OPENING OF THE PYRIDINE RING OF COMPOUNDS OF THE HYDROXYQUINOLINE SERIES*

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The nitrosation of 2-, 3-, and 4-hydroxyindoles was investigated. The Beckmann rearrangement with opening of the pyridine ring to form anthranilic acids or their derivatives occurs during the action of benzenesulfonyl chloride in alkaline media on 3-nitroso-4-hydroxycarbostyrils.

The Beckmann rearrangement with opening of the benzene ring to give (3-cyano-2-pyridyl)acrylic acids [2] occurs during the action of acylating agents in alkaline media on 5-nitroso-6-hydroxyquinolines.

The possibility of the application of this method for the opening of heteroaromatic rings has as yet received little study. It is known only that the β-oximes of isatin and substituted isatins can be converted to the corresponding anthranilonitriles by this route. In this connection, we carried out a series of experiments involving the synthesis and Beckmann rearrangement of compounds containing both hydroxyl and nitroso groups in the pyridine ring.

As models we initially took 2-methyl-4-hydroxyindoline (I) and 4-methylcarbostyril (II), in which electrophilic substitution at the 3-position usually proceeds readily [3]. However, we found that the nitrosation of these compounds in both mineral acids and acetic acid with an equimolecular amount or excess of sodium nitrite leads to the formation of resinous reaction products. In order to direct the electrophilic attack at the 4-position, we synthesized 3-hydroxy-2-(p-bromophenyl)quinoline (III), but this substance could not also be converted to the necessary nitroso derivative under various conditions.

We then decided to use 4-carboxycarbostyril (IV). It should, however, be noted that the direct route to the synthesis of compounds of the IV type (the tautomeric form of 2,4-dihydroxyquinoline) from aniline and malonic acid or their derivatives is usually accompanied by the formation of a number of side products, primarily the corresponding pyranocarbostyril [4,5]. We carried out the reaction of methylaniline and diphenylamine with malonic ester by heating them in Dowtherm [6], but almost exclusive formation of pyranocarbostyrils was found in both cases. However, we obtained 4-hydroxycarbostyril from aniline, malonic acid, and phosphorus oxychloride in the presence of naphthalene [7]. We synthesized 1-methyl- (V) and 1-phenyl-4-hydroxycarbostyril (VI) from the appropriate anthranilic acids.

Carbostyrils IV, V, and VI are readily nitrosated to form VII-IX, respectively. Maxima at 252 and 340 nm are observed in the UV spectrum of VII, which characterizes the o-quinoneoxime structure apparently chelated at the oxygen atom in the 4-position. In acid media the absorption curve changes sharply, which can be explained by the appearance of the o-nitroso form. The introduction of a methyl or phenyl group to the nitrogen atom (VIII and IX) leads to a shift of the maxima to the long-wave region with a certain increase in the extinction.

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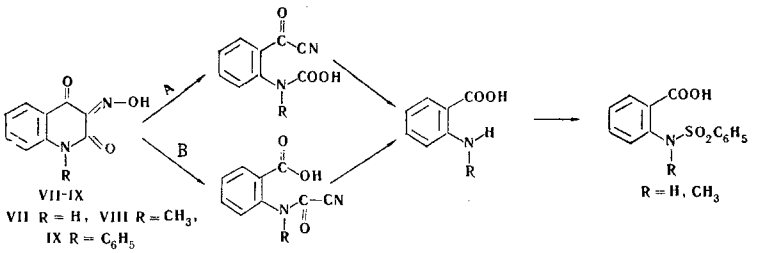

When VII-IX are subjected to the action of benzenesulfonyl chloride in alkaline media, the pyridine ring is opened to give the corresponding anthranilic acids. Chromatography of the reaction mixture demonstrated that N-acylation occurs simultaneously with the rearrangement. Thus, in several experiments, the major product proved to be the N-phenylsulfonyl derivative of anthranilic acid.

The rearrangement may occur a priori with cleavage of the C_2-C_3 bond (path A) or C_3-C_4 bond (path B). The available data do not make it possible to give a definite answer to the problem, but in analogy with the rearrangement of isatin β-oxime, in which the process occurs with cleavage of the C_2-C_3 bond, we consider path A to be the preferred one. The possibility of initial opening of the lactam ring cannot be excluded from consideration, although this should proceed considerably more slowly.

EXPERIMENTAL

Chromatography on a loose layer (2 mm) of activity-II aluminum oxide was carried out to evaluate the course of the reaction and the purities of the compounds. A benzene–absolute ethanol system (9:1) was used for I and II, ethanol–5% ammonium hydroxide (4:1) was used for IV-IX and rearrangement products VII and IX, and benzene–glacial acetic acid (20:3) was used for the rearrangement products of VIII. The spots were developed with iodine vapors. The UV spectra of 10^{-4} M solutions were recorded with an SF-4A spectrophotometer.

2-Methyl-4-hydroxyquinoline (I). This was obtained from aniline and acetoacetic ester in benzene–glacial acetic acid with subsequent cyclization immediately after removal of the benzene by distillation and had mp 234-235° (from water) [8] and R_f 0.5. UV spectrum: λ_{max}, nm ($\log \varepsilon$), in 80% ethanol: 234 (4.35), 314 (4.00), 326 (3.97).

4-Methylcarbostyril (II). This was synthesized by the cyclization of acetoacetanilide in concentrated H_2SO_4 and had mp 221-222° (from ethanol) [9] and R_f 0.59. UV spectrum, λ_{max}, nm ($\log \varepsilon$), in 80% ethanol: 226 (4.79), 268 (3.83), 324 (3.82).

3-Hydroxy-2-(p-bromophenyl)cinchoninic Acid. The minimum amount of a solution of 8.5 g (0.21 mole) of sodium hydroxide in 27.5 ml of water was added to a suspension of 7.35 g (0.05 mole) of isatin in 60 ml of water. A solution of 9.08 g (0.035 mole) of p-bromophenacyl acetate [11] in 50 ml of hot ethanol and the remaining portion of the sodium hydroxide solution were added to the resulting solution. The mixture was refluxed for 3 h and allowed to stand overnight. It was then diluted with 130 ml of water and filtered. Concentrated hydrochloric acid (16.5 ml) and 5.5 ml of glacial acetic acid were added to the filtrate with thorough stirring, and the mixture was allowed to stand overnight at room temperature. The precipitate was collected on a large-diameter Buchner funnel, washed with four 5-ml portions of cold water, and transferred to a flask with 150 ml of water. The precipitate was dissolved by the addition of 4.5 ml of 25% ammonium hydroxide, and the undissolved material was removed by filtration. A total of 10 ml of 6 N acetic acid was added to the filtrate, and the mixture was allowed to stand at room temperature for 1-2 h. The precipitate was removed by suction filtration, washed four times with 8-ml portions of water, and dried first at room temperature and then at 60° to give 6.4 g (50%) of a dark-yellow powder with mp 217-218° (dec., from ethanol) and R_f 0.35 [ethanol–25% ammonium hydroxide–water (2:1:2)] that was soluble in hot dimethylformamide and slightly soluble in hot ethanol. Found %: N 3.8, 3.9; Br 23.4, 23.6. $C_{16}H_{10}BrNO_3$. Calculated %: N 4.1; Br 23.2.

3-Hydroxy-2-(p-bromophenyl)quinoline (III). A solution of 6.4 g (0.02 mole) of 3-hydroxy-2-(p-bromophenyl)cinchoninic acid in 20 ml of boiling dimethyl succinate was added in portions with stirring in 2-3 min, and the mixture was refluxed until CO_2 evolution ceased and the mixture was completely homogenized. The mixture was then cooled, and 40 ml of diethyl ether was added. The precipitate was removed by filtration and washed on the filter with ether to give 3.0 g (50%) of a product with mp 249.5-250° (from

xylene). The product was a light-colored powder with R_f 0.55 [benzene–absolute ethanol (15:1)] that was soluble in hot toluene and ethanol and slightly soluble in hot water. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 226 (4.87), 232 (4.69), 240 (4.41), 256 (4.53), 295 (3.92), 342 (4.03). Found %: N 4.4, 4.5; Br 26.4, 26.6. $C_{15}H_{10}BrNO$. Calculated %: N 4.7; Br 26.6.

The nitrosation was carried out in acetic acid with equimolar and double amounts of sodium nitrite at 2-3°, but no nitroso derivative could be detected in the course of the reaction. Only the starting compound was isolated after stirring for 3 h.

4-Hydroxycarbostyril (IV). A mixture of 4.8 g (0.05 mole) of aniline, 7.8 g (0.075 mole) of malonic acid, 17 g of phosphorus oxychloride, and 6 g of naphthalene was heated at 95-100° for 20 min. It was then decomposed with water and made alkaline to pH 10. The undissolved material was removed by filtration, and the filtrate was acidified to pH 3. A rapidly moving impurity, which was lost after two recrystallizations from glacial acetic acid, was seen during chromatography of the isolated product. The yield of product with mp > 300° [7] was 2.8 g (35%). The light-colored powder was soluble in hot ethanol and hot glacial acetic acid and slightly soluble in hot water. R_f 0.65. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 226 (4.89), 282 (3.78), 300 (3.84).

1-Methyl-4-hydroxycarbostyril (V). A mixture of 13.7 g (0.09 mole) of N-methylanthranilic acid, 40.8 ml (0.4 mole) of acetic anhydride, and 50 ml of glacial acetic acid was heated on a metal bath at 140-150° for about 6 h. The solution was cooled, 20% sodium hydroxide solution was added until the mixture was alkaline, and the mixture was refluxed for 2 h. Acidification with acetic acid to pH 3 gave 7.5 g (48%) of a product with mp 268-269° (from 50% ethanol) [12] as a light-yellow, acicular powder that was quite soluble in hot ethanol, soluble in hot dioxane, and slightly soluble in hot water. R_f 0.65. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 224 (4.58), 230 (4.51), 274 (3.85), 282 (3.88), 312 (3.83).

1-Phenyl-4-hydroxycarbostyril (VI). A mixture of 19.17 g (0.09 mole) of N-phenylanthranilic acid, 40.8 ml (0.4 mole) of acetic anhydride, and 50 ml of glacial acetic acid was heated at 165° for about 12 h. The mixture was cooled, and 20% sodium hydroxide was added until the mixture gave an alkaline reaction. It was then refluxed for 2 h. Acidification with acetic acid gave 14.2 g (66%) of a product with mp 292° (from dimethylformamide) [13]. The light-colored powder was soluble in hot ethanol and hot xylene and insoluble in water. R_f 0.73. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 234 (4.58), 283 (3.99), 306 (3.96).

3-Nitroso-4-hydroxycarbostyril (VII). A total of 7.2 ml of dilute hydrochloric acid (1:1) was added in 15 min to a cooled (to 3-4°) solution obtained from 1.61 g (0.01 mole) of IV and 0.42 g (0.015 mole) of sodium hydroxide in 60 ml of water and 0.865 g (0.012 mole) of sodium nitrite, and the mixture was stirred for 1 h and worked up to give 1.7 g (89%) of a red-orange powder with mp 205-206° (dec., from glacial acetic acid) [13] that was soluble in hot ethanol, hot dioxane, and hot acetone. R_f 0.25. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 228 (4.22), 240 (4.08), 252 (4.23), 340 (4.12).

3-Nitroso-1-methyl-4-hydroxycarbostyril (VIII). A solution of 1.04 g (0.015 mole) of sodium nitrite in 10 ml of water was added to a cooled (to 3-4°) solution of 2.41 g (0.013 mole) of V in 120 ml of glacial acetic acid and 50 ml of distilled water in 25 min, the mixture was stirred for 1 h, and worked up to give 2.5 g (94%) of an orange powder with mp 212-213° (dec., from ethanol) [15] that was soluble in hot dioxane and hot glacial acetic acid; R_f 0.27. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 226 (4.23), 256 (4.34), 340 (4.23).

3-Nitroso-1-phenyl-4-hydroxycarbostyril (IX). This compound [4.5 g (85%)] was similarly obtained from 4.74 g (0.02 mole) of VI, 0.84 g (0.03 mole) of sodium hydroxide in 35 ml of distilled water, and 1.73 g (0.024 mole) of sodium nitrite by the addition of 15.6 ml of dilute (1:1) hydrochloric acid. The orange powder had mp 197-198° (dec., from glacial acetic acid) and was soluble in hot ethanol, hot acetone, and hot dioxane. R_f 0.51. UV spectrum, λ_{max}, nm (log ε), in 80% ethanol: 224 (4.43), 228 (4.43), 254 (4.32), 340 (4.15). Found %: N 10.3, 10.3. $C_{15}H_{10}N_2O_3$. Calculated %: N 10.5.

Rearrangement of VII. A mixture of 1.4 g (0.0075 mole) of VII, 1.15 ml (0.009 mole) of benzenesulfonyl chloride, and 50 ml of acetone was stirred and heated to the boiling point. Heating was discontinued, and a solution of 1.02 g of sodium hydroxide in 10.2 ml of water was added cautiously in portions. The mixture was then refluxed for 10 min, cooled to room temperature, and neutralized with 12% hydrochloric acid to pH 7. The acetone was evaporated on a water bath. Anthranilic acid and its phenylsulfonyl derivative were detected in the reaction mixture by chromatography; from the R_f values, fluorescence in UV light, and

color in iodine vapors, these were identical to reference spots obtained by another route [15]. The solution was acidified to pH 3, and 1 g of potassium bicarbonate and 20 ml of water were added to the filtered precipitate. The material was decolorized by refluxing with activated charcoal, the mixture was filtered, and the product was reprecipitated with 12% hydrochloric acid to give 0.3 g (15%) of N-phenylsulfonylanthranilic acid with mp 212-213° [16] and R_f 0.63, which was identical to an authentic sample.

Rearrangement of VIII. As in the rearrangement of VII, 4.75 g (0.023 mole) of VIII, 3.85 ml (0.03 mole) of benzenesulfonyl chloride, 100 ml of acetone, and 3.4 g of sodium hydroxide in 34 ml of water were allowed to react. According to chromatography, the major product in the reaction mixture was one for which the R_f value (0.73) and fluorescence in UV light coincided with that observed for a genuine sample of N-methylanthranilic acid [17]. Reprecipitation gave 1.5 g (43%) of N-methylanthranilic acid with mp 177-178° (after two recrystallizations from ethanol); R_f 0.74. The N-phenylsulfonyl derivative had mp 180-181° (from glacial acetic acid) and R_f 0.64.

Rearrangement of Nitroso Compound IX. This was carried out as in the rearrangement of VII from 3.99 g (0.015 mole) of VI, 2.31 ml (0.018 mole) of benzenesulfonyl chloride, 60 ml of acetone, and 2.04 g of sodium hydroxide in 20.4 ml of water. The chief compound detected by chromatography was N-phenylanthranilic acid [18]. The yield of product with mp 183° (from cyclohexane) and R_f 0.61 was 2.5 g (78%). This product did not depress the melting point of a genuine sample.

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