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A NEW SYNTHESIS
OF
PARA-AMINOSALICYLIC ACID
HYDROCHLORIDE

by

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Presented in partial fulfillment of the requirement
for the degree of Master of
Science.

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Introduction

Following the initial report by Lehmann⁽¹⁾ that para-aminosalicylic acid possesses tuberculostatic activity, a series of derivatives and analogues of the substance have been synthesized and their in vitro tuberculostatic activities against H₃₇RV strain of *Mycobacterium tuberculosis* have been determined.

In the presence of salicylic acid⁽²⁾, pathogenic strains of *Mycobacterium tuberculosis* have been found to show an increased uptake of oxygen. Some sixty derivatives of benzoic and salicylic acids have been tested in attempts to find a drug which will inhibit this increase in respiration and possibly also inhibit growth. The most active tuberculostatic compound thus far found is 2-hydroxy-4-amino-benzoic acid (para-aminosalicylic acid), which has been found to prevent the growth of the tubercle bacillus in cultures at concentrations of $10^{-5.5}$ M (0.5mg./100cc).⁽²⁾ The action is more fundamental than a mere interference with respiration, since para-aminosalicylic acid also inhibits the growth of non-pathogenic strains of the tubercle bacillus, such as the B. C. G. strain which shows no salicylate effect. In vitro tuberculostatic behavior of para-aminosalicylic acid and related compounds has been reported by Goodaere and his colleagues⁽³⁾. It became apparent to these researchers from the following table (Table 1) that, with a few exceptions, substitution by simple radicals in the para-aminosalicylic acid molecule has but little effect on tuberculostatic activity. This fact appears to be especially borne out by the activities of the compounds in the groups B, C and D. The low activity of compound 9 proved somewhat surprising and it was hoped to comment more fully on this in a later paper. Although the esters of para-aminosalicylic

Table 1

Inhibition Concentrations of Para-Aminosalicylic acid and Related Compounds. Inoculum of 0.001gm./cc. of H₃₇RV Strains of Mycobacterium Tuberculosis.

	Substance	Inhibition Conc. mg./100cc.
Group A	Standard	
1	Para-aminosalicylic acid	0.0487-0.0243
2	Para-aminobenzoic acid	100-50
3	Sodium salicylate	50-25
4	Meta-aminophenol	12.5-6.25
Group B	Esters and Amides of p-aminosalicylic acid	
5	Methyl ester	0.0487-0.0243
6	Ethyl ester	0.0487-0.0243
7	n-Propyl ester	0.0487-0.02433
8	Isobutyl ester	0.0243-0.0121
9	Para-aminosalicylamide	50-25
Group C	Acyl Derivatives of Para-aminosalicylic Acid	
	$\text{RNH} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \\ \diagdown \quad \diagup \end{array} \begin{array}{c} \text{COOH} \\ \text{OR}^1 \end{array}$	
10	N-Acetyl	0.78-0.39
11	N-Benzoyl	1.56-0.78
12	N-Sulfanilyl	6.25-3.125
13	O-, N-Diacetyl	3.125-1.56
14	N-Succinyl	50-25
Group D	Acyl Esters of Para-aminosalicylic Acid	
	$\text{RNH} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \\ \diagdown \quad \diagup \end{array} \begin{array}{c} \text{COOR}^{\text{II}} \\ \text{OR}^1 \end{array}$	
15	N-Acetyl, n-propyl (R=CH ₂ CO, R ^I =H, R ^{II} =C ₃ H ₇)	0.195-0.0975
16	N-Benzoyl, methyl (R=C ₆ H ₅ CO, R ^I =H, R ^{II} =CH ₃)	0.78-0.39
Group E	Nuclear Substituted Derivatives	
17	3,5-Dibromo-4-aminosalicylic acid	12.5-6.25
Group F	Derivatives of Para-nitrosalicylic acid	
18	Para-nitrosalicylic acid	25-12.5
19	Isopropyl ester	3.125-1.56
20	Acetyl-p-nitrosalicylic acid	6.25-3.125
21	Methyl ester	12.5-6.25
22	Isobutyl ester	25-12.5
Group G	Analogues	
23	3-Amino-4-hydroxybenzoic acid	3.125-1.56
24	4-Amino-3-hydroxybenzoic acid	3.125-1.56
25	2-Amino-4-hydroxybenzoic acid	50-25
26	Methyl-2-amino-4-hydroxybenzoate	25-12.5
27	2,4-Diaminobenzoic acid	25-12.5

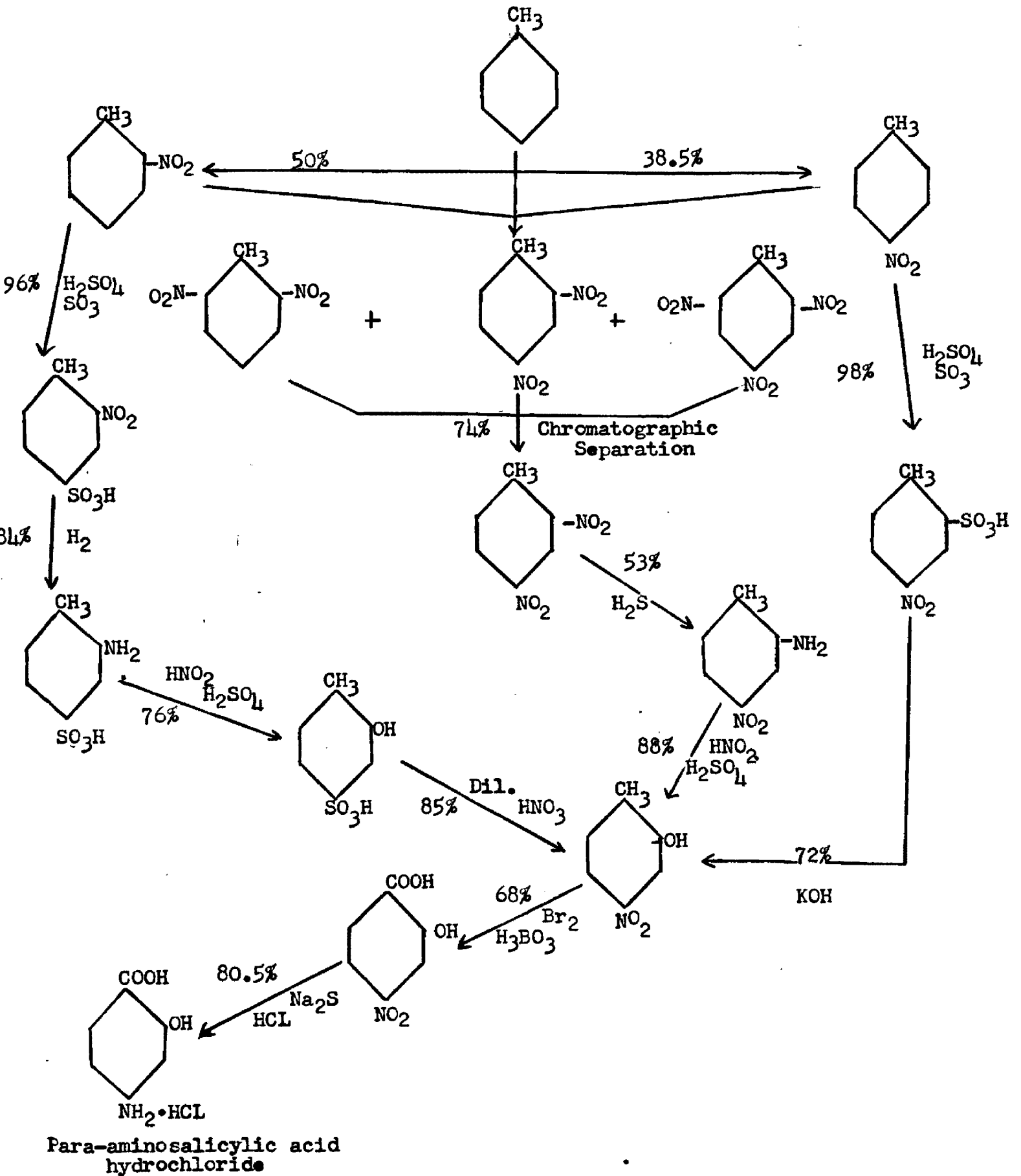
acid do not appear to possess a marked advantage over the free acid itself from these in vitro data, they were considered worthy of animal study. It was also felt that compound 14 might possess in vivo activity by analogy with the carboxy-acyl sulfonamides. The results described under group 6 confirmed the original findings of Lehmann, namely that the particular configuration displayed by para-aminosalicylic acid is probably the most active of the possible isomers. Compound 25 is of particular interest since it has been suggested as being formed during carboxylation of meta-aminophenol, a process utilized in one of the syntheses of para-aminosalicylic acid⁽⁴⁾. It should be noted that no difference in tuberculostatic activity was observed between samples of para-aminosalicylic acid synthesized by the various methods.

Clinically⁽⁵⁾ some eighty-two adult patients with various forms of tuberculosis were treated with para-aminosalicylic acid, usually in oral doses of respectively 5, 3, 3 and 5 grams of the hydrochloride at 4 hour intervals (14gm. per day), in order to maintain the average blood levels at 3-6mg. per 100cc. for 3 to 4 weeks, with one week intervals without treatment. The results in pulmonary tuberculosis were generally good. Of forty-seven cases, thirty-three improved, nine did not improve and five died. In the favorable cases there was a gradual decline in fever, and a diminution in sedimentation rates, as well as a rise in hemoglobin and a disappearance of tubercle bacilli from the sputum. The Roentgen picture also improved. In other forms of tuberculosis the results were likewise favorable, except in meningitic tuberculosis (a total of six cases) which all terminated fatally. The toxicity of para-aminosalicylic acid was found to be low. In some cases gastro-intestinal

discomfort and diarrhea occurred; in isolated cases there occurred some kidney irritation accompanied by a slight albuminuria. Para-aminosalicylic acid proved very beneficial when a 5 or 10% solution was used to fill extra-pleural post-operative cavities infected with the tubercle bacillus. Recently it has been recommended⁽⁶⁾ that para-aminosalicylic acid be administered clinically as the sodium salt and/or with adequate amounts of sodium bicarbonate to guard against crystalluria, acidosis and to decrease nausea.

Para-aminosalicylic acid has been prepared by the alternative syntheses of Seidel and Bittner^(7,8) involving the carboxylation of meta-aminophenol. Some workers in Switzerland, Germany, Sweden, England and America have all published their carboxylation conditions, which differ somewhat from those of the original procedure. Another practical preparative method starting with 4-nitro-2-aminotoluene and involving 4-nitro-2-chloro-benzoic acid as an intermediate has recently been reported by Wenig and Gardner⁽⁹⁾.

The starting material of the method worked out in this laboratory and herein reported was toluene, which through the series of reactions shown in the following diagram (Chart 1) resulted in good yields of para-aminosalicylic acid.



Theoretical Considerations

The mixture of ortho- and para-nitrotoluenes resulting from the nitration of toluene with mixed acid (H_2SO_4 and HNO_3) may readily be separated on a technical scale by fractional distillation in vacuum, for the isomers differ sufficiently in their boiling points ($16^\circ C.$ at $760mm.$).⁽¹⁰⁾ It is furthermore possible by a combination of distillation and crystallization to effect a separation of the ortho and para isomers and to thus obtain the pure ortho as well as para compounds. The monosubstitution results in yields of the ortho and para isomers in a ratio varying somewhat with the temperature of the procedure. The mixture also contains a small quantity of meta-nitrotoluene eliminated in the fractional distillation and crystallization.

The preparation of 2,4-dinitrotoluene may be accomplished by nitrating toluene with mixed acid (H_2SO_4 and HNO_3), usually in two steps, with the utilization of the spent acid from the dinitration for the mononitration. The main end product, the 2,4-dinitro derivative is formed through the ortho- and para-nitrotoluenes⁽¹¹⁾. The para compound yields 2,4-dinitrotoluene exclusively by a substitution ortho to the methyl and meta to the nitro groups; while in the ortho-nitro isomer, comparable positions are available at carbons 4 and 6, but in this case substitution occurs preponderantly at the point of the stronger para direction by the methyl group yielding the same 2,4-isomer; 2,6-dinitrotoluene is produced only in minor amounts. Under controlled conditions the quantity of 2,4,6-trinitrotoluene also formed in the nitrations may be reduced to negligible proportions. The isolation of the 2,4-dinitrotoluene from the reaction mixture may be accomplished readily by the aid of chromatography. In this investigation magnesium oxide was used as the adsorbent

and acetone as the solvent. The trinitrotoluene is strongly adsorbed producing a violet zone at the top of the column; 2,4-dinitrotoluene is poorly adsorbed forming a green zone at the bottom of the column; other nitrotoluenes present pass out into the filtrate.

Theoretically sulfonation of ortho- and para-nitrotoluenes should produce 2-nitrotoluene-4-sulfonic acid and 4-nitrotoluene-2-sulfonic acid respectively. This is due to the varied though synergistic actions of the methyl and nitro groups. In the case of para-nitrotoluene, the nitro group deactivates position 3 very strongly and activates position 2, and since the latter is also under the ortho (activating) influence of the methyl group, it should be the exclusive site of monosubstitution on sulfonation. Similarly in the case of ortho-nitrotoluene the expected sites of substitution should be at the positions 4 and 6, which are para and ortho respectively to the methyl and meta to the nitro groups. Since para orientation is ordinarily stronger than the ortho, a predominance of attack at position 4 should therefore be anticipated. In this work sulfonation of ortho-nitrotoluene was found to produce exclusively the 4 sulfonic acid, the reaction mechanism evidently being analogous to that of the dinitration.

A particular important use of the products of sulfonation is the preparation of phenols which may be accomplished by fusion with potassium or sodium hydroxide. At temperatures ranging between 250-300°C. the sulfonic acid group is replaced by the "OK" or "ONa" group from which the phenol is obtained by treating the cooled melt with ice and hydrochloric acid. The reaction however does not proceed as simply as might be anticipated. Oxidative side reactions occur simultaneously with the normal exchange reaction, about 10% of para-nitrosalicylic acid being

formed in the procedure as conducted in this work.

The hydrolysis of the diazonium salt of 2-aminotoluene-4-sulfonic acid by means of boiling sulfuric acid results in good yields ortho-cresol 5-sulfonic acid, which may be converted into 5-nitro-ortho-cresol by the heating of its aqueous solution with diluted nitric acid in the presence of a small amount of sulfuric acid as a catalyst. The replacement of the sulfonic acid group by the nitro group is of considerable technical importance. It is successful chiefly with phenol- and naphthol- sulfonic acids⁽¹²⁾.

The selective reduction of one group in polynitro compounds may often be accomplished by the use of calculated amounts of sodium, ammonium or hydrogen sulfide. In this operation, on dissolving the 2,4-dinitrotoluene in alcoholic ammonia and passing in hydrogen sulfide until certain conditions were attained, the reagent reduced one group completely before attacking the other. The resulting mixture of 2-nitro-4-aminotoluene and 4-nitro-2-aminotoluene obtained in the reaction was easily separated into its components by taking advantage of their different solubilities in water⁽¹³⁾.

The conversion of 4-nitro-2-aminotoluene into 5-nitro-ortho-cresol may successfully be accomplished by diazotization followed by hydrolysis.

Whenever 5-nitro-ortho-cresol is treated with bromine at reflux temperatures preferably with exposure to a light source, the halogen enters the methyl side chain and on prolonged action yields the tribromo derivative. Hydrolysis of the product with boric acid⁽¹²⁾ or lime in the presence of iron powder as a catalyst at 150°C. followed by acidification produces quantitatively the corresponding acid (para-nitrosalicylic acid).

Reduction of para-nitrosalicylic acid with tin or zinc and hydro-

ehloric acid or with stannous ehloride always leads to meta-aminophenol.⁽¹⁴⁾
The satisfactory method of reduction employed in this research utilized for a prolonged time the mild reducing action of sodium sulfide in alkaline solution. Yields exseedng 80% of para-aminosalicylic acid were obtained.

The final product, para-aminosalicylic acid is a yellowish powder melting at 140-150°C.^(15,16,17) It is soluble in water and alcohol and moderately soluble in ether. Its hydroehloride is a stable white crystalline powder melting at 223-226°C. with decomposition⁽⁹⁾. It is unstable in alkaline solution, decarboxylating to meta-aminophenol in solution above 80°C.⁽¹⁶⁾ The dried sodium salt darkens in a few days.

Experimental

PARA- AND ORTHO-NITROTOLUENES FROM TOLUENE

120gm. (138cc.) of toluene was placed in a 1 L. flask, a cooled mixture of 150cc. concentrated sulfuric acid (sp. gr. 1.84) and 100cc. of nitric acid (sp. gr. 1.42) was then added in small portions, the contents of the flask being shaken vigorously and cooled after each addition. The temperature was maintained below 50°C. throughout the process. After the acid had all been added, vigorous shaking was continued for ten minutes. The reaction mixture was then poured into about 2 L. of water. The liquid nitrotoluene layer was finally separated from the acid solution by decantation, washed with water to remove acid then rendered water free by being placed over anhydrous calcium chloride.

The mixed nitrotoluenes were fractionally distilled at diminished pressure. The fractions distilling over at 108-115°C. 19mm. and 120-135°C. 19mm. were collected separately, each being subsequently redistilled at 19mm. pressure. The collected 110-112°C. fraction which boiled at 220°C. under ordinary conditions, was identified as ortho-nitrotoluene. Yield 89gm. or 50%. The fraction distilling at 126-130°C. was recrystallized from alcohol and air dried. The product, a pale yellow crystalline powder. m.p. 51.8°C. was identified as para-nitrotoluene. Yield 68.6gm. or 38.5%.

2,4-DINITROTOLUENE FROM TOLUENE

120gm. of toluene was placed in a 1 L. flask, a cooled mixture of 500cc. sulfuric acid (sp. gr. 1.84) and 320cc. nitric acid (sp. gr. 1.42) was added in small portions. The contents of the flask were shaken vigorously and cooled after each addition to prevent loss of toluene by evaporation. After all of the acid was added, the reaction mixture was poured into about

three volumes of cold water with vigorous stirring until solidification occurred. The solid material was separated and washed well on a suction filter with cold water to remove the oily liquid (mono-nitrotoluene) as completely as possible. On recrystallization from the least possible quantity of hot alcohol, a yield of 220gm. of slightly yellow crystals was obtained, m.p. 62-89°C.

50gm. of the crude product was dissolved in 300cc. of acetone. The solution was allowed to run through a column (3.2cm. in diameter) of 80gm. pure magnesium oxide at the rate of not more than one drop per second. As the solution passed through the adsorbent two colored zones appear, a violet layer (about 1/8 of the column) was at the top, the rest of the column being green colored. After developing with 350cc. of acetone, the column was dried. The violet layer was cut off and rejected. The green layer containing the 2,4-dinitrotoluene was extracted with 95% alcohol. The acetone filtrate was passed through a series of eight columns similar to the one previously described or until a green colored zone no longer appeared in the adsorbent. The columns were then extracted with alcohol. The alcoholic extractions were combined and concentrated on a water bath by evaporation. On cooling, 39.5gm. of pale yellow needles, 2,4-dinitrotoluene were obtained, m.p. 71.5°C. Yield 74% (from toluene).

4-NITROTOLUENE-2-SULFONIC ACID FROM PARA-NITROTOLUENE

50gm. of para-nitrotoluene was added to 90cc. of fuming sulfuric acid (20% SO₃) with vigorous shaking. After heating on a water bath for 30 minutes, the mixture was allowed to cool, and then poured into 200cc. of cold water. Pale yellow needles crystallized out on standing. On recrystallization from 70% alcohol, the pure product was obtained as the dihydrate,

m.p. 131°C. Yield 87gm. or 98%.

2-NITROTOLUENE-4-SULFONIC ACID FROM ORTHO-NITROTOLUENE

The procedure used was similar to that used in preparing 4-nitrotoluene-2-sulfonic acid. 80gm. of ortho-nitrotoluene was used, and a yield of 124gm. (96% yield) of 2-nitrotoluene-4-sulfonic acid was obtained in the form of long pale yellow needles, m.p. 91.5°C.

5-NITRO-ORTHO-CRESOL FROM 4-NITROTOLUENE-2-SULFONIC ACID

A mixture of 50gm. of potassium hydroxide, 15cc. of water and 10gm. of anhydrous 4-nitrotoluene-2-sulfonic acid was melted in a nickel crucible and heated with stirring for 30 minutes at 250-300°C. The crucible was tightly covered to prevent oxidation of the melt. After the resulting dark colored reaction mass was allowed to cool, it was decomposed with 250cc. of 15% hydrochloric acid, followed by concentrated hydrochloric acid until there was no further effervescence. After the addition of 300cc. of water, the mixture was heated until everything except a small amount of resin-like matter was dissolved. After filtration of the cooled mixture, 5-nitro-ortho-cresol and a small amount of para-nitrosalicylic acid crystallized out. The mother liquor was concentrated by further evaporation, and additional crystals were obtained. The combined mixed crystals were washed with diluted sodium carbonate solution (5%) to remove para-nitrosalicylic acid then recrystallized from alcohol. 5gm. of yellow crystals of 5-nitro-ortho-cresol was obtained. M.P. 118.5°C. Yield 72%.

2-AMINOTOLUENE-4-SULFONIC ACID FROM 2-NITROTOLUENE-4-SULFONIC

ACID

80gm. of 2-nitrotoluene-4-sulfonic acid was dissolved in 250cc. of alcohol, 100cc. of concentrated ammonium hydroxide solution (28%) was added with shaking. Hydrogen sulfide gas was passed rapidly through the mixture under the hood until the odor of hydrogen sulfide was pronounced and then continued 30 minutes longer. The mixture was then heated on a water bath under the hood for 10 minutes; 250cc. of concentrated hydrochloric acid and 100cc. of water was added, and the heating continued for 45 minutes longer. On cooling the precipitated sulfur was removed by filtration and the filtrate neutralized with sodium carbonate solution (congo red used as the indicator). 2-Aminotoluene-4-sulfonic acid precipitated in the form of crystals containing one molecule of water of hydration. This compound lost water and decomposed on heating. Yield 54.5gm. or 84%.

ORTHO-CRESOL-5-SULFONIC ACID FROM 2-AMINOTOLUENE-4-SULFONIC ACID

A mixture of 100cc. concentrated sulfuric acid (sp. gr. 1.84) and 180cc. of water was added to 50gm. of finely powdered 2-aminotoluene-4-sulfonic acid. After diazotization by the usual procedure, the product was added rapidly to an actively boiling mixture of 200cc. concentrated sulfuric acid and 300cc. of water. After all of the nitrogen gas had escaped, the solution was boiled for an additional 15 minutes and then cooled. 300cc. of alcohol was finally added. Ortho-cresol-5-sulfonic acid precipitated in the form of needle crystals which were collected, washed with alcohol and then air dried. M.P. 79-80°C. Yield 35gm. or 76%.

5-NITRO-ORTHO-CRESOL FROM ORTHO-CRESOL-5-SULFONIC ACID

34gm. of ortho-cresol-5-sulfonic acid was dissolved in 200cc. of boiling water. A solution of 60cc. of concentrated nitric acid diluted with 60cc. of water was added, followed by 5cc. of concentrated sulfuric acid as a catalyst. After boiling until the spontaneous reaction was over (approximately 15 minutes), the solution was allowed to cool. 5-Nitro-ortho-cresol separated in the form of yellow crystals. These were recrystallized from alcohol and air dried. M.p. 118-119°C. Yield 24gm, or 85%.

4-NITRO-2-AMINOTOLUENE FROM 2,4-DINITROTOLUENE

35gm. of 2,4-dinitrotoluene was dissolved in 80cc. of hot alcohol. The solution was allowed to cool and 50cc. of concentrated ammonium hydroxide (28%) was then added with vigorous shaking. Hydrogen sulfide gas was passed rapidly through the mixture under the hood until the odor of the reagent was strong. After heating on a water bath under the hood for 15 minutes, the mixture was poured into 500cc. of cold water. The resulting precipitate was collected and washed with cold water. A sufficient quantity of water was then added to form a thin paste. This was followed by 60cc. of concentrated hydrochloric acid. The undissolved sulfur was removed by suction filtration, and the filtrate neutralized with an excess of concentrated ammonium hydroxide. The resulting precipitate was collected and recrystallized from hot water to remove the more soluble 2-nitro-4-aminotoluene. 15gm of yellow colored fine needle crystals (4-nitro-2-aminotoluene) was obtained. M.P. 98°C. Yield 53%.

5-NITRO-ORTHO-CRESOL FROM 4-NITRO-2-AMINOTOLUENE

15gm. of 4-nitro-2-aminotoluene was dissolved in 20cc. of concentrated hydrochloric acid and 50cc. of water at 80°C. To this was added an

additional 30cc. of concentrated hydrochloric acid, and the entire solution was cooled to 5°C. A solution of 7.5gm. of sodium nitrite in 15cc. of water at 25°C. was added as rapidly as the reaction could take up the nitrous acid. This was checked with starch-iodide paper.

The diazonium mixture was added as rapidly as possible to an actively boiling mixture of 50cc. concentrated sulfuric acid and 50cc. of distilled water. After all of the nitrogen gas had escaped, the solution was boiled for an additional 15 minutes. Yellow crystals of 5-nitro-ortho-cresol separated out after cooling. On recrystallization from alcohol, a yield of 13gm. (Or 88%) (M.P. 118°C) was obtained.

PARA-NITROSALICYLIC ACID FROM 5-NITRO-ORTHO-CRESOL

24gm. of 5-nitro-ortho-cresol was placed into a 500cc. 3-necked round bottom flask under sunlight and heated in an oil bath to 120-130°C. until the crystals just melted. The contents of the flask were maintained at this temperature and 200gm. (64cc.) of bromine was then added drop by drop, with constant stirring, the hydrogen bromide gas produced during the reaction being allowed to escape through a reflux condenser. At the completion of the reaction, 40gm. of powdered boric acid was added to the contents of the flask, and the mixture was heated on an oil bath at 150°C. more hydrogen bromide gas being evolved. After continuous heating for 5 hours, the bath temperature was increased to 200°C. On cooling, the mixture was extracted four times with ether and the combined ether extractions were concentrated. The resulting para-nitrosalicylic acid crystallized out in the form of yellow crystals which were then dissolved in 5% sodium carbonate solution. This was finally neutralized by addition of diluted hydrochloric acid to reprecipitate the purified product. Yield 20gm. or 68%,

m.p. 226-228°C.

PARA-AMINOSALICYLIC ACID HYDROCHLORIDE FROM PARA-NITROSALICYLIC
ACID

A mixture of 20gm. of para-nitrosalicylic acid and 9gm. of anhydrous sodium carbonate was heated with 80cc. of water until dissolved. 35gm. of sodium sulfide dissolved in 150cc. of water was gradually added to the boiling sodium para-nitrosalicylate solution. After heating six hours at 110°C. under a reflux condenser, 50cc. of water was added, followed by 80cc. of concentrated hydrochloric acid. The resulting mixture was heated at 100°C. for two hours, then cooled and filtered to remove the precipitated sulfur. The filtrate was rendered neutral (congo red) with powdered sodium carbonate. Para-aminosalicylic acid was precipitated in the form of a yellowish amorphous powder. This was separated on a filter and dissolved in an excess of concentrated hydrochloric acid. 300cc. of alcohol was finally added. The precipitated para-aminosalicylic acid hydrochloride was filtered off and washed with 100cc. of concentrated hydrochloric acid. The excess hydrochloric acid was removed by washing with alcohol and finally with ether. The crude product was recrystallized from boiling water. Yield 18gm. (or 80.5%) M.P. 221-224°C. with decomposition. Nitrogen found: 7.29% (Calc. 7.4%).

Conclusions

Para-aminosalicylic acid has been synthesized in this laboratory by a satisfactory procedure from toluene through para- and ortho-nitrotoluenes and 2,4-dinitrotoluene. The processes are simple, readily performed with a minimum of apparatus and the yields are excellent.

Bibliography

- (1) Lehmann, *Lancet*, 251, 15, (1946).
- (2) Jorgen Lehmann, *Svenska Lakartidn*, 43, 2029-41, (1946).
- (3) Goodacre, Mitchell and Seymour, *Quant. J. Pharma. and Pharmaco.*
21, 3, 301-305, (1948).
- (4) Martin, Spring, Dempsey, Goodacre and Seymour, *Nature*, 161,
435, (1948).
- (5) Gylfe Vallentin, *Svenska Lakartidn*, 43, 2047-58, (1946).
- (6) Way, Smith, Howie, Weiss and Swanson, *J. Pharmaco. and Experi.*
Therap. 93, 3, (1948).
- (7) Seidel and Bittner, *Monatsh*, 23, 431, (1902).
- (8) Seymour, *Quant. J. Pharma. and Pharmaco.* 21, 3, 413, (1948).
- (9) Wenis and Gardner, *J. A. Ph. A*, 38, 1, (1949).
- (10) Lucas, *Org. Chem.*
- (11) Fieser and Fieser, *Org. Chem.* (1944).
- (12) Weygand, *Organic Preparations, English Edition*, (1945).
- (13) Hodgman, *Handbook of Chemistry and Physics*, (1939).
- (14) Ghielmetti, *Farm. Sci.* 3, 51-2, (1948).
- (15) McAnally and Seymour, *Lancet*, 254, 305, (1948).
- (16) O'Connor, *ibid.* 254, 191, (1948).
- (17) Whittet, *Pharm. J.* 105, 133, (1947); *Lancet*, 254, 268, (1948).