6-30-1954

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Edward Jacob Mach
New Jersey Institute of Technology

Recommended Citation

Mach, Edward Jacob, "The preparation of 2-aminophenol-4-sulfonic acid from sulfanilic acid" (1954). *Theses*. 2265.
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THE PREPARATION OF
2-AMINOPHENOL-4-SULFONIC ACID
FROM SULFANILIC ACID

by

Edward J. Mach

Submitted in Partial Fulfillment
of the Requirements
for the Degree of
MASTER OF SCIENCE
in Chemical Engineering
in the
Graduate Division
at the
Newark College of Engineering

June 1954

ACKNOWLEDGEMENT

The author expresses his appreciation to Professor James A. Bradley, of the Newark College of Engineering, for his guidance during the course of this investigation.

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ABSTRACT

Sulfanilic acid (I) was examined for purity and character. Sodium and potassium salts were acetylated and their isolation and yields were investigated.

The salts were nitrated with mixed acids and the reaction mixtures were treated in various ways to ascertain a good method for isolating the desired 2-nitrosulfanilic acid (II). An attempt was made to characterize the reaction products, and to devise quantitative methods to estimate the yield of 2-nitrosulfanilic acid. A previously unreported by-product of the nitration, 2,4,6-trinitroaniline (IIe), was isolated. Several new salts of 2-nitrosulfanilic acid were prepared, and a possible new derivative was observed from the reaction of phenanthraquinone and the diamine obtained by the reduction of the nitro group in 2-nitrosulfanilic acid.

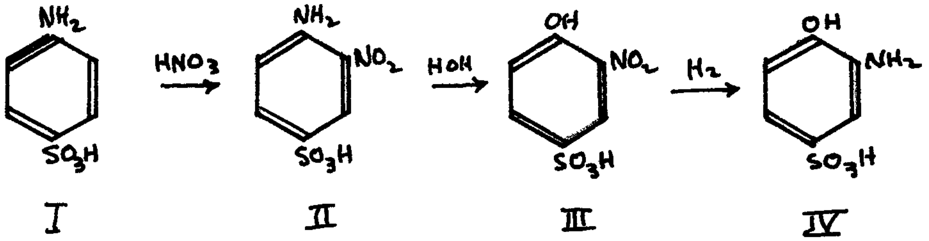
Conversion of the 2-nitrosulfanilic acid (II) to 2-nitrophenol-4-sulfonic acid (III) was accomplished by the replacement of the amino group by hydroxyl with boiling alkali, and the rate was estimated from the ammonia evolved.

Reduction of the nitro group with hydrogen gave the desired 2-aminophenol-4-sulfonic acid (IV).

DISCUSSION

GENERAL CONSIDERATIONS

The steps in the preparation of 2-aminophenol-4-sulfonic acid from sulfanilic acid as concerns this project are shown in the following simplified outline:



The various compounds and reactions involved are known or have been described in the literature. However, this particular overall method, involving the above steps, has not been reported.

Minnevitch (5) describes a method employing chlorobenzene as the starting material. His method involves sulfonation, nitration, hydrolysis of the chloro to hydroxyl, and finally reduction of the nitro group to give the 2-aminophenol-4-sulfonic acid. This method is also the subject of a thesis by Milazzo (6) who studied in detail the hydrolysis step, and was studied for details of nature and yield by Conradi and Bradley (29).

Many reports in the literature, in describing compounds encountered in this synthesis, are inconclusive regarding proof of identity and yields based thereon thus establishing a general phase of this investigation: proof of identity and determination of yields of compounds of proven identity.

SULFANILIC ACID. (I)

The original sample of sulfanilic acid obtained was a grey powder, obviously impure. It was purified by recrystallizing from water, and alternatively, by precipitating the free acid from an aqueous solution of the sodium salt with concentrated hydrochloric acid. Precipitation gave a higher weight yield, but the product was contaminated with sodium chloride. Subsequent starting material obtained was anhydrous and nearly pure.

Sulfanilic acid is reported as a monohydrate (18), and as a dihydrate (7). In both cases dehydration is reported to occur at 100°C. However, crystals obtained from dilute aqueous (1%), and also from concentrated (7%) aqueous solution showed no dehydration on prolonged drying at 120°C, followed by further drying at 155°C.

The acid does not melt. The decomposition point (7) is not sharp enough for use as a criterion of purity. Estimation of sulfanilic acid purity is best made by determination of the neutral equivalent (10), an by a diazotization titration (9). The amino group cannot be titrated with acid since it is too weakly basic to form salts.

2-NITROSULFANILIC ACID. (II)

Conditioning Sulfanilic Acid for Nitration.

Several methods for the preparation of 2-nitrosulfanilic acid are described, and are considered here briefly for comparison:

1) 1-bromo-2-nitrobenzene-4-sulfonic acid is treated with alcoholic ammonia (11).
2) 1-chloro-2-nitrobenzene-4-sulfonic acid is treated with alcoholic ammonia (13).
3) Sulfonation of o-nitroaniline (12).
4) Sulfonation and nitration of acetanilide (2),(3).
5) Nitration of sulfanilic acid (2)(4)(14).

In this project, only the preparation by nitration of sulfanilic acid is applicable.

The direct nitration of sulfanilic acid has been found to lead to ambiguous results (14).

Sulfanilic acid has an inner salt structure (15)(16). The powerfully acidic sulfonic acid group inductively neutralizes and predominates over the feebly basic amino substituent. Nitration of the free acid with nitric acid alone has the weakly meta-directing ionized amino (NH_3^+) group competing with the strong meta-directing sulfonic acid group. Substitution of a nitro group in the ortho position to the amino group would predominate, but some meta nitro would be expected. The amino group is also sensitive to oxidation, and considerable destruction would occur.

A salt of the sulfonic acid destroys the inner salt structure, creating a strong ortho directing non-ionized amino (NH_2) group, which is, however, still susceptible to oxidation. Solution in concentrated sulfuric acid stabilizes against oxidation, but reforms the ionized amino group. Acetylation forms an ortho directing group almost as strong as the non-ionized amino group, and also protects against oxidation.

Thus, conditioning sulfanilic acid for nitration to yield optimum ortho nitroamino substitution consists of forming a salt, acetylating, and then dissolving in concentrated sulfuric acid.

Nietzki and Benckiser (2), and Sakellarios and Jatrides (4) employed essentially the technique described to prepare 2-nitrosulfanilic acid (II). No isomers are reported.

Nietzki and Benckiser (15) report failure to acetylate free sulfanilic acid with acetic anhydride. This was confirmed. Of note is one experiment by the author which became uncontrollable and expelled the contents of the flask.

However, the acetylation of an alkali metal salt is simple and convenient (4)(17). Only the sodium and the potassium salts were investigated.

The dry sodium salt, and its aqueous solution, were acetylated with acetic anhydride (1)(4)(15)(17). The sodium salt is difficult to isolate pure since it is very soluble in water and is obtained by concentrating the reaction mixture to dryness. The residue contains about 90-95% sodium N-acetylsulfanilate. Acetic acid is difficult to remove. Schroeter (1) washed with ether, dried over soda-lime and then in an air stream at 150-160°C for ten hours. Fortunately, for nitration, such complete removal of acetic acid is unnecessary. For other purposes, such as analytical, it has been found that Schroeter's procedure can be avoided by washing the dry residue with acetonitrile, followed by several anhydrous ether washes, and then drying at 110°C. Another successful method consists of triturating the dry residue with benzene and distilling at atmospheric pressure to remove the benzene-acetic acid azeotrope, repeating if necessary.

The potsaaium salt was acetylated with acetic anhydride, essentially according to the procedure of Sakellarios and Jatrides (14). This appeared to be the better method. The potassium salt is obtained in nearly quantitative yield, and is easy to isolate because it crystallizes well from water. Merely cooling the acetylating mixture deposits a good crop of material requiring only quick washes with acetic anhydride, acetonitrile, and anhydrous ether to obtain an essentially pure product.

The acetyl group is stable to hydrolysis in cold dilute aqueous solution (17). In cold concentrated aqueous solution, or in warm dilute, the hydrolysis rate increases. This, in the case of the sodium salt treatment for isolation, could contribute to impurities.

Nitration of N-Acetylsulfanilic Acid Salts.

The general procedure used for nitration was as follows (4): the salt was dissolved in concentrated sulfuric acid and the solution was cooled to the desired nitration temperature. With stirring and external cooling, the nitrating mixture (nitric acid in concentrated sulfuric acid) was added at a rate to maintain the desired reaction temperature. The reaction was stirred at ice-bath temperature for a time. Then after storage at room temperature, or in the refrigerator, the mixture was poured on ice. In many cases a water insoluble material in small quantity resulted. Examination of this orange product showed it to be trinitroaniline. The average amount was equivalent to about 5% of the starting material.

It was observed to result only in the nitration of the potassium salt. Its presence could be detected qualitatively by Janovsky's reaction (26). This color test was also reported by Bost and Nicholson (27), but curiously, according to their stipulations the test should be negative for a compound of this structure. The compound had the characteristics reported for trinitroaniline, and after recrystallizing from acetonitrile-water the yellow crystals melted at 189-191°C. Nitration at 25-30°C gave approximately twice the amount of trinitroaniline obtained from nitrations at 0-5°C.

The diluted nitration mixture was treated with barium or calcium compounds to remove sulfuric acid as an insoluble sulfate. Barium and calcium salts of 2-nitrosulfanilic acid (II) are moderately soluble in water and are not precipitated. After adding a filter aid, the hot slurry was filtered. The filter cake was washed with hot water and the cake was discarded. The combined filtrates were concentrated to a low volume of solution from which the 2-nitrosulfanilic acid (II) could be isolated.

The free acid was isolated by precipitating from a concentrated aqueous solution with concentrated hydrochloric acid. It was purified by dissolving in hot 99.5% ethanol, filtering off insolubles, and evaporating the filtrate to dryness followed by reprecipitation as above.

Another method of isolating the free acid consists of passing a solution of a salt thru a cation resin exchanger. The raffinate is concentrated to dryness, redissolved in hot 99.5% ethanol, and filtered from insolubles which may remain (infrequently obtained from a properly operated column). Ethanol is removed, and precipitation from concentrated aqueous solution with concentrated hydrochloric acid yields the purified free acid. Yields from hydrochloric acid precipitations may be improved somewhat by saturating the cold mixture with dry hydrochloric acid gas and cooling well before filtering. After filtering, the 2-nitrosulfanilic acid is washed on the filter, in succession, with concentrated HCl, several times with dry acetonitrile, and finally with anhydrous ether.

Altho requiring more time and effort, the ion exchange method insures a product which is free of possibly co-precipitated salts, a source of contamination in HCl precipitated salt solutions. An impressive performance was observed in the treatment of a solution of a bulk of various types of crude materials obtained from about ten nitrations with Amberlite IR-120 (H form). The column capacity was calculated on the basis of assuming 100% barium salt of 2-nitrosulfanilic acid being present. No ethanol insoluble material was obtained, and the neutral equivalent of the product indicated a purity of 100%.

The isolation of the acid as a salt was best accomplished via the potassium salt, which is salted out of a concentrated aqueous solution with a concentrated solution of potassium acetate. After cooling and filtering the salt is washed with 99.5% ethanol, in which potassium acetate is quite soluble. A wash with anhydrous ether gives a dry product after a short air dry.

Hydrolysis of the sulfonic acid group with boiling strong sulfuric acid solution gave a 72% yield of o-nitroaniline (IId)(19) indicating that nitration was predominantly in the position ortho to the amino group, and only one nitro group was introduced. This inference was substantiated by a determination of the neutral equivalent which agreed with the calculated value for 2-nitrosulfanilic acid.

The amide of II was prepared (11)(25) and was found to have a melting point of 207-209°C. The melting point is reported as 206-207°C by Fischer (13) who found that Goslich's (11) value of 155-156°C was incorrect.

The sodium salt of 2-nitrosulfanilic acid(II) reduced quantitatively with hydrogen over Raney nickel, and the resultant diamine was reacted with phenanthraquinone (18)(20)(21)(22)(23) to give, apparently, a new derivative: the sodium salt of dibenzo [a,c] phenazine-11-sulfonic acid (VII). This is an established behavior of ortho diamines. The derivative, however, could not be characterized at this time.

Similarly, an attempt was made to react the diamine with glyoxal, and with N-acetyl isatin. Neither substance gave a water insoluble derivative, and the investigation of any possible water soluble derivatives was deferred at this time.

The disulfonate of benzidine (V) was prepared as a possible means of quantitatively estimating yields of 2-nitrosulfanilic acid, as was the p-toluidine salt(VI). Both are unreported. The p-toluidine salt proved to be too soluble in water to be used for quantitative precipitation, but a relatively well defined melting point of 193-194°C is of value in characterizing 2-nitrosulfanilic acid.

The benzidine salt (V) was found to have a solubility in water at 25°C of 0.35%, a value which could probably be adapted for quantitative estimations of 2-nitrosulfanilic acid. However, it was observed in attempts to employ the salt for specific and quantitative precipitation of 2-nitrosulfanilic acid that its behavior was erratic in relatively crude solutions from nitrations. Major factors, such as presence of dissolved salts, appeared to be without effect. A more detailed investigation had to be curtailed.

Several other organic bases were tried for precipitating a water insoluble salt of 2-nitrosulfanilic acid (judged on an arbitrary basis of producing almost immediately a crystalline precipitate in large quantity). Piperazine (28), and benzylaniline gave nothing, while 4,4'-diaminodiphenylmethane began to precipitate on initial addition but subsequently redissolved on further addition of the amine hydrochloride solution. Structural comparison with benzidine suggested a possibly better precipitant.

Proposed, but not tried because the reagent could not be available in time, was the use of 4,4'-diaminotolan as a precipitant. It is claimed (30) that its sulfonic acid salts are less soluble than the benzidine salts.

Another analytical approach, which was contemplated but not tried due to lack of time, was to estimate yields on the basis of an analytical determination of potassium in the potassium salts of the sulfonic acid by the method of Suzuki (31) which employs tartaric acid in place of the otherwise expensive reagents.

2-NITROPHENOL-4-SULFONIC ACID (III)

The labilizing effect of a nitro group, ortho or para to an amino group on the benzene ring, was employed to prepare 2-nitrophenol-4-sulfonic acid (III)(3). King (24) reports a different method of preparation via nitration of sodium phenol-4-sulfonate, which is of comparative interest.

An aqueous solution of the salt of 2-nitrosulfanilic acid was boiled with alkali until ammonia was no longer given off. The hydrolysis rate was estimated by measuring the amount of ammonia given off. It appeared that an increase in the concentration of the alkali increased the hydrolysis rate, but at the same time increased the amount of sodium 2-nitrophenol-4-sulfonate which has a relatively low solubility. The precipitated salt was the cause of some extremely violent bumping at times, especially in reactions with alkali concentrations approaching the upper portion of the 5 to 19% range.

Hydrolysis was effected to the extent of about 80-85% of theory when pure 2-nitrosulfanilic acid was used as starting material.

Hydrolysis of crude solutions resulting from nitration of relatively pure N-acetylsulfanilic acid sodium or potassium salts showed the general effect of increased hydrolysis rate and total hydrolysis with an increase in the alkali concentration. The estimated overall yield of 2-nitrophenol-4-sulfonic acid based on hydrolysis measurements varied from about 47% to about 78% (calculated on the basis of theoretical overall yields from the N-acetylsulfanilate).

The 2-nitrophenol-4-sulfonic acid was isolated as the sodium salt from concentrated aqueous solution. the free acid was obtained by stripping the sodium salt in an Amberlite IR-120 (H form) ion exchange column. The acid was obtained by concentrating the aqueous column raffinate on a steam bath under water vacuum pressure. The acid was usually of a yellow color, but curiously, one preparation of the free acid after concentrating to a heavy sirup solidified to a crystalline mass having an intense dark blue color. The blue material, however, gave a deep yellow aqueous solution.

The free acid is too soluble in water to be isolated by means of precipitation with concentrated hydrochloric acid.

The free acid is reported by King (24) as a trihydrate melting at 51.5°C, but this form was not encountered. Only material melting at 122°C was isolated, which is the value reported by King for the anhydrous 2-nitrophenol-4-sulfonic acid.

2-AMINOPHENOL-4-SULFONIC ACID (IV)

Reduction of the nitro group in 2-nitrophenol-4-sulfonic acid (III) results in the desired 2-aminophenol-4-sulfonic acid (IV). An investigation of the many available methods for reducing nitrogroups to amino is beyond the scope of this project, but without doubt, most could be successfully employed for the preparation of 2-aminophenol-4-sulfonic acid.

Reduction was accomplished with zinc and hydrochloric acid, and with hydrogen over Raney nickel. In both cases the progress of the reduction was indicated by the gradual dissappearance of the yellow color of the solution, with complete reduction resulting in a nearly colorless solution of 2-aminophenol-4-sulfonic acid.

The reaction mixure after reduction with zinc is worked up in the usual manner, the acid then being precipitated with concentrated hydrochloric acid. Isolation can also be effected by use of the ion exchanger.

2-nitrophenol-4-sulfonic acid is reduced by hydrogen over Raney nickel catalyst in aqueous solution at atmospheric pressure and room temperature (25°C), accompanied by the usual decolorization of the solution. A reduced absorption rate was observed in an attempt to reduce a crude alkaline solution from a sodium hydroxide hydrolysis of II.

Reduction of the free acid requires only filtration of the catalyst and concentration of the aqueous solution to low volume from which the sparingly soluble 2-aminophenol-4-sulfonic acid crystallizes. The normally white crystals have occasionally a lavender tint.

A solution of a salt of the reduced acid can be treated with hydrochloric acid as previously described to yield the free acid.

Passing a solution of a salt of 2-aminophenol-4-sulfonic acid resulting from a Raney nickel reduction thru an Amberlite IR-120 (H form) column yields the free acid in solution. The free acid is crystallized by concentration.

2-Aminophenol-4-sulfonic aicd is similar in nature to sulfanilic acid in that it is sparingly soluble in water and does not melt. It may be characterized by the neutral equivalent, and a positive test with Tollen's reagent.

EXPERIMENTAL PROCEDURES

(All observed melting points are corected)

Sulfanilic Acid (I)

Purification by Recrystallization: 210 grams of crude sulfanilic aicd were dissolved in 3 liters of boiling water. The solution was treated with charcoal, and filtered rapidly while hot. The white crystals which deposited on cooling were filtered off, sucked dry as possible, and air dried, giving 164 grams of product which contained 98% sulfanilic acid (diazotization titration) (9). On a recovered weight basis, the yield was 77%. Neutral equivalent: Found, 176; Calc., 173.

Purification by Precipitation: 17.3 grams (0.1 mole) of crude sulfanilic acid were dissolved in 100 cc of 1 N sodium hydroxide solution with the aid of heat. The solution was treated with charcoal, and filtered brilliant. To the filtrate was added 15 cc of conc. HCl. The precipitated white crystals were filtered off, after cooling the mixture, and air dried, giving 16.3 grams of product found to contain 91% sulfanilic acid; the yield on a recovered weight basis was 85%. Neutral equivalent: found, 176; calc., 173.

Water Content: 10 grams of water recrystallized sulfanilic acid were dried in an oven at 110°C for 1 day.

Weight lost by the sample was 0.029 gram. This is equivalent to 1.7% of theory if 2 H_2O were originally present, and to 3.1% of theory if 1 H_2O was originally present.

Solubility: At its boiling point, 99.5% ethanol dissolved less than 0.1% of pure anhydrous sulfanilic acid. The acid is insoluble in most common organic solvents. It is moderately soluble in formamide, and in dimethyl formamide. The sodium and potassium salts are readily soluble in water.

Other Characteristics: The acid does not melt. At about 300°C it begins to sinter and become dark in color, and at about 320-330°C the material is so dark that observation is difficult. The neutral equivalent, and titration with sodium nitrite (9) can be used for estimating sulfanilic acid. It can be detected qualitatively with nitrite in the presence of alpha-naphthylamine oxoalate as an indicator (8) by the red color developed by the solution.

Sodium N-Acetylsulfanilate (Ic)(1)

Sodium sulfanilate, 92 grams (0.47 mole) and 51 grams (0.50 mole) of acetic anhydride were mixed in a flask. No reaction occured. An additional 51 grams of acetic anhydride were added. After a short while, spontaneous reaction occured giving sufficient heat to reflux the acetic anhydride. The mixture was heated on a steam bath for one half hour, cooled, and filtered. The solid was washed once with acetic anhydride, and 3 times with anhydrous ether. Drying at 110-115°C for 1 day gave 121.2 grams. Theory for 1 H_2O is 120 grams. Further drying for 2 days at 155°C gave 107.7 grams. Theory for the anhydrous salt is 111 grams. Titration with sodium nitrite showed 97.5% acetylation. The net yield was 94.5%.

Potassium N-Acetylsulfanilate (Id) (4)

51.9 grams (0.3 mole) of sulfanilic acid (I) were dissolved in 100 cc of water with the aid of 20.7 grams (0.15 mole) of potassium carbonate. The solution was warmed to 50°C, and with stirring, 33.6 grams (0.33 mole) of acetic anhydride were added at a rate to maintain the reaction temperature between 65 and 70°C. The mixture was allowed to cool with stirring after the addition. Crystals began to appear when the mixture had cooled to about 50°C. After storage at 4°C, the crystals were filtered, washed 2 times with 99.5% ethanol, and 2 times with anhydrous ether. Overnite drying at 114°C gave 63 grams. The filtrate gave an additional 12 grams. The product contained 99.5% acetylated material, and the net yield was 98.4%. The alpha-naphthylamine nitrite test was negative altho diazotization titration showed 0.5% non-acetylated material present (experimental error?).

2-Nitrosulfanilic Acid (II) (4)

75.9 grams (0.3 mole) of potassium N-acetylsulfanilate (Id) were added to 225 grams of concentrated sulfuric acid in portions, with stirring, to maintain a temperature of less than 60°C. The solution was cooled to 5°C with an ice-salt bath. To the stirred solution was added a mixture of 21.3 grams of 90% nitric acid (10% excess) and 22.5 grams of concentrated sulfuric acid at a rate to maintain the reaction temperature around 5°C, assisted by external cooling. The reaction mixture was then stirred at about 4°C for about 4 hours, and then allowed to warm up to room temperature on storage overnite.

The reaction mixture was poured on ice. It gave a deep yellow colored solution with a strong acetic odor (warming the solution results in rapid de-acetylation and the solution becomes deep orange). The solution, roughly 2 liters, was heated in a 14 quart enameled pail on an electric hot plate and vigorously stirred while 283 grams of calcium carbonate were added quite rapidly in fairly large portions. Water additions, in conjunction with the carbonate additions, were made as required to maintain fluidity of the slurry. (Note: a large volumes ratio, of container to solution, is of considerable value, along with high speed stirring in the control of frothing and reducing the time required to effect the neutralization. And if, in addition, very finely powdered calcium carbonate is added as a slurry in water, the neutralization can be completed in a few minutes.)

The neutral slurry was brought to a boil, and the heat was turned off. About 1 liter of Hyflo filter aid (measured loose and dry) was stirred in, and the slurry was filtered. The filter cake was washed with hot water on the filter by rinse-thru until most of the color was gone (about 3 times). The filtrate, about 4 liters, was flash concentrated to a volume of approximately 500 cc, which after transfer and rinse measured 630 cc.

<u>Free Acid</u>: A 200 cc aliquot was treated with 400 cc of concentrated HCl. After cooling and filtering, the crystals were washed once with conc. HCl, 2 times with dry acetonitrile, and then 2 times with anhydrous ether. Drying at 115°C gave 10.1 grams (49%) of 2-nitrosulfanilic acid, having a purity of about 99%.

<u>Potassium Salt (IIc)</u>: To a 200 cc aliquot was added 200 cc of a concentrated potassium acetate solution. Crystals formed quickly, and after storage in the refrigerator, they were filtered, and washed with 99.5% ethanol, and then with anhydrous ether. Drying at 115°C yielded 20.0 grams of the potassium salt. The filtrate gave an additional 1 gram. Total crude yield was 85%.

A 97% recovery of free acid from an analytical stripping of the crude potassium salt in an acid form Amberlite IR-120 ion exchange column resulted in a net yield of 82% of potassium 2-nitrosulfanilate (IIc).

o-Nitroaniline (IId) from 2-nitrosulfanilic Acid (II); Evidence of Structure.

If nitration had occured in the ortho position to the amino group in sulfanilic acid, then hydrolysis of the sulfonic acid group should yield o-nitroaniline (IId), (19).

2.18 grams (0.01 mole) of 2-nitrosulfanilic acid (II) were added to a hot mixture of 7.75 cc of conc. sulfuric acid and 9.5 cc of water. The solution was refluxed for one and one half hours, poured into cold water, and the yellow precipitate was collected and dried. Yield was 1 gram (72%). The melting point was 67-68°C. A mixed melting point of 68-70°C was obtained with an authentic sample of o-nitroaniline which melted at 69-71°C.

Benzidine Salt of 2-Nitrosulfanilic Acid. (V)

4.36 grams (0.02 mole) of 2-nitrosulfanilic acid were dissolved in 30 cc of water. To this solution was added 125 cc of benzidine reagent (9). A precipitate formed immediately. The solution was cooled and filtered. The salt was washed 2 times on the filter with small amounts of cold water, and then dried at 115°C. The yield was 5.5 grams (89%). The crude material had a decomposition point of about 289°C (very dark and difficult to observe). A sample recrystallized from water was observed to decompose at 293-295°C. The color of the salt was bright yellow.

The solubility of the benzidine salt in water at 25°C was 0.35% (grams in 100 cc of water). It was found to be considerably more soluble in hot water, from which it crystallized well for purification.

The salt is slightly soluble in acetone, 99.5% ethanol, methanol, and acetonitrile. It is insoluble in anhydrous ether, and in petroleum ether (b.p. 30-60°C).

The salt can be quantitatively titrated with standard sodium hydroxide solution, by means of which a neutral equivalent of 309 was observed. This agreement with a calculated value of 310.3 for the assumption that both amino groups react for salt formation, confirms the structure as a disulfonate of benzidine. (V).

p-Toluidine Salt of 2-Nitrosulfanilic Acid. (VI)

The salt was prepared by mixing aqueous solutions of the acid and p-toluidine hydrochloride. Cooling and scratching induced crystallization. After recrystallizing several times from ethanol-ether, the yellow salt melted at 193-195°C. It is moderately soluble in water, ethanol, and acetone; only slightly soluble in acetonitrile, and ethyl acetate; and is insoluble in anhydrous ether. The observed neutral equivalent obtained by titrating with standard sodium hydroxide agrees with the calculated value for the p-toluidine salt of 2-nitrosulfanilic acid.

Dibenzo [a,c] phenazine-11-sulfonic Acid Sodium Salt. (VII)(29)

1,2-phenylenediamine-4-sulfonic acid (IIa) obtained by reducing 2-nitrosulfanilic acid (II) with hydrogen over Raney nickel was reacted with phenanthraquinone bisulfite.

Jones and Robinson (21) describe a similar procedure using zinc and hydrochloric acid for the reduction. An adaptation of their method is used in the preparation herein described.

1.28 grams (0.005 mole) of 2-nitrosulfanilic acid (II) was dissolved in 15 cc of water, and 5 cc of concentrated HCl were added. To the boiling solution was added 3 grams of zinc dust, and the boiling was continued. After a few minutes, 3 grams more of zinc dust were added, and the solution was boiled until it became nearly colorless. It was diluted with water and filtered. To the hot filtrate was added sodium acetate followed by a hot solution of phenanthraquinone in sodium bisulfite (containing added sodium acetate). Boiling for a short time resulted in the formation of a voluminous precipitate. Microscopic examination revealed a mass of long yellow filaments. The product was collected by filtration.

1,2-Phenylenediamine-4-sulfonic Acid. (IIa)

1.09 grams (0.005 mole) of 2-nitrosulfanilic acid (II) were dissolved in about 10 cc of water and titrated to neutral with 50 cc of 0.1 N sodium hydroxide (1 equivalent) to form the sodium salt. Approximately 1/4 teaspoon of water wet Raney nickel catalyst was added and the reduction was performed in a burette type apparatus at room temperature (24°C) and atmospheric pressure. The compound showed a normal reduction curve, and adsorption was 98% complete in about 3 hours, during the course of which the solution gradually became colorless. The reduction was performed only to estimate its general nature for use as a possible analytical tool. The product was not isolated; the formation of the characteristic long filaments with phenanthraquinone was accepted as sufficient evidence, in this case, of reduction to the diamine.

2-Nitrosulfanilamide. (IIb)

With Shriner and Fuson's (25) procedure as a guide, 5 grams of 2-nitrosulfanilic acid (II) and 10 grams of phosphorus pentachloride were heated together in a flask in an oil bath at 150-180°C for a half hour. The reaction was cooled and 50 cc of dry benzene were added. (Ether also added to assist solution). The benzene-ether solution was washed with cold water, and dried with anhydrous sodium sulfate. The dried solution was then poured into cold concentrated ammonium hydroxide solution with vigorous stirring. No precipitate was formed. The mixture was evaporated to dryness in vacuum and the residue was dissolved in warm water. After charcoal treatment, the solution was cooled. The crystals were filtered off. The crude amide melted at 201-207°C. Recrystallization from hot water gave plates which melted at 207-209°C, with slight decomposition. Fischer (13) reports the melting point of the amide as 206-207°C.

2-Nitrophenol-4-sulfonic Acid. (III)

Rate of Hydrolysis of 2-Nitrosulfanilic Acid.

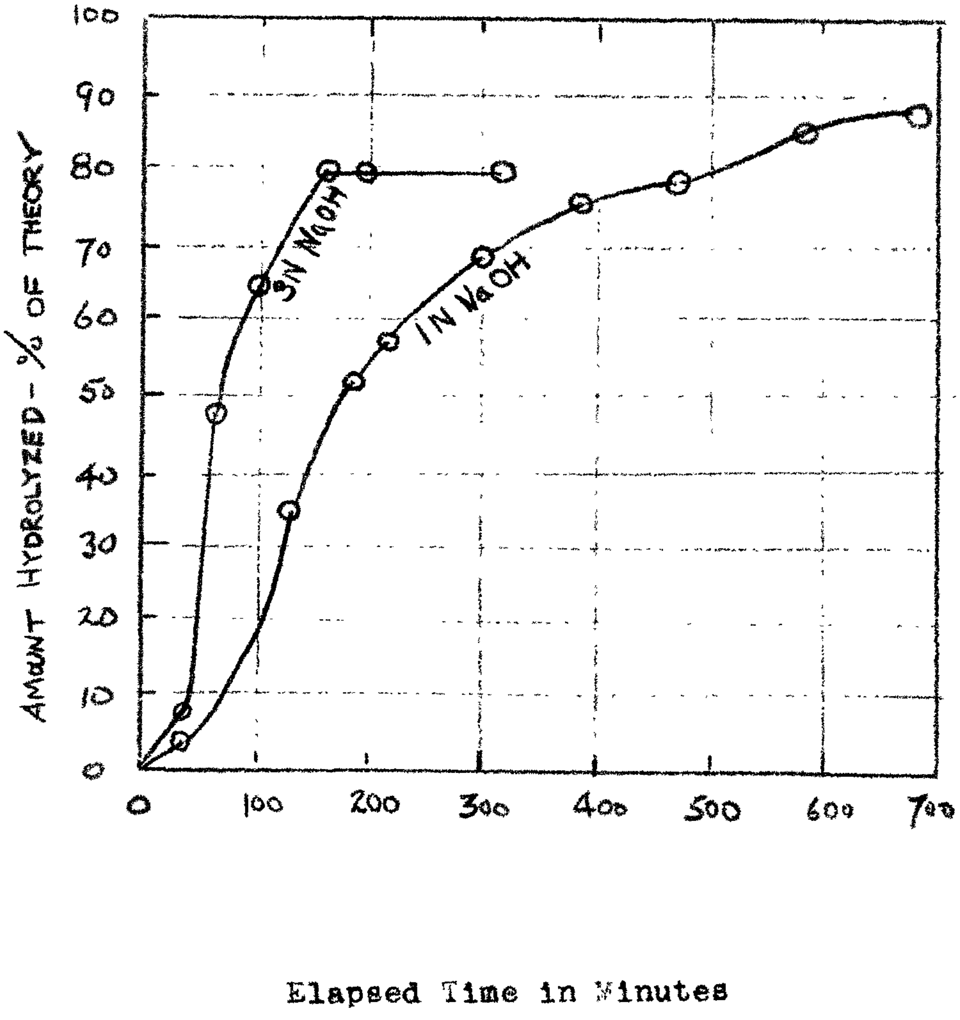
2.18 grams (0.01 mole) of 2-nitrosulfanilic acid (II) and 60 cc (0.06 mole) of 1 N sodium hydroxide were placed in a reflux apparatus connected to a system for collecting evolved ammonia in standard hydrochloric acid. The solution was boiled and the gases were drawn gently thru measured amounts of 0.1 N HCl. At intervals, aliquots of the standard acid were withdrawn and titrated with standard 0.1 N sodium hydroxide. The values were used to calculate the rate and the amount of ammonia evolved. The results are shown graphically in figure 1 on page 29.

The hydrolysis was repeated under the same conditions as above except that an equivalent amount of 3 N sodium hydroxide was used. The results are also shown in figure 1 on page 29 for comparison.

The data available for the evaluation of the hydrolysis was limited due to mechanical problems encountered with respect to apparatus refinement and sampling methods, and can only used for a broad generalization of the nature of the hydrolysis.

Figure 1.

Hydrolysis rate of 2-nitrosulfanilic acid to 2-nitrophenol-4-sulfonic acid with 1 N and 3 N sodium hydroxide.



2-Nitrophenol-4-sulfonic Acid.(III)

Isolation.

The aqueous solution from the alkaline hydrolysis experiment described above was neutralized with acetic acid and concentrated to a low volume. After cooling, the solution was filtered. The crystals were carefully washed with cold 99.5% ethanol, then anhydrous ether, and dried at 110°C. The yield was 1.7 grams (70%).

A solution of the sodium salt in water was passed thru an Amberlite IR-120 column, and concentrated to dryness under water pump vacuum on a steam bath. The residue was treated several times by trituration with acetonitrile and distilling off volatiles, and finally heated on a steam bath under water pump vacuum for a while. A sample of the dried brown residue melted at 121-123°C (24). (Note: another preparation of the free acid in the same manner gave a deep blue product which melted at 122°C). King (24) reports a melting point of 122°C for anhydrous(III).

2-Aminophenol-4-sulfonic. (IV)

2.4 grams (0.01 mole) of sodium 2-nitrophenol-4-sulfonate were dissolved in about 50 cc of water and about 1/4 teaspoon of water wet Raney nickel catalyst was added. Reduction with hydrogen over a period of about 3 hours showed an adsorption of 236 cc of hydrogen measured at 27°C and atmospheric pressure. The maximum pressure during the reduction was 100 cm of water. Theory requires 246 cc of hydrogen measured as above. The adsorption was 95% of theory.

The catalyst was filtered off. The solution was diluted with water to about 200 cc and warmed to about 50°C. The warm solution of the sodium salt was passed thru an Amberlite IR-120 column, and the raffinate on concentration and cooling yielded a total of about 1.6 grams of the free acid. Yield: about 85-90%.

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Position Numbering of the Parent Ring:

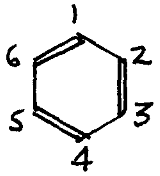

Table of Substitutions and Positions:

Compound Number	Ring Positions of Substituents (No entry H)					
	1	2 (o)	3 (m)	4 (p)	5	6
I	NH_2	-	-	SO_3H	-	-
Ia	NH_2	-	-	SO_3Na	-	-
Ib	NH_2	-	-	SO_3K	-	-
Ic	$NHCOCH_3$	-	-	SO_3Na	-	-
Id	$NHCOCH_3$	-	-	SO_3K	-	-
II	NH_2	NO_2	-	SO_3H	-	-
IIa	NH_2	NH_2	-	SO_3Na	-	-
IIb	NH_2	NO_2	-	SO_2NH_2	-	-
IIc	NH_2	NO_2	-	SO_3K	-	-
IId	NH_2	NO_2	-	-	-	-
IIe	NH_2	NO_2	-	NO_2	-	NO_2
III	OH	NO_2	-	SO_3H	-	-
IIIa	OH	NO_2	-	SO_3Na	-	-
IV	OH	NH_2	-	SO_3H	-	-

(Continued of next page)

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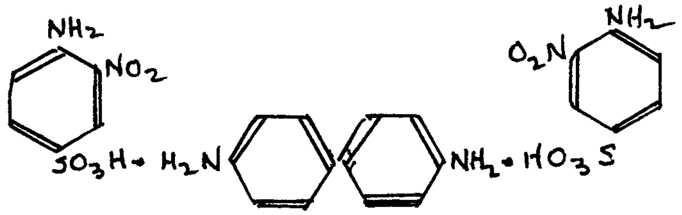
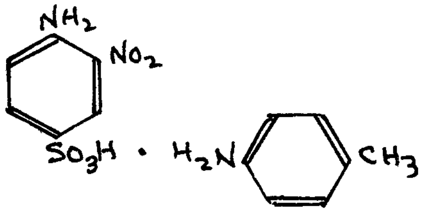
(continued)

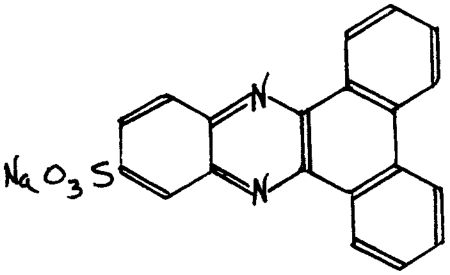
Cmpd. V



Cmpd. VI



Cmpd. VII



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