A STUDY OF SOME OF THE PROPERTIES OF TETRABROMOANTHRANILIC ACID AND TETRACHLOROANTHRANILIC ACID

A thesis submitted to the Chemistry Department of Washington and Lee University as a partial fulfillment of the requirements for the degree of Bachelor of Science in Chemistry.

May 31, 1941

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(Under the direction of Dr. L. H. Farinholt)

INTRODUCTION

The original purpose of this thesis was twofold; to prepare tetrabromoanthranilic acid and study its chemical reactions, and to study the reactions of tetrachloroanthranilic acid, especially its behavior in diazotization. The first was of interest because of the possible effects the bromine atoms on a benzene ring might have on the carboxyl and amino groups attached; the second was undertaken to see if diazotization of such a highly negative nucleus could be accomplished; and if it could be, whether this reaction could be employed to make tetrachlorosalicylic acid, which this laboratory has been unable to obtain by direct halogenation of salicylic acid. The preparation of tetrabromophthallic anyhdride was undertaken jointly by the two authors, after which Adams prepared the tetrabromoanthranilic acid from it, and studied the properties of the bromine compounds, while Godehn studied the properties of the chlorine compounds. It was originally intended to compare the properties of the two halogenated compounds, and to some extent this was done.

The original purpose of this thesis was carried out in part, as we succeded in making and identifying the tetrachlorosalicylic acid. However, this original purpose was modified to some extent, since after experimental work was begun, it was realized that the

preparation of the tetrabromoanthranilic acid in itself combined many of the facts pertinent to the chemistry of the compound, and various methods of preparation were employed in efforts to improve yields and to correlate facts concerning the action of the various groups in the compound. However, the chief interest remained in the reactions of the amino and carboxyl groups of the tetrabromophthalic acid and anthranilic acid derivatives.

The following paper presents the work we have done in carrying out these ends, and includes the points of interest encountered in doing this work.

At this time we wish to express our gratitude to Dr. L. H. Farinholt for his invaluable guidance in this work, and for the ready aid he has offered us in overcoming the difficulties which we encountered; and also to Mr. J. R. Taylor who has given us much valuable assistance.

MONOGRAPH

The purpose of this monograph was to collect the data available on the tetrabromination and tetrachlorination of phthallic anhydride, the formation of tetrabromo and tetrachloro-phthalimides, and the formation of tetrachloro and tetrabromo-anthranilic acids. Data on the reactions of the halogen substituted anthranilic acids and methods of diazotization have also been collected, as a basis upon which the laboratory experimental work was founded.

I BROMINATION OF PHTHALIC ANHYDRIDE

A[1] Tetrabromophthalic anhydride can be prepared by dissolving phthalic anhydride in fuming sulfuric acid containing 50% free SO_3, adding a small amount of iodine as a carrier and excess Br_2. The bromine is added in portions of decreasing amounts in the ratio 5:3:1:1, the first addition at 70° until bromine is absorbed, the second at 100°, the third at 130°, and the last at 170° where the temperature is maintained for about half an hour. After cooling, the mixture is poured over cracked ice, filtered, and purified by dissolving in warm, dilute sodium hydroxide and re-precipitation with hydrochloric acid. This gives tetrabromophthalic acid contaminated with considerable quantities of the mono-sodium salt. This salt is decomposed by steaming the acidified solution vigorously for about half an hour before filtering off the tetra-

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(1) Pratt and Shupp: J.A.C.S. 40 1416 (1918)

bromophthalic acid. The dried acid is converted into the anhydride by crystallizing from xylene in which it is soluble in the ratio 1:6. A 75-85% yield is obtained in this manner with the anhydride melting at from 273.5 to 274°. Lower brominated derivitaves are effectually removed by the above procedure.

B[2] Tetrabromophthalic anhydride can be prepared from tetrabromophthalic acid by sublimation.

II PREPARATION OF TETRACHLOROPHTHALIC ANHYDRIDE

A[3] Tetrachlorophthalic anhydride is obtained by heating naphthalene and chlorosulfonic acid for ten hours at 180°. Melting point - 255°.

III PREPARATION OF TETRABROMOPHTHALIMIDE

A[4] Tetrabromophthalimide can be prepared by dissolving tetrabromophthalic anhydride in nitrobenzene and boiling for half an hour with formamide. On cooling the imide crystallizes out in yellow blades which, when washed free of solvent and dried, give a 75% yield of the imide. This crude product is purified by recrystallization from xylene using bone black and from glacial acetic acid giving bright yellow blades.

IV PREPARATION OF TETRAHALOGENATED ANTHRANILIC ACID

A[5] Tetrabromoanthranilic acid can be prepared by the action of KOH and KOCl on tetrabromophthalimide. The imide is dissolved in dilute KOH and cooled to 0-5° and chlorine led in. The ppt. formed is a yellow

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(2) Blumberg: Berichte 17 2494
(3) Georg Walter: Monatsh 64 287-8 (1934)
(4) J.A.C.S. 40 1417 (1918)
(5) Lesser and Weiss: Berichte 46 3942

powder when dried and is purified by heating with charcoal, dissolving and recrystallizing from acetic acid. Melting point is 204-205°. It is readily soluble in alcohol and ethyl acetate and difficultly soluble in acetic acid, chloroform, and xylol.

B[6] Tetrachloroanthranilic acid can be prepared readily by use of the Hoffman reaction from the acid amide of tetrachlorophthalic acid. Tetrachlorophthalic anhydride, finely pulverized, is added with stirring into 20% ammonia. The mixture warms by itself to 50° and the anhydride goes completely into solution. With stronger ammonia or with different (cooler) temperatures the ammonium salt of tetrachlorophthalimidic acid precipitates in part. The solution obtained is immediately poured into excess dilute H_2SO_4 mixed with ice whereby the phthalimidic acid precipitates out in white flakes. These flakes are immediately washed with water on a suction filter, for on standing they change to tetrachlorophthalic acid. The moist acid is dissolved in water and ice and the exact amount of NaOH alkaline hypochlorite solution is allowed to flow into the liquid cooled to 0-5°, the hypochlorite solution composed of 1 mol NaOCl and 2 mols NaOH. The end of the reaction is recognized by a test with aniline water giving a smooth blue color. The excess hypochlorite is removed by adding a small amount of bisulfite and heating to 75° for three hours. Excess HCl is added to the warm solution to precipitate the tetrachloro-

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(6) Villiger and Blangey: Ber. 42 3549-52 (1909)

anthranilic acid. These crystals are purified by dissolving the crude acid in hot 12% Na_2CO_3 solution and the same volume of saturated NaCl solution is added, and the precipitate is dissolved in hot water, then reprecipitated with HCl.

The tetrachloroanthranilic acid is quite insoluble in cold water, difficultly soluble in cold glacial acetic acid and benzene, and easily dissolves in alcohol, methanol, and ether, and crystallizes out of these solutions in long needles, melting at 182-3° with frothing. The substance recrystallized from warm glacial acetic acid shows a considerably lower melting point. For analysis the substance is dried and crystallized out of methanol on the water bath. Heating above the melting point converts the acid quantitatively to 2,3,4,5-tetrachloroaniline. With bases it gives well defined salt crystals.

C[7] Tetrachloroanthranilic acid can be prepared by passing through tetrachlorobenzoic acid and nitro-tetrachlorobenzoic acid.

V DIAZOTIZATION BY THE "INVERTED METHOD"

A[8] Schmitt, who discovered diazobenzene-p-sulfonic acid, obtained it by Griess's method, but as many of the monoamino-sulfonic and carboxylic acids are insoluble in water, and so can be acted on but solwly by nitrous acid, and the diazo salts themselves are also aparingly soluble, reaction may soon come to a halt. The reactivity

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(7) Tust: Ber. 20 2441 (1887)
(8) Saunders, "The Aromatic Diazo Compounds"; 9 (1936)

of the acid can be increased by precipitating it in a fine state of division by adding acid to a solution of its salt, but a better alternative is to add the nitrite to the alkaline solution of the amino-acid and then run the mixture steadily into the chilled acid. Diazotization takes place instantly, and the insoluble substance which separates is the diazo compound.

Diazotization of sulfanilic acid.

Sodium sulfanilate (23 g. = 0.1 mol) and sodium nitrite (7 g.) are dissolved in water (120 ml) cooled with ice, and then poured with stirring into sulfuric acid (17 ml., sp. gr. 1.81) diluted with water (100 ml.) The diazo compound is precipitated and reaction is complete almost as soon as the last of the solution is added to the acid.

INTRODUCTION TO EXPERIMENTAL WORK

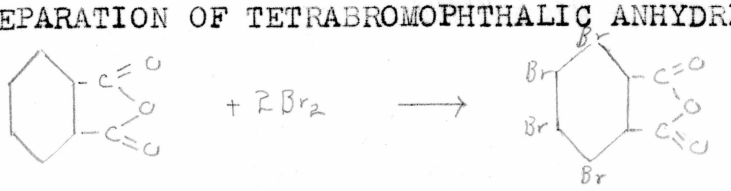
In the study of the derivatives of tetrabromoanthranilic acid several general procedures were used. For analysis of the compounds obtained, melting points and Parr bomb analyses for bromine were chiefly used. All melting points listed in the following pages were taken on the same thermometer and the corrections are included in the values listed. Parr bomb determinations of bromine were carried out as suggested in JACS 39, 2069, with a Volhard titration for excess silver added or potentiometric titrations as described in this thesis.

The starting materials used were technical products and yields obtained were at no time considered in any exactitude. However, methods for obvious improvement of yields have been considered in all of the work done.

The nature of the work necessary for the study of the preparation of tetrabromoanthranilic acid has prevented any close similarity to the work done on the previously prepared tetrachloroanthranilic acid. However, diazotization of the compounds and effects of a few reagents on each compound have been noted.

EXPERIMENTAL WORK

I PREPARATION OF TETRABROMOPHTHALIC ANHYDRIDE



Method: The method of Pratt and Shupp (1) was used with modifications indicated below.

To 100 g. of phthallic anhydride in a three neck flask fitted with a dropping funnel, water condenser, and a stirring rod through a mercury seal, 600g. of technical 60% fuming sulfuric acid was added. The mixture was stirred for 2½ hours until all of the anhydride had dissolved; then 2 g. of iodine crystals were added and the flask heated to 80°. 125 ml. of bromine in the dropping funnel were run into the solution with the dropping funnel going under the solution - about 1 drop per sec. After a few minutes bromine began to appear in the condenser and the rate of addition was slowed down considerably.

After 8 hours one-third of the bromine had been added and bromine was no longer taken up. Iodine crystals were noticed appearing in the condenser and especially on the rubber stopper connections. The flask was cooled spontaneously with stirring and was then immersed in a cold water bath for five minutes. A slurry of orange-yellow crystals appeared on cooling. About 0.7 g. of iodine crystals wer added to the cold mixture and about one-third of the remaining bromine

(1) JACS 40 1416 (1918)

was run in with stirring. The water bath was heated to 87°, maintained at this temperature for two hours, and bromine fumes again became prolific. The flask was cooled once more and then taken to 98° for 20 min. when once more bromine fumes came off rapidly, and the flask was allowed to cool.

100 ml. of fuming sulfuric acid was added and the flask heated for 2½ hours at 98° with the addition of 15 ml. of bromine. On cooling, brown crystals formed. 10 ml. more of bromine was added with the flask heated at 98° for 2 hours. On cooling, brown crystals filled the lower nine-tenths of the system.

The flask was heated for three hours at 98° with the slow addition of another 15 ml. of bromine and again the flask was cooled. Crystals were still present and when the flask was at room temperature the rest of the bromine was added along with 75 ml. of fuming sulfuric acid. The flask was reheated on the water bath with a "cold finger" in the end of the condenser for continual refluxing of the bromine for 1¾ hours. Then the oil bath was substituted for the water bath and the temperature slowly raised over an hour and a half to 164°, and the bath held at this temperature for ½ an hour. Bromine refluxed far into the condenser and an increase in temperature would have allwed the escape of free bromine from the end of the condenser. The flame was then removed and the flask allowed to

cool spontaneously. After three hours the flask was at room temperature.

The contents of the flask were filtered leaving a heavy brown precipitate rich in bromine fumes. The filtrate was poured onto ice in a two liter crock. After the ice had melted, the contents of the crock were filtered through a sintered glass funnel leaving a grayish-black precipitate. This was discarded as too impure for use. The original ppt. was treated with glacial acetic acid and filtered leaving a gray ppt. This was dried and weighed 160 g. A small portion was recrystallized from acetic acid and a Parr bomb run on this sample for bromine.

Results - Parr bomb analysis

Weight of sample	0.3041 g.	
Silver nitrate added	42.13 ml.	- 0.100 N.
KSCN titration	36.25 ml.	- 0.0500 N
Found:		63.3% bromine

Theoretical:

tetrabromophthalic anhydride	68.9%
tetrabromophthalic acid	66.4%
tribromophthalic anhydride	62.3%

The crude gray ppt. from above was treated by two methods:

1. One portion of this gray ppt. was dissolved in xylene at 80°. This was recrystallized by evaporation of the xylene leaving a gray ppt. as before. One sample was used for determination of bromine

Results: Parr bomb analysis

Weight of sample	0.3005 g.
Silver nitrate added	50.0 ml - 0.100 N.
KSCN titration	51.17 ml. - 0.050 N.
Found	64.9% bromine

Theoretical:

tetrabromophthalic anhydride	68.9%
" acid	66.4%
tribromophthalic anhydride	62.3%
" acid	59.4%

2. The rest of the gray ppt. was dissolved in NaOH solution and the precipitate from xylene above was added also. The mono-sodium salt seemed insoluble, so the ppt. was dissolved in 400 ml. of 2 N. NaOH solution. This solution was treated with decolorizing carbon black, heated to boiling, cooled and filtered. After washing the ppt., the filtrate was acidified with excess concentrated sulfuric acid (70 ml.) A white ppt. was immediately formed which was allowed to stand overnight and was then filtered and dryed on an evaporating dish over a water bath.

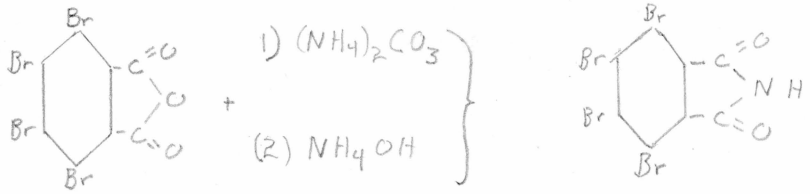
The dried white crystals were treated with acetic anhydride in an 800 ml. round bottom flask and heated for 2½ hours to a temp. of 120° over an oil bath. White crystals resulted.

Melting point -

Recorded M. P. -

Experiment II - PREPARATION OF TETRABROMOPHTHALIMIDE FROM THE CRUDE TETRABROMOPHTHALIC ANHYDRIDE FROM I.

Method: Two methods were attempted for obtaining the imide.

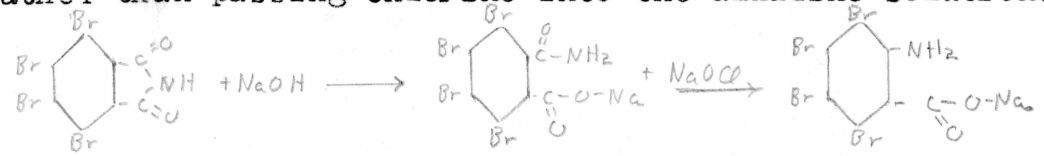


A) 25 g. of crude tetrabromophthalic anhydride were heated in a 500 ml. round bottomed flask with 7.97 g. of ammonium carbonate for 2½ hours over an oil bath with the temp. slowly raised to 300°. A yellow solid was obtained, partly colored with white crystals. After cooling, the solid was treated with water and broken up with a yellow murky-white mixture resulting. This was filtered and washed, and the ppt. was treated with acetic acid and allowed to stand. A white suspension resulted which after several filtrations gave a yellowish-gray ppt. weighing 21.9 g. Theoretical yield - 24.9 g.

B) 20 g. of tetrabromophthalic anhydride in excess conc. ammonium hydroxide were heated in a 500 ml. round bottom flask on the waterbath until the anhydride dissolved. The solution was evaporated almost to dryness and then heated over an oil bath to 300° with an air condenser attached. A yellow solid resulted. After treatment with water and acetic acid, as above, the mixture was filtered. Yellow crystals resulted which were washed and dried. Yield was 18.1 g. Theoretical yield - 19.9 g.

III PREPARATION OF TETRABROMOPHTHRANILIC ACID FROM TETRABROMOPHTHALIMIDE.

Method: The method of Lesser and Weiss was used (1) with modifications. Sodium Hydroxide was used rather than KOH, and commercial 5% "Chlorox" (NaOCl) was used rather than passing chlorine into the alkaline solution.



To 25 g. of crude tetrabromophthalimide in a 500 ml. beaker, 15.9 g. of NaOH and 55.5 ml. of water were added. The beaker was cooled in an ice bath to 3° and after the NaOH had dissolved, 79.3 g. of 5% NaOCl solution was added. After half an hour the mixture was heated in the beaker on a water bath to 80° for 30 minutes. An orange colored solution resulted which gave orange-red crystals on cooling. The mixture was neutralized with hydrochloric acid and treated with excess glacial acetic acid. The orange crystals were filtered and washed, with acetic acid and water. Yield: 24.1 g. Theoretical: 24.2 g.

IV ANALYSIS OF PRODUCTS OBTAINED IN EXPERIMENTS.

A Analysis of Tetrabromophthalic Acid.

Crude tetrabromophthalic acid obtained from the original tetrabromophthalic anhydride was boiled with acetic acid, a little HCl, and 50% water. The compound

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(1) Berichte: 46 3942

slowly hydrolyzes and goes into solution. The solution was filtered and water was added to the filtrate. On cooling white crystals were precipitated. If the acid is dissolved in glacial acetic acid and heated it changes over to the anhydride. The white crystals were filtered, and then they were washed with acetic acid and water. Some crude tetrabromophthalic acid already prepared by our advisor, Dr. L. H. Farinholt, was recrystallized in the same manner. Small samples of each were dried in an oven at 100° for Parr bomb analyses.

1. Parr bomb on recrystallized tetrabromophthalic acid prepared by in experiment I holt

Wt. of sample	0.3040 g.
Silver nitrate added	43.52 ml. - 0.100 N
KSCN titration	37.50 ml. - 0.050 N
Found	65% bromine
Theoretical	66% bromine

2. Parr bomb on recrystallized tetrabromophthalic acid prepared by Dr. L. H. Farinholt.

Wt. of sample	0.3030 g.
Silver nitrate added	40.04 ml. - 0.100 N
KSCN titration	32.04 ml. - 0.050 N
Found	63.5%
Theoretical	66%

The discrepancies in these Parr bomb analyses were laid to traces of the mono-sodium salt, for in neither case was the crude acid steamed in solution as proposed by Pratt and Shupp (1)

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(1) JACS 40 1416

B Analysis of Prepared Tetrabromoanthranilic Acid

The impure tetrabromoanthranilic acid obtained in experiment III (21 g.) was pulverized and heated with glacial acetic acid to boiling. Most of the substance seemed to go into solution. The mixture was filtered and the filtrate heated with carbon black to boiling, refiltered, and diluted with water. A very small amount of white crystals resulted. The precipitates above were again treated with glacial acetic acid, heated to boiling, cooled, filtered, and diluted. A much smaller amount of precipitate was obtained, but the procedure was carried out once more. The total precipitate on drying weighed 2 g. It melted at 196°. Recorded M. P. 204-5.

The exceptionally small amount of tetrabromo-anthranilic acid appearing was of great interest, although it was not a particularly desireable result. Since only slightly more than one g. of the substance was on hand, another preparation was necessary.

V REPREPARATION OF TETRABROMOANTHRANILIC ACID FROM REPURIFIED TETRABROMOPHTHALIC ACID.

20 g. of analyzed tetrabromophthalic acid was dissolved in excess cond. ammonium hydroxide. The solution was heated on an oil bath until the water had evaporated from the flask, and the flask was then fitted with an air condenser and heated solwly to 300°. The resulting yellow solid was treated with water, filtered and washed with water. The ppt. was dried over a steam bath and weighed 17.9 g. Theoretical 18.9

This imide, 25 g. of NaOH and 100 ml. of water were shaken in a beaker until the NaOH dissolved. The imide did not seem soluble even on warming to 35°. The solution was cooled to 4° in an ice bath and NaOCl added in excess. No reaction seemed to occur, so the beaker was removed from the ice bath after half an hour and warmed gradually. At 60° a reddish color appeared, and the yellow imide crystals became darker. The mixture was heated to 80° for two hours and taken to 100°. After cooling, the mixture was filtered giving a dark red filtrate and a pink ppt. The precipitate was washed with water and heated on a steam bath. On drying, the pink crystals gave no melting point at 300° and were insoluble in conc. HaOH, dil. NaOH, conc. HCl, and glacial acetic acid. However, conc. NaOH acquired a red color on boiling with this substance and gave a yellow ppt. on neutralization and acidification with hydrochloric acid. This red solution gave no ppt. on acidification with acetic acid. When the HCl ppt. was treated with acetic acid it readily dissolved.

The filtrate was neutralized with hydrochloric acid evolving a good deal of gas in a foam. Acetic acid was added in excess and the solution heated to boiling. During heating a precipitate formed which dissolved on stirring. After cooling, the solution was acidified with HCl until profuse orange-yellow crystals filled the beaker. These crystals were filtered

and dried, weighing 2 g. A portion was recrystallized by dissolving in a large volume of glacial acetic acid with heating and precipitating by evaporation and cooling. These melted at approximately 200°. Recorded M.P. - 204°.

These results were an indication of the absence of the basicity usually found with an amino group, for the tetrabromoanthranilic acid is insoluble in acid. Acetic acid probably shows a solvent effect here.

It was becoming obvious that this method of preparation was not leading to yields of tetrabromoanthranilic acid expected, so new methods of preparation were attempted. The first was a modification of the method previously used, and the second was derived from the method of preparation of tetrachloroanthranilic acid by Villiger and Blangey (1).

VI NEW PREPARATIONS OF TETRABROMOANTHRANILIC ACID.

A Since it has been shown that tetrachloroanthranilic acid is converted quantitatively to tetrachloroaniline on heating (1), the previous method of preparation of tetrabromoanthranilic acid was carried out without allowing the temperature to rise above 60°. 25 g. of analyzed tetrabromophthalic acid was dissolved in ammonia, heated to 250° over an oil bath, and the imide obtained as before (2). The imide was dissolved

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(1) Berichte 42 3549-52 (1909)
(2) This thesis

in cold 12 Molar NaOH solution over a period of three hours, and the solution was filtered. The clear filtrate was cooled to zero degrees and excess NaOCl added with stirring. The temp. was kept below 5° for three hours, and the beaker containing the solution was then removed and allowed to warm to room temperature. The solution was stirred at room temp. for two hours, then cooled to about 5° in an ice bath and neutralized with HCl. On acidification, white crystals resulted which were filtered and dried over a water bath at 65-70°. These crystals turned slightly pink around the edge of the evaporating dish where heat was greatest, and the entire mass became darker to a tan-white color. A portion of these crystals recrystallized from acetic acid melted at 202°.

B Villiger and Blangey in preparation of tetrachloroanthranilic acid used a slightly different method in which the acid amide is isolated. 25 g. of tetrabromophthalic anhydride was dissolved in 20% ammonia with stirring. This solution was poured into a mixture of ice and dilute sulfuric acid, and white flakes were precipitated. These were filtered and washed with water immediately and were then dissolved in NaOH and cooled to zero degrees. NaOCl was added in excess and the mixture allowed to warm to room temperature and stand for three hours. The solution was then heated to 60° with sodium bisulfite to remove excess NaOCl. Hydrochloric acid was added to precipitate the anthranilic acid and white crystals resulted.

These were filtered and dissolved in hot 12% sodium carbonate solution for purification. Saturated NaCl solution was added while hot to precipitate the acid on cooling. This precipitate was dissolved in a hot very slightly alkaline solution of NaOH and the acid precipitated with HCl added very slowly. The ppt. was washed thoroughly and dried in a dessicator.

Melting pt. - 202° Theoretical - 204°

C For further study of tetrabromoanthranilic acid and to check the first part of this experiment, a large batch of tetrabromoanthranilic acid was prepared with the following results.

50 g. of tetrabromophthalic acid was heated with 75 ml. of 15 Molar ammonia and 75 ml. of water and went into solution. This solution was dried by evaporation and placed in a round bottom flask fitted with an air condenser and heated in an oil bath to 300°. After cooling, the yellow imide was washed from the condenser into the flask with water, shaken thoroughly and treated with NaOH in the cold until the solution was about 8 molar. This was allowed to stand for 24 hours and was then heated slowly to 60° for 2 hours. There was little or no sign of the imide dissolving, but a small amount of ammonia was evolved (litmus turned blue) with the original addition of NaOH. The mixture was cooled to 5° and NaOCl added liberating a large amount of gas with only a faint odor of chlorine and no test for oxygen with glowing splints. This mixture was

taken to 60° for 2 hours.

The NaOCl mixture was allowed to cool and stand for 2 days and was then filtered. The filtrate was made acid with HCl, and a yellowish-white ppt. identical in color with the precipitate from the NaOCl solution resulted. This was dried over a boiling water bath and allowed to stand.

D Experimental recrystallization of crudes from tetrabromoanthranilic acid preparations.

About 100 g. of crude insoluble substance from various preparations of anthranilic acid was heated with glacial acetic acid and filtered. The precipitate was treated with NaOH and gave an orange colored solution above a large mass of insoluble substance. This alkaline solution was filtered and its filtrate acidified with HCl giving white crystals.

The original acetic acid filtrate was orange-red in color and on dilution and evaporation gave orange-yellow crystals.

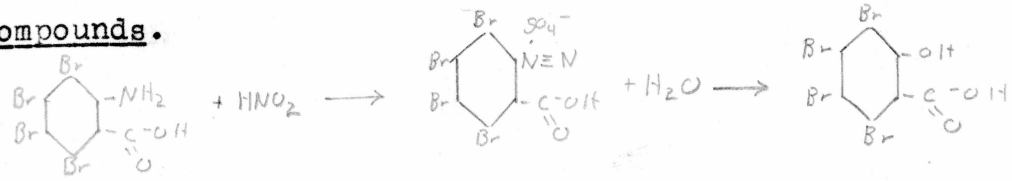
The large mass of red-pink precipitate from the alkaline solution was again treated with acetic acid and filtered. The results were the same as before on dilution and evaporation. The preceding procedure was carried out four times, but a large amount of a pink residue was insoluble.

On drying, the acid precipitates after filtration about 28 g. of recrystallized tetrabromoanthranilic acid was obtained.

The substance insoluble in NaOH and acetic acid was also found to be insoluble when boiled with water, but it turns a definite orange. On boiling with very dilute HCl soln. the pink residue is turned white.

VII AN ATTEMPT TO PREPARE TETRABROMOSALICYLIC ACID FROM TETRABROMOANTHRANILIC ACID.

In order to study the action of the $-NH_2$ group in tetrabromoanthranilic acid, diazotization was carried out as suggested by Saunders in his Aromatic Diazo Compounds.



Two attempts at diazotization were made with the following experimental results:

A 5 g. of recrystallized tetrabromoanthranilic acid, 0.7 g. of $NaNO_2$, and 0.4 g. of NaOH were dissolved in about 100 ml. of water and diluted to 250 ml. An orange red color resulted. The mixture was cooled to zero degrees and 7 ml. of conc. sulfuric acid in water were added slowly, the temp. not going above 7^o at any time. A yellow ppt. formed. On warming, this ppt. disappeared and gas was evolved. After most of the gas had been evolved, the solution was allowed to cool to room temperature, white crystals resulting. These were filtered and gave less than 1 g. of precipitate.

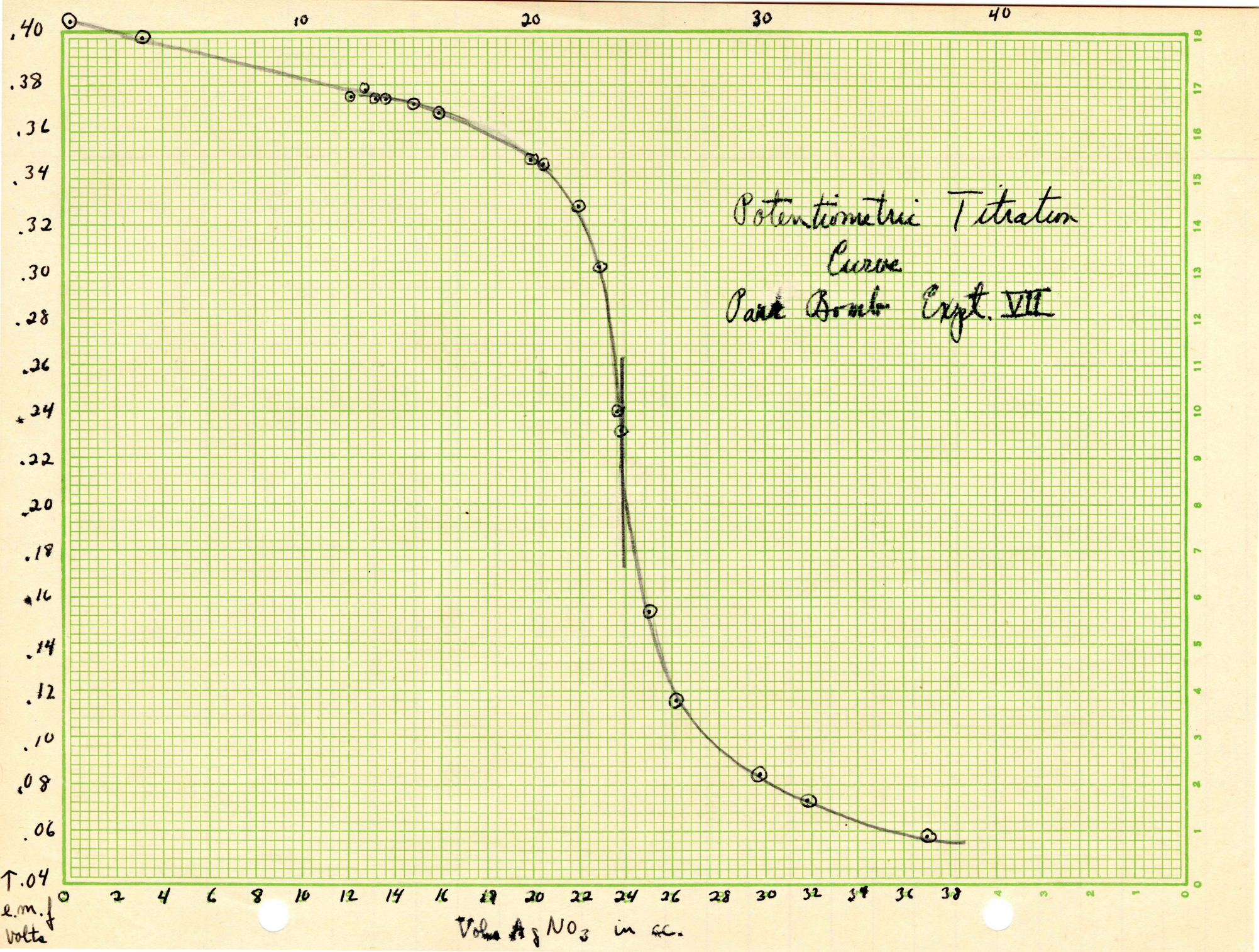
B Repreparation of Tetrabromosalicylic Acid.

12.5 g. of tetrabromoanthranilic acid, 2.5 g. of

NaOH and 3 g. of $NaNO_2$ were dissolved in about 200 ml. of water. This solution was cooled to zero and sulfuric acid added. Brown fumes came off. The mixture was allowed to warm to room temperature and was heated to 60°. A small amount of brown-red crystals were precipitated and filtered. These were dissolved in NaOH, filtered and acidified. This ppt. was filtered, treated with ether and then shaken with NaOH. The mixture was filtered and the ether portion extracted. The NaOH portion was acidfied giving brown red crystals. These crystals were dried in a dessicator and analyzed for bromine.

Parr bomb analysis for bromine - potentiometric titration (sample curve on following page)

Wt. of sample		0.3026 g.
Ml. of $AgNO_3$		24
Percent bromine found		63.7%
Theoretical:	Tetrabromosalicylic acid	70.6%
	Tribromosalicylic acid	63.9%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Volts
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
Vols $AgNO_3$ in cc.
10 20 30 40

SUMMARY OF EXPERIMENTS ON TETRABROMOANTHRANILIC ACID

Several positive results have been obtained in the work on tetrabromoanthranilic acid. It has been shown that the yield of the tetrabromoanthranilic acid can be greatly improved by working at temperatures below sixty degrees. A by-product which becomes the main product of the reaction has been effectively removed by this method. It has also been shown that the diazotization of tetrabromoanthranilic acid leads to unexpected results in the formation of a compound corresponding closely to tribromosalicylic acid. The basic effect of the organic amino group in tetrabromoanthranilic acid has been found to be negligible as far as chemical reactions are concerned, and the action of the carboxyl group as an acid is hindered.

The tendency for removal of the carboxy group in tetrabromoanthranilic acid on heating may be responsible for increase in yields of the acid form the imide at low temperatures. The removal of one bromine atom in diazotization has also been postulated (1). The negativity of the bromine atoms in tetrabromoanthranilic acid undoubtedly has a great effect on the usually positive amino group, and stearic hindrance may also enter in. The formation of the many colored complexes found throughout the work presents many interesting problems, but time did not allow a sufficient consideration of this subject to postulate any theories of mechanism.

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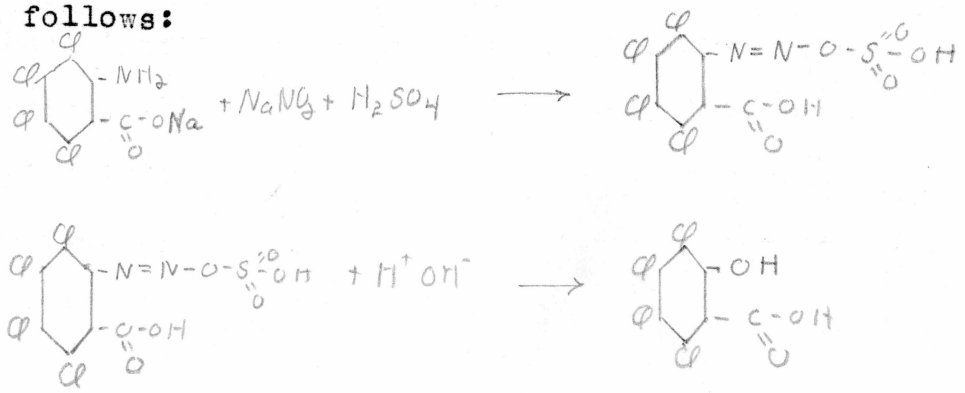
(1) Saunders: Aromatic Diazo Compounds p 55

REACTIONS OF TETRACHLOROANTHRANILIC ACID

After working on the tetrabromination of phthallic anhydride, and the preparation from that of tetrabromophthallic acid in conjunction with R. H. Adams, I had as the object of my work the studying of the properties and reactions of tetrachloroanthranilic acid, particularily the diazotization of this acid. It developed that the attempts at diazotization were so time consuming that this was the only reaction studied.

The possibility of diazotizing and subsequently hydrolizing off the diazonium group and replacement by hydroxyl, thus producing tetrachlorosalicylic acid was suggested by my advisor in this work, Dr. L. H. Farinholt. This reaction was of particular interest as tetrachlorosalicylic acid had not been prepared before. The work of Farinholt, Stuart, and Twiss[1] showed that salicylic acid could not be directly chlorinated beyond the trichloro derivative. However, it was successfully prepared by the diazotization and subsequent hydrolysis of tetrachloroanthranilic acid. The mechanism of the reaction is as follows:



(1) J.A.C.S. 62 1237 (1940)

Some difficulty was anticipated in the diazotization of tetrachloroanthranilic acid, for it is known that the ease of diazotization of an amine is lessened if there is a carboxyl group in the nucleus, and further that the addition of halogen also has a retarding effect on this reaction.

After consulting the literature for the best method of diazotization, the "inverted method" described by Saunders (see monograph, V-A) was decided to be the most feasible. However, this method was somewhat modified to meet the needs of the occasion. It was found that the sodium salt of tetrachloroanthranilic acid was insoluble in the small amount of water indicated, so a much larger volume of water was necessary. In view of this fact, the sulfuric acid was poured into the basic solution of the amino acid, instead of the opposite way as described.

As raw material for my experiments, I used some impure tetrachloroanthranilic acid furnished by Dr. Farinholt. I was not able to find its history.

All analyses were done by analysing for halogen content using a Parr bomb. However, in the Volhard titration for halogen, a great deal of difficulty was found in determining the end point, so the titration was done by directly adding silver nitrate, using a potentiometric method for determining the end point. Titration was done against a silver electrode, and as a reference electrode, since I was titrating chloride,

I did not use a calomel half cell, but rather one of mercuric sulfate, with .25 N sodium sulfate in the salt bridge. Extremely good curves were obtained using this method, although the precaution must be taken to stir vigorously in the neighborhood of the silver electrode, so that the silver chloride will not deposit on it. This method furnished an accurate and very rapid method of titrating, a complete Parr bomb analysis taking only an hour.

I am indebted to Mr. J. R. Taylor for helping me work out the details of this titration.

EXPERIMENTAL

I PURIFICATION OF TETRACHLOROANTHRANILIC ACID

The crude tetrachloroanthranilic acid of Dr. Farinholt was found to be soluble in glacial acetic acid, so it was purified from this. 10 g. of the impure acid was dissolved in glacial acetic acid, and the impurities filtered off. Then the solution was diluted with water, on which the anthranilic acid came down as a yellow precipitate. It was dried and determined pure by melting point experiment.

Observed melting point	Recorded melting point
182°	182°

II PURIFICATION OF TETRACHLOROANTHRANILIC ACID

An attempt to diazotize impure tetrachloroanthranilic acid was conducted on a small scale. As this was to be a test tube experiment, no record was kept of the amount of reagents used. The impure acid was added to a solution of sodium hydroxide, but it did not dissolve readily. Water was added to bring it to a clear solution, but the amount necessary was very great. (About 1 liter of water for 1 g. of acid.) Sodium nitrite was added and the solution cooled to 0°. Then it was acidified with sulfuric acid, a yellow solid coming down. This was heated over a steam bath, filtered, and dried over a steam bath. On taking its melting point it was found to be pure tetrachloroanthranilic acid, this having precipitated in the large volume of solution

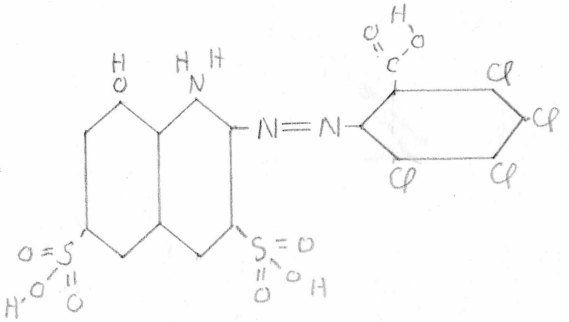
rather than the diazo reaction taking place. From then on, this method was used to purify the raw material.

Observed melting point	Recorded melting point
182°	182[3]

The following two test tube reactions were carried out to see whether tetrachloroanthranilic acid could be diazotized. I decided to carry out the diazo reaction and then coupld the product and determine whether or not anything happened.

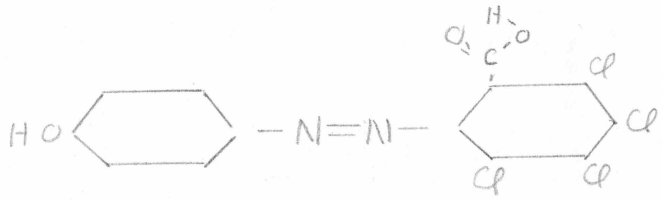
III DIAZOTIZATION AND COUPLING WITH H ACID.

About .5 g. of tetrachloroanthranilic acid was dissolved in 100 ml. of water. A clear solution was not obtained, but in view of (II), it was thought unwise to use any more water. A small amount of sodium nitrite was added, the solution cooled to 0° and acidified with sulfuric acid. A brownish-pink insoluble precipitate came down. To this was added an aqueous solution of H acid. After a short time, the precipitate dissolved, and a dark red-brown solution was the result. From this I concluded that diazotization and coupling had occurred, with the probable formation of the following dye:



IV DIAZOTIZATION AND COUPLING WITH PHENOL

The same procedure as in (III) was carried out, with the exception that phenol was used instead of H acid. The result in this case was a yellow solution, which acted as an indicator, being yellow in acidic solution and brown in basic solution. The following is the probable product.



The products in both the above reactions were quite soluble, and there being an extremely small amount of them, contaminated with a large amount of sodium sulfate, no attempt was made to isolate and purify them. However, the important conclusion was inferred that we would be able to diazotize tetrachloroanthranilic acid.

All further experiments were devoted to the attempt to make tetrachlorosalicylic acid.

V ATTEMPTED PREPARATION OF TETRACHLOROSALICYLIC ACID

7.4 g. of tetrachloroanthranilic acid and 1.38 g. of sodium nitrite were added to a solution of .79 g. of sodium hydroxide in 50 ml. of water. The volume of the solution was made up to 800 ml. before the anthranilic acid would dissolve. This solution was

cooled to 0°. Then, with constant stirring, 3.38 ml. of concentrated sulfuric acid in 20 ml. of water was quickly added, the volume of the solution being so great that the temperature did not rise. A white precipitate immediately formed which turned pink in about 30 seconds.

This was allowed to stand for an hour, during which time it gradually turned brown. It was then heated to boiling and allowed to cool. A brown, gummy precipitate formed in lumps, which were filtered off. This gum was purified by dissolving in glacial acetic acid, filtering, and reprecipitating with water. The brown crystals resulting were dried at 55° for two days. This product was analysed for chlorine © ntent by use of a Parr bomb, the results being as follows:

Calculated for tetra-chlorosalicylic acid	Found
51.5%	58.9%

This high percent of chlorine was quite astonishing, and in looking for the reason I came across the following possible explanation:

According to Villiger and Blangey[1] tetrachloro-anthranilic acid, when heated above its melting point is converted quantitatively into 2,3,4,5-tetrachloro-aniline. Thus, I assume that in heating my product, the carboxyl group split off, leaving 2,3,4,5-tetra-

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(1) Ber. 42 3549-52 (1909)

chlorophenol. The percent of chlorine in tetrachloro phenol, 60.7%, checked with my results. On taking its melting point, part of it decomposed a little below 100°, to which temperature it had been heated during the hydrolysis, and the rest melted at about 120°, the phenol melting at 110°.

In light of this experience, all subsequent work was done at a temperature below 60°.

VI ESTABLISHMENT OF METHOD OF PURIFICATION

The diazotization was carried out exactly as in the preceding experiment, but in the hydrolysis, the solution was heated only to 60°. This was a decided improvement, for instead of the gummy mass forming, a flocculent mass of fine brown crystals came down. These were purified by dissolving in 6N sodium hydroxide, filtering, and reprecipitating with 6N sulfuric acid. However, on drying, the material did not look at all pure. Therefore this material was used to develop a method of purification. Glacial acetic acid and water did not seem to do so well, so the following method was developed:

The solid was dissolved in 6N sodium hydroxide, and diluted to complete solution. This solution was a deep blood red. Part of the solid did not dissolve, so this was filtered off, and the clear solution was acidified precipitating flocculent brown crystals. This wet solid was dissolved in ethyl ether, and the inorganic salts, being insoluble, were filtered off. The

ethereal solution was again deep blood red. This ethereal solution was shaken several times with dilute sodium hydroxide, which formed the sodium salt of the acid, insoluble in ether, but soluble in the aqueous solution. These aqueous extracts were separated by means of a separatory funnel and combined. Then they were placed in a vacuum oven to boil off the small amount of ether in the solution. The clear red solution was then acidified with sulfuric acid, pale brown crystals coming down. These crystals were dried at room temperature, but there was so little material that nothing further was done with it.

At this time Adams called to my attention that if wet, freshly reprecipitated anthranilic acid were used, instead of the dried material which I had been using, it would dissolve in a much smaller volume of water. He had discovered this fact while working with his tetrabromoanthranilic acid.

VII PREPARATION OF TETRACHLOROSALICYLIC ACID.

8 g. of impure tetrachloroanthranilic acid were dissolved in sodium hydroxide, filtered, and then precipitated with sulfuric acid and washed. This wet paste was placed in a beaker and neutralized with 6N sodium hydroxide. Then it was dissolved in 1 g. of sodium hydroxide in 200 ml. of water and 1.5 g. of sodium nitrite was added. The solution was cooled to 0° and, with constant stirring, 4 ml. of concentrated

sulfuric acid in 20 ml. of water was rapidly added. Immediately a thick pink precipitate came down. This was allowed to stand in the ice bath for ten minutes, during which time the precipitate turned brown. It was then taken out of the ice bath and allowed to stand at room temperature for two hours. Placed on a water bath, it was heated to 40°, and with stirring, allowed to cool to room temperature. The reddish-brown precipitate was then filtered and washed. The precipitate was dissolved in sodium hydroxide, giving the deep red coloration, filtered, the filtrate acidified with sulfuric acid, and the brown crystals filtered off and washed. This wet mass was dissolved in ethyl ether, the insoluble residue being filtered off. The clear red solution was extracted with several portions of sodium hydroxide. This aqueous solution was placed in a vacuum to remove the ether, and acidified with sulfuric acid, a pale tan precipitate coming down. The precipitate was filtered, washed with 500 ml. of water, and dried in a dessicator. Yeild:- about .8 g.
A Parr bomb analysis was run, the titration being carried out potentiometrically.

Calculated for tetrachlorosalicylic acid	Found
51.5%	52.35%

A melting point of the material was tried, but it decomposed at about 145°. This result proves conclusively the preparation of tetrachlorosalicylic

acid. The decomposition on heating agrees with the behavior of tetrabromosalicylic acid.

VIII REPREPARATION OF TETRACHLOROSALICYLIC ACID.

Another diazotization and hydrolysis of anthranilic acid was carried out to reproduce the preparation of tetrachlorosalicylic acid. The procedure was carried out in every detail like the one just preceding, with the exception that at no time was the temperature allwed to go over 25°. The Parr bomb result was 53.7% chlorine, which is not as close as that in the previous experiment, but still close enough, in view of the fact that any other possible compound produced would not have a chlorine content anywhere near this figure.

SUMMARY

By means of the diazotization of tetrachloroanthranilic acid, and the hydrolysis of its diazo group, leading to the introduction of a hydroxyl group, tetrachlorosalicylic acid has finally been prepared. However, the yield was extremely poor, and some work must be done to improve it. The acid seemed somewhat soluble in water. The yield yould undoubtedly be improved if some means were found to carry out diazotization in a much smaller volume of solution, and a better means of purification were found.

An interesting subject for study would be the formation of the red compound when this acid is in solution.

CONCLUSION

Since our work parallelled only in the diazotization we can hardly draw any general conclusions from a comparison of the two. However, there is one striking point. In the diazotization of tetrachloroanthranilic acid, the product is tetrachlorosalicylic acid, while in the diazotization of tetrabromoanthranilic acid, the product is apparently tribromosalicylic acid. The bromine atoms are less strongly held to the aromatic nucleus, which seems strange, since they are less negative than chlorine atoms, which we should expect to come off more readily, if the rule of "like charges repel" holds good.

Another difference noted between the two compounds is that the tetrachlorodiazonium compound was quite insoluble, wheras the tetrabromodiazonium salt dissolved on warming! Perhaps this can be explained on the grounds that one of the bromine atoms split off, leaving a compound which was more soluble.

The study of the peculiarities of these compounds has proven fascinating to both of us. It has raised some large and interesting questions that we are unable to answer. It is hoped that in the near future the answers to them will be found.