NITROALKENE-ANTHRANILIC ACID ADDITION PRODUCTS

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The long-known synthesis (1) of 3-nitro-4-hydroxyquinoline (II) by dehydration of 2-(2'-nitro-1'-ethylidenamino)benzoic acid (I) suggested that similar dehydrations of 2-(2'-nitro-1'-alkylamino)benzoic acids (III) might lead to the formation of 3-nitro-4-keto-1,2,3,4-tetrahydroquinolines (IV), valuable for synthetic purposes and of interest in antimalarial research.



We have found that compounds of type III are readily obtainable from the reactions of anthranilic acid with 2-nitro-1-alkenes (V). Initial experiments on this condensation were performed with anthranilic acid and 2-nitro-1-butene (V, $\mathbf{R} = C_2\mathbf{H}_5$). Condensation occurs readily on heating and yields 2-(2'-nitro-1'-butylamino)benzoic acid (III, $\mathbf{R} = C_2\mathbf{H}_5$). This synthesis was later modified in order that the more stable 2-nitro-1-butyl acetate could be substituted for 2-nitro-1-butene as a reagent. The former is readily decomposed to the latter by warm water or basic salts (2), and when this decomposition takes place in the presence of anthranilic acid the latter reacts with the 2-nitro-1-butene as it is formed to give good yields of the desired product. Another compound of this type, 2-(2'-nitro-1'-ethylamino)benzoic acid (III, $\mathbf{R} = \mathbf{H}$) was synthesized by a similar decomposition of 2-chloro-1-nitroethane (3) in the presence of sodium anthranilate. Attempts to extend the synthesis to include secondary

¹Present address: duPont Experimental Station, E. I. duPont de Nemours and Company, Wilmington, Delaware. nitroalkenes such as 2-nitro-2-butene and 4-nitro-3-heptene or the acetates of the corresponding nitro alcohols were unsuccessful.

The 2-(2'-nitro-1'-alkylamino)benzoic acids (III) are insoluble in water and dilute acids but soluble in concentrated mineral acids and may be quantitatively recovered from the latter solutions by dilution with water. On the other hand, they are very unstable toward alkali, and solutions of their ammonium or sodium salts rapidly decompose to regenerate the original nitroalkene and salts of anthranilic acid.

All attempts to cyclize the 2-(2'-nitro-1'-alkylamino)benzoic acids to the corresponding tetrahydroquinoline derivatives were unsuccessful. Refluxing with acetic anhydride and sodium acetate causes extensive decomposition and at lower temperatures the only reaction is acetylation of the aminoid nitrogen; this derivative was isolated in the case of 2-(2'-nitro-1'-butylamino)benzoic acid. Concentrated sulfuric or phosphoric acids fail to cause any change at 150°, and the compounds may be quantitatively recovered by dilution with water. Thionyl chloride and the phosphoric halides react vigorously with the nitro acids, III, presumably converting them to the corresponding acid chlorides. However, no cyclization occurs and the original nitro acids are regenerated on dilution with water. Treatment of the acid chlorides with alkali, pyridine, or anhydrous aluminum chloride also fails to cause cyclization.

Both of the nitro acids were subjected to catalytic hydrogenation in the hope that simultaneous reduction and cyclization might occur, but only the corresponding amino acids (VI) were obtained.

$$\begin{array}{c} \begin{array}{c} \begin{array}{c} H \\ NCH_{2}CHR \\ \\ CO_{2}H NO_{2} \end{array} + 3H_{2} \longrightarrow \begin{array}{c} \begin{array}{c} H \\ NCH_{2}CHR \\ \\ CO_{2}H NH_{2} \end{array} + 2H_{2}O \\ \end{array} \\ \end{array}$$

Attempts to cyclize the methyl ester (VII) of the aforementioned 2-(2'-nitro-1'-ethylamino)benzoic acid by aqueous alkali and by sodium methoxide in methanol result only in the same type of decomposition noted with the acid itself. Methanol-free sodium methoxide in absolute ether gives a precipitate of the sodium salt of the nitronic acid (VIII) which is unchanged after 48 hours refluxing in ether.



It is difficult to understand the resistance of the 2-(2'-nitro-1'-alkylamino) benzoic acids (III) to cyclization in view of the ease with which 2-(2'-nitro-1'-ethylidenamino) benzoic acid (I) is cyclized. Although the -N=CH-grouping in I undoubtedly acts as a powerful activator for the methylenic hydrogens,

those of III are sufficiently labile to form a sodium derivative in nonpolar solvents. Further investigation of this phenomenon is indicated.

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EXPERIMENTAL

All melting points are corrected.

2-(2'-Nitro-1'-butylamino)benzoic acid (III, $R = C_2H_5$). A mixture of 32.2 g. (0.20 mole) of 2-nitro-1-butyl acetate (2), 13.2 g. (0.22 mole) of glacial acetic acid, 35 ml. of water, 30.1 g. (0.22 mole) of anthranilic acid, and 16.4 g. (0.20 mole) of sodium acetate was stirred continuously and heated at 90-95° for one hour, then allowed to cool to room temperature. The crystalline product (41 g. of crude, m.p. 138-140°) was filtered off, washed with water and dried at 60°. It was dissolved in hot benzene, boiled with charcoal, filtered through a preheated funnel and cooled slowly to 15-20°. The product was filtered off, rinsed with benzene, and dried at 60°; yield 34-37 g. (71-78%) of pale tan needles, m.p. 142-143°. Repeated crystallization and decolorization failed to remove the faint color or change the melting point.

Anal. Calc'd for C₁₁H₁₄N₂O₄: C, 55.44; H, 5.92; N, 11.76; neut. equiv., 238.1.

Found: C, 55.45, 55.48; H, 5.91, 6.02; N, 11.75, 11.86; neut. equiv., 238.0, 238.1. $2 \cdot (2' \cdot Nitro-1' \cdot ethylamino) benzoic acid (III, R = H)$. A solution of 8.1 g. (0.059 mole) of anthranilic acid in 25 ml. of methanol was stirred with 5.0 g. (0.06 mole) of sodium bicarbonate and 15 ml. of water, warmed until the evolution of carbon dioxide was complete, and cooled to room temperature. Then 5.9 g. (0.053 mole) of 2-chloro-1-nitroethane (3) was added and the mixture was stirred for 30 minutes. It was then diluted with 200 ml. of hot water, allowed to cool to room temperature, and finally filtered; yield 10.9 g. of crude product, m.p. 150-151°. Recrystallization from 300-350 ml. of benzene gave 10.0 g. (90%) of white crystals, m.p. 155-156°.

Anal. Calc'd for C₉H₁₀N₂O₄: C, 51.40; H, 4.81; N, 13.33.

Found: C, 51.45, 51.54; H, 4.87, 4.91; N, 13.39, 13.47.

Methyl 2-(2'-nitro-1'-ethylamino)benzoaie (VII). A solution of 3.8 g. (0.025 mole) of methyl anthranilate, 2.7 g. (0.025 mole) of 2-chloro-1-nitroethane, and 2.5 ml. (0.03 mole) of pyridine in 10 ml. of methanol (99-100%) was refluxed for 90 minutes. The solution was then diluted with 50 ml. of water and allowed to cool to room temperature. The product was filtered off, washed with water, and dried at room temperature; yield 5.4 g. of crude material, m.p. 70-75°. It was recrystallized from 125 ml. of ligroin, (b.p. 90-100°) giving 4.1 g. (73%) of pale yellow needles, m.p. 84°. Several recrystallizations from ligroin gave a white product but no change in m.p.

Anal. Calc'd for C₁₀H₁₂N₂O₄: C, 53.55; H, 5.40; N, 12.50.

Found: C, 53.58, 53.59; H, 5.37, 5.42; N, 12.57, 12.60.

2-N-(2'-nitro-1'-butyl) acetylaminobenzoic acid. A mixture of 6.0 g. (0.025 mole) of 2-(2'-nitro-1'-butylamino) benzoic acid and 15 ml. of acetic anhydride was stirred while 2.0 g. (0.025 mole) of anhydrous sodium acetate was added. When the spontaneous reaction subsided the mixture was stirred and heated to 80°, then allowed to cool. It was diluted with 50 ml. of water and neutralized with solid potassium carbonate, then acidified with excess concentrated hydrochloric acid. The precipitated oil was extracted with ether, which was then carefully evaporated. The residue was mixed with water and allowed to crystallize; yield 3.5 g. (50%) of white crystals, m.p. 119-120° (decomp.). Recrystallization from a mixture of benzene and ligroin gave white needles with the same m.p.

Anal. Calc'd for C₁₃H₁₆N₂O₅: C, 55.69; H, 5.75; N, 10.00.

Found: C, 55.77, 55.80; H, 5.74, 5.68; N, 10.01, 10.09.

2-(2'-Amino-1'-butylamino) benzoic acid (VI, $R = C_2H_5$). A mixture of 6.0 g. (0.025 mole)

of 2-(2'-nitro-1'-butylamino)benzoic acid and Raney nickel catalyst in 75 ml. of 67% alcohol was shaken under hydrogen at an initial pressure of 4 atm. until the absorption of hydrogen ceased. The solution was warmed, filtered, then boiled with charcoal, filtered again, evaporated to incipient crystallization at the boiling point, and finally diluted with an equal volume of hot alcohol. After standing overnight the product was filtered off and dried at 100°; yield 3.8 g. (73%) of a faintly pink powder, m.p. 221-223° (decomp.). Recrystallization from water caused no change in m.p.

Anal. Calc'd for C₁₁H₁₆N₂O₂: C, 63.43: H, 7.74; N, 13.46.

Found: C, 63.47, 63.48; H, 7.71, 7.62; N, 13.54, 13.63.

2-(2'-Amino-1'-ethylamino)benzoic acid (VI, R = H). A mixture of 2.1 g. (0.01 mole) of 2-(2'-nitro-1'-ethylamino)benzoic acid, 125 ml. of water, and Raney nickel catalyst was shaken under hydrogen at an initial pressure of 4 atm. until the absorption of hydrogen ceased. The catalyst was filtered off, the filtrate was boiled with charcoal, filtered, evaporated to incipient crystallization and diluted with equal volume of alcohol. After standing overnight the product was filtered off, washed with alcohol, and dried at 100°; yield 1.4 g. (78%) of white crystals which slowly darkened, and melted about 220-225° (decomp.).

Anal. Calc'd for $C_9H_{12}N_2O_2 \cdot 1/3H_2O$: C, 58.06; H, 6.86; N, 15.05.

Found: C, 58.06, 58.13; H, 6.81, 6.92; N, 15.04, 15.14.

SUMMARY

1. The reactions of anthranilic acid with 2-nitro-1-alkenes and their derivatives are described.

2. The character of the products and a number of their reactions are discussed.

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