Tsizin and M. V. Rubtsov, Khim. Geterotsikl. Soed., 637 (1970).
3. G. Budzikiewicz, K. Djerassi, and D. Williams, Interpretation of the Mass Spectra of Organic Compounds [Russian translation], Mir, Moscow (1966), pp. 204 and 248.
4. H. Raudniz and G. Puluj, Ber., 64, 2212 (1931).
5. L. F. Fieser, J. L. Hartwell, and A. M. Seligman, J. Am. Chem. Soc., 58, 1223 (1936).
6. S. H. Hooker, J. Am. Chem. Soc., 58, 1212 (1936).
7. K. Chandrasenan and R. H. Thomson, Tetrahedron, 27, 2529 (1971).
8. Yu. S. Tsizin, N. B. Karpova, and O. V. Efimova, Khim. Geterotsikl. Soed., 418 (1971).