[Contribution from the Departments of Chemistry of the University of Georgia and Northwestern University]

THE ACTION OF ARENESULFONYL CHLORIDES ON PHTHALOHYDROXAMIC ACID, SUCCINOHYDROXAMIC ACID AND "PHTHALIC ANHYDRIDE OXIME"

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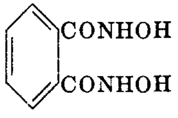
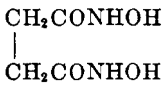
Recently (1) the action of arenesulfonyl chlorides on simple hydroxamic acids has been found to result in rearrangement as follows:

Equation 1: $2\ RCONHONa + C_6H_5SO_2Cl \rightarrow RCONHOCONHR + C_6H_5SO_3Na + NaCl$

The present work reports the application of this reaction to phthalohydroxamic acid, I, and succinohydroxamic acid, II (2).

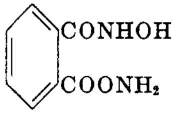


I

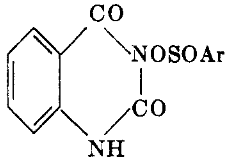


$$\begin{array}{l} CH_2CONHOH \\ | \\ CH_2CONHOH \end{array}$$

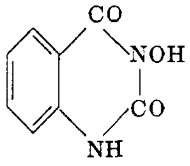
II



III



IV a: Ar = C_6H_5
b: Ar = $p\text{-}C_7H_7$



V

Treatment of sodium phthalohydroxamate (I, disodium salt) with benzenesulfonyl or *p*-toluenesulfonyl chloride results in the formation of the corresponding 3-arenesulfonoxy-1*H*-quinazolinedione as follows:

Equation 2: $C_6H_4(CONHONa)_2 + 2\ ArSO_2Cl \rightarrow IV + ArSO_3H + 2\ NaCl$

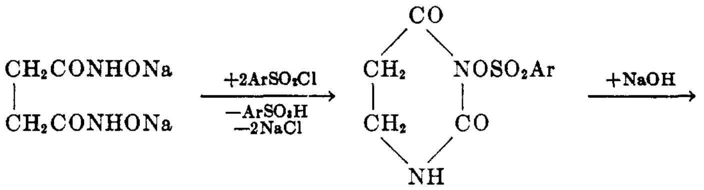
A probable course of the reaction is that attack of the sulfonyl chloride involves rearrangement of one of the hydroxamic acid groups to an isocyanato group which then interacts with the neighboring hydroxamic acid group. The final product, IV, is obtained by further action of the sulfonyl chloride. The structure of IV was established by elemental analysis and alkaline hydrolysis to 3-hydroxy-1*H*-quinazolinedione (V, 2a). It was shown previously (2a) that sodium phthalohydroxamate as prepared was contaminated with the sodium salt of an isomeric acid, III. Compound IV could not arise from this impurity, III.

In agreement with Equation 2, the reaction mixture was observed to become acidic as the reaction progressed. When triethylamine or pyridine was incorporated in the reaction mixture, improved yields of IV were realized. Further evidence for Equation 2 was provided by the isolation of the arenesulfonic acids as *S*-benzylthiuronium salts.

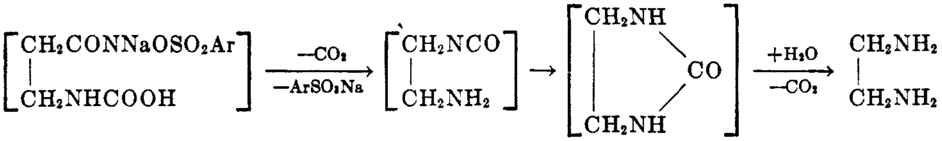
The action of sulfonyl chlorides on sodium succinohydroxamate (II, disodium salt) was observed to proceed with rearrangement similar to that observed with phthalohydroxamic acid, affording arenesulfonoxy derivatives of 5,6-dihydrouracil, VI. Yields of VI were not improved by the use of tertiary amines.

In contrast to the results obtained with IV, alkaline hydrolysis of VI followed by treatment with hydrochloric acid results in further rearrangement to ethylenediamine, isolated as the benzoyl derivative. These results are in agreement with the known stability of the quinazolinedione nucleus to acids and alkalies.

The reactions involved may be interpreted as follows:



VI a: Ar = C_6H_5
b: Ar = p-C_7H_7



At one time in the course of this work, it was thought that IVa and IVb might be derivatives of the so-called "phthalic anhydride oxime", $C_8H_5NO_3$ (3). The previously unreported benzenesulfonyl, VIIa, and p-toluenesulfonyl, VIIb, derivatives of the colorless variety of this compound were prepared for comparison but, as evidenced by physical properties and analysis, were different from IVa and IVb.

The action of aqueous alkalies on VIIa and VIIb yielded mixtures which were not separated, but potassium hydroxide in approximately 85% ethanol caused rearrangement of VIIa to a mixture of ethyl o-carboxycarbanilate (4) and an oil which could be hydrolyzed to anthranilic acid, probably ethyl anthranilate. These results compare with the rearrangement of both colorless and yellow forms of "phthalic anhydride oxime" in low yields to anthranilic acid by potassium hydroxide in amyl alcohol (3a).

EXPERIMENTAL

Melting points reported herein are uncorrected.

Sodium phthalohydroxamate (2a) and sodium succinohydroxamate (2) were prepared as described previously. Other materials employed were good commercial grades.

Reaction of sodium phthalohydroxamate with benzenesulfonyl chloride. Experiment Ia. To 3.65 g. of freshly prepared, powdered sodium phthalohydroxamate suspended in 30 ml. of chloroform was added slowly with mechanical stirring a solution of 5.0 g. of benzenesulfonyl chloride in 20 ml. of chloroform while the temperature of the mixture was held between 25° and 30° (approximately 30 minutes). The mixture was stirred for an additional 15 minutes and allowed to stand for one hour. The insoluble material was separated by filtration, triturated with hot ethanol, and again filtered while hot. On being cooled, the alcoholic filtrate yielded 1.8 g. of sodium benzenesulfonate, identified as the *S*-benzylthiuronium salt, m.p. and mixture m.p. with an authentic specimen, 146–147° (5).

The chloroform solution was evaporated to dryness and the residue was dissolved in the minimum amount of hot 95% ethanol. The cooled solution yielded a precipitate which was separated by filtration, washed, and dried affording 0.88 g. of 3-benzenesulfonoxy-1*H*-quinazolinedione (IVa), colorless prisms, m.p. 233–235°. By concentration of the filtrate, a second crop weighing 0.42 g. (m.p. 200–205°) was obtained. The total yield of the crude product was thus 1.30 g. or 29%. By recrystallization of the product from ethanol containing a little benzene, the melting point of the product was raised to 235–236°.

Anal. Calc'd for $C_{14}H_{10}N_2O_5S$: C, 52.82; H, 3.17; N, 8.80.

Found: C, 53.03; H, 3.21; N, 8.95.

Experiment IIa. By the method described in the preceding experiment, 2.7 g. of sodium phthalohydroxamate in chloroform was allowed to react with 4.0 g. of benzenesulfonyl chloride. Then 1 ml. of triethylamine was added. The mixture was allowed to stand for 30 minutes and was evaporated to dryness. The residue was washed with water and crystallized from 95% ethanol yielding two crops of IVa weighing 1.20 g. and 0.30 g., m.p. 235–236°, representing a 42% yield.

Reaction of sodium phthalohydroxamate with p-toluenesulfonyl chloride. Experiment Ib. According to the procedure described under Experiment Ia, 3.65 g. of sodium phthalohydroxamate was caused to react with 6.0 g. of *p*-toluenesulfonyl chloride in chloroform yielding 2.0 g. of sodium *p*-toluenesulfonate, identified as the *S*-benzylthiuronium salt, m.p. 179–180° (5), and 0.85 g. of 3-*p*-toluenesulfonoxy-1*H*-quinazolinedione, IVb, as colorless prisms, m.p. 279–280° (17% yield). The melting point of the product was raised to 280–281° by recrystallization from ethanol to which a little benzene had been added. The analytical sample was further recrystallized from glacial acetic acid resulting in no change of the melting point.

Anal. Calc'd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43.

Found: C, 54.70; H, 3.72; N, 9.01.

Experiment IIb. When 2.6 g. of sodium phthalohydroxamate in 25 ml. of chloroform was mixed with 2 ml. of pyridine, a light yellow mixture was formed. To this mixture was added 4.5 g. of solid *p*-toluenesulfonyl chloride in small portions so that the temperature was maintained below 35°. The resulting mixture was worked up as described under Experiment IIa yielding 1.35 g. of IVb, m.p. 280–281° (38%).

Hydrolysis of IVa *and* IVb. A 0.42 g. quantity of IVa was dissolved in a 10% excess of warm aqueous 1% sodium hydroxide. The solution was heated to boiling, cooled, and acidified with hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from water yielding 0.18 g. of 3-hydroxy-1*H*-quinazolinedione, V, as long needles. The melting point and mixture melting point with an authentic specimen (2a) in an open capillary was 308–310°. The melting point observed in a sealed capillary was 320–322°. A sample mixed with *o*-phenyleneurea (6) melted at 250–255°.

Alkaline hydrolysis of IVb yielded the identical product in similar yield.

3-Benzenesulfonoxy-5,6-dihydrouracil, VIa, was obtained as previously described (1). The sample employed was recrystallized several times from 2-propanol and water and melted at 165–166°.

Treatment of sodium succinohydroxamate with p-toluenesulfonyl chloride. 3-*p*-Toluenesulfonoxy-5,6-dihydrouracil, VIb, was prepared similarly. Using 3.6 g. of sodium succinohydroxamate and 8.7 g. of *p*-toluenesulfonyl chloride, there was obtained 1.22 g. of VIb, m.p. 164–166°. The product was obtained as prisms melting at 167–168° after recrystallization from ethanol. The melting point was depressed by the addition of VIa.

Anal. Calc'd for $C_{11}H_{12}N_2O_5S$: C, 46.31; H, 4.59; N, 9.82.

Found: C, 46.67; H, 4.28; N, 9.71.

When trimethylamine or pyridine was incorporated in the reaction mixture, a product which was difficult to purify was obtained.

Rearrangement of VIa *and* VIb. An exothermic reaction occurred when 1.92 g. of VIa (1) was added to a solution of 0.4 g. of potassium hydroxide in 10 ml. of water. The solution was kept at 100° for 30 minutes and then worked up in two separate experiments, using identical quantities, as follows:

(*a*) To the solution was added 20 ml. of concentrated hydrochloric acid and the resulting solution was heated under reflux for five hours, concentrated to about half its bulk *in vacuo*, cooled overnight at 5°, and then carefully basified with pellets of potassium hydroxide while the temperature was kept below 25°. The alkaline solution was benzoylated using 4 ml. of benzoyl chloride. The derivative which settled rapidly was separated and washed with water. Recrystallization from acetic acid afforded colorless needles (1.4 g.), m.p. 246–247°, undepressed on admixture with an authentic sample of the benzoyl derivative of ethylenediamine. The mother liquor was diluted with water, yielding a second crop (m.p. 242–244°; 0.1 g.). The total yield (1.5 g.) represents an 80% conversion of VIa.

(*b*) The alkaline solution was treated with 11.5 g. of potassium hydroxide in 20 ml. of water. The resulting solution was refluxed for four hours, cooled overnight, benzoylated (4 ml. of benzoyl chloride), and processed as above, affording 0.8 g. of the benzoyl derivative of ethylenediamine, m.p. 247°. The second crop weighed 0.1 g., m.p. 242–244°. Yield: 0.9 g.; 48%.

Similar treatment of 0.15 g. of VIb with a solution of 0.020 g. of sodium hydroxide in 3 ml. of water, followed by the work-up of procedure (*a*) above, yielded 0.08 g. of the benzoyl derivative of ethylenediamine, m.p. 245–246°.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01.
Found: C, 71.21; H, 6.03.

Benzenesulfonyl (VIIa) *and p-toluenesulfonyl* (VIIb) *derivatives of "phthalic anhydride oxime"*. Into an orange-red solution of 0.5 g. of triethylamine and 0.20 g. of the colorless form of "phthalic anhydride oxime", m.p. 230–232° (3b), in 15 ml. of chloroform was dropped benzenesulfonyl chloride until the color was discharged. The solution was then evaporated to dryness and the residue was crystallized and recrystallized from ethanol, yielding 0.20 g. of VIIa as colorless rods, m.p. 189–190°.

Anal. Calc'd for $C_{14}H_9NO_5S$: N, 4.62. Found: N, 4.40.

The *p*-toluenesulfonyl derivative was prepared similarly (0.23 g. of the derivative from 0.20 g. of "phthalic anhydride oxime") and found to melt at 162–163° (prisms).

Anal. Calc'd for $C_{15}H_{11}NO_5S$: N, 4.42. Found: N, 4.53.

Reaction of VIIa *with ethanolic potassium hydroxide.* To a solution of 1.0 g. of VIIa in 50 ml. of benzene was added 100 ml. of 95% ethanol and 50 ml. of water. The mixture was brought to boiling and a solution of 0.36 g. of potassium hydroxide in 20 ml. of water was added. After five minutes an additional 100 ml. of water was added and the mixture was distilled. The cloudy distillate was collected from the time the temperature of the residue reached 90° until the volume of the residue remaining was approximately 50 ml. The residue was cooled and acidified with hydrochloric acid which precipitated 0.19 g. of ethyl *o*-carboxycarbanilate, $C_6H_4(COOH)NHCOOEt$, m.p. 124–125° (4), soluble in dilute alkali but insoluble in dilute mineral acids.

Samples of the cloudy distillate were clarified by the addition of dilute hydrochloric acid, but the oily product was not soluble in excess, dilute potassium hydroxide. Alkaline hydrolysis of the bulk of the distillate, which possessed the odor typical of ethyl anthranilate, yielded 0.08 g. of anthranilic acid, m.p. and mixture m.p., 143–144°.

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SUMMARY

The action of arenesulfonyl chlorides on phthalohydroxamic and succinohydroxamic acids results in rearrangement of one of the hydroxamic acid groups. Thus, sodium phthalohydroxamate yields 3-arenesulfonoxy-1*H*-quinazolinediones; sodium succinohydroxamate, 3-arenesulfonoxy-5,6-dihydrouracils.

3-Arenesulfonoxy-1*H*-quinazolinediones hydrolyze smoothly with alkali, but 3-arenesulfonoxy-5,6-dihydrouracils rearrange under the influence of alkali to ethylenediamine.

The preparation of the benzenesulfonyl and *p*-toluenesulfonyl derivatives of "phthalic anhydride oxime" is reported. Alcoholic potassium hydroxide converts the benzenesulfonyl derivative to ethyl *o*-carboxycarbanilate.

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