NITROSOPHENOLS AND THEIR REARRANGEMENT PRODUCTS

IV.* 6-METHYL-3-CYANO-2-PYRIDYLACRYLIC ACIDS

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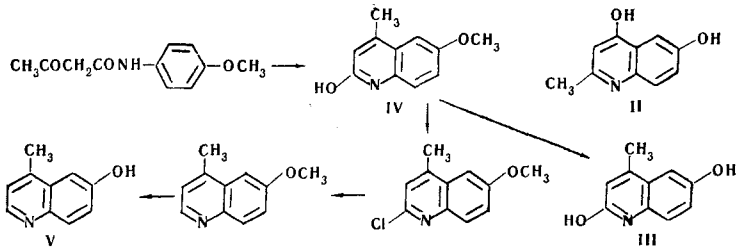
Under the usual conditions, 6-hydroxyquinolines which have a substituent in the 4-position do not form 5-nitroso derivatives; this is explained by steric factors. 5-Nitroso-6-hydroxyquinaldine is obtained from 2-methyl-6-hydroxyquinoline; under the conditions of the Beckmann rearrangement it forms cis- and trans-β-(6-methyl-3-cyano-2-pyridyl)acrylic acids, which were separated by thin-layer chromatography. The cis isomer is readily isomerized to the trans isomer in both alkaline and acidic media.

Several acids of the pyridine series (nicotinic and pyridylacetic acid) are capable of raising the fibrinolytic potential of blood, which may be of substantial importance in combating thromboses [2, 3]. The search for new synthetic routes and new models in this field has therefore taken on great significance for medicinal chemistry.

We recently showed [4, 5] that 5-nitroso-6-hydroxyquinoline is converted to β-(3-cyano-2-pyridyl)-acrylic acid by the action of benzenesulfonyl chloride in aqueous alkali apparently via a scheme involving rearrangement of 1-nitroso-2-naphthol [6], i.e., through a step involving isomerization to an o-quinone monooxime with subsequent Beckmann rearrangement of the second type. The geometry (cis or trans form) of the acid obtained depends substantially on the conditions used to carry out the reaction [5].

In order to evaluate the generality of this route to the synthesis of cyanopyridylacrylic acids and to study their transformations we obtained a number of compounds of the quinoline series. 6-Hydroxyquinaldine (I) was obtained by the Doebner-Miller synthesis from p-aminophenol and crotonaldehyde. We used the Conrad-Limpach cyclization of β-(p-hydroxyphenylamino)crotonic ester to synthesize 4,6-dihydroxyquinaldine (II). The isomeric 2,6-dihydroxylepidine (III) is more conveniently obtained by demethylation of 2-hydroxy-6-methoxylepidine (IV), synthesized by the cyclization of p-acetoacetanisidide. Replacement of the hydroxyl group in the 2-position of IV by chlorine, elimination of halogen, and demethylation led to 6-hydroxylepidine (V).



Like 6-hydroxyquinoline, 6-hydroxyquinaldine is readily nitrosated at the 5-position to form nitroso compound VI. The nitrosation of II and III is complicated by oxidative processes. The high-melting, yellow-red, slightly soluble substances formed in low yields do not give chelates with heavy metal ions. This is

*See [1] for communication III.

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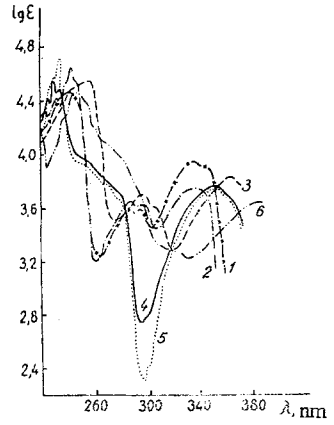


Fig. 1

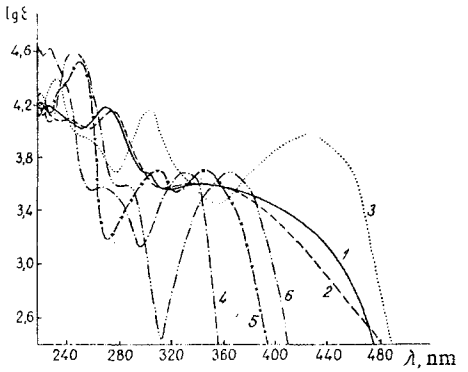


Fig. 2

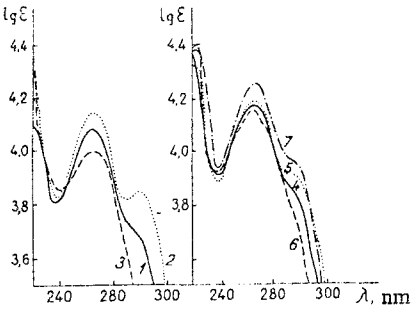


Fig. 3

Fig. 1. Absorption spectra (in 80% ethanol): 1) 4,6-dihydroxyquinaldine (II); 2) II (0.01 N HCl in 80% ethanol); 3) II (0.01 N KOH in 80% ethanol); 4) 2,6-dihydroxylepidine (III); 5) III (0.01 N HCl in 80% ethanol); 6) III (0.01 N KOH in 80% ethanol).

Fig. 2. Absorption spectra (in 80% ethanol): 1) 5-nitroso-6-hydroxyquinaldine (VI); 2) VI (0.01 N HCl in 80% ethanol); VI (0.01 N KOH in 80% ethanol); 4) 6-hydroxyquinaldine (I); 5) I (0.01 N HCl in 80% ethanol); 6) I (0.01 N KOH in 80% ethanol).

Fig. 3. UV spectra (in water): 1) cis-β-(6-methyl-3-cyano-2-pyridyl)acrylic acid (cis-VII); 2) cis-VII (0.01 N HCl); 3) cis-VII (0.01 N KOH); 4) trans-β-(6-methyl-3-cyano-2-pyridyl)acrylic acid (trans-VII); 5) trans-VII (0.01 N HCl); 6) trans-VII (0.01 N KOH); 7) methyl trans-β-(6-methyl-3-cyano-2-pyridyl)acrylate (VIII).

apparently also associated with the steric effect of the substituent in the 4-position, since nitrosation of 4-methyl-6-hydroxyquinoline (V) does not proceed under the usual conditions.

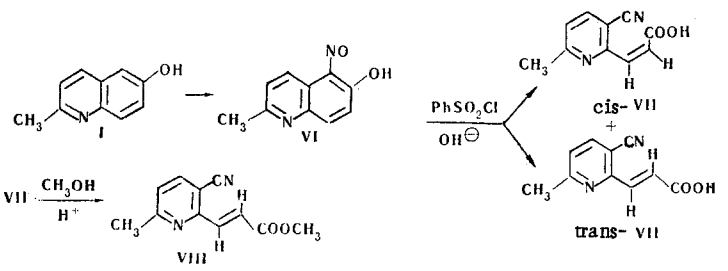
The ease of tautomeric transformation of the hydroxyquinolines to the corresponding quinoline form has been discussed repeatedly (see [7], for example). The UV spectra of II and III (Fig. 1) indicate the characteristic change in the curves on passing to the alkaline region (the appearance of maxima at 240-260 and 360-380 nm with a curve inflection at 270-280 nm), which is typical for quinoid structures. When there is no hydroxyl group in the pyridine ring [for example, in I (Fig. 2) and V], a bathochromic shift of all of the maxima at 248, 288, and 364 nm is observed in alkali, while only the long-wave maxima are shifted in acid (due to protonation of the heteroatom).

The introduction of a nitroso group into the 5-position of the ring results (in VI) in a pronounced increase in the absorption intensity at 272 nm (Fig. 2). The o-quinone oxime grouping, which exists in alkaline media, is manifested in a shift of the maximum to 306 nm and subsequent intensification of the absorption to form a maximum at 426 nm. The quinone oxime form is apparently realized to only a small extent in neutral media. In acidic media, VI exists in the nitrosohydroxyquinoline form with absorption maxima at 232, 272, and 334 nm.

The cis and trans isomers of β-(6-methyl-3-cyano-2-pyridyl)acrylic acid (VII) are formed by the action of benzenesulfonyl chloride in aqueous acetone on nitroso compound VI; the isomers are readily separated by chromatography on loose aluminum oxide. If iodine vapors are used to develop the chromatogram, it is readily noted that the cis isomer forms a colored compound in about 2 min, while trans-VII gives a brightly colored spot in 30 sec. The absorption spectra of these isomers are close in the UV region, but their extinctions differ somewhat (Fig. 3). For cis-VII the absorptions in neutral, acidic, and alkaline media differ somewhat, while the absorption intensity as a function of the medium remains almost constant for trans-VII. The appearance of a small maximum at 300 nm is apparently characteristic only for cis-pyridylacrylic acids in acidic media.

The trans isomer is readily formed by heating cis-VII with pyridine. Correspondingly, esterification of both cis- and trans-VII with methanol in acidic media results in the same trans ester (VIII). We have

already noted a similar phenomenon for 3-cyano-2-pyridylacrylic acid [5]. An increase in the extinction and a 3-nm shift in the absorption maximum as compared with trans-VII are observed in the UV spectrum of VIII.



A quartet of peaks (6.72, 6.93, 7.39, and 7.61 ppm) with spin-spin interaction constant J = 13 Hz, which corresponds to cis-ethylene protons, is observed in the PMR spectrum of cis-VII. The spectrum of trans-VII contains a quartet of peaks (7.18, 7.45, 7.93, and 8.20 ppm) with J = 16 Hz. A quartet of peaks (7.11, 7.38, 7.80, and 8.08 ppm) with spin-spin interaction constant J = 16.5 Hz, which confirms the trans configuration [8], is observed for VIII.

EXPERIMENTAL

The UV spectra of 10^{-4} M solutions were obtained with an SF-4A spectrometer. 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.

Compound I, ethyl β-(p-hydroxyphenylamino)crotonate, 6-methoxy-4-hydroxyquinaldine, IV, and V were chromatographed on a thin layer of activity II aluminum oxide (0.2-mm thick) with a benzene–absolute ethanol (9 : 1) system; II and III were chromatographed with a benzene–absolute ethanol (4 : 1) system; the nitroso derivatives and VII were chromatographed with an ethanol–25% ammonium hydroxide–water (20 : 1 : 4) system with application of 20-40γ of the compound. The following systems of eluants were used for chromatography on Leningrad "B" paper by the ascending method: ethanol–25% ammonium hydroxide–water (20 : 1 : 4) for I and VI; isopropyl alcohol–25% ammonium hydroxide–water (8 : 1 : 1) for VII. The spots were detected in UV light and with iodine vapors.* Yellow (I, III, and V), light-blue (II and IV), or light-violet fluorescence (6-methoxy-4-hydroxyquinaldine) were observed in UV light.

The potentiometric titration of 0.01 N solutions of VII was carried out with an LPU-01 pH meter with carbonate-free 0.01 N sodium hydroxide at 20° using a glass-calomel electrode couple. The pK_a values were taken to be equal to the pH at the half-neutralization point.

6-Hydroxyquinaldine (I). A mixture of 29.4 g (0.27 mole) of p-aminophenol in 40 ml of concentrated hydrochloric acid was heated on a water bath for 10-15 min, and 24 ml (0.34 mole) of crotonaldehyde (six to seven portions in 30 min) was added with shaking of the flask by hand after each addition. The mixture was heated on a water bath for another 2.5-3 h. Water (200 ml) was added, the mixture was cooled to room temperature, and 10% sodium carbonate was added until a resinous clump appeared in the solution. Subsequent addition of the sodium carbonate solution was carried out carefully until resin formation ceased (i.e., up to pH 7). The turbid solution was rapidly poured off from the resinous substances and filtered after 0.5-1 h. The precipitate on the filter was washed with hot water (60-70°), squeezed, and dried to give 10-12 g (23-28%) of product. The yields were 10-12% when paraldehyde was used. Repeated recrystallization from xylene gave a product with mp 211-212° [9]. The crystalline powder was quite soluble in ethanol and ether, soluble in hot benzene, and slightly soluble in cold water. R_f 0.81 (paper), 0.47 (Al_2O_3).

5-Nitroso-6-hydroxyquinaldine (VI). A solution of 2.1 g (0.03 mole) of sodium nitrite in 10 ml of water was added in the course of 0.5-1 h with stirring and cooling to +2° to 4.5 g (0.028 mole) of I in 6.5 ml (0.11 mole) of acetic acid and 25 ml of distilled water. Stirring was continued for another 1.5-2 h, and the precipitate was filtered, washed with water, squeezed, and dried to give 4.5-5 g (85-94.5%) of a product with mp 159-160° (decomp., from ethanol). The crystalline powder was soluble in hot dioxane, hot glacial acetic acid, and hot acetone. R_f 0.70 (paper), 0.48 (Al_2O_3). Found%: N 14.6. $C_{10}H_8N_2O_2$. Calculated %: N 14.9.

*A 0.05% alcohol solution of Bromphenol Blue was used to develop VII (on paper).

trans-β-(6-Methyl-3-cyano-2-pyridyl)acrylic Acid (trans-VII). A mixture of 9.4 g (0.05 mole) of VI, 7.7 ml (0.06 mole) of benzene–sulfonyl 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 portions. Heating was continued, and the mixture was refluxed for another 10 min. The reaction mixture was cooled to room temperature, neutralized to pH 7 with 12% hydrochloric acid, and the acetone was removed by distillation on a water bath. The solution was acidified to pH 4, the resulting precipitate was filtered, and 6 g of sodium bicarbonate and 40 ml of water were added. The solution was decolorized by boiling with activated charcoal, filtered, and again precipitated with 12% hydrochloric acid (pH 4) to give 6.0-7.0 g (64-74.5%) of acid with mp 200-201° (decomp.). Crystallization from water yielded needle-shaped crystals which were quite soluble in hot ethanol, soluble in hot water, and slightly soluble in cold water and had mp 203-204° (decomp.). R_f 0.61 (paper), 1.43 (Al_2O_3). pK_a 4.25 ± 0.05 (water). Found %: N 15.0; mol. wt. 187.5. $C_{10}H_8N_2O_2$. Calculated %: N 14.9; mol. wt. 188.19.

cis-β-(6-Methyl-3-cyano-2-pyridyl)acrylic Acid (cis-VII). A total of 5.1-6.0 g (54-64%) of a substance with mp 173-174° (decomp.) was obtained from 9.4 g (0.05 mole) of VI, 7.7 ml (0.06 mole) of benzenesulfonyl chloride, 200 ml of acetone, and 6.8 g of sodium hydroxide in 68 ml of water (as in the preceeding method but immediately upon mixing of the components). Repeated recrystallization from absolute ethanol gave a product with mp 193-194° (decomp.). The crystalline powder was quite soluble in acetone and soluble in hot ethanol, hot water, and hot xylene. It was more soluble in water than trans-VII but less soluble in ethanol. R_f 0.49 (paper), 0.46 (Al_2O_3). pK_a 4.95 ± 0.05 (water). Found %: N 14.9; mol. wt. 187.03. $C_{10}H_8N_2O_2$. Calculated %: N 14.9; mol. wt. 188.19.

Conversion of cis-VII to trans-VII. A mixture of 0.94 g (0.005 mole) of cis-VII 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, 5 ml of water was added, and the mixture was acidified with 2.1 ml of 12% hydrochloric acid. The precipitate was filtered, washed with water, and dried to give 0.56 g (58.5%) of trans-VII with mp 196-197° (decomp.). Recrystallization from water gave a product with mp 202-203° (decomp.). The chromatographic data and UV spectrum corresponded to the trans isomer.

Methyl trans-β-(6-Methyl-3-cyano-2-pyridyl)acrylate (VIII). A total of 1.5-1.6 g (75-80%) of a substance with mp 140-141° (from carbon tetrachloride) was obtained from 1.88 g (0.01 mole) of trans-VII, 10 ml of absolute methanol, and 1 ml of concentrated sulfuric acid after refluxing for 3 h, cooling, addition of 20 ml of water, alkalization with 10% sodium carbonate to pH 8, and washing the precipitate on the filter with water. The crystalline powder was quite soluble in dioxane, soluble in hot ethanol, and slightly soluble in water. R_f 0.41 [Al_2O_3, benzene–heptane (4:1)]. Found %: N 13.6. $C_{11}H_{10}N_2O_2$. Calculated %: N 13.8.

The same compound was obtained in 40-50% yield by methylation of cis-VII under similar conditions.

Ethyl β-(p-Hydroxyphenylamino)crotonate. p-Aminophenol [27.25 g (0.25 mole)], 31.6 ml (0.25 mole) of acetoacetic ester, 50 ml of benzene, and 1 ml of glacial acetic acid were placed in a 0.25 liter flask connected to a Dean-Stark water separator fitted with a reflux condenser. The mixture was heated on an oil bath to 125°, and the water was decanted from the water separator (4.8 ml). Upon completion of water separation, petroleum ether (bp 70-100°) was added to the cooled solution until a substance began to precipitate. The precipitate was filtered, washed with petroleum ether, and dried to give 52-53 g (94-95%) of a product with mp 88-89° (from cyclohexane). The pale-yellow, crystalline substance was soluble in ether, ethanol, hot benzene, and hot carbon tetrachloride. R_f 0.61 (Al_2O_3). Found %: N 6.5. $C_{12}H_{15}NO_3$. Calculated %: N 6.3.

4,6-Dihydroxyquinaldine (II). A. Ethyl β-(p-hydroxyphenylamino)crotonate was added with stirring to a mixture of diphenyl and diphenyl ether heated to the boiling point. The mixture was boiled and stirred for another 10 min. It was then cooled to room temperature, and the liquid was decanted from the residue and washed with petroleum ether. A total of 200 ml of 10% sodium hydroxide was added to the mixture, and it was heated until the residue dissolved. Traces of Dowtherm were extracted with ether. The aqueuous layer was acidified to pH 4 with acetic acid. The precipitate was filtered, washed with water, and dried to give 7.3-7.5 g (41.7-43%) of a product which melted above 290° (decomp., from water). The fibrous substance was soluble in hot ethanol and slightly soluble in benzene and chloroform. R_f 0.25 (Al_2O_3). Found %: N 8.1. $C_{10}H_{11}NO_2$. Calculated %: N 8.0.

B. A mixture of 18.9 g (0.1 mole) of 6-methoxy-4-hydroxyquinaldine [10] and 100 ml of 48% hydrobromic acid was refluxed for 8 h. The mixture was cooled, 25 g of sodium hydroxide dissolved in 100 ml

of water was added to the precipitate, and the mixture was stirred and acidified to pH 4 with acetic acid to give 15-16 g (86-91%) of product [7].

Nitrosation of 1.22 g (0.007 mole) of II in 50% acetic acid at +2° yielded about 0.1 g (7%) of a substance which decomposed above 290°. The red amorphous powder was soluble in hot dimethylformamide and slightly soluble in hot ethanol. R_f 0.46 (Al_2O_3). An analytically pure substance could not be obtained.

6-Methoxy-4-hydroxyquinaldine. A total of 92-95 g (48.7-50%) of a substance which melted above 290° (decomp., from ethanol) [10] was obtained like II by the cyclization of ethyl β-(p-methoxyphenylamino)-crotonate [from 92.2 g (0.75 mole) of p-anisidine and 94.8 ml (0.75 mole) of acetoacetic ester] in 300 ml of refluxing diphenylmethane after cooling of the mixture, addition of 300 ml of benzene, filtration of the precipitate, washing with ethanol and ether, and drying. The fibrous, crystalline powder was quite soluble in hot dimethylformamide and soluble in hot ethanol. R_f 0.36 (Al_2O_3). UV spectrum in 80% ethanol, λ_{max}, nm (log ε): 226 (4.28); 240 (4.52); 284 (3.61); 294 (3.62); 328 (3.99); 340 (3.96); 0.01 N HCl in 80% ethanol: 236 (4.63); 242 (4.88); 286 (3.68); 294 (3.68); 328 (3.77).

Acetoacetic Acid p-Hydroxyanilide. A mixture of 54.5 g (0.5 mole) of p-aminophenol and 78 ml (0.6 mole) of acetoacetic ester was heated on a metal bath at 145° for 6 h with a reflux condenser. It was then poured with stirring into 0.5 liter of hot water (about 70°), and allowed to stand overnight. The precipitate was filtered, washed with hot water, squeezed, and dried. Acetoacetic acid p-hydroxyanilide and ethyl β-(p-hydroxyphenylamino)crotonate and p-aminophenol impurities were detected by chromatography of the substance in a benzene–ethanol (9:1) system (Al_2O_3). Crystallization from boiling benzene yielded 15 g (15%) of pure substance with mp 91.5° (from 5% acetic acid). R_f 0.49 [Al_2O_3, benzene–acetic acid (4:1)]. Found %: N 6.4. $C_{10}H_{11}NO_3$. Calculated %: N 6.6.

2,6-Dihydroxylepidine (III). A. Concentrated sulfuric acid (5 ml) was added with stirring in the course of 5-10 min to 6.0 g (0.03 mole) of acetoacetic acid p-hydroxyanilide, and the mixture was heated at 100° for 4-5 h. It was then diluted with water, and the precipitate was filtered, washed on the filter with water, and suspended in 100-150 ml of water. After standing for 1-2 h, the precipitate was filtered, squeezed, washed with water, and dried to give 4.0 g (74.3%) of a product which melted above 300° (from glacial acetic acid). R_f 0.52 (Al_2O_3).

B. A total of 21 g (78%) of a substance whose chromatographic and spectral data corresponded to the 2,6-dihydroxylepidine [11] obtained in experiment A was obtained after 12 h refluxing of 28.4 g (0.15 mole) of 6-methoxy-2-hydroxylepidine in a mixture of 100 ml of glacial acetic acid and 150 ml of 48% hydrobromic acid, addition of 150 ml of water, and neutralization with ammonium hydroxide and stirring.

A total of 0.1 g (14%) of a yellow powder with mp 234-236° (decomp., from glacial acetic acid) was obtained by nitrosation of 0.61 g (0.0035 mole) of III in 200 ml of glacial acetic acid and 30 ml of water by the addition of 1.0 g (0.014 mole) of sodium nitrite in 10 ml of water. The product was soluble in hot dimethylformamide. R_f 0.83 (Al_2O_3). It did not form chelates with aluminum ions.

6-Methoxy-2-hydroxylepidine (IV). A total of 94.6 g (78%) of a substance with mp 266-267° (from isobutyl alcohol) [12] was obtained by cyclization of 125 g (0.64 mole) of p-acetoacetanisidide in 68.8 ml of concentrated sulfuric acid (as for III). R_f 0.45 (Al_2O_3). UV spectrum in 80% ethanol, λ_{max}, nm (log ε): 222 (4.77); 230 (5.03); 234 (4.88); 348 (3.90); 0.01 N HCl in 80% ethanol: 226 (5.03); 234 (4.94); 346 (3.88).

6-Hydroxylepidine (V). A total of 4.0-4.1 g (87-89%) of V with mp 214-216° [13] and R_f 0.48 (Al_2O_3) was obtained after the reaction of IV with phosphorus oxychloride, reduction of the 2-chloro derivative with excess zinc dust in acetic acid, and demethylation of 5.0 g (0.029 mole) of the thus obtained 6-methoxylepidine by refluxing with 25 ml of 48% hydrobromic acid for 8 h. UV spectrum in 80% ethanol, λ_{max}, nm (log ε): 224 (4.80); 228 (4.85); 280 (3.55); 330 (3.68); 0.01 N KOH in 80% ethanol: 224 (4.18); 230 (4.17); 248 (4.64); 292 (3.63); 352 (3.85).

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