[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Piria Reaction. III.[1] Mechanism Studies[2]

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A. Intermediate Nitroso Group Formation

Pinnow[3] reduced 3-nitro-4-dimethylaminotoluene with tin and hydrochloric acid and obtained 1,5-dimethylbenzimidazole, the formation of which was accounted for by assuming the removal of a molecule of water between a methyl group and an intermediate nitroso group. A sodium bisulfite reduction of 3-nitro-4-dimethylaminotoluene described in the present work led to the same benzimidazole, pointing to the intermediate formation of a nitroso group in this reaction also. In view of the fact that there are two competing reactions (ring closure and further reduction), it is perhaps not surprising that the yield of the benzimidazole was only 18%. If the first step in the bisulfite reduction of a nitro compound is the formation of a nitroso compound, corresponding nitro and nitroso compounds should give the same products in the over-all Piria reaction and nuclear sulfonation should take place at or beyond the nitroso stage of reduction. This is in agreement with our findings. In the present study, *p*-nitrosotoluene was reduced with various mixtures of sodium bisulfite and sodium sulfite. The results are shown in Table I.

TABLE I

REDUCTIONS OF *p*-NITROSOTOLUENE

	Yield of *p*-toluidine, %	Yield of *p*-toluidine sulfonic acid, %
$NaHSO_3$	55.5	11.3
	55.5	6.8
	54.2	5.7
$NaHSO_3 \cdot 0.25NaOH$	46	11.2
	44	7.5
	45	14.8
	44.5	13.0
$NaHSO_3 \cdot 0.5NaOH$	54	12.4
	53	13.7
$NaHSO_3 \cdot 0.75NaOH$	55.5	9.3
	54	10.1
Na_2SO_3	73	..
	67	6.0

The values previously obtained[4] from a one-quarter neutralized sodium bisulfite reduction of *p*-nitrotoluene are *p*-toluidine, 72 and 67%; *p*-toluidine sulfonic acid, 11 and 12%. Likewise, Brick[5] reduced nitrosobenzene with sodium bisulfite and obtained aniline (23%) and sulfanilic acid (67%). Nitrobenzene, under similar conditions yielded the same two products: aniline (19%) and sulfanilic acid (35%).[1]

Reduction of 3-Nitro-4-dimethylaminotoluene.—The sulfate (2.265 g.) melting at 176–177° with decomposition,[3a] and sodium sulfite (2.5 g.) in 100 cc. of water was refluxed for five days and after the addition of concentrated hydrochloric acid (6 cc.) was boiled further. From the mixture, made alkaline with sodium hydroxide, benzimidazole was extracted with ether and isolated as the tartrate; yield 18.3% (0.461 g.); m. p. 185.2–185.8° with decomposition.

Anal. Calcd. for $C_{13}H_{16}O_6N_2 \cdot 2H_2O$: C, 46.96; H, 6.07. Found: C, 46.78; H, 6.06.

The benzimidazole was also converted to its picrate (m. p. 248–250° in a sealed tube).

Reduction of *p*-Nitrosotoluene. Sample Reduction.—Sixteen and six-tenths grams of sodium sulfite was dissolved in 200 cc. of water and heated to 60°. Four grams of *p*-nitrosotoluene (m. p. 47.5–48.5°) was added and the reaction mixture shaken until the green color had disappeared (*ca.* five minutes). Fifteen cubic centimeters of concentrated hydrochloric acid was added and the solution was evaporated to 50 cc. On cooling, a solid formed which was filtered off, triturated with water, refiltered, dried and weighed (0.45 g. = 6% *p*-toluidine sulfonic acid). The filtrates were made alkaline with sodium hydroxide and extracted with ether, the extracts dried and the ether evaporated. The remaining *p*-toluidine weighed 2.4 g. (67%). All of the reductions of *p*-nitrosotoluene are summarized in Table I.

B. The Final Products of the Bisulfite Reduction of *p*-Nitrotoluene

The treatment of a nitro compound with bisulfite yields water soluble organic compounds, and amines and aminosulfonic acids can be isolated only after treatment with a mineral acid. The view that the amines are formed from sulfaminates ($RNHSO_3Na$) is supported by the actual preparation of a number of sulfaminates from the

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(1) (a) I. Hunter and Sprung, THIS JOURNAL, **53**, 1432–43 (1931); (b) II, *ibid.*, **53**, 1443–1447 (1931).

(2) The work described in this paper formed part of a thesis submitted to the Graduate Faculty of the University of Minnesota by Carl M. Langkammerer in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1934.

(3) (a) *Ber.*, **28**, 3041 (1895); (b) **30**, 3119 (1897); (c) *J. prakt. Chem.*, [2] **63**, 352 (1901); (d) **65**, 579 (1902).

(4) Ref. 1b, p. 1438; Langkammerer, Ph.D., Thesis, University of Minnesota, 1934.

(5) Brick, "The Reduction of Nitroso and Hydroxylamino Compounds with Sodium Bisulfite," Senior Thesis, University of Minnesota, 1929.

corresponding nitro compounds[6] and a demonstration that they are hydrolyzed quantitatively to amines and sulfuric acid.[1b] The present work describes the isolation of nuclear sulfonated sulfaminates and demonstrates the fact that they are hydrolyzed quantitatively to yield the corresponding aminosulfonic acids. In addition, the amounts of sulfaminates and sulfonated sulfaminates actually isolated from the reduction of *p*-nitrotoluene before acidifying are congruent with the amounts of amine and aminosulfonic acid formed in the over-all Piria reaction. Finally the sulfonated sulfaminate structure previously assumed is now supported by an independent synthesis, employing the Baumgarten N-pyridinium sulfaminic acid sulfonation.[7] Thus, the immediate antecedents of the reaction products appear to be sulfaminates and nuclear sulfonated sulfaminates.

Isolation of the Sulfaminate and Sulfaminate–sulfonate from the Bisulfite Reduction of *p*-Nitrotoluene.—One mole (137 g.) of *p*-nitrotoluene, 520 g. (5 moles) of sodium bisulfite, and 50 g. (1.25 moles) of sodium hydroxide were placed in a 3-liter, round-bottomed flask with 2500 cc. of water. After refluxing for five hours, the mixture was neutralized with 37 cc. of 5 *N* sodium hydroxide solution, evaporated to 1000 cc., cooled and filtered. The filtrate was evaporated further, cooled and filtered. This process was repeated until the volume of the filtrate was 150 cc. The filtrate was then poured into 300 cc. of 95% alcohol and the precipitate filtered off. The alcoholic filtrate was evaporated to dryness and 36.4 g. (11.7% yield) of sulfaminate–sulfonate was obtained.

Anal. Calcd. for $C_7H_7O_6NS_2Na_2\cdot H_2O$: Na, 14.0. Found: Na, 14.35.

The substance was purified by dissolving in 95% alcohol, adding an equal volume of absolute alcohol, evaporating to one-half the original volume, cooling and filtering. This procedure was carried out several times and the analyses on various fractions were close to 14% sodium. A more complete analysis on one fraction is given.

Anal. Calcd. for $C_7H_7O_6NS_2Na_2\cdot H_2O$: Na, 14.0; C, 25.50; H, 2.76; sulfaminate S, 9.74; sulfonate S, 9.74. Found: Na, 13.91, 14.02; C, 25.24; H, 2.83; sulfaminate S, 9.82, 9.91, 10.13; sulfonate S, 9.61, 9.37, 9.33.

Sulfaminate sulfur was determined by hydrolyzing with dilute hydrochloric acid in the presence of barium chloride, filtering, and weighing the barium sulfate obtained. Sulfonate sulfur was then determined by treating the resulting filtrate with an excess of bromine, filtering, and washing the organic material out of the second precipitate of barium sulfate with ether, drying and weighing.

All of the precipitates obtained previous to that of the sulfaminate–sulfonate in the original separation were extracted with 2500 cc. of boiling 95% alcohol. The extract was evaporated to 200 cc., cooled, and filtered, 105.5 g. of sulfaminate being obtained. The filtrate on evaporation to dryness yielded 62.0 g. more of sulfaminate, or a total of 167.5 g. (73.5% yield assuming one molecule of water of crystallization). A sample of the sulfaminate of *p*-toluidine was recrystallized from 95% alcohol and dried in a vacuum desiccator for analysis.

Anal. Calcd. for $C_7H_8O_3NSNa$: Na, 11.00. Found: Na, 11.02, 11.00.

Synthesis of the Sulfaminate–Sulfonates. Sample Experiment.—The sulfaminate of *p*-toluidine sulfonic acid: five grams of the sodium salt of *p*-toluidine sulfonic acid (prepared by baking *p*-toluidine sulfate) and 3.5 g. of sodium carbonate were dissolved in 150 cc. of water and cooled to 10°. Four and five-tenths grams of N-pyridinium sulfaminic acid[7] was added and the solution was shaken for two hours at 10°. After all the solid had dissolved the reaction mixture was placed in the ice-box for another hour, made neutral to phenolphthalein, extracted twice with ether and evaporated to 15 cc. The precipitate which formed on cooling was discarded. Eighty-five cubic centimeters of 95% alcohol was added and the inorganic precipitate was again discarded. On pouring into 300 cc. of acetone 2.2 g. of material was obtained.

Anal. Calcd. for $C_7H_7O_6NS_2Na_2\cdot H_2O$: Na, 14.0; C, 25.50; H, 2.76. Found: Na, 14.17, 14.23; C, 25.65; H, 3.08.

In another run a fraction was obtained which analyzed quite closely for the sulfaminate–sulfonate with one-half a molecule of water.

Anal. Calcd. for $C_7H_7O_6NS_2Na_2\cdot 0.5H_2O$: Na, 14.37; C, 26.24; H, 2.52; sulfaminate S, 10.01; sulfonate S, 10.01. Found: Na, 14.27, 14.32; C, 26.12, 26.68, 26.59; H, 2.67, 2.70, 2.81; sulfaminate S, 10.11, 9.85; sulfonate S, 10.11, 10.20.

The sulfaminate–sulfonates of sulfanilic acid, metanilic acid, 2-aminotoluene-5-sulfonic acid and naphthionic acid were prepared in a similar way. The analytical data are presented in Table II.

Comparison of the Sulfaminate–sulfonate from *p*-Toluidine Sulfonic Acid and the One Obtained from the Bisulfite Reduction of *p*-Nitrotoluene.—We are indebted to Dr. E. B. Sandell of the Analytical Division of the University of Minnesota for the following crystallographic report. "The refractive indices of the two preparations were compared. Although all the needles did not have the same orientation, it was found that many crystals of the two preparations agreed in exhibiting the indices 1.575–1.580 and 1.595–1.600. It is concluded that they are identical."

C. The Position Taken by the Incoming Sulfonic Acid Group

A complete review of the cases in which the structures of the aminosulfonic acids formed in over-all Piria reactions has been determined would require a considerable amount of space. However, one can make the general statement that in all previous cases in which the structure

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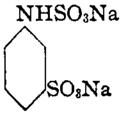
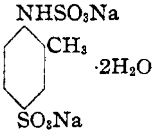
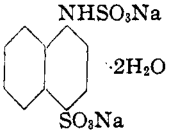
(6) Weil and Moser, *Ber.*, **55**, 732 (1922); Weil and Wassermann, *ibid.*, **55**, 2533 (1922).

(7) Baumgarten, *ibid.*, **59**, 1976–1983 (1926).

TABLE II

THE SULFAMINATE-SULFONATES

Compound					
Yield, %		68	58	53	45
C, %	Calcd.	24.23	24.23	24.2	31.31
	Found	24.30	23.8 24.3	24.6	31.3
H, %	Calcd.	1.70	1.70	3.14	2.89
	Found	2.23	2.26 2.24	3.37	3.13
Na, %	Calcd.	15.48	15.48	13.25	12.00
	Found	15.39	15.33	13.14 12.92	11.87
Sulfaminate S, %	Calcd.	10.79	10.79	9.22	...
	Found	10.59	9.78	8.95	...
Sulfonate S, %	Calcd.	10.79	10.79	9.22	...
	Found	10.83	...	9.07	...
H_2O, %	Calcd.	...	...	10.38	9.40
	Found	...	...	9.99	9.33

has been *proved definitely*, the sulfonic acid group entered either ortho or para to the amino group. Earlier workers were mostly of the opinion that sulfonation *always* occurred ortho or para to the nitro group which was being reduced. Weil, however, was skeptical of the structure of the aminosulfonic acid from *p*-nitroaniline; and Engel,[8] who reduced azophenols with bisulfite, concluded that the sulfonic acid group entered meta to the amino group and ortho to the hydroxyl.

With these things in mind we undertook a structure proof of the aminosulfonic acid obtained from the bisulfite reduction of *p*-nitrophenol. The method used involved removal of the amino group by diazotization and subsequent treatment of the diazonium compound with alcohol. The resulting phenolsulfonic acid would be the meta compound if sulfonation occurred ortho to the amino group and the ortho compound if sulfonation took place meta to the amino group. Bromination of phenol-*m*-sulfonic acid[9] produces 2,4,6-tribromophenol-*m*-sulfonic acid, the sulfonic acid group remaining intact. Phenol-*o*-sulfonic acid, on the other hand, yields 2,4,6-tribromophenol on bromination,[10] the sulfonic acid group being split off. Bromination of the phenolsulfonic acid obtained by de-amination of the *p*-aminophenolsulfonic acid from *p*-nitrophenol gave 2,4,6-tribromophenol, proving that it was the 1-amino-4-hydroxybenzene-3-sulfonic acid.

A second example of meta sulfonation is afforded by 5-nitrosalicylic acid which was reduced by bisulfite to yield 1-amino-4-hydroxy-3-carboxybenzene-5-sulfonic acid and 5-aminosalicylic acid.

Thus it has been demonstrated that the sulfonic acid group can enter in a position meta to the amino group in the case of *p*-nitrophenols and it is possible that it does so by means of a 1,4-addition of sodium bisulfite to the —N═C–C═C— system present in the quinone-oxime form of the intermediate *p*-nitrosophenol.

Bisulfite Reduction of *p*-Nitrophenol.—Five tenths of a mole (69.5 g.) of *p*-nitrophenol, 238 g. of sodium metabisulfite (2.5 moles) and 125 cc. of 5 *N* sodium hydroxide (0.625 mole) were dissolved in a liter of water in a two-liter three-necked round-bottomed flask equipped with a mechanical stirrer. Twenty grams of solid sodium hydroxide was then added and a stream of purified nitrogen was passed into the flask. The solution was then boiled for eleven hours. Stirring was discontinued after the solution became homogeneous. At the end of eight hours the addition of hydrochloric acid to a small portion of the reaction mixture gave no precipitate, but refluxing was continued for three more hours.

Concentrated hydrochloric acid (150 cc.) was added slowly from a separatory funnel to decompose the intermediate products of the reaction and the excess bisulfite. The reaction mixture was then concentrated to 600 cc. by distillation in an atmosphere of nitrogen. The solid which was filtered off after cooling to 0° weighed 68 g., but it was contaminated with inorganic matter and some *p*-aminophenol hydrochloride.

Since we were interested only in the structure of the aminophenol sulfonic acid, this fraction will be the only one discussed. Other fractions were obtained on successive evaporations but they were chiefly *p*-aminophenol hydrochloride contaminated with inorganic salts.

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[8] Engel, THIS JOURNAL, **51**, 2986–2994 (1929).

[9] Lauer and Langkammerer, *ibid.*, **56**, 1629 (1934).

[10] Obermiller, *Ber.*, **42**, 4365 (1909).

The 68-g. precipitate was taken up in 400 cc. of water, a few drops of hydrochloric acid added, and the solution heated to boiling. The material which did not dissolve was filtered off. It weighed 29.9 g. (31.7% yield). It left no ash on ignition and contained no chloride or sulfate ions.

A sample of this material was dissolved in sodium hydroxide solution, filtered, and reprecipitated with hydrochloric acid. The precipitate was washed with water, alcohol, and then ether and finally dried in an oven at 120° for analysis.

Anal. Calcd. for $C_6H_7O_4NS$: S, 16.95. Found: S, 17.4.

Determination of the Constitution of the Aminophenol Sulfonic Acid.—One and eighty-six hundredths grams of the aminophenol sulfonic acid was dissolved in a mixture of 5 cc. of concentrated hydrochloric acid and 15 cc. of water, and 0.85 g. of potassium nitrite added. The diazonium compound was filtered off and refluxed with 80% alcohol for two hours. All of the solid dissolved. After cooling to room temperature, 2 cc. of bromine was added and the solution heated to 80°. One hundred cubic centimeters of water was added and the alcohol removed under diminished pressure. One and six-tenths grams (50%) of tribromophenol was obtained. After purification it melted from 84–87°. Mixed with a known sample of tribromophenol it melted from 86–87°.

Bisulfite Reduction of 5-Nitrosalicylic Acid.—Eighty-four grams of 5-nitrosalicylic acid was reduced in five hours by a procedure similar to that described for *p*-nitrophenol. Hydrochloric acid was added and the solution evaporated to 800 cc. On cooling, a 56-g. precipitate was obtained, which was separated by filtration and dried at 120°. Further evaporations yielded other fractions but since we were interested only in the structure of the aminosulfonic acid the first precipitate is the only one considered.

The precipitate (56 g.) was placed in 300 cc. of boiling water and filtered hot. There remained 6.96 g. (6.5%) of the aminosulfosalicylic acid. When recrystallized from 250 cc. of boiling water, it was sulfate and chloride free.

Anal. Calcd. for $C_7H_7O_6NS$: S, 13.7. Found: S, 13.03.

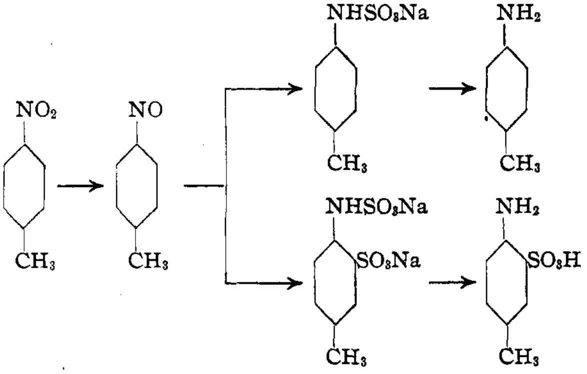
Determination of the Constitution of the Aminosulfosalicylic Acid.—One gram of the material was placed in a 50-cc. Erlenmeyer flask with 10 cc. of 2 *N* hydrochloric acid and potassium nitrite added until diazotization was complete. The diazonium compound was filtered off and washed with alcohol and ether. It decomposed from 263–268°.

Twenty-six hundredths of a gram of the diazonium compound was refluxed with 20 cc. of 80% alcohol for four hours. The alcohol was evaporated *in vacuo* and a little cold water was added. The solution was treated with bromine vapors and the solid filtered off. After one crystallization from alcohol, it melted at 86–88°. Mixed with tribromophenol it melted at 88–89°.

As a check, 5-amino-3-sulfosalicylic acid was prepared from 5-nitro-3-sulfosalicylic acid by reduction. This was carried through the de-amination and bromination and tribromophenol was again obtained.

Summary

1. Evidence has been presented which indicates that the Piria reaction on *p*-nitrotoluene goes through the stages.



It is suggested that the sulfonation occurs by means of a 1,4-addition of bisulfite to the nitroso compound.

2. In the case of *p*-nitrophenols the sulfonic acid group may enter meta to the amino group.

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