INVESTIGATION OF HETEROCYCLIC QUINONES

XXIII.* 2-CHLOROQUINOLINEQUINONES

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UDC 547.831.8

A number of 2-substituted quinoline-5,6-quinones were synthesized by oxidative amination of 2-substituted 6-hydroxyquinolines. 2-Chloroquinolinequinones, in which the halogen is activated owing to the joint effect of the carbonyl group and the heteroatom, were obtained from 2-chloro-4-methyl-6-hydroxyquinoline.

The few known 2-substituted quinolinequinones are usually obtained by traditional methods [2]. In connection with the search for methods for the synthesis of the antibiotic streptonigrin [3] and its analogs, interest has been displayed in these compounds, but only 2-piperidino(morpholino)quinoline-5,8-quinones could be obtained by a multistep synthesis [4].

Continuing our study of the oxidation of heterocyclic phenols with oxygen in the presence of a Cu^{2+}-secondary amine complex, we obtained a number of 2-substituted quinolinequinones in one to two steps from the appropriate 6-hydroxyquinolines. 2-Chloro-4-methyl-6-hydroxyquinoline (IV), as one of the most accessible 2-chloro-6-hydroxyquinolines, was used as the starting compound. Compound IV was converted by the usual methods to 2-morpholino-4-methyl-6-hydroxyquinoline (I) and 2-phenoxy-4-methyl-6-hydroxyquinoline (VII).

Quinones IIa and IIb are formed in yields of 64 and 76%, respectively, in the oxidation of I with oxygen in the presence of a copper–piperidine(morpholine) complex.

Quinones IIb and IIc, containing identical secondary amine residues attached to $C_{(2)}$ and $C_{(8)}$, were obtained by oxidation of IV (Table 1). As in the case of 4-chloro-6-hydroxyquinolines [5], substitution of chlorine occurs under mild conditions owing to the acceptor effect of $C_{(5)}=O$. In contrast to IV, substitution of the phenoxy group by an amine residue does not occur in the oxidation of VII, and 2-phenoxyquinones VIII are formed. In all cases, the oxidation was carried out with a 6-hydroxyquinoline to secondary amine ratio of 1:4 to 1:8.

By decreasing the amount of amine it proved possible to stop the oxidation of IV at the step involving the formation of 2-chloro-4-methyl-8-piperidino(morpholino)quinoline-5,6-quinone (Va, b). Thin-layer chromatography showed that quinones V are formed when the ratio of IV to secondary amine is 1:1. Until very recently, 2-(or 4-)haloquinolinequinones had not been obtained, although they are of interest in view of the high lability of the halogen. The first quinone of this type – 2-methyl-4-chloroquinoline-5,6-quinone – was described in [5]; it is unstable and rapidly decomposes on storage. Quinones V are more stable but also decompose on standing in solutions and in the solid state, particularly in light.

It should be noted that the oxidative amination of 2-methyl-4-chloro-6-hydroxyquinoline (IX), an isomer of IV, gives almost exclusively the 4,8-diaminoquinones previously obtained in [5], even in the presence of 1 mole of secondary amine. This is apparently explained by the low solubility of IX in methanol and dimethylformamide, which were used as the solvents, owing to which there is always an excess of the secondary amine in solution. Consequently, 2-(or 4-)chloroquinolinequinones can be obtained by this method only from 2-(or 4-)chloro-6-hydroxyquinolines that are sufficiently soluble in the reaction medium.

*See [1] for communication XXII.

E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1700-1704, December, 1973. Original article submitted January 23, 1973.

TABLE 1. 2,8-Disubstituted 4-Methylquinoline-5,6-quinones

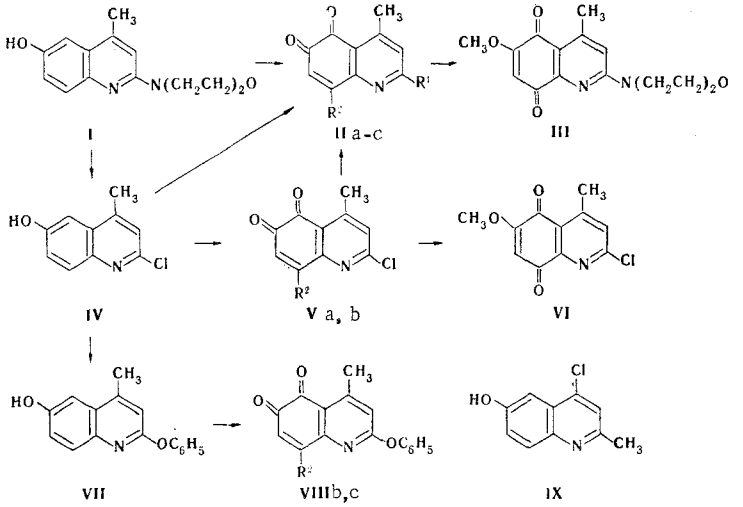
Compound	Starting compound	mmole of secondary amine	Reaction time, h	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	IR spectrum	Yield, %
IIa	I	40	2,0	202—202,5	$C_{19}H_{23}N_3O_3$	67,0	6,8	12,4	66,8	6,8	12,3	1663m, 1622 s, 1592s, 1550s	64
	IV	80	2,0										47
IIc	I	40	2,2	196—197	$C_{18}H_{21}N_3O_4$	63,0	6,3	12,3	63,0	6,2	12,2	1665m, 1625 s, 1592 s, 1565 s	76
	IV	40	4,0										36
IIb	IV	80	2,0	173—174,5	$C_{20}H_{25}N_3O_2$	71,1	7,6	12,1	70,8	7,4	12,4	1668 m, 1640s, 1592 s, 1575s	48
Va	IV	10	0,75	154—156	$C_{15}H_{15}ClN_2O_2$*	—	—	9,2	—	—	9,6	1692m, 1622s, 1580m, 1550 s	65
Vb	IV	11	1,5	160—161	$C_{14}H_{13}ClN_2O_3$†	—	—	9,3	—	—	9,6	1690 m, 1650 s, 1580 m, 1554 s	32
VIIIb	VII	40	2,0	201—202	$C_{20}H_{18}N_2O_4$	—	—	8,2	—	—	8,0	1680 m, 1630 s 1570 s	80
VIIIc	VII	40	1,0	184—185	$C_{18}H_{16}N_2O_3$	—	—	9,3	—	—	9,1	1680 m, 1622 s 1570 s	72

*After vacuum drying (for 3 h at 70° and 2 mm): found: Cl 12.6%; calculated: Cl 12.2%. Before drying: Cl 21.0; N 8.7%. $C_{15}H_{15}ClN_2O_2 \cdot \frac{1}{3} CHCl_3$. Calculated: Cl 21.5; N 8.5%. Loss in weight on drying: found 11.5%; calculated: 12.0%.

†Found: Cl 12.2%. Calculated: Cl 12.1%.

The halogen in quinones V is labile and is readily substituted by the action of nucleophilic reagents. Thus Va in methanol containing an excess of morpholine undergoes more than 50% conversion to IIa in 90 min at 20°; the conversion of Va to IIb under similar conditions proceeds even more rapidly — in 30 min (monitored by TLC).

The results show that the sequence of reactions during the oxidative amination of IV is as follows: initially there is 1,4-addition of the secondary amine to intermediate quinone X, after which the resulting 5,6-dihydroxy derivative is oxidized to 2-chloroquinone V, and the latter reacts with excess amine to give II (see [6, 7]).



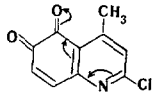
II a $R^1 = N(CH_2CH_2)_2O$, $R^2 = N(CH_2)_5$; b $R^1 = R^2 = N(CH_2)_5$; c $R^1 = R^2 = N(CH_2CH_2)_2O$;

V, VIII a $R^2 = N(CH_2)_5$; b $R^2 = N(CH_2CH_2)_2O$; c $R^2 = N(CH_3)_2$

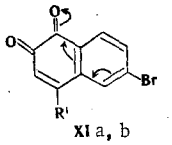
The substituents attached to $C_{(2)}$ have a pronounced effect on the position of the band of carbonyl absorption of the quinones: while it is found at ~1690 cm^{-1} in the spectra of 2-chloroquinones V, the carbonyl maximum of 2-piperidino(morpholino)quinones II is at 1663-1668 cm^{-1} (Table 1); this indicates transmission of the mesomeric effect.

o-Quinones II and V are converted to 6-methoxyquinoline-5,8-quinones (III and VI, respectively) on heating in methanol in the presence of sulfuric acid via the method in [8].

The high reactivity of chlorine in quinones V and VI can be used to obtain other 2-substituted quinoline-quinones from them.



X



XI a, b

XI a $R' = N(CH_2)_5$

b $R' = N(CH_2CH_2)_2O$

2-Hydroxy-6-bromonaphthalene was oxidized in order to obtain a qualitative evaluation of the contribution of the carbonyl group to activation of the halogen. In this case, only quinones XI were obtained, even with a large excess of secondary amines, i.e., substitution of bromine in naphthoquinones does not occur under the conditions of oxidative amination. Alkaline saponification of quinones XI leads to the previously described 2-hydroxy-6-bromo-1,4-naphthoquinone (XII). Thus it was shown that activation of the halogen in quinones V is insured owing to the joint effect of the carbonyl group and the nitrogen heteroatom.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. Thin-layer chromatography on Silufol plates (Czechoslovakian SSR) in methanol–chloroform (1:20) was used to monitor the course of the reactions and determine the purity of the quinones. The colorless substances were developed with iodine vapors or in UV light.

2-Chloro-4-methyl-6-hydroxyquinoline (IV). A solution of 4.0 g (19 mmole) of 2-chloro-4-methyl-6-methoxyquinoline [9] in a mixture of 20 ml of concentrated H_2SO_4 and 11.4 ml of water was refluxed for 5 h, cooled, diluted with 80 ml of water, and made alkaline with 25% ammonium hydroxide. The precipitate was separated, washed with water, and recrystallized from 50% aqueous alcohol to give 2.9 g (76%) of colorless crystals that were quite soluble in alcohol and acetone and slightly soluble in benzene and ether. The product had mp 193.5-194.5°. Found: C 62.2; H 4.2; Cl 18.1; N 7.4%. $C_{10}H_8ClNO$. Calculated: C 62.0; H 4.2; Cl 18.3; N 7.2%.

2-Morpholino-4-methyl-6-hydroxyquinoline (I). A solution of 19.3 g (100 mmole) of IV in 50 ml (0.58 mole) of morpholine was refluxed for 5 h, cooled, and poured into 500 ml of water. The aqueous mixture was extracted with chloroform (four 50-ml portions), and the extract was washed with water, dried with Na_2SO_4, and evaporated to a volume of 50 ml. It was then treated with 100 ml of hexane, and the precipitate was separated and dried to give 22.9 g (94%) of colorless crystals that were quite soluble in alcohol and acetone and moderately soluble in benzene and ether. The product had mp 169-170° (from toluene). Found: C 68.9; H 6.5; N 11.7%. $C_{14}H_{16}N_2O_2$. Calculated: C 68.8; H 6.6; N 11.5%.

2-Phenoxy-4-methyl-6-hydroxyquinoline (VII). A mixture of 1.93 g (10 mmole) of IV, 10 g (106 mmole) of phenol, and 0.44 g (11 mmole) of NaOH was refluxed for 1 h and 10 min, after which it was cooled and transferred into 150 ml of water. The aqueous mixture was treated with 0.5 ml of acetic acid, and the precipitate was triturated, removed by filtration, washed with water, dried, and recrystallized from toluene to give 1.70 g (68%) of colorless crystals (mp 191-193°) that were quite soluble in alcohol and acetone and moderately soluble in benzene. The product had mp 191-193°. Found: C 76.8; H 5.1; N 5.5%. $C_{16}H_{13}NO_2$. Calculated: C 76.5; H 5.2; N 5.6%.

Oxidation of I, IV, and VII. A 10-mmole sample of I (or IV or VII) was added to a solution of 0.1 g of cupric acetate in a mixture of 12 ml (40 ml in the preparation of VIIIb) of methanol and n mmole of a secondary amine (see Table 1). The reaction mixture was stirred in an oxygen atmosphere until gas absorption had ceased. The solid material was separated, washed with a small amount of methanol and ether, and dried in a desiccator. The yield based on the material that precipitated is indicated in Table 1. An additional amount of quinone can be obtained by dilution of the filtrate with water and extraction with chloroform. The chloroform solution was washed successively with water, 3% acetic acid, and water, dried with Na_2SO_4, evaporated to a small volume, and chromatographed on silicic acid with elution of the quinone with chloroform (monitoring by TLC). The quinones were crystallized from chloroform–hexane (from benzene in the case of Vb and VIIIc); they were obtained as crystalline substances of various shades of red, melted with decomposition, were quite soluble in chloroform (except for VIIIb) and acetic acid, were less soluble in alcohol, and moderately or only slightly soluble in ether. Some of the compounds were crystallized with a solvent, which was removed by heating in vacuo. The properties of the substances are presented in Table 1.

Reaction of V with Amines. A 2-mmole sample of piperidine (or morpholine) was added to a solution of 0.2 mmole of V in 1 ml of methanol, and the mixture was stirred at 20° with removal of a sample for TLC every 10 min. Control spots on the thin-layer chromatogram were compared with a genuine mixture of V and II (1 : 1). Compound V gave the same pattern on the chromatogram as a known mixture with piperidine after 30 min (conversion to IIb) and after 90 min with morpholine (conversion to IIa).

2-Morpholino-4-methyl-6-methoxyquinoline-5,8-quinone (III). A solution of 0.75 g (2.2 mmole) of IIc in a mixture of 7.5 ml of methanol and 0.5 ml of concentrated H_2SO_4 was refluxed for 45 min, cooled, and treated with 30 ml of chloroform and 20 ml of water. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (two 10-ml portions). The combined chloroform extracts were washed with water (three 10-ml portions), dried with Na_2SO_4, evaporated to 2 ml, and diluted with 20 ml of hexane. The precipitate was separated, washed with hexane, and dried to give 0.42 g (67%) of orange crystals that were quite soluble in alcohol and benzene and had mp 163-165° (dec., from ethyl acetate–hexane). IR spectrum: 1660 s, 1590 s (broad). Found: N 9.9%. $C_{16}H_{18}N_2O_3$. Calculated: N 9.8%.

2-Chloro-4-methyl-6-methoxyquinoline-5,8-quinone (VI). A solution of 1.00 g (3.4 mmole) of Va in a mixture of 8 ml of methanol and 0.6 ml of concentrated H_2SO_4 was refluxed for 30 min (yellow needles of VI began to precipitate immediately after heating was begun). The reaction mixture was cooled and diluted with 30 ml of water, and the precipitate was removed by filtration, washed with water, and dried to give 0.48 g (59%) of bright-yellow needles that were moderately soluble in acetic acid and only slightly soluble in benzene, ethyl acetate, and alcohol. The product had mp 252° (dec.; the compound began to change at 225°; from acetic acid). IR spectrum: 1685 s, 1656 s, 1611 s, 1570 s. Found: C 55.2; H 3.9; Cl 14.7%. $C_{11}H_8ClNO_3$. Calculated: C 55.6; H 3.4; Cl 14.9%.

4-Piperidino- and 4-Morpholino-6-bromo-1,2-naphthoquinones (XIa and XIb). These compounds were obtained as described for I by oxidation of 10 mmole of 6-bromo-2-naphthol in the presence of 40 mmole of piperidine (morpholine).

Quinone XIa. This compound, with mp 170-171° (from benzene–hexane), was obtained in 88% yield as red crystals. IR spectrum: 1695 s, 1630 s (broad), 1576 s, 1535 s. Found: N 4.7%. $C_{15}H_{14}BrNO_2$. Calculated: N 4.4%.

Quinone XIb. This compound, with mp 191-192° (from benzene), was obtained in 60% yield as red crystals. Found: N 4.1%. $C_{14}H_{12}BrNO_3$. Calculated: N 4.3%.

2-Hydroxy-6-bromo-1,4-naphthoquinone (XII). A suspension of 3 mmole of XIa (or XIb) in a solution of 0.8 g (20 mmole) of NaOH in 12 ml of 50% aqueous alcohol was stirred at room temperature for 3 h. The resulting suspension of the sodium salt of the hydroquinone was acidified to pH 2 by stirring with dilute (1 : 1) hydrochloric acid, and after 1 h the precipitate was removed by filtration, washed with water, and dried to give 85-90% of gold crystals with mp 203-205° (from acetic acid). Found: Br 31.6%. $C_{10}H_5BrO_3$. Calculated: Br 31.3% (according to [10], this compound has mp 204-205°).

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