A STUDY OF HETEROCYCLIC QUINONES

IV. 4-Carboxy-2-phenylquinoline Quinones*

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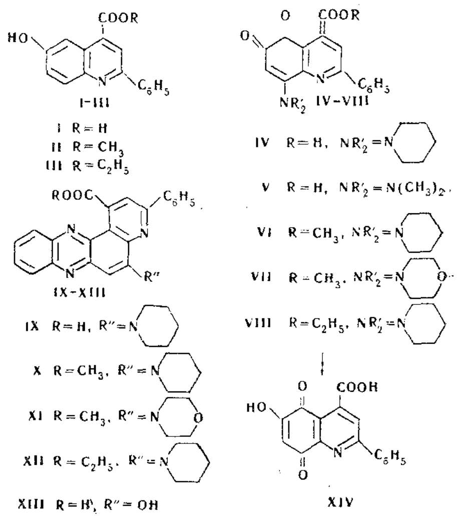
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 4, pp. 687–689, 1969

UDC 547.831.6.8.9:542.943

The oxidation of 6-hydroxy-2-phenylquinoline-4-carboxylic acid and its esters to the corresponding quinoline quinones has been studied.

In studying the oxidation of 6-hydroxyquinolines with oxygen in the presence of a Cu^{++}–secondary amine complex [1–3], it appeared of interest to determine how the presence of electron-accepting substituents in the pyridine nucleus is reflected in the course of the reaction. We have studied the oxidation of 6-hydroxy-2-phenylquinoline-4-carboxylic acid and its esters (I–III). It was to be expected that the oxidation both of the free acid and of its esters would take place in the presence of catalytic amounts of copper ions since, in contrast to derivatives of 4-hydroxyquinoline [3], the reaction products cannot form stable copper complexes. In actual fact, the oxidation of I–III takes place exceptionally readily, giving high yields of the corresponding quinones IV–VIII. The oxidation of the free acid I takes place satisfactorily only in the presence of highly basic secondary amines (piperidine, dimethylamine), while with the less basic morpholine the reaction takes place far more slowly and ceases after the absorption of 40–50% of the calculated amount of oxygen.



Mild alkaline saponification of the quinones IV–VIII leads to 4-carboxy-6-hydroxy-2-phenylquinoline 5,8-quinone (XIV), which behaves as a dibasic acid. Potentiometric determination of the ionization constants in 50% ethanol at 20° C gave pK_1 3.03 ± 0.03 and pK_2 4.61± ± 0.09.

With o-phenylenediamine, all the quinones obtained form phenazines (IX–XIII). The IR spectra of IV–VIII and XIV contain, in addition to the bands of the carbonyl absorption of quinones (in the 1600–1690 cm^{-1} region) bands that can be assigned to the carbonyl absorption of the carboxyl (or alkoxycarbonyl) group (in the 1705–1740 cm^{-1} region) (Table 1).

EXPERIMENTAL

The IR spectra were taken in paraffin oil on a UR-10 spectrophotometer and the pK_a values were calculated from the potentiometric titration curves obtained on a LPU-01 pH-meter.

6-Hydroxy-2-phenylquinoline-4-carboxylic acid (I). This was obtained by Lutz's method from p-aminophenol, benzaldehyde, and pyruvic acid. Yield 35%. Mp 328–330° C (decomp.), which corresponds with literature data [5].

Methyl 6-hydroxy-2-phenylquinoline-4-carboxylate (II). A solution of 10 g (38 mM) of I in a mixture of 50 ml of methanol and 5 ml of conc H_2SO_4 was boiled for 8 hr, cooled, poured into 500 ml of ice-water, and neutralized with sodium carbonate solution. The precipitate was separated off, washed with water, and recrystallized from aqueous (1 : 2) methanol. Yield 7.8 g (74%). Yellow crystals with mp 166–167° C. Found, %: C 73.28; H 4.73; N 5.08. Calculated for $C_{17}H_{13}NO_3$, %: C 73.11; H 4.69; N 5.02.

Ethyl 6-hydroxy-2-phenylquinoline-4-carboxylate (III). This was obtained in a similar manner to II from I and ethanol. Yield 61%. Yellow crystals with mp 166–167° C. Found, %: N 4.82. Calculated for $C_{18}H_{15}NO_3$, %: N 4.78.

4-Carboxy-2-phenyl-8-piperidinoquinoline 5,8-quinone (IV) and 4-carboxy-8-dimethylamino-2-phenylquinoline 5,8-quinone (V). A solution of 4.0 g (15 mM) of I and 0.05 g of copper acetate in 30 ml of a methanolic solution of a secondary amine (piperidine, dimethylamine) was stirred at 15–20° C and 760 mm in an atmosphere of oxygen. The reaction mixture immediately became red and its temperature rose to 30–35° C. After 1 hr, when ~580 ml of oxygen had been absorbed, the evolution of heat and the absorption of gas ceased. The reaction mixture was acidified with cooling and stirring, using a mixture of 15 ml of 4 N HCl and 30 ml of ethanol. After 30 min, the precipitate of quinone was filtered off, washed with water (20 ml), methanol (10 ml), and ether (20 ml), and dried in the desiccator. It formed dark red crystals sparingly soluble in the majority of organic solvents and in water. The compound decomposed when an attempt was made to recrystallize it from acetic acid. For analysis, a small amount of the substance was recrystallized from ethanol (Table 1).

Oxidation of esters of 6-hydroxy-2-phenylquinoline-4-carboxylic acid. Preparation of VI–VIII. To a solution of 0.05 g of copper acetate in a mixture of 20 mM of a secondary amine and 10 ml of methanol was added 10 mM of II (or III) and the mixture was stirred in an atmosphere of oxygen until the absorption of the gas ceased (about 2 hr). The precipitate of quinone was filtered off, washed with ethanol (5 ml), and ether (10 ml) and dried in the desiccator. This gave red crystals soluble in chloroform and insoluble in water and petroleum ether (Table 1).

4-Carboxy-6-hydroxy-2-phenylquinoline 5,8-quinone (XIV). A) A solution of 14.5 g (40 mM) of IV in 120 ml of 1 N caustic soda was heated at 40° C for 30 min and then 90 ml of acetone was added and it was acidified with 48 ml of 4 N HCl. The mixture was cooled, and

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*For part III, see [3]

Table 1
4-Carboxy- and 4-Alkoxycarbonyl-8-dialkylamino-2-phenylquinoline 5,6-Quinones

Compound	Solvent for recrystallization	Absorption in the IR spectrum, cm^{-1}		Decomp. p., °C	Empirical formula	Found, %			Calculated, %			Yield, %
		$\nu_{C=O}$(COOR)	$\nu_{C=O}$,			C	H	N	C	H	N	
IV	Ethanol	1720	1690, 1605	200	$C_{21}H_{18}N_2O_4$	69.86	5.22	7.60	69.60	5.01	7.73	85
V	Ethanol	1720	1690, 1600	208—210	$C_{18}H_{14}N_2O_4$	66.68	4.58	—	67.07	4.38	—	93
VI	Benzene	1740, 1730	1690, 1625	192—193	$C_{22}H_{20}N_2O_4$	70.44	5.13	7.36	70.20	5.36	7.44	74
VII	Chloroform-hexane (1 : 1)	1737	1690, 1630	200—201	$C_{21}H_{18}N_2O_5$	66.54	4.74	7.03	66.66	4.80	7.40	78
VIII	Ethanol	1735	1690, 1615	171—172	$C_{23}H_{22}N_2O_4$	70.83	5.56	7.39	70.75	5.68	7.18	97

Table 2
Pyrido[3,2-a]phenazines

Compound	Solvent for recrystallization	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IX	Dioxane-water (2 : 1)	248—250, разл.	$C_{27}H_{22}N_4O_2 \cdot 1/2H_2O$	73.27	5.52	13.00	73.12	5.23	12.63	90
X	Benzene-hexane (1 : 1)	189—191	$C_{28}H_{24}N_4O_2$	75.35	5.46	12.85	74.98	5.39	12.49	95
XI	Dioxane	244—245	$C_{27}H_{22}N_4O_3$	72.31	5.01	12.07	71.98	4.92	12.44	96
XII	Ethanol	166—167	$C_{29}H_{26}N_4O_2$	75.44	5.98	11.93	75.30	5.67	12.11	82
XIII	Dioxane-water (1 : 1)	297—298, decomp.	$C_{22}H_{13}N_3O_3$	72.26	3.82	11.25	71.93	3.57	11.44	61

the precipitate was filtered off, washed with 50 ml of water, and dried in the desiccator. Yield of 10.6 g (84.6%). Yellow crystals readily soluble in dimethylformamide, moderately soluble in dioxane, sparingly soluble in ethanol, ethyl acetate, and acetic acid, insoluble in ether and benzene. Mp 241–243° C (decomp., from dioxane). Found, %: C 61.70; H 3.60; N 4.74. Calculated for $C_{16}H_9NO_5 \cdot H_2O$, %: C 61.34; H 3.54; N 4.47. IR spectrum: ν 1720, 1705, 1680 and 1650 cm^{-1}.

B) A suspension of 1.3 g (3.5 mM) of **VI** in a mixture of 10.5 ml of 1 N caustic soda, 15 ml of water, and 25 ml of ethanol was stirred at 18–20° C for 3 hr, and the resulting solution was acidified with 20 ml of 1 N HCl. The precipitate was filtered off, washed with water, and dried. Yield 1.0 g (92%). Mp 242–243° C (decomp., from dioxane). It gave no depression of the melting point with the sample obtained in experiment (A).

Methyl 3-phenyl-5-piperidinopyrido[3, 2-a]phenazine-1-carboxylate (X). A solution of 0.38 g (1 mM) of **VI** in 6 ml of ethanol heated to the boil was treated with 0.12 g (1.1 mM) of o-phenylenediamine and the mixture was heated to the boil for 10 min. After 2 hr, the precipitate was separated off, dried, and recrystallized from benzene-hexane (1:1). Orange crystals, readily soluble in benzene and dioxane, moderately soluble in acetone, and ethyl acetate, sparingly soluble in ether and petroleum ether, and insoluble in water.

The phenazines **IX** and **XI–XIII** (Table 2) were obtained similarly.

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15 February 1967

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