NITROSOPHENOLS AND THEIR REARRANGEMENT PRODUCTS

II.* OPENING OF THE BENZENE RING OF 5-NITROSO-6-HYDROXYQUINOLINE

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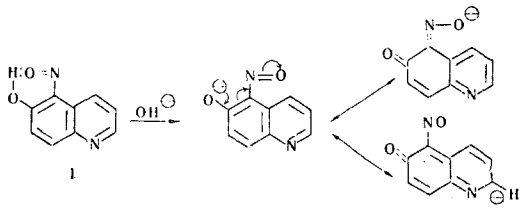
It is shown that the benzene ring is opened (via the scheme of the Beckmann rearrangement) during the nitrosation of 6-hydroxyquinoline and subsequent reaction with acylating agents; the products are β-(3-cyano-2-pyridyl)acrylic acids.

The comparative instability of one of the rings of a two-ring system is sometimes used for the synthesis of some compounds which are difficult to obtain. Thus the benzene ring of quinoline or isoquinoline is oxidized to obtain pyridinecarboxylic acids [2]. 2-Carboxy-3-pyridylglyoxylic acid can be obtained by the selective oxidation of 8-hydroxyquinoline [3], while 6-hydroxyquinoline can similarly be converted to β-(3-carboxy-2-pyridyl)glyceric acid [4]. In more complex cases, the oxidative destruction proceeds ambiguously and is therefore unsuitable.

1-Nitroso-2-naphthol and its substituted derivatives are converted to o-cyanocinnamic acids (see [1], for example) by the action of acylating agents via the scheme of a Beckmann rearrangement of the second type with opening of the benzene ring. This reaction has not been investigated until recently as applied to heterocyclic structures. Recently two of us [5] were able to show that 5-nitroso-6-hydroxyquinoline (I) forms β-(3-cyano-2-pyridyl)acrylic acid (II) under the conditions of the Beckmann rearrangement. This process is the subject of this investigation.

6-Hydroxyquinoline is readily converted to nitroso compound I by the action of nitrous acid. It is apparent from a comparison of the UV spectra (Fig. 1) of the starting material and the nitroso compounds that the absorption maximum at 232 nm has become indistinct, while the absorption region has been extended to the visible portion of the spectrum. The maximum at 292 nm undergoes a bathochromic shift to 304 nm, while an intense absorption, as a consequence of the formation of an orthoquinoid chelated structure, appears at 420 nm. Protonation of 6-hydroxy-quinoline induces a considerable bathochromic shift of both absorption maxima, especially the short-wave one, while in the nitroso compound an acidic medium has practically no effect on the character of the absorption. In alkaline media the spectrum of 6-hydroxyquinoline itself is characterized by a sharp bathochromic shift of both maxima (λ_{max} 292 and 362 nm) due to the quinoid character of the structure. This is seen to an even greater extent in the spectrum of nitroso compound I, in which both ortho- and para-quinoid forms can be realized.



I

*See [1] for communication I.

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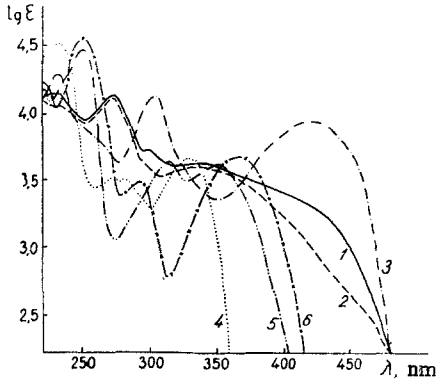


Fig. 1

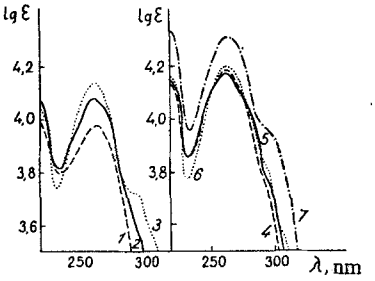


Fig. 2

Fig. 1. UV spectra (in 80% ethanol): 1) I; 2) I (0.01 N HCl in 80% ethanol); 3) I (0.01 N KOH in 80% ethanol); 4) 6-hydroxyquinoline; 5) 6-hydroxyquinoline (0.01 N HCl in 80% ethanol); 6) 6-hydroxyquinoline (0.01 N KOH in 80% ethanol).

Fig. 2. UV spectra (in water): 1) cis-II (0.01 N KOH); 2) cis-II; 3) cis-II (0.01 N HCl); 4) trans-II (0.01 N KOH); 5) trans-II; 6) trans-II (0.01 N HCl); 7) III.

Depending on the conditions, the cis or trans isomer of acid II is formed by the action of benzenesulfonyl chloride on nitroso compound I in aqueous acetone in the presence of alkali. If the process is carried out vigorously by the rapid addition of alkali to a mixture of the reagents, the major product is cis acid II with mp 190-191°. If, however, the alkali is introduced slowly, the major product is trans II with mp 217-218°.

The cis configuration of the acid with mp 190-191° was determined on the basis of the PMR spectrum, in which a quartet of peaks (6.77, 6.96, 7.43, and 7.62 ppm) with spin-spin interaction constant J = 13 Hz is observed. The isomeric acid with mp 217-218° also has a quartet of peaks with chemical shifts of 7.08, 7.35, 7.87, and 8.12 ppm but with J = 16 Hz.

Acid cis-II has a lower mobility than trans-II during chromatography on both aluminum oxide and on paper. This makes it possible to detect traces of the isomers and separate them. Their reactivities also differ substantially. The cis isomer requires an exposure of several minutes during development of the chromatogram with iodine vapors, while trans-II gives a brightly colored spot after 15-30 sec.

Both the cis and trans acids form the same trans methyl ester (III) on methylation (methanol in acid); the PMR spectrum of III contains, in addition to a singlet from the CH_3 group (3.95 ppm) and a multiplet from the protons of the pyridine ring (8.1-8.4 and 8.8-9.2 ppm), a quartet (7.10, 7.40, 7.85, and 8.15 ppm) with J = 16 Hz.

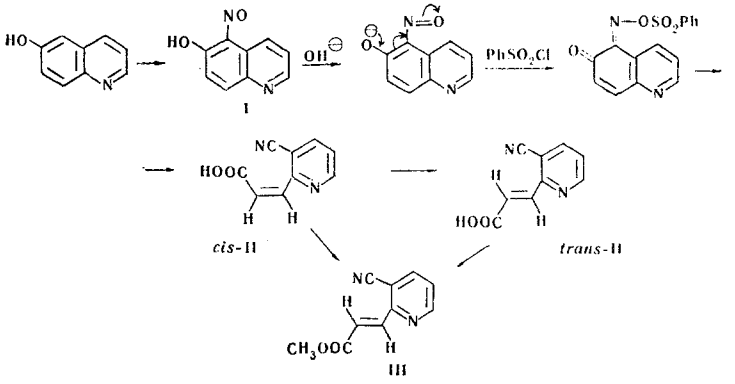
A small amount of the cis ester is chromatographically detected in the case of the cis acid. Heating the cis acid (1.5 h at 150°) with an equimolar amount of pyridine converts it completely to the trans isomer, just as in the cis-trans isomerization of cinnamic acids [1].

The structure of ester III is confirmed by the mass spectrum which has an intense peak with m/e 188 which corresponds to the molecular ion. Molecular ion M^+ disintegrates with cleavage of a CH_3 group (peak with m/e 173) or a CH_3O group (peak with m/e 157). The latter process is confirmed by the metastable ion with m* 132.8. The subsequent loss of a CO group (metastable ion with m* 106.2) results in an ion with m/e 129 which splits out HCN (ion with m/e 102 and metastable ion with m* 80.8) or CN (ion with m/e 103 and metastable ion with m/e 82).

The absorption maxima in the UV spectra of the cis- and trans-II in water (see Fig. 2) are close (262 and 264 nm, respectively), but the trans form has a somewhat larger extinction. A slight maximum is also observed for the cis form in acid at 294 nm. Methylation results in a bathochromic shift of 2 nm and a further increase in the extinction.

Thus the rearrangement of 5-nitroso-6-hydroxyquinoline (I) apparently proceeds in the same way as in the naphthol series, i.e., through a step involving the monooxime of the corresponding o-quinone. The normal reaction product is the cis acid (cis-II), but it is isomerized to the thermodynamically more stable

trans-II by the action of pyridine or in the presence of compounds of the pyridine series. A similar effect is induced by protonation of the pyridine nitrogen atom.



Experiments with similar opening of the rings of 7-hydroxyquinoline were less successful. The major product in the Skraup synthesis from m-aminophenol is 7-hydroxyquinoline, but it also contains 5-hydroxyquinoline. Chromatography on aluminum oxide did not make it possible to detect this contaminant, but it was readily manifested after nitrosation (appearance of two spots on the chromatogram). After nitrosation, purified 7-hydroxyquinoline forms an infusible, amorphous, chromatographically homogeneous powder which on attempts to carry out the Beckmann rearrangement by the action of benzenesulfonyl chloride in alkali gave only traces of a substance which, from its chromatographic behavior on aluminum oxide and on paper, corresponds to β-(2-cyano-3-pyridyl)acrylic acid.

EXPERIMENTAL

The UV spectra (10^{-4} mole/liter) were obtained with an SF-4A spectrophotometer. The PMR spectra in trifluoroacetic acid (with hexamethyldisiloxane as the internal standard) were obtained with an RS-60 spectrometer with an operating frequency of 60 MHz. Paper chromatography was carried out by the ascending method using Leningrad "B" paper and applying 20-40γ of the substances. The hydroxyquinolines and their nitroso derivatives were chromatographed with an ethanol–25% ammonium hydroxide–water (20:1:4) system with development by UV irradiation (6-hydroxyquinoline gave a yellowish fluorescence, while 7-hydroxyquinoline gave a blue fluorescence). Isopropyl alcohol–25% ammonium hydroxide–water (8:1:1) was used for the acids with development with a 0.05% solution of Bromphenol Blue or (at higher concentrations) UV light. Chromatography in a thin layer of aluminum oxide (activity II) was carried out with a benzene–absolute ethanol (9:1) system for the hydroxyquinolines and with an ethanol–25% ammonium hydroxide–water (20:1:4) system for the nitroso derivatives and acids with development in UV light or with iodine vapors.

6-Hydroxyquinoline. Boric acid [25 g (0.40 mole)] was dissolved by heating in 150 g (1.63 mole) of glycerol (sp. gr. 1.26) and added to a mixture of 44.7 g (0.41 mole) of p-aminophenol, 14 g of crystalline ferrous sulfate, and 29.5 g (0.24 mole) of nitrobenzene. A total of 69.8 ml of concentrated sulfuric acid (sp. gr. 1.83-1.84) was added slowly with stirring, and the mixture was brought to the boiling point. Heating was discontinued for 10-15 min since the mixture boiled spontaneously. Refluxing was continued for 10 h, and the boiling point of the mixture was about 135-140°. The flask contents were then cooled, diluted with 100 ml of water, and 300 ml of 50% sodium hydroxide was added with cooling until the mixture gave a strongly alkaline reaction (universal indicator, pH 10). The volatile substances were steam distilled from the mixture until the distillate became clear. The residual hot mixture was filtered, acidified to pH 2 (universal indicator), and again filtered. A 20% solution of sodium carbonate was added to the filtrate until it gave an alkaline reaction (universal indicator, pH 8). The precipitate was filtered, washed with water, and dried to give 33-38 g (55-64%) of a product with mp 192-193° (from dilute ethanol) [6]. The brown-gray crystalline powder was quite soluble in alkalies and acids, soluble in ethanol, and slightly soluble in chloroform, ether, and benzene. R_f 0.77 (paper), 0.43 (Al_2O_3).

5-Nitroso-6-hydroxyquinoline (I). A solution of 9.7 g (0.14 mole) of sodium nitrite in 30 ml of water was added with stirring in the course of 1 h to a solution of 20.8 g (0.14 mole) of 6-hydroxyquinoline in 12 ml (0.14 mole) of concentrated hydrochloric acid (sp. gr. 1.18) and 50 ml of distilled water cooled to 2°.

Stirring was continued for another 2 h. The resulting precipitate was filtered, washed on the filter with water, and dried to give 21-23 g (86-94%) of product with mp 198-200° (decomp., from ethanol). The golden-yellow crystalline powder was soluble in hot ethanol and hot concentrated acetic acid and slightly soluble in ether. R_f 0.64 (paper, 0.60 (Al_2O_3). Found %: N 16.10, 16.08. $C_9H_6N_2O_2$. Calculated %: N 16.09.

trans-β-(3-Cyano-2-pyridyl)acrylic Acid (trans-II). A mixture of 8.70 g (0.05 mole) of I, 7.70 ml (0.06 mole) of benzenesulfonyl chloride, and 200 ml of acetone was heated to the boiling point with stirring. Heating was discontinued, and a solution of 6.8 g of sodium hydroxide in 68 ml of water was added carefully in the course of 3-4 min. The mixture began to boil spontaneously after the addition of each dose of alkali, and I gradually dissolved. After the addition of all of the alkali, heating was continued and the mixture was held at the boiling point for another 10 min. The reaction mixture was cooled to room temperature, neutralized with 12% hydrochloric acid (pH 7, universal indicator), and the acetone was removed by heating on a water bath. The solution was filtered, the filtrate was acidified with 12% hydrochloric acid to pH 4, and 6 g of sodium bicarbonate and 40 ml of water were added to the filtered precipitate. The solution was decolorized by boiling with activated charcoal, filtered, and again precipitated by the addition of 12% hydrochloric acid to pH 4 to give 4.4-5 g (50-57%) of a product with mp 210-211° (decomp.). Two recrystallizations from water gave a product with mp 217-218° (decomp.). Chromatography indicated that it did not contain the cis isomer. The colorless, brilliant crystalline substance was quite soluble in hot ethanol and hot water and slightly soluble in benzene and cold water. R_f 0.54 (paper), 0.54 (Al_2O_3). Found %: N 16.11, 16.15. $C_9H_6N_2O_2$. Calculated %: N 16.09.

cis-β-(3-Cyano-2-pyridyl)acrylic Acid (cis-II). Compound I [8.70 g (0.05 mole)] was similarly treated with 7.70 ml (0.06 mole) of benzene–sulfonyl chloride, 200 ml of acetone, and 6.8 g of sodium hydroxide in 68 ml of water. The only difference was that the sodium hydroxide solution was added rapidly (in 0.5-1 min) in such a way as to maintain a reaction that was not too violent. After addition of the alkali, the mixture was refluxed for 15-20 min. Reprecipitation (as for the trans isomer) yielded 3.5-4.0 g (40-46%) of cis-II with mp 177-178° (decomp.). Repeated recrystallization from absolute ethanol made it possible to obtain a sample which did not contain the trans isomer and had mp 190-191° (decomp.). The white, brilliant, fibrous substance was quite soluble in hot water and hot toluene, soluble in hot ethanol, and slightly soluble in benzene. R_f 0.45 (paper), 0.46 (Al_2O_3). Found %: N 16.19, 16.18. $C_9H_6N_2O_2$. Calculated %: N 16.09.

Methyl trans-β-(3-Cyano-2-pyridyl)acrylate (III). A. A mixture of 1.74 g (0.01 mole) of trans-II, 10 ml (0.3 mole) of absolute methanol, and 1 ml of concentrated sulfuric acid was refluxed without access to moisture for 3 h. The hot mixture was transferred to a conical flask, cooled, 20 ml of water was added, and 10% sodium carbonate was added to pH 8 (universal indicator). The precipitate was filtered, washed with water, and dried to give 1.4-1.5 g (76-80%) of a product with mp 116-117° (from water).

B. Dry hydrogen chloride was passed into a solution of 1.74 g (0.01 mole) of trans-II and 20 ml (0.6 mole) of absolute methanol cooled to room temperature until it was completely saturated (~1.5 h). The solution was evaporated to dryness on a water bath. The dry residue was dissolved in water, and 10% sodium carbonate was added to pH 8 (universal indicator). The precipitate was filtered, washed with water, and dried to give 1.0-1.2 g (53-64%) of ester with mp 116-117° (from water). The colorless, brilliant substance was quite soluble in ether, acetone, and ethyl acetate, soluble in hot ethanol and carbon tetrachloride, and slightly soluble in cold water. R_f 0.33 [benzene–heptane (4:1), Al_2O_3]. Found %: N 15.00, 15.10. $C_{10}H_8N_2O_2$. Calculated %: N 14.89.

Methyl ester III was obtained in 15-20% yield from cis-II under the conditions of experiment A. It was also obtained in 42-53% yield under the conditions of experiment B and had mp 116-117° (from water). The elementary analysis and the chromatographic spectral data correspond to structure III.

Conversion of cis-II to trans-II. A mixture of 0.87 g (0.005 mole) of cis-II and 0.4 ml (0.005 mole) of dry pyridine was heated on a metal bath at 150° for 1.5 h. It was then cooled, diluted with 5 ml of water, and acidified to pH 4 with 2.1 ml of 12% hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried to give 0.70-0.71 g (80-82%) of trans-II with mp 215-216° (decomp.). Recrystallization from water gave a product with mp 216-217° (decomp.). The elementary analysis and chromatographic data corresponded to the trans-II structure.

7-Hydroxyquinoline. This was obtained like 6-hydroxyquinoline from 44.7 g (0.41 mole) of m-aminophenol, 14 g of crystalline ferrous sulfate, 29.5 g (0.24 mole) of nitrobenzene, and 25 g of boric acid dis-

solved in 150 g (1.63 mole) of glycerol and 69.8 ml of concentrated sulfuric acid. After steam distillation of the volatile substances, the filtered alkaline solution was acidified strongly with concentrated hydrochloric acid (pH 1, universal indicator) to give 30-36 g (50-60%) of product. Recrystallization from chlorobenzene gave 25-30% of a product with mp 237-238° (compare with [7]). R_f 0.74 (paper), 0.48 (Al_2O_3). The picrate had mp 242-243° (from ethanol).

A total of 5-6 g (20-24%) of a dark-brown, amorphous, powdery nitroso compound was obtained from 20.8 g (0.14 mole) of 7-hydroxyquinoline, 12 ml (0.14 mole) of hydrochloric acid (sp. gr. 1.18), and 9.7 g (0.14 mole) of sodium nitrite in 30 ml of water (as in the synthesis of I) after dissolving the precipitate in 70 ml of acetic acid, filtration, and neutralization to pH 7 with ammonium hydroxide.

An attempt to carry out the Beckmann rearrangement with such an impure substance gave traces of a compound with R_f 0.70 (paper), 0.62 (Al_2O_3).

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