INVESTIGATION OF HETEROCYCLIC QUINONES

XIX.* SYNTHESIS AND PROPERTIES OF 2-PHENYL-4-METHOXYQUINAZOLINE QUINONES

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UDC 547.856'864.07

A number of substituted 2-phenyl-4-methoxyquinazoline quinones were synthesized from 2-phenyl-4-methoxy-6-hydroxyquinazoline by oxidative amination. Two isomeric substances, to one of which an o-quinoid structure was assigned, were isolated in the preparation of 2-phenyl-4-methoxy-6-anilinoquinazoline 5,8-quinone.

The application of oxidative amination to 6-hydroxyquinazolines makes a new class of heterocyclic quinones – quinazoline quinones [2] – accessible. Within our plan to synthesize compounds containing structural elements responsible for antibiotic activity [3], we obtained a number of 2-phenyl-4-methoxy-6-aminoquinazoline 5,8-quinone derivatives (VII) and studied some properties of 4-methoxyquinazoline quinones; in particular, we made a qualitative estimate of the ease of nucleophilic attack at C_4.

2-Phenyl-4-methoxy-6-hydroxyquinazoline (I) was oxidized with oxygen in the presence of piperidine and cupric acetate to 2-phenyl-4-methoxy-8-piperidinoquinazoline 5,6-quinone (II) in 82% yield. Compound II displays the usual properties of amino-o-quinones: it forms 1-methoxy-3-phenyl-5-piperidinopyrimido-[5,4-a]phenazine (III) with o-phenylenediamine, undergoes reductive acetylation on reaction with zinc dust and acetic anhydride, and has two characteristic bands at 1600-1700 cm^{-1} in its IR spectrum. It might have been expected that the carbonyl groups in quinone II, which have a pronounced effect on the distribution of the electron density in the pyrimidine ring [2], facilitate nucleophilic attack at C_4. However, replacement of the methoxy group by piperidine does not occur under either the oxidation conditions or on prolonged refluxing of an alcohol solution of quinone II with piperidine. The methoxy group is not involved in the alkaline saponification of II, and 2-phenyl-4-methoxy-6-hydroxyquinazoline 5,8-quinone (V) is formed. Saponification of the methoxy group occurs only under acid hydrolysis conditions. It is known that 4-methoxyquinazolines are converted to 4-quinazolones by the action of acids [4]. We carried out the acid hydrolysis of quinones II and V, and, for comparison, the hydrolysis of the starting 6-hydroxyquinazoline (I). Monitoring with thin-layer chromatography (TLC) on silicic acid demonstrated that complete hydrolysis of I to 2-phenyl-6-hydroxy-4-quinazoline occurs only after refluxing for 2 h in aqueous alcoholic hydrochloric acid. Under these conditions, quinones II and V are also saponified, while 2 h are required for the complete saponification of V. Heating of II in aqueous alcoholic hydrochloric acid for 10 min leads to a mixture of V and VI, from which the latter quinone was isolated in ~50% yield. Thus the presence of a quinoid ring is not reflected substantially in the reactivity of the 4 position of the quinazoline ring.

The method that we developed in [3] was used to convert II to VII. Quinone II gives 2-phenyl-4,6-dimethoxyquinazoline 5,8-quinone (IV) when it is heated in methanol in the presence of concentrated sulfuric acid. The 6-methoxy group in quinone IV is readily replaced by an amine residue on reaction with primary and secondary amines. The reaction proceeds at room temperature with piperidine, methylamine, and butylamine, but proceeds on heating with a weaker base – morpholine. A second quinone, which is

*See [1] for communication XVIII.

E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 841-845, June, 1972. Original article submitted April 27, 1971.

TABLE 1. N-Substituted 2-Phenyl-4-methoxy-6-aminoquinazoline 5,8-Quinones*

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		
			C	H	N
VIIa	183—184 (benzene – hexane, 1 : 1)	$C_{20}H_{19}N_3O_3$	68,9	5,6	12,2
VIIb	210—212 (benzene)	$C_{19}H_{17}N_3O_4$	65,2	5,3	12,0
VIIc	184—185 (alcohol – water, 1 : 1)	$C_{19}H_{18}N_3O_3$	67,5	5,7	12,2
VIId	262—264 (dioxane)	$C_{16}H_{13}N_3O_3$	65,0	4,7	14,3
VIIe	241—243 (benzene)	$C_{21}H_{15}N_3O_3$	70,6	4,4	11,6
VIIf	244—245 (chloroform – hexane, 2 : 1)	$C_{21}H_{15}N_3O_3$	70,8	4,3	11,3

TABLE 1 (continued)

Compound	Calc., %			IR spectrum at 3200-3600 and 1600-1700 cm^{-1}	UV spectrum, λ_{max}, mm (log ε)	Yield, %
	C	H	N			
VIIa	68,8	5,5	12,0	1676 1632 (C=O)	220 (4,35), 245 sh (4,12), 310 (4,33), 350 (4,11)	80
VIIb	65,0	5,0	12,0	1684 1626 (C=O)	220 (4,33), 245 sh (4,12), 303 (4,29), 350 (4,16)	89
VIIc	67,8	5,4	12,5	3358, 3250 b (NH) 1682, 1636 (C=O)	220 (4,31), 253 sh (4,14), 300 (4,36), 348 (4,26)	45
VIId	65,1	4,4	14,3	3342 (NH) 1686, 1650 sh (C=O)	220 (4,28), 258 sh (4,15), 300 (4,33), 349 (4,25)	63
VIIe	70,7	4,2	11,8	3335 (NH) 1693, 1633 (C=O)	220 (4,23), 257 (4,13), 307 (4,17), 350 (4,03)	18
VIIf	70,7	4,2	11,8	3612 vw 3356 (OH) 1675 (C=O), 1640 (C=N)	220 (4,49), 283 (4,34), 304 (4,36), 355 (4,23)	55

*Abbreviations: b is broad, sh is shoulder, and vw is very weak.

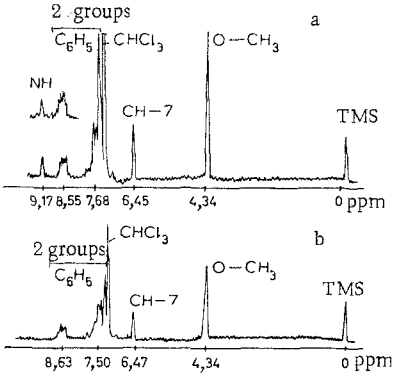
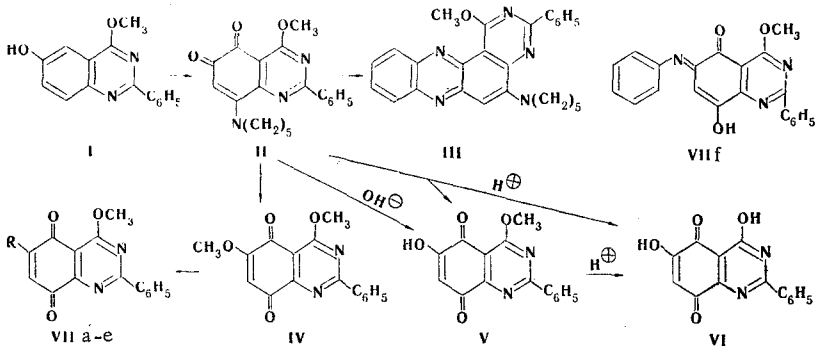


Fig. 1. PMR spectra in $CDCl_3$: a) 2-phenyl-4-methoxy-6-anilinoquinazoline 5,8-quinone (VIIe); b) 2-phenyl-4-methoxy-8-hydroxyquinazoline 5,6-quinone 6-anil VIIf).

detected in the filtrate by TLC, is formed along with the major product (which precipitates) in the reaction of IV with methylamine and butylamine. Treatment of IV with alcoholic ammonia gives a mixture, from which individual substances could not be isolated; TLC demonstrated the presence of quinone V and another three more polar substances with low R_f values. Interesting results were obtained in the reaction of IV with aniline. The reaction does not proceed in methanol even on heating. Brief refluxing of IV in acetic acid with 20% excess aniline gives a mixture of two substances [VIIe and VIIf, by TLC with chloroform–methanol (20 : 1): R_f 0.45 and 0.60, respectively], which was separated chromatographically on silicic acid. Heating of IV in acetic acid with 3 mole of aniline gives VIIf and traces of VIIe. Compounds VIIe and VIIf have close melting points (241-243 and 243-245°, respectively). Their UV spectra differ appreciably, and their IR spectra, although they are close, display distinct differences at 3300-3600 and 1600-1700 cm^{-1} (see Table 1). The elementary analyses of the two substances fit empirical formula $C_{21}H_{15}N_3O_3$, which corresponds to 2-phenyl-4-methoxy-6-anilinoquinazoline 5,8-quinone (VIIe). Quinone VIIf is gradually converted to VIIe on heating in acetic acid, which is readily observed by means of TLC. The product of the conversion of VIIf was isolated by means of preparative TLC on silicic acid and was identified from the IR spectrum as VIIe.

We assumed that tautomeric relationships exist between the compounds obtained and that one of them has a p-quinoid structure, while the other has an o-quinoid structure (VIIe and VIIf, see the scheme below). It is known that amino- and hydroxyquinones can exist in two tautomeric forms [5]. As a rule, one isomer exists in the solid state. A communication regarding the isolation of both tautomers of hydroxycarbostyryl quinone appeared only recently [6]; unfortunately, exhaustive proof of the structures of the isomers was not presented in this paper. In the case of VIIc-e, the o-quinoid form can be stabilized through the formation of a chelate hydrogen bond. In the 6-anilinoquinone there is an

additional possibility of stabilization of the o-quinoid structure (VIIf) through conjugation of the phenyl group of the aniline residue with the heteroring



a R=N(CH$_2$)$_5$; b R=N(CH$_2$CH$_2$)$_2$O; c R=HNC$_4$H$_9$-*n*; d R=NHCH$_3$; e R=NHC$_6$H$_5$

The PMR spectra (Fig. 1) of VIIe and VIIf were recorded to establish their structures. Both substances display singlets that correspond to the protons of the methoxy group and protons attached to C_7 as well as multiplets at 7.6 and 8.6 ppm that correspond to the protons of the aniline residue and the phenyl group attached to C_2. In addition, the PMR spectrum of VIIe has a signal at 9.17 ppm, which can be assigned to the proton attached to the nitrogen atom of the aniline residue, which confirms the p-quinoid structure of VIIe. The signal from the 8-OH proton of VIIf is situated at 7-7.5 ppm [7] and is overlapped by a multiplet from the phenyl protons. With this sort of interpretation of the PMR spectra, the bands in the IR spectra of these compounds can be assigned as indicated in Table 1. The IR spectrum of VIIf contains bands of the stretching vibrations of free and associated OH groups, just as in the case of 8-hydroxyquinoline and its derivatives [8].

EXPERIMENTAL

The PMR spectra of deuterochloroform solutions of the compounds were obtained with an RS-60 spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. The UV spectra of alcohol solutions were recorded with a Unicam^{SP} 800 spectrophotometer. The IR spectra of mineral-oil suspensions were obtained with a UR-20 spectrophotometer. Monitoring of the course of the reactions and determination of the purity of the substances were accomplished by thin-layer chromatography (TLC) on silicic acid with chloroform–methanol (20 : 1) (the chloroform–methanol ratio for V and VI was 2 : 1). The colorless substances were developed in iodine vapors or in UV light.

2-Phenyl-4-methoxy-6-hydroxyquinazoline (I). A 2-g (6.7 mmole) sample of 2-phenyl-4-chloro-6-acetoxyquinazoline [9] was added to a solution of sodium methoxide obtained from 0.46 g (0.02 g-atom) of sodium and 20 ml of methanol, and the mixture was refluxed for 2 h, diluted with 100 ml of water, treated with charcoal, and neutralized with acetic acid. The precipitate was removed by filtration, washed with water, and dried to give 1.3 g (77%) of a colorless substance that was quite soluble in methanol, acetone, alcohol, and ethyl acetate, moderately soluble in benzene, and insoluble in petroleum ether, and had mp 219-220° [from ethyl acetate–heptane (1 : 2)]. Found: C 71.8; H 4.8; N 11.3%. $C_{15}H_{12}N_2O_2$. Calculated: C 71.4; H 4.8; N 11.1%.

2-Phenyl-4-methoxy-8-piperidinoquinazoline 5,6-quinone (II). A 1.26-g (5 mmole) sample of I was oxidized with oxygen in methanol in the presence of 20 mmole of piperidine and 0.05 g of cupric acetate via the method described in [2] to give 1.38 g (79%) of red crystals that were quite soluble in alcohol, acetone, chloroform, dioxane, and ethyl acetate, moderably soluble in methanol and benzene, and slightly soluble in ether, and had mp 192-193° (dec., from benzene). IR spectrum, cm^{-1}: 1688, 1624 (C=O). UV spectrum, λ_{max}, nm (log ε): 220 (4.36), 272 (4.23), 308 (4.27), 360 (4.10). Found: C 69.1; H 5.4; N 12.0%. $C_{20}H_{19}N_3O_3$. Calculated: C 68.8; H 5.5; N 12.0%.

1-Methoxy-3-phenyl-5-piperidinopyrimido[5,4-a]phenazine (III). This compound was obtained as yellow crystals with mp 216-217° (from ethyl acetate) via the method in [2] from II. Found: C 73.9; H 5.4; N 16.6%. $C_{26}H_{23}N_5O$. Calculated: C 74.1; H 5.5; N 16.6%.

2-Phenyl-4-methoxy-5,6-diacetoxy-8-piperidinoquinazoline. A mixture of 0.35 g (1 mmole) of II, 25 ml of acetic anhydride, 2 ml of pyridine, and 2 g of zinc dust was refluxed for 10 min, during which the solution became colorless. The reaction mixture was cooled, the zinc dust was removed by filtration, and the filtrate was vacuum-evaporated to dryness. The residue was extracted with dioxane, and water was added to the extract until crystallization commenced to give 0.4 g (92%) of light-yellow crystals with mp 187-189° (from aqueous dioxane) that were quite soluble in alcohol, slightly soluble in benzene, and insoluble in water. IR spectrum, cm^{-1}: 1756 (C=O). Found: C 66.1; H 6.1; N 9.7%. $C_{24}H_{26}N_3O_5$. Calculated: C 66.0; H 6.0; N 9.6%.

2-Phenyl-4-methoxy-6-hydroxyquinazoline 5,8-quinone (V). A solution of 0.4 g (10 mmole) of sodium hydroxide in 2 ml of water was added to a suspension of 0.7 g (2 mmole) of II in 10 ml of alcohol, and the mixture was stirred at 20° for 1.5 h and neutralized with 3 ml of 4 N hydrochloric acid. The precipitate was separated, washed with water, and dried to give 0.47 g (83%) of yellow crystals that were quite soluble in acetone, ethyl acetate, chloroform, dioxane, moderately soluble in benzene, and had mp 201-203° (from benzene). IR spectrum, cm^{-1}: 3170 s (associated OH), 1690, 1643 (C=O). Found: C 64.3; H 4.1; N 10.1%. $C_{15}H_{10}N_2O_4$. Calculated: C 64.1; H 3.7; N 9.9%.

Saponification of 2-Phenyl-4-methoxy-6-hydroxyquinazoline (I). A 0.018-g (0.07 mmole) sample of I was refluxed in a mixture of 0.08 ml of 4 N hydrochloric acid and 0.5 ml of methanol. After 2 h (as monitoried by TLC every 20 min), I (R_f 0.7) was conferted to 2-phenyl-6-hydroxy-4-quinazolone [1] (R_f 0.5).

2-Phenyl-4,6-dihydroxyquinazoline 5,8-quinone (VI). A) A suspension of 0.7 g (2 mmole) of II in a mixture of 8 ml of methanol and 2 ml of 4 N hydrochloric acid was refluxed for 10 min. The substance initially dissolved, and a precipitate formed after 5 min. The suspension was cooled, and the precipitate (a mixture of quinones V and VI) was separated. Quinone V was extracted with 40 ml of hot benzene. The benzene solution contained V [R_f 0.8 in chloroform–methanol (2:1)]. The insoluble portion was removed by filtration and dried to give 0.24 g (46%) of VI as light-yellow crystals that were moderately soluble in methanol, alcohol, acetone, and dioxane, and insoluble in benzene and chloroform, and had R_f 0.5. After recrystallization from dioxane, the product decomposed above 240° and was identical (with respect to the IR spectra and R_f values) to the substance obtained in [1]. IR spectrum, cm^{-1}: 3100 b (associated OH), 1692, 1655, 1630 (C=O). Found: C 61.0; H 4.3%. $C_{14}H_8N_3O_4$. Calculated: C 60.7; H 4.5%.

B) A suspension of 0.28 g (1 mmole) of V was refluxed in a mixture of 4 ml of methanol and 1 ml of 4 N hydrochloric acid for 2 h. The mixture was cooled, and the precipitate was removed by filtration and worked up as described in method A to give 0.24 g (88%) of product.

2-Phenyl-4,6-dimethoxyquinazoline 5,8-Quinone (IV). A 1-g (2.86 mmole) sample of II in a mixture of 10 ml of methanol and 0.5 ml of concentrated sulfuric acid was refluxed for 10 min and cooled. The resulting precipitate was separated, washed with 5 ml of methanol and 5 ml of ether, and dried to give 0.6 g (71%) of yellow crystals with mp 275-277° (dec., from dioxane) that were quite soluble in chloroform and dioxane and moderately soluble in methanol and ethyl acetate. IR spectrum, cm^{-1}: 1690, 1653 (C=O). Found: C 64.7; H 4.4; N 9.3%. $C_{16}H_{12}N_2O_4$. Calculated: C 64.8; H 4.1; N 9.4%.

N-Substituted 2-Phenyl-4-methoxy-6-aminoquinazoline 5,8-Quinones (VIIa-d). A mixture of 3 mmole of IV, 9 mmole of amine (6 mmole in the case of butylamine), and 20 ml of methanol was stirred at 20° (under reflux in the case of morpholine) until the mixture no longer gave the color reaction for methoxyquinones with cyanoacetic ester and ammonia [10]. The precipitate was separated, washed with methanol and ether, dried, and recrystallized. Quinones VII are red or dark-red crystals that are moderately soluble in alcohol, chloroform, and benzene, and insoluble in ether and petroleum ether. Quinone VIId was insoluble in alcohol and benzene and moderately soluble in chloroform and dioxane. The characteristics of the compounds obtained are presented in Table 1.

Reaction of IV with Aniline. A) A mixture of 0.90 g (3 mmole) of IV and 0.3 ml (3.6 mmole) of aniline in 30 ml of acetic acid was refluxed until it no longer gave a reaction for IV (~30 min), and it was then evaporated in vacuo to dryness. The residue was chromatographed with a column (2.5 by 30 cm) filled with silicic acid with elution initially with 200 ml of benzene followed by 200 ml of chloroform. The benzene eluate was evaporated to give 0.5 g (55%) of VIIf with mp 243-245° [from chloroform–hexane (2:1)] and R_f 0.60. The chloroform eluate yielded 0.20 g (18%) of VIIe with mp 241-143° (from benzene) and R_f 0.45 (see Table 1).

B) A 0.27-g (0.9 mmole) sample of IV and 0.25 ml (2.7 mmole) of aniline in 9 ml of acetic acid were refluxed for 40 min, and the mixture was cooled and diluted with 50 ml of water. The precipitate was separated, washed with water, and dried to give 0.25 g (78%) of VIIf with R_f 0.60.

Conversion of Quinone VIIf to VIIe. A solution of 0.02 g of VIIf in 1 ml of acetic acid was refluxed for 2 h and cooled. Chloroform (10 ml) was added, and the chloroform solution was washed with water until it was neutral (twice with 5-ml portions). It was then dried with sodium sulfate and evaporated. The residue (a mixture of quinones VIIf and VIIe) was subjected to preparative chromatography on a loose layer of silicic acid with elution with chloroform–methanol (20 : 1) to give 0.005 g of a substance with R_f 0.45 that was identical to VIIe according to the IR spectra.

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