A STUDY OF HETEROCYCLIC QUINONES

V. The Mannich Reaction with Substituted 6-Hydroxyquinoline 5,8-Quinones

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A series of Mannich bases has been obtained from 2- and 4-substituted 6-hydroxyquinoline 5,8-quinones, and their structure has been demonstrated by an analysis of their PMR spectra and by oxidation with hydrogen peroxide. A consideration of the ionization constants of the Mannich bases permits the conclusion that they have a zwitterionic structure.

It has been shown previously that 6-hydroxyquinoline 5,8-quinone readily takes part in the Mannich reaction [1] under the same conditions as 2-hydroxy-1,4-naphthoquinone [2, 3]. In the course of an investigation of quinoline quinones, we have obtained a series of 2- and 4-substituted 6-hydroxyquinoline 5,8-quinones [4–7]. In this paper we describe the preparation of Mannich bases from these compounds. The reaction was carried out with the hydroxyquinoline quinones, formalin, and secondary amines—dimethylamine, diethylamine, piperidine, and morpholine. One of the hydroxyquinones that we used is a derivative of quinaldine and the other of 4-hydroxyquinaldine. It is known that quinaldine [8] and 4-hydroxyquinaldine [9,10] take part in the Mannich reaction with the replacement by a dialkylaminomethyl group of, in the first case, the hydrogen of the methyl group and, in the second case, the hydrogen at C_3. Consequently, we had to show that when the Mannich reaction was performed with 6-hydroxyquinaldine 5,8-quinone and 4,6-dihydroxyquinaldine 5,8-quinone the hydrogen at atom C_7 of the quinoline ring was replaced.

The structure of II (Table 1) was confirmed by its PMR spectrum, in which signals of the following groups were observed: singlets with δ_{CH_3} 2.96 ppm and δ_{CH_2} 4.20 ppm, and doublets of the protons at C_3 and C_4—8.19 and 8.90 ppm, respectively. Such a spectrum would not be observed with the alternative structure since in this case the signal of the methyl group would be absent and signals of two interacting methylene groups and, in the weak-field region (at $\delta \geq 5.5$) a singlet corresponding to the proton at C_7 would be observed.

The structure of compounds III and IV was shown chemically. On oxidation with hydrogen peroxide, they formed 4-hydroxy-2-methylpyridine-5,6-dicarboxylic acid, which was identical with the product of the oxidation of 4,6-dihydroxyquinaldine 5,8-quinone.

The products of the Mannich reaction are orange or red crystalline substances insoluble in ether, benzene, and hexane, and sparingly soluble in alcohols. Compounds I–IV are readily soluble in water, acids, and alkalis, while the higher-molecular-weight compounds V–VIII are insoluble in water but are soluble in acids and alkalis. In contrast to the other compounds of this series, V gives a hydrochloride sparingly soluble in hydrochloric acid which is hydrolyzed by water. In an

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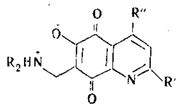
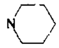
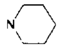
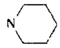
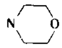
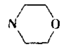
*For part IV, see [7].

Table 1

2- and 4-Substituted 7-Dialkylaminomethyl-6-hydroxyquinoline 5,8-Quinones*



Compound	R′	R″	NR_2	Solvent for recrystallization	. пл., ° С	Empirical formula	Found, %			Calculated, %			Yield, %
							C	H	N	C	H	N	
I	CH_3	H	$N(CH_3)_2$	Ethanol-ether (1 : 1)	223—225 (decomp.)	$C_{13}H_{14}N_2O_3 \cdot \frac{1}{2}H_2O$	61.05	6.40	10.81	61.16	5.92	10.98	81
II	CH_3	H		Ethanol-ether (1 : 1)	184—185 (decomp.)	$C_{16}H_{18}N_2O_3$	67.04	6.61	9.51	67.11	6.34	9.79	89
III*	CH_3	OH	$N(CH_3)_2$	Water	181—182 (decomp.)	$C_{13}H_{14}N_2O_4 \cdot 3H_2O$	49.86	6.37	8.56	49.36	6.50	8.86	71
IV	CH_3	OH		Ethanol-water (8 : 1)	350	$C_{16}H_{18}N_2O_4$	63.67	6.07	9.51	63.56	6.00	9.27	86
V**	C_6H_5	COOH		***	200—202 (decomp.)	$C_{22}H_{20}N_2O_5 \cdot 2H_2O$	62.03	5.50	6.63	61.67	5.65	6.54	51
VI	C_6H_5	COOH		****	190—191 (decomp.)	$C_{21}H_{18}N_2O_6 \cdot H_2O$	61.63	5.34	6.70	61.16	4.89	6.79	85
VII	C_6H_5	COOH	$N(C_2H_5)_2$	****	172 (decomp.)	$C_{21}H_{20}N_2O_5 \cdot H_2O$	63.00	5.85	6.75	63.30	5.57	7.03	83
VIII	CH=CH—C_6H_5	H		****	155 (decomp.)	$C_{22}H_{20}N_2O_4 \cdot 2H_2O$	61.50	5.90	6.40	61.38	6.09	6.51	72

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*Hydrochloride, $C_{13}H_{14}N_2O_4 \cdot 2HCl \cdot H_2O$: mp 203–205° C (decomp., from ethanol with ether). Found, %: Cl 20.06; N 7.95. Calculated, %: Cl 20.07; N 7.93.

**Hydrochloride, $C_{22}H_{20}N_2O_5 \cdot HCl$: mp 167–168° C (decomp., from ethanol with ether). Found, %: Cl 8.28; N 6.53. Calculated, %: Cl 8.27; N 6.53.

***Purified via the hydrochloride by hydrolyzing it with water.

****For purification the substance was dissolved in 4 N HCl, and the solution was filtered and neutralized with an equivalent amount of 1 N NaOH.

anhydrous medium, compound III forms a yellow dihydrochloride.

The initial hydroxyquinoline quinones are comparatively strong acids [4, 6, 7]. The introduction into position 7 of strongly basic substituents leads to the formation of compounds existing in the form of zwitterions. In the determination of the ionization constants of compounds II–IV, a phenomenon characteristic for zwitterions is observed: the pK_a value of the basic group determined by titrating the substance with alkali and the pK_a value of the acid group by titration with acid [11]. The following values of pK_a were obtained for compounds **II**, **III**, and **IV**, respectively: 3.16, 1.95, and 2.47 (addition of a proton), and 11.31, 9.19, and 9.46 (detachment of a proton). The initial 6-hydroxyquinaldine 5,8-quinone [4] and 4,6-dihydroxyquinaldine 5,8-quinone [6] had pK_a values of, respectively, 4.18 and 3.21, while the pK_a values of the substituents were of the order of 10, and, therefore, the assignment of the constants can be made unambiguously.

The IR spectra of compounds II–VIII and their salts had bands in the 1600–1800 cm^{-1} region that are characteristic for the carbonyl groups of quinones, while those of V–VII had, in addition, bands ascribable to the carbonyl of a carboxyl group.

EXPERIMENTAL

The PMR spectra were obtained on an INM 4H 100 spectrometer with a working frequency of 100 MHz using D_2O as solvent and dioxane (δ 3.70) as internal standard. The ionization constants were calculated from the curves of titration with 0.001- and 0.01-molar aqueous solutions. The pH measurements were carried out on a LPU-01 pH-meter. The IR spectra were taken in paraffin oil on a UR-10 spectrophotometer.

Preparation of the Mannich bases. A suspension of 10 mM of a hydroxyquinoline quinone in 50 ml of anhydrous ethanol was treated with 11 mM of a secondary amine, and the mixture was cooled to 5–10° C and 0.95 ml of 40% formalin was added with stirring. Stirring at room temperature was continued for 3–4 hr and then the mixture was left overnight, and the precipitate was filtered off, washed with a small amount of ethanol and ether, and purified. In the preparation of compounds **I** and **II** a smaller amount of ethanol (15 ml) was used, since the reaction products are moderately soluble in it.

4-Hydroxy-2-methylpyridine-5,6-dicarboxylic acid. A) To 0.70 g (2.2 mM) of **III** (or the equivalent amount of **IV**) in a solution of 0.4 g of sodium bicarbonate in 20 ml of water was added 2.5 ml of 40% hydrogen peroxide, and the mixture was heated at 70–80° C and stirred until it had become decolorized (~20 min). Then it was acidified with dil (1 : 1) HCl to pH 1 and was cooled. The colorless crystals that deposited were separated off, washed with water (1 ml), and dried in a desiccator over $CaCl_2$. Yield 0.29 g (61%). The substance is moderately soluble in water, acetic acid, and ethanol, sparingly soluble in acetone, chloroform, and benzene, and insoluble in ether and petroleum ether. The substance melted at 160–161° C, and then solidified and began to decompose from 220° C. Found, %: C 44.53; H 4.27; N 6.62. Calculated for $C_8H_7NO_5 \cdot H_2O$, %: C 44.65; H 4.22; N 6.51. Equivalent on titration with 0.1 N NaOH: found 106.5–107.2. Calculated 107.6.

Table 2

Absorption of Compounds II–VIII in the 1600–1800 cm^{-1} Region

Compound	$\nu_{C=O}$ (of quinones)	$\nu_{C=O}$ (of quinones)	$\nu_{C=O}$ (COOH)
II	—	1680	1620
III	—	1690	1650
III · 2HCl	—	1695	1625
IV	—	1670	1645
V	1720, 1735	1690	1615
V · HCl	1745	1675	1650, 1620
VI	1738	1690	1610
VII	1730	1690	1615
VIII	—	1680	1640, 1610

B) The oxidation of 0.50 g (2.1 mM) of 4,6-dihydroxyquinaldine 5,8-quinone [6] as described above yielded 0.35 g (73%) of an acid. After recrystallization from water, it melted at 160–161° C, and then solidified and began to decompose at 220° C. It gave no depression of the melting point with a sample obtained by method (A).

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