INVESTIGATION OF HETEROCYCLIC QUINONES

XXIV.* AMINATED ISOQUINOLINE-7,8-QUINONES

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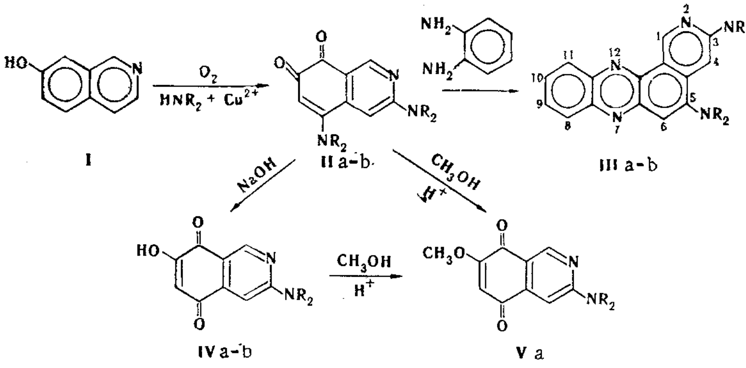
3,5-Bis(dialkylamino)isoquinoline-7,8-quinones are formed by oxidative amination of 7-hydroxyisoquinoline. The o-quinones are converted to 3-piperidino(morpholino)-7-hydroxy(methoxy)isoquinoline-5,8-quinones.

The corresponding o-quinones with a secondary amine residue in the quinoid ring are usually formed in the oxidation of heterocyclic phenols with oxygen in the presence of a Cu^{2+}-secondary amine complex [2], although in some cases the reaction is also accompanied by amination of the heterocyclic portion of the molecule [3, 4]. It is important that amination of quinazolinequinones occurs at the C-2 atom, although the C-4 atom is the most electrophilic atom in quinazoline [5, 6].

It should be noted that amination of the heterocyclic portion of the molecule does not occur in the oxidative amination of the closest analog of 6-hydroxyquinazoline – 6-hydroxyquinoline [7]. It seemed of interest to accomplish the oxidative amination of 7-hydroxyisoquinoline (I).



a $R_2=(CH_2)_5$; b $R_2=(CH_2)_4O$

o-Quinone derivatives of isoquinoline have not been described in the literature. Isoquinoline-5,8-quinones were first obtained in 1964 (see [8] and the literature cited in it).

The oxidation of I with oxygen in the presence of copper acetate and secondary amines of different basicities (piperidine, morpholine) gives good yields of isoquinoline-7,8-quinones (IIa-b) containing two secondary amine residues. About 2 moles of oxygen, which corresponds to the calculated amount [4], is absorbed during the reaction.

The structure of quinone IIa was established from the PMR spectrum. There are three unresolved multiplets at strong field at 1.44-2.03 (12H), 3.04-3.40 (4H), and 3.54-3.90 (4H) ppm that correspond to the protons of the β,γ-methylene groups and two pairs of nonequivalent α-methylene groups of the piperidine residues, respectively. In addition, the PMR spectrum of IIa contains three singlets at 8.66 (H-1), 6.60 (H-4), and 5.94 (H-6) ppm. The signal of the vicinal proton (H-6) is found in this same region in the spec-

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[*] See [1] for communication XXIII.

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tra of similar quinones (see [4]), while the H-3 and H-4 protons would show up as doublets in the case of amination at C-1 (see [8]).

Thus, the second electrophilic center (in addition to C-5) in isoquinoline-7,8-quinones is found at C-3. For this case, the analogy between amination of heterocyclic quinones and the Chichibabin reaction [3, 4] is inappropriate, inasmuch as the C=N bond does not participate in the reaction here. The results speak in favor of a mechanism including 1,6-addition of the secondary amine with the participation of the quinone carbonyl group [4]. The transfer of the electrophilic center from C-4 to C-2 on passing from quinazolines to quinazoline-5,6-quinones and from C-1 to C-3 for isoquinolines and isoquinolines to isoquinoline-7,8-quinones can be explained by the presence in the quinolines in the peri position relative to C-4 and C-1, respectively, of a strongly electronegative carbonyl oxygen atom that hinders nucleophilic attack in these positions. Amination of the heterocyclic portion of the molecule does not occur in the oxidation of 6-hydroxyquinoline, apparently because of the reduced electrophilicity of the 2-position due to conjugation with the $C_3{=}C_4$ bond.

Quinones II display characteristic maxima at 1600-1700 cm^{-1} in their IR spectra. They also react readily with o-phenylenediamine to give bright-yellow phenazine derivatives (III), which are convenient for identification purposes. Phenazines III are the first representatives of the previously undescribed pyrido-[3,4-*a*]phenazine heterocyclic system.

On brief heating with dilute NaOH solution, quinones II are saponified to 3-piperidino(morpholino)-7-hydroxyisoquinoline-5,8-quinones (IV), which, like other hydroxyquinones, display acidic properties and dissolve readily in aqueous sodium bicarbonate solution or amine solutions to give salts.

Heating of IIIa in methanol in the presence of sulfuric acid gives 3-piperidino-7-methoxyisoquinoline-5,8-quinone (Va). This same compound is formed by heating quinone IIa in methanol with sulfuric acid by the method in [9]. The structure of product Va is confirmed by its PMR spectrum, which contains two unresolved multiplets at 1.82-2.12 (6H, β,γ-CH_2) and 3.64-4.04 (4H, α-CH_2) ppm, which correspond to the signals of protons of the piperidine residues, and four singlets at 3.9 (3H, OCH_3), 6.27 (1H, H-6), 7.38 (1H, H-4), and 8.57 (1H, H-1) ppm.

In conclusion, it should be noted that the problem of the possibility of amination of isoquinoline-5,8-quinones in the heterocyclic ring remains unsolved. Jouliie and Puthenpurayil [8] obtained only 7-morpholinoisoquinoline-5,8-quinone by the action of excess morpholine (3 moles) on isoquinoline-5,8-quinone in diglyme. In addition, in the oxidation of 6-hydroxyquinazoline in the presence of a Cu^{2+}-secondary amine system, amination proceeds at C-2 after the formation of the quinazolinequinone and amination of the quinone ring [4]. In the case of isoquinoline-7,8-quinones, the sequence of steps is apparently similar, and it may be expected that under the conditions of the oxidative amination the p-quinones of the isoquinoline series will be aminated at C-3 owing to the effect of $C_8{=}O$.

EXPERIMENTAL

The IR spectra of mineral-oil pastes of the compounds were studied with a UR-20 spectrometer. The PMR spectra of the quinones were recorded as follows: with a JNM-4H-100 spectrometer for IIa in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard, and with a Varian T-60 spectrometer for Va in CF_3COOH with TMS as the external standard. The reactions were monitored and the purity of the quinones was determined by means of thin-layer chromatography (TLC) on Silufol plates in a methanol–chloroform (1 : 20) system.

3-Hydroxybenzylideneaminoacetaldehyde Dimethylacetal. This compound was obtained in 92% yield from m-hydroxybenzaldehyde and aminoacetaldehyde dimethylacetal by a method similar to that described for the diethylacetal [10]. The colorless crystals had mp 77-78° (benzene–heptane). IR spectrum: 3300 m (associated OH), 1652 s (C=N), and 1600 s (arom.) cm^{-1}. Found, %: N 6.7. $C_{11}H_{15}NO_3$. Calculated, %: N 6.9.

7-Hydroxyisoquinoline. This compound, with mp 225-227°, was obtained by cyclization of 3-hydroxybenzylideneaminoacetaldehyde dimethylacetal by the method in [10].

3,5-Dipiperidinoisoquinoline-7,8-quinone (IIa). A 1.45-g (10 mmole) sample of 7-hydroxyisoquinoline in 12 ml of methanol was oxidized with oxygen in the presence of 22 mmole of piperidine and 0.05 g of copper acetate by the method in [4]. After 1 h, 406 ml of O_2 had been absorbed. The precipitate was removed by filtration, washed successively with methanol (2 ml) and ether (5 ml), and dried in a desiccator to give 2.04 g (63%) of red crystals with mp 207-208° (decomp., from alcohol) that were quite soluble in chloroform and acetic acid, moderately soluble in alcohol and benzene, and only slightly soluble in water. IR spectrum: 1670 s and 1630 s cm^{-1}. Found, %: C 70.2; H 6.9; N 13.3. $C_{19}H_{23}N_3O_2$. Calculated, %: C 70.1; H 7.1; N 12.9.

3,5-Dimorpholinoisoquinoline-7,8-quinone (IIb). The method used to prepare quinone IIa was used to obtain this compound [2.3 g (70%)], with mp 228-229° (decomp., from dioxane), by oxidation of 1.45 g of 7-hydroxyisoquinoline in the presence of morpholine. The orange-red crystals were quite soluble in acetic acid, moderately soluble in chloroform, and only slightly soluble in alcohol, benzene, and ether. IR spectrum: 1670 s and 1635 s cm^{-1}. Found, %: C 61.6; H 5.8; N 13.0. $C_{17}H_{19}N_3O_4$. Calculated, %: C 62.0; H 5.8; N 12.8.

3,5-Dipiperidinopyrido[3,4-*a*]phenazine (IIIa). A 0.13-g (1.2 mmole) sample of o-phenylenediamine was added to a heated (to the boiling point) solution of 0.32 g (1 mmole) of quinone IIa in a mixture of 7.5 ml of alcohol and 0.5 ml of acetic acid, and the mixture was refluxed for 10 min. It was then cooled, and the precipitated IIIa was removed by filtration, washed with alcohol, and dried to give 0.3 g (75%) of yellow crystals with mp 226-227° (from alcohol). Found, %: C 75.5; H 6.8; N 17.9. $C_{25}H_{27}N_5$. Calculated, %: C 75.5; H 6.9; N 17.6.

3,5-Dimorpholinopyrido[3,4-*a*]phenazine (IIIb). The method used to prepare IIIa was used to obtain 0.24 g (60%) of IIIb from 1 mmole of quinone IIb. The yellow crystals had mp 285-286° (from alcohol). Found, %: C 69.3; H 5.7; N 17.4. $C_{23}H_{23}N_5O_2$. Calculated, %: C 68.8; H 5.8; N 17.5.

3-Piperidino-7-hydroxyisoquinoline-5,8-quinone (IVa). A 0.98-g (3 mmole) sample of quinone IIa was added to a solution of 0.6 g (15 mmole) of NaOH in 10 ml of 50% aqueous alcohol, and the mixture was refluxed for 15 min. It was then cooled, diluted with 10 ml of water, and acidified to pH 3 with 10% HCl. The resulting precipitate was removed by filtration, washed with water, and dried in a desiccator to give 0.71 g (92%) of brown-red crystals with mp 227-229° (from benzene). IR spectrum: 3360 m, 3305 s (broad, associated OH), 1652 m, and 1630 m cm^{-1}. Found, %: N 10.5. $C_{14}H_{14}N_2O_3$. Calculated, %: N 10.8.

3-Morpholino-7-hydroxyisoquinoline-5,8-quinone (IVb). The method used to prepare IIa was used to obtain 0.73 g (94%) of this compound by saponification of 0.99 g (3 mmole) of IIb. The orange crystals had mp 242-244° (dioxane–hexane). IR spectrum: 3130 s (broad, associated OH), 1664 s, and 1638 sh cm^{-1}. Found, %: C 60.0; H 5.0; N 10.5. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60.0; H 4.7; N 10.8.

3-Piperidino-7-methoxyisoquinoline-5,8-quinone (Va). A) A solution of 1.0 g (3.9 mmole) of IVa in 10 ml of methanol containing three drops of concentrated H_2SO_4 was refluxed for 3 h, after which it was cooled and poured into 100 ml of water. The quinone was extracted with chloroform (four 20-ml portions). The combined chloroform extracts were washed with water, dried with Na_2SO_4, and evaporated. The residue was chromatographed on silicic acid with elution of 0.6 g (57%) of Va with benzene–acetone (10 : 1). The dark-red crystals had mp 172-174° (from alcohol). IR spectrum: 1665 s and 1647 m (C=O) cm^{-1}. Found, %: N 10.3. $C_{15}H_{16}N_2O_3$. Calculated, %: N 10.3.

B) A solution of 1.3 g (4 mmole) of IIa in a mixture of 15 ml of methanol and 2 ml of concentrated H_2SO_4 was refluxed for 3 h, after which it was cooled to 0° and transferred to a solution of 3.5 ml of pyridine in 50 ml of chloroform. The chloroform solution was washed with water (30 ml), and the aqueous layer was extracted with chloroform (three 10-ml portions). The combined chloroform extracts were washed successively with water (10 ml), acetic acid (20 ml), and water (10 ml), dried with Na_2SO_4, and evaporated to a small volume. The residual solution was chromatographed on silicic acid with elution of Va [0.54 g (49%)] by benzene–acetone (10 : 1). The product was identical to the product obtained by method A.

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