HETEROCYCLIC QUINONES

IX. SUBSTITUTED 4-AMINOQUINOLINEQUINONES*

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Oxidation of substituted 4-amino-6-hydroxyquinaldines and 4-chloro-6-hydroxiquinaldine with oxygen in the presence of Cu^{++}–secondary amine complexes has yielded a new group of compounds, substituted 4-aminoquinoline-5,6-quinones. The reaction intermediate, 4-chloroquinaldine-5,6-quinone, has been prepared and oxidized. The effects of substituents on the course of the oxidation have been examined, and some properties of the compounds obtained have been investigated.

A number of 6,7-disubstituted quinoline-5,8-quinones are known to possess valuable antibacterial, antifungal, and cytostatic properties [2,3]. Some N-substituted 4-aminoquinolines also have high physiological activity. Quinolinequinones possessing an amino group in the 4 position have not been described in the literature, although they are of interest as potential chemotherapeutic agents. The synthesis of these compounds by conventional methods is difficult.

The object of this work to investigate the possibility of obtaining substituted 4-aminoquinolinequinones by oxidation of the corresponding 4-amino-6-hydroxyquinolines with oxygen in the presence of Cu^{++}–secondary amine complexes [4]. The starting materials were 6-hydroxyquinaldines bearing variously substituted amino groups in the 4 position (V-VIII). Compounds V-VIII were obtained by known methods from 4-chloro-6-hydroxyquinaldine (III), or by dimethylation of the corresponding methoxy derivatives.

The oxidation of V and VII proceeded readily with catalytic amounts of copper acetate, giving the corresponding quinones IX and XI. Oxidation of VI and VIII, however, proceeded only in the presence of an equivalent amount of copper acetate. This was not unexpected, since we have previously shown [5] that when the reaction product binds copper ions as chelates, the oxidation requires equivalent amounts of divalent copper. In the oxidation of VI, the starting material itself is capable of binding Cu^{++} as a complex, since it contains a β-alanine residue. Since oxidation of VII occurs with a catalytic amount of copper, but oxidation of VIII does not, it is suggested that steric factors are of considerable importance in the formation of complexes with quinones XI and XII. It should be noted that the velocity and completeness of the oxidation depend to a considerable extent on the basicity of the amine used in the reaction (see [4]). In the presence of morpholine (pK_a 8.7) oxidation of V and VII proceeds much more slowly than it does in the presence of piperidine (pK_a 11.2), and VI is oxidized only in the presence of piperidine.

The oxidation of 4-chloro-6-hydroxyquinaldine (III) was investigated further. The use of piperidine led to the formation of the quinone XIII in good yield, but use of morpholine gave the quinone IX in lower yield. We explain this as follows. According to the assumed stepwise course of the reaction [4,6], the quinone IV must be formed as an intermediate in the oxidation of III. The carbonyl group increases the lability of the halogen in IV so much that, despite the mild reaction conditions, nucleophilic substitution

* For part VIII, see [1].
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TABLE 1. Oxidation of compounds III-VIII

Reaction product	Starting material	$Cu(OAc)_2$, g-eq (initial), mole	Duration of reaction, hr	mp, °C (decomp)	Characteristic frequencies in the IR spectrum, cm^{-1}			Molecular formula	Found, %			Calculated, %			Yield, %
					$\nu_{C=O}$ (Quinone)	$\nu_{C=O}$ COOR	ν_{N-H}		C	H	N	C	H	N	
IX	V	0.017	4	182—183	1670, 1620	—	—	$C_{18}H_{21}N_3O_4$*	63.0	5.8	12.2	63.0	6.2	12.2	55
IX†	III‡	0.017	6	182—183	1670, 1620	—	—		—	—	—	—	—	—	29
X	VI‡	1.0	5.5	170	1646, 1605	1715	3310	$C_{18}H_{21}N_3O_4 \cdot 0{,}5H_2O$	61.4	6.4	11.8	61.3	6.3	11.9	21
XI	VII	0.017	3.5	196—197	1645, 1605	1740	3270	$C_{18}H_{21}N_3O_5$	59.9	6.1	11.4	60.2	5.9	11.7	53
XII	VIII	1.0	2.5	198—199	1635, 1605	—	3420, 3300, 3280	$C_{15}H_{17}N_3O_2$	66.4	6.5	15.8	66.4	6.3	15.5	50
XIII	III	0.017	2.5	189—191	1678, 1620	—	—	$C_{20}H_{25}N_3O_2$	71.1	7.5	12.2	70.8	7.4	12.4	62
XIII†	IV	0.017	0.2	189—191	1678, 1620	—	—	—	—	—	—	—	—	—	64

* After drying over P_2O_5 (3 hr, 10 mm, 70° C). Before drying, found, %: C 61.4; H 7.0; N 11.2. Calculated for $C_{18}H_{21}N_3O_4 \cdot C_2H_5OH$, %: C 61.7; H 7.0; N 10.8. Loss in weight on drying, 12.1% (calculated, 11.8%).

† The compound was identical with the previous one by TLC, IR spectrum, and mp.

‡ Filtration after extraction with chloroform gave 46-49% of unreacted starting material (III or VI).

occurs at C_4. In 4-chloroquinolines, a similar reaction occurs only on heating. In order to confirm these assumptions, compound IV was prepared, and its behavior under the oxidations conditions was examined. Nitration of III, followed by reduction, gave 4-chloro-5-amino-6-hydroxyquinaldine (II), which was oxidized by chromic acid to IV. The haloquinone IV was a somewhat unstable, deep-violet crystalline compound, which decomposed on standing. The few known quinoline-5,6-quinones are also extremely unstable [7,8]. The quinone XIII was obtained in good yield by oxidation of IV in the presence of piperidine and a catalytic amount of copper acetate, indicating the advantage of the formation of IV as an intermediate in the oxidation of III.

The diaminoquinones IX-XIII are crystalline compounds of varying shades of red. They are stable in the dark. The greater stability of the 8-dialkylaminoquinoline-5,6-quinones compared with the other quinoline-5,6-quinones is explained by the fact that these compounds, being vinyl amides, possess a much lower oxidation potential, and the 8-position, at which condensation reactions can take place, is occupied by the amino group.

The IR spectra of the quinones IX-XIII confirm their structures (see Table 1). The spectrum of the chloroquinone IV shows two strong maxima in the region of the carbonyl absorption, at 1705 and 1683 cm^{-1}. The substantial shift toward shorter wavelengths is caused by the negative inductive effect of the chlorine atom.

The quinones IX-XIII are readily hydrolyzed. Acid or alkaline hydrolysis of XIII gives 4-piperidino-6-hydroxyquinaldine-5,8-quinone (XV). Hydrolytic fission of the piperidine residue in the 4-position is not observed. 4-Amino-6-hydroxyquinoline-5,8-quinone is readily obtained in this way. It is interesting that the diaminoquinones IX-XIII give phenazine derivatives with o-phenylenediamine only in the presence of acetic acid.

EXPERIMENTAL

4-Chloro-6-hydroxyquinaldine (III). A solution of 40 g (0.19 mole) of 4-chloro-6-methoxyquinaldine [9] in a mixture of 200 ml of conc. H_2SO_4 and 114 ml of water was boiled for 5 hr, and the mixture was then cooled, diluted with 800 ml of water, and made basic, with cooling and stirring, by adding

25% NH_3. The precipitate was filtered off, washed with water, dried, and recrystallized from isobutanol to give 28.4 g (76%) of colorless crystals which were readily soluble in acetic acid, but sparingly soluble in methanol, ethanol, dioxane, acetone, and ethyl acetate, and insoluble in hexane, chloroform, and water. mp 210-212° C (decomp, from isobutanol). Found, %: C 62.1; H 3.9; Cl 18.2; N 7.4. Calculated for $C_{10}H_8ClNO$, %: C 62.0; H 4.2; Cl 18.3; N 7.2. Acetate, mp 148-149° C (from alcohol). Found, %: N 6.0. Calculated for $C_{12}H_{10}ClNO_2$, %: N 5.9.

4-Chloro-5-nitro-6-hydroxyquinaldine (I). To a solution of 10 g (53 mmole) of III in 100 ml of conc. H_2SO_4 was added, with stirring at 0° C during 5 min, 5.7 g (56 mmole) of potassium nitrate. The reaction mixture was stirred for 1 hr 30 min, the temperature rising gradually to 20° C, and the mixture was poured into 1 liter of water. The precipitate was filtered off, dissolved in 250 ml of 1 N NaOH, treated with charcoal, and acidified with acetic acid. The product which separated was isolated, washed with water, and dried to give 9.8 g (79%) of yellow crystals, mp 198-200° C (decomp, from isobutanol). Found, %: Cl 15.0; N 11.6. Calculated for $C_{10}H_7ClN_2O_3$, %: Cl 14.8; N 11.7.

4-Chloro-5-amino-6-hydroxyquinaldine (II). A suspension of 3.0 g (12.5 mmole) of I in 36 ml of isobutanol was hydrogenated in the presence of 1.0 g of Raney nickel at 20° C and atmospheric pressure. After 3 moles (840 ml) of H_2 had been taken up, the mixture was heated to dissolve the precipitate, the catalyst filtered off and washed on the filter with 10 ml hot isobutanol, and 6 ml of 20% alcoholic HCl was added to the combined filtrate and washings. The precipitated hydrochloride was filtered off after cooling, washed with ether, and dried to give 2.7 g (87%) of red crystals which were moderately soluble in water, acetic acid, and methanol, but sparingly soluble in ethanol and chloroform, and insoluble in ether and hexane, mp above 320 °C (decomp). Found, %: Cl 28.5. Calculated for $C_{10}H_9ClN_2O \cdot HCl$, %: Cl 28.9. The free base was obtained by treatment of an aqueous solution of the hydrochloride with ammonia, as a bright-yellow solid, mp 162-163° C. Found, %: Cl 14.5; N 11.5. Calculated for $C_{10}H_9ClN_2O \cdot 2H_2O$, %: Cl 14.5; N 11.9.

4-Chloroquinaldine-5,6-quinone (IV). This was obtained by oxidation of II with potassium dichromate in H_2SO_4, as in [10], in 23% yield. Deep-violet, acicular crystals, readily soluble in chloroform, acetic acid, methanol, and ethanol, but insoluble in water, ether, and hexane. The compound decomposed on standing into substances with much lower R_f values. Mp above 320° C (decomp, from 1:3 chloroform–hexane mixture). Found, %: Cl 17.2; N 6.6. Calculated for $C_{10}H_6ClNO_2$, %: Cl 17.1; N 6.7.

4-Morpholino-6-hydroxyquinaldine (V). A solution of 12.9 g (50 mmole) of 4-(N-morpholino)-6-methoxyquinaldine [11] in 60 ml of 48% HBr was boiled for 6 hr, then cooled and made basic with 10% NH_3. The viscous precipitate was transferred into 40 ml of alcohol, the mixture was brought to the boil, cooled, and the precipitate was filtered off, washed with water, and dried to give 8.3 g (68%) of colorless crystals, mp 278-280° C (decomp, from alcohol), which were readily soluble in acetic acid, moderately soluble in methanol and ethanol, and insoluble in ether, acetone, and benzene. Found, %: C 68.5; H 6.4; N 11.7. Calculated for $C_{14}H_{16}N_2O_2$, %: C 68.8; H 6.6; N 11.5.

4-(β-Carboxyethylamino)-6-hydroxyquinaldine (VI). A mixture of 10 g (0.052 mole) of III, 10 g (0.112 mole) of β-alanine, and 40 g of phenol was heated at 160-165° C with stirring for 1 hr. The phenol was removed by steam distillation, and the residue was filtered off, washed with water, and dried to give 8.2 g of VI. The filtrate and washings were made basic with ammonia, extracted with 3 × 30 ml of ether, and acidified with acetic acid to give a further 1.5 g of VI. Yield 9.7 g (71%) of a finely crystalline, colorless solid, sparingly soluble in most organic solvents and in water. Mp 318-319° C (decomp, from 1:1 acetic acid-water mixture). Found, %: C 57.3; H 6.1; N 10.2. Calculated for $C_{13}H_{14}N_2O_3 \cdot 1.5H_2O$, %: C 57.1; H 6.3; N 10.2.

4-(β-Methoxycarbonylethylamino)-6-hydroxyquinaldine (VII). A mixture of 3.0 g (11 mmole) of VI and 30 ml of 10% methanolic HCl was heated at the boil for 6 hr, the crystals which separated on cooling were filtered off, washed with ether, and dried to give 2.7 g (75%) of colorless crystals, mp 222-223° C (decomp, from methanol). Found, %: C 54.5; H 6.1; Cl 11.1; N 8.7. Calculated for $C_{14}H_{16}N_2O_3 \cdot HCl \cdot CH_3OH$, %: C 54.8; H 6.4; Cl 10.8; N 8.5.

4-Amino-6-hydroxyquinaldine (VIII). A solution of 4.0 g (21 mmole) of 4-amino-6-methoxyquinaldine [12] in 20 ml of 48% HBr was boiled for 6 hr, cooled, and the precipitate was filtered off, washed with ether, and dried to give 4.95 g (91%) of colorless crystals which were readily soluble in water, methanol, and ethanol, and insoluble in acetone and ether. Mp 315° C (decomp, from 1:2 alcohol–ether mixture). Found, %: Br 31.2; N 11.1. Calculated for $C_{10}H_{10}N_2O \cdot HBr$, %: Br 31.3; N 11.0. The free base was obtained by

treating an aqueous solution of the hydrobromide with NH_3. Yield 96%, acicular crystals, mp 105-107° C (decomp, from water, air-dried). Found, %: C 45.9; H 7.8; N 10.9. Calculated for $C_{10}H_{10}N_2O \cdot 5H_2O$, %: C 45.4; H 7.6; N 10.6.

Oxidation of III-VIII (general method). A 15 mmole quantity of the compound to be oxidized was added to a solution of copper acetate (see table 1) in a mixture of 30 ml of methanol and 60 mmole of the secondary amine (piperidine or morpholine), and the mixture stirred in an atmosphere of oxygen until no further uptake of gas occurred. The reaction mixture was diluted with water (60 ml), acidified with 2 N HCl, and extracted with 4 × 40 ml of chloroform. The chloroform extract was washed with water, dried over Na_2SO_4, concentrated in vacuo to a volume of 20 ml, and 100 ml of petroleum ether was added. The precipitate was filtered off, and dried in a vacuum desiccator. In the oxidation of IV, 1 mmole of compound was used. Compounds IX-XIII were crystalline solids, soluble in chloroform and alcohols, sparingly soluble in ether, and insoluble in hexane. Recrystallization of the quinones IX and XI-XIII was carried out using alcohol, and for X a 2:1 alcohol-water mixture was used. Quinones IX and X were moderately soluble in water. The results are given in Table 1.

1,5-Di(piperidino)-3-methylpyrido[3,2-*a*]phenazine (XIV). To a hot solution of 0.68 g (2 mmole) of XIII in a mixture of 10 ml of alcohol and 1 ml of acetic acid was added 0.25 g (2.3 mmole) of o-phenylenediamine, and the solution was boiled for 10 min. After 2 hr, the reaction mixture was made basic with 10% ammonia; the precipitate was filtered off, dried, and recrystallized from dioxane to give 0.42 g (51%) of yellow crystals, mp 209-210° C, readily soluble in acetic acid, methanol, ethanol, chloroform, and benzene, sparingly soluble in ether and hexane, and insoluble in water. Found, %: C 76.3; H 7.2; N 17.0. Calculated for $C_{26}H_{29}N_5$, %: C 75.9; H 7.1; N 17.0.

4-Pyridino-6-hydroxyquinaldine-5,8-quinone (XV). A) To a suspension of 3.4 g (10 mmole) of XIII in 15 ml of dioxane was added 15 ml of 10% HCl, and the mixture was heated at 80° C with stirring for 10 min. After 1 hr, the precipitate was isolated, washed with acetone and ether, and recrystallized from water to give 1.8 g (57%) of red crystals, mp 192-194° C (from water), readily soluble in acetic acid, methanol, and water, moderately soluble in ethanol, sparingly soluble in chloroform, acetone, benzene, and dioxane, and insoluble in ether and hexane. Found, %: C 56.5; H 6.3; N 8.7. Calculated for $C_{15}H_{16}N_2O_3 \cdot 2.5H_2O$, %: C 56.8; H 6.7; N 8.8.

B) A 3.4 g (10 mmole) quantity of XIII was boiled with a solution of 1.4 g (25 mmole) of KOH in 25 ml of 90% ethanol for 5 min. The reaction mixture was cooled, acidified with 5-N HCl, and the precipitate filtered off and recrystallized from water to give 1.45 g (46%) of material which was identical by TLC and mixed mp with that obtained in A) above. Both samples gave the phenazine XVI with o-phenylenediamine.

1-Piperidino-3-methyl-5-hydroxypyrido[3,2-*a*]phenazine (XVI). Obtained in the same way as XIV from 0.63 g (2 mmole) of XV in alcohol. Yield 0.53 g (77%), yellow crystals, readily soluble in acetic acid, chloroform, and benzene, moderately soluble in methanol, ethanol, acetone, and ethyl acetate, sparingly soluble in ether and hexane, and insoluble in water. Mp 197-198° C (from heptane). Found, %: C 73.6; H 5.8; N 15.8. Calculated for $C_{21}H_{20}N_4O$, %: C 73.2; H 5.8; N 16.3.

All the compounds were dried in a vacuum desiccator over calcium chloride and paraffin; exceptions are mentioned in the text. IR spectra were taken on a UR-10 spectrophotometer as suspensions in Vaseline oil. The progress of the reactions and the purity of the quinones were determined by thin layer chromatography on silicic acid, using a methanol-chloroform mixture (1:20). The R_f values (IV > XIII > XI > IX > XII > X > XV) were as expected from the polarity of the compounds.

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