INVESTIGATION OF HETEROCYCLIC QUINONES

XXI.* SUBSTITUTION OF A METHYL GROUP DURING OXIDATIVE AMINATION

N. B. Karpova and Yu. S. Tsizin

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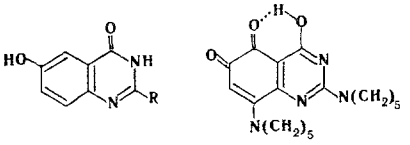
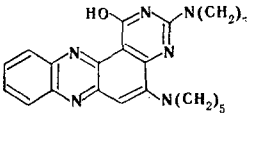
Substitution of the methyl group by an amine residue to give 2,8-dipiperidino-4-hydroxyquinazoline-5,6-quinone occurs in the oxidative amination of 2-methyl-6-hydroxy-4-quinazolone in the presence of a Cu^{2+}–piperidine complex. The possible mechanism of the reaction is discussed.

In a continuation of our investigation of quinazolinequinones, we carried out the oxidative amination of 2-methyl-6-hydroxy-4-quinazolone (Ia) in the presence of a copper–piperidine complex. Like other 6-hydroxy-4-quinazolones, Ia is oxidized only with an equivalent amount of metal salt, since copper is bonded to the resulting quinone as a chelate complex [2]. Acidification of the reaction mass with a strong acid is necessary to decompose the latter. The reaction is accompanied by increased oxygen absorption (2.5 mole) and leads to a mixture of quinones, from which 2,8-dipiperidino-4-hydroxyquinazoline-5,6-quinone (II) is isolated in ~20% yield after chromatography on silicic acid.



Ia, b

II



III

Ia R = CH_3; b R = H

The structure of II was confirmed by the results of elementary analysis, by IR spectroscopy, and by a comparison of it with a sample previously obtained by oxidation of Ib [2]. The phenazine derivatives (III) of both quinones are also identical. The PMR spectrum of II shows, in addition to signals of protons of piperidine residues, the singlet of a proton attached to $C_{(7)}$ (δ 6.05 ppm) and a singlet at weak field (δ 12.95 ppm), which corresponds to the proton of a hydroxyl group linked by a strong intramolecular hydrogen bond.

Substitution of a methyl group in the process is an unusual phenomenon. Elimination by oxidation of the methyl group to a carboxyl group and subsequent decarboxylation should be excluded, since we did not detect carbonate ions in the reaction mass. A mechanism based on the assumption that the effect of the quinoid ring is transmitted through the pyrimidine ring is more acceptable. This assumption is completely correct, since amination of benzothiazole- [3] and quinazolinequinones [4] at $C_{(2)}$, which was previously observed, is also readily explained by transmission of the effect of the carbonyl groups of quinones. It is known that substitution of alkyl groups by an amine residue can occur in the reaction of alkyl-o-benzoquinones with aromatic amines [5, 6]. In this case, it is assumed that the amines react with alkylquinones in the hydroxyquinomitide form to give aminomethyl derivatives [5, 7]. There is no single opinion in connection with what the mechanism of splitting out of an aminomethyl group is, but it has been established that it is split out as formaldehyde [5, 8].

On the basis of the analogy with benzoquinones and having in view the increased consumption of oxygen, we can assume that quinone IV, which in tautomeric form V adds piperidine to give VI, is initially

*See [1] for communication XX.

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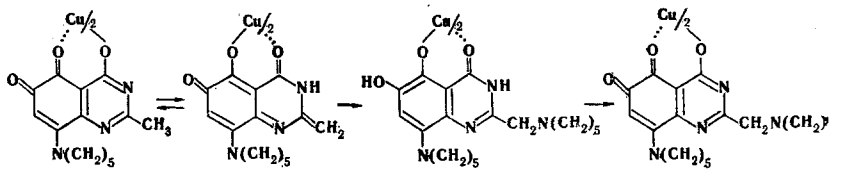
formed in the oxidation of Ia. Compound VI is oxidized to quinone VII, after which either direct substitution of the piperidinomethyl group occurs [5] or a reverse Mannich reaction occurs initially, followed by amination of the free $C_{(2)}$ position [8].



IV V VI VII

The formation of IV is accompanied by the consumption of 1.5 mole of O_2, while another mole of O_2 is necessary for the conversion of VI to II; thus the overall consumption of oxygen is 2.5 mole, as experimentally observed.

EXPERIMENTAL

The PMR spectra of deuterochloroform solutions were recorded with a JNM-4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions of the compounds were determined with an SF-4 spectrophotometer. The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) in a loose layer of silicic acid in chloroform–methanol (20 : 1).

2-Methyl-6-methoxy-4-quinazolone. This compound, with mp 264-265° (mp 257° [9]), was obtained in 22% yield by condensation of N-acetyl-p-anisidine with ethyl carbamate in the presence of phosphorus pentoxide by the method described in [9].

2-Methyl-6-hydroxy-4-quinazolone (Ia). A solution of 5.4 g (28 mmole) of 2-methyl-6-methoxy-4-quinazolone in 76 ml of 48% HBr was refluxed for 48 h. The mixture was then cooled and poured over ice, and the precipitate was separated and dissolved in 20 ml of 5% NaOH. The solution was treated with charcoal and neutralized with 15 ml of acetic acid. The precipitate was removed by filtration and dried to give 3.2 g (65%) of a colorless substance that did not change on heating to 330° (from alcohol). Found: C 61.2; H 4.9; N 16.0%. $C_9H_8N_2O_2$. Calculated: C 61.4; H 4.6; N 15.9%.

2,8-Dipiperidino-4-hydroxyquinazoline-5,6-quinone (II). A 1.8-g (10 mmole) sample of Ia was added to a solution of 1 g (0.5 mmole) of copper acetate in a mixture of 8 ml (80 mmole) of piperidine and 12 ml of methanol, and the suspension was stirred under an oxygen atmosphere. After 1.5 h, the mixture had adsorbed 560 ml of O_2 (25 mmole). It was then cooled to 5°, diluted with 50 ml of chloroform, and acidified with 27 ml of 4 N HCl. The chloroform solution was washed with water, dried with sodium sulfate, and evaporated. The residue (1.4 g) was chromatographed with a column (5 by 30 cm) filled with silicic acid with elution with benzene–chloroform (4 : 1) to give 0.6 g (18%) of violet crystals that were quite soluble in alcohol and chloroform, moderately soluble in ethyl acetate, dioxane, and benzene, and insoluble in ether and petroleum ether. The product had mp 195-196° [from ethyl acetate–heptane (1 : 1)]. No melting-point depression was observed for a mixture of this product with a sample obtained from Ib [2]. IR spectrum, ν, cm^{-1}: 1628, 1605. UV spectrum, λ_{max}, nm (log ε): 246 (4.32), 280 (4.14), 390 (4.26). PMR spectrum: signal at δ 1.79 ppm (12H, β, γ-CH_2), signals at 3.74 and 3.94 ppm (8H, α-CH_2), singlet at 6.05 ppm [1H attached to $C_{(7)}$], singlet at 12.95 ppm (OH group). Found: C 63.0; H 6.5; N 16.6%. $C_{18}H_{22}N_4O_3$. Calculated: C 63.1; H 6.5; N 16.3%.

A special experiment was set up to determine the presence of carbonate ions in the reaction medium; in this experiment, after O_2 absorption had ceased, the reaction mass was carefully acidified with 2 N H_2SO_4, without connecting the system to the atmosphere, with simultaneous bubbling of oxygen through it and then through a bottle filled with barium hydroxide solution. No barium carbonate precipitation was observed.

1-Hydroxy-3,5-dipiperidinopyrimido[5,4-a]phenazine (III). This compound, with mp 239-240° (from dioxane), was obtained by heating 1 mmole of quinone II with 1.2 mmole of o-phenylenediamine in acetic acid. The product was identical to the compound described in [2]. Found: N 20.3%. $C_{24}H_{26}N_6O$. Calculated: N 20.3%.

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