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A review of the bromination of intermediate compounds in the preparation of 4 - bromo - 2 - sulphimide benzoic acid and the preparation of 4 - iodo - 2 - sulphimide benzoic acid.

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A REVIEW OF THE BROMINATION OF INTERMEDIATE COMPOUNDS IN THE PREPARATION OF 4 - BROMO - 2 - SULPHIMIDE BENZOIC ACID AND THE PREPARATION OF 4 - IODO - 2 - SULPHIMIDE BENZOIC ACID.

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A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL OF THE UNIVERSITY OF LOUISVILLE IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF ARTS

DEPARTMENT OF CHEMISTRY

by

Robert E. Johnson, Jr.

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1. Introduction

Since the objective of the research presented here is the selection of the best point in the preparation of halogen derivatives of saccharin for introducing the halogen into the nucleus and the preparation of 4 - iodo - 2 - sulphimide benzoic acid, it might be best to start with a short review of the history and general properties of saccharin, including some of its halogen derivatives.

The anhydride of orthosulphamide - benzoic acid, more commonly called saccharin, was first prepared in 1878, in the laboratories of Remsen at Johns Hopkins University. It is a crystalline powder, nearly odorless, having an intensely sweet taste even in dilute solutions. 1 gram of saccharin should dissolve in 290 mls. of water and 31 mls. of alcohol at 25 C; also in about 25 mls. of boiling water. The aqueous solution of saccharin is acid to litmus paper and if made of strength of 1 part in 10,000 parts, should have a distinctly sweet taste comparable with that of an aqueous solution of sugar, 1 part in 20. Saccharin melts when heated to a temperature between 219 C and 222 C. It is easily soluble with evolution of carbon dioxide in a solution of sodium bicarbonate, the sodium salt of saccharin being formed. This is the form known as soluble saccharin and is the compound most commonly found on the market. (1)

The principal use of saccharin has been as a sweetening agent. It is used as a substitute for sugar in the case of diabetics where it is essential to curtail the intake of sugar.

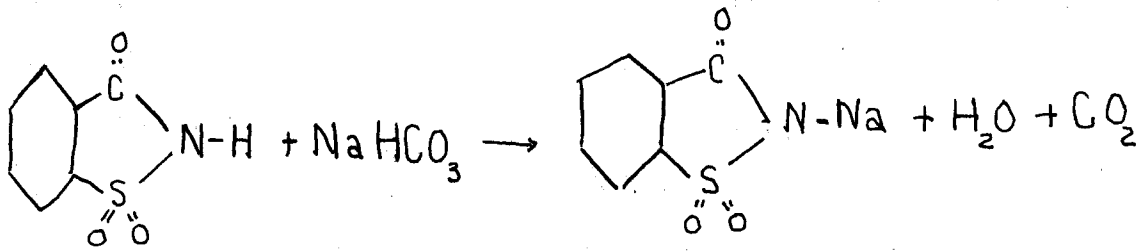
Many objections have been raised to its use, some investigators claiming that it has a toxic effect when used over long periods of time. It is reported that saccharin acting in the mouth decreases appetite and gastric secretion, acting in the stomach it increases gastric secretion and decreases peptic digestion, acting in the small intestine it decreases absorption, acting on the erythrocytes it decreases hemolysis. Saccharin in the blood, in proportion to its concentration, passes into the lymph, cerebro - spinal fluid, saliva, tears and mammary secretion. The continuous and general use of saccharin is not regarded as harmless, and such use of it is not thought advisable. (2).

In Report No. 94 of the Referee Board of Consulting Scientific Experts of the U. S. Department of Agriculture the conclusion was reached that relatively large doses of saccharin (over 0.3 gram, and especially over 1 gram daily), if continued for considerable periods of time (months), are liable to induce disturbances of digestion. On the other hand, small doses of saccharin (0.3 grams or less) may be taken daily during the long periods of time (months) by normal adults without any detriment to health ascertainably by available methods of study. No evidence was attainable that the addition of saccharin to the food altered the quality or strength of the food. On the other hand, it is obvious that if saccharin be added to the food with intention of replacing glucose or some other foodstuffs, this must be regarded as a substitution involving the reduction of the food value of the sweetened product, and hence as a reduction in its quality. (3)

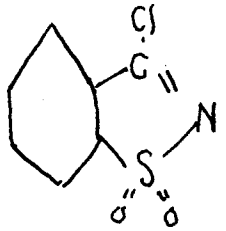
This would seem to indicate that saccharin should not be used as a sweetening agent except where it is essential to decrease the amount of glucose or other sugars consumed in the daily diet.

Edward Bonjean, in a study of the influence of saccharin solutions on the dog and man, reports that below a concentration of one-tenth percent saccharin is practically without effect when made up with tablets commercially supplied (60 parts saccharin, 40 parts $NaHCO_3$). The acidity of saccharin alone is likely to affect these processes when in smaller doses. Failure to take into account this acid function is responsible for disagreement in the literature. Saccharin is considered harmless in doses permitted by taste. (4) It is also reported that saccharin is eliminated from the body unchanged. (5)

Many derivatives have been prepared from saccharin, although they consist principally of the metallic salts such as the sodium salt formed by the action of sodium bicarbonate which has already been mentioned.

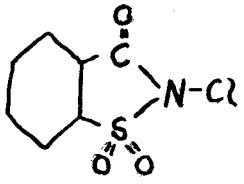


It has been found that phosphorous pentachloride converts saccharin into pseudosaccharin - chloride.



This compound melting at 149°C. (6)

When chlorine is passed into a potash solution of saccharin the products formed depend on the quantity of alkali present. If an equivalent amount of saccharin is used, the sparingly soluble cholride,



m. p. 152° , separates. This substance is not sweet, is similar in taste to a hypochlorite and in odor to chloral. If excess of alkali is present, the solution remains clear, and if an acid is added a precipitate is formed which may be o - sulphamchlor - amidobenzoic acid or o - sulphon - di - chloramido benzoic acid, or a mixture of both, depending on the quantity of chlorine used. (7)

William Davies, of the University of Oxford, prepared 6 - chlore - 2 - benzoic sulphimide. He converted 6 - chlore - o - toluenesulfonyl chloride to the amide. The amide was then oxidized in an alkaline solution by potassium permanganate to form "Chlorosaccharin." It was obtained in small shiny plates melting at 210°-2°C. and was about half as sweet as saccharin, but with an astringent taste, except in very great dilution. (8)

Remsen and Bayley prepared 4 - brome - 2 - sulfimide benzoic acid by heating 4 - brome - 2 - sulphamide toluene with a solution of potassium permanganate. They obtained long needle-like crystals melting at 217° C. and subliming at 200° C. It was easily soluble in

alcohol and hot water, but insoluble in hydrochloric acid. The taste at first was very sweet and then very bitter. (9)

4 - brome - 2 - sulphimide benzoic acid has also been prepared by treating 4 - brome - 2 - sulphamide benzonitril with sodium hydroxide. (10)

11. Objective.

As a basis for the preparation of the iodine derivative of saccharin it was decided to run a series of brominations to determine the best point in the procedure for the introduction of the halogen in the nucleus.

Since the preparation of saccharin by the method technically employed can be resolved into the following four stages:

(1) The Preparation and Purification of Toluene - ortho - sulphonic acid,

(2) Preparation and Purification of Toluene - ortho - sulphonchloride,

(3) Preparation and Purification of Toluene - ortho - sulphonamide,

(4) Oxidation of Toluene - ortho - sulphonamide to Saccharin, (11) it was thought advisable to try brominating at each stage except, of course, stage (4).

In addition, "bromosaccharin" (4 - bromo - 2 - sulphimide benzoic acid) was prepared from 4 - bromo toluene by using a modification of the method referred to above for the manufacture of saccharin. This was prepared to determine the influence of the bromine atom in the nucleus on the various stages in the preparation.

III. Experimental

A. Preparation of "Bromosaccharin".

The Preparation of Bromosaccharin from p - bromotoluene:

"Bromosaccharin" was prepared from p - bromotoluene in four stages.

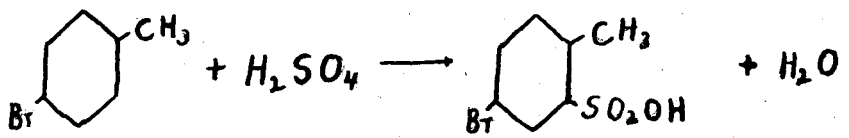
(1) The preparation and purification of 4 - bromotoluene - 2 - sulphonic acid.

(2) The preparation of 4 - bromotoluene - 2 - sulphonchloride.

(3) The preparation of 4 - bromotoluene - 2 - sulphonamide.

(4) The oxidation of 4 - bromotoluene - 2 - sulphonamide to 4 - bromo - 2 - sulphonamide benzoic acid with its acidification to form 4 - bromo - 2 - sulphonamide benzoic acid anhydride or p - bromo saccharin.

1. The preparation and purification of 4 - bromotoluene - - 2 - sulphonic acid:



The 4 - bromo - toluene - 2 - sulphonic acid was prepared by treating para - bromo - toluene with 30 percent fuming sulphuric acid at 0° to 5°C. This temperature was more favorable for the formation of the ortho compound. Six parts by weight (114 grams with sp.g. of 1.9) of 30 percent fuming sulphuric acid was employed to one part by weight (19 grams or 0.1 mol) of para - bromo - toluene, as this concentration was found to facilitate the reaction of the

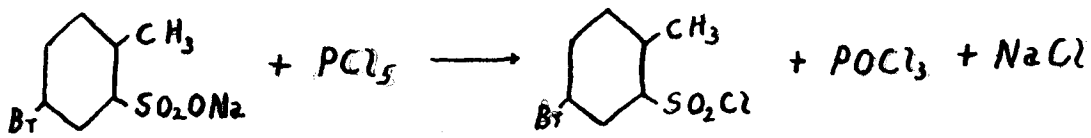
hydrocarbon with the acid.

The para-bromo - toluene was placed in a 500 ml. round bottomed flask equipped with a mechanical stirrer and placed in an ice bath. After the temperature of the para - bromo - toluene had been lowered to 0° C. to 5°C., the fuming sulphuric acid was added slowly, care being taken to prevent charring. The mixture was stirred constantly throughout the reaction, the temperature at no time being allowed to rise above 5°C. The reaction was permitted to run until a test portion dissolved completely in water. This was found to take fifteen hours.

The sulphonation mixture was then poured into 500 ml. of iced water and neutralised with 192.95 grams (1.12 mol) of barium hydroxide. The precipitated barium sulphate was then removed by filtration. The filtrate contained the barium salts of 4 - bromo - toluene - 2 - sulphonic acid and 4 - bromo - toluene - 3 - sulphonic acids. These isomeric acids were separated by the differences in solubility of their barium salts. The ortho salt is much less soluble than the meta salt, therefore, crystallising from the solution first. (12) The filtrate was placed in a large evaporating dish and heated on a waterbath. The solution was evaporated to 100 ml. and allowed to cool to permit crystallization. 29 grams (0.0428 moles) of the 4 - bromo - toluene - 2 - barium sulfonate salt was obtained. 500 ml. of water was added to this salt and it was then treated with 9.2 grams (0.068 moles) of sodium carbonate. The precipitated barium carbonate was removed by

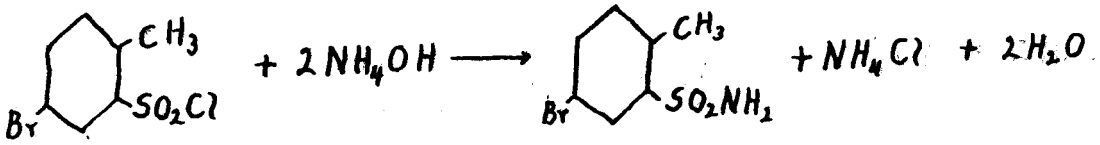
filtration and the filtrate evaporated to dryness to obtain the sodium salt. 23 grams (0.078 mol) of the sodium salt being obtained, giving a yield of 79 percent.

2. The preparation of 4 - bromo - toluene - 2 - sulphonchloride.



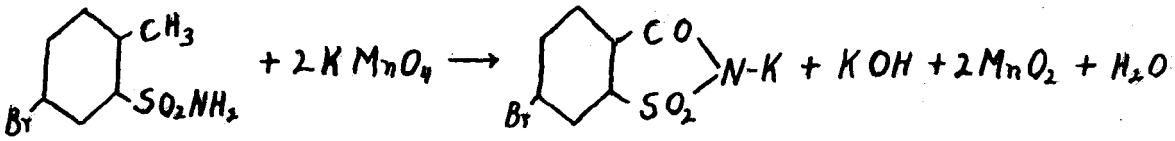
The 23 grams (0.078 moles) of dry 4 - bromo - toluene - - 2 - sodium sulphonate was treated with 30 grams of phosphorus pentachloride in a liter round bottomed flask under a hood. The phosphorus pentachloride was first ground to fineness in a morter and then slowly added to the 4 - bromo - toluene - 2 - sodium sulphate. Two silicate marbles were added to facilitate mixing and the flask shaken by hand with a rotating motion. The mixture was cooled during the reaction by the use of an ice bath, the temperature being kept below room temperature. After the completion of the reaction, which took about fifteen minutes, the mixture was allowed to reach room temperature and then one liter of iced water was added and the mixture shaken vigorously. The 4 - bromo - toluene - 2 - sulphonchloride formed a solid layer in the bottom of the flask. The wash water, containing the dissolved phosphorus oxychloride and sodium chloride, was then decanted, leaving the 4 - bromo - toluene - 2 - sulphonchloride in the flask. (13)

3. The preparation of 4 - brom - toluene - 2 - sulphonamide.



500 ml. of 27 percent ammonium hydroxide was then poured into the flask containing the 4 - brom - toluene - 2 - sulphonchloride. The mixture was cooled by surrounding the flask with ice. The reaction mixture was allowed to set over night. The reaction was then completed by heating gently for ten minutes. Upon cooling, the 4 - brom - toluene - 2 - sulphonamide formed crystallised and was removed by filtration. A yield of 13 grams (0.052 mol.) was obtained. The product was washed with cold water and then purified by crystallising from 500 ml. of cold water. A product was obtained having a m. p. of 164°C. which is close to that given (166° - 167°C.) in the literature for this compound. (14)

4. The oxidation of 4 - bromo - toluene - 2 - sulphonamide to 4 - bromo - 2 - sulphonamide benzoic acid anhydride.



The oxidation of the 4 - bromo - toluene - 2 - sulphonamide to 4 - bromo - 2 - sulphonamide benzoic anhydride was carried out by the use of potassium permanganate. 13 grams (0.052 mol) of 4 - bromo - toluene - 2 - sulphonamide was dissolved in 2.08 grams (0.052 mol) of sodium hydroxide and 133.38 grams (7.41 mol) of water contained in a 500 ml. round bottomed flask. The mixture was heated to 40° - 50° C. and 1.026 grams (0.0[illegible]8 mol) of potassium permanganate was added with stirring and in small quantities at a time. The addition of the permanganate was spread out over the whole period of eight hours required for the oxidation. The excess was destroyed by the addition of sodium hydrogen sulphite. The solution was then filtered from the precipitated manganese dioxide, which was washed with water until the addition of conc. hydrochloric acid to the filtrate no longer produced a precipitate of "bromosaccharin."

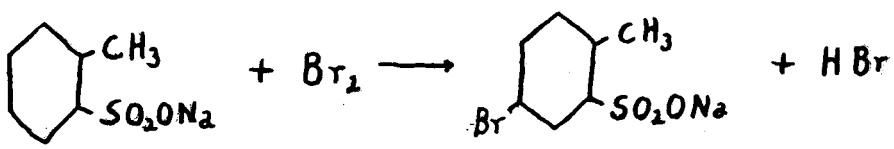
The combined filtrate and washings were cooled to 15° - 18°C. and made neutral, to methyl orange, with conc. hydrochloric acid. The excess of 4 - bromo - toluene - 2 - sulphonamide was thereby precipitated and filtered off. From the filtrate, "bromosaccharin"

was precipitated by the addition of a further quantity of conc. hydrochloric acid about 10 ml. being added. The "bromosaccharin" was filtered off, washed with cold water and dried at a temperature of 35°- 40°C. A yield of 10.5 grams (0.04 moles) being obtained with a m. p. of 219°C.

B. Brominations.

Since the main interest was in the comparative values, no attempt was made to gain the highest possible yields. In order to give the results a higher interpretative value, the same method of bromination was employed for each run. A modification of the method employed in Organic Syntheses for the preparation of p - bromphenol was used. (15)

1. Bromination of sodium - ortho - toluene - sulphonate.



42 grams (0.242 moles) of sodium - ortho - toluene - sulphonate was dissolved in 250 mls. of Carbon disulfide. The mixture was placed in a three hole 1000 ml. round bottomed flask equipped with a reflux condensor mercury - sealed mechanical stirrer, and separatory funnel. The top of the reflux condensor was connected with a calcium chloride tube leading to a funnel suspended in a beaker of a dilute solution of sodium hydroxide. The round bottomed flask was surrounded by an ice bath to keep the temperature below 5°C. The mechanical stirrer was started and about ten minutes allowed for the cooling of the solution to 5°C. In the meantime, 39 grams (0.243 moles) or 12.5 mls. of bromine dissolved in 125 mls. of carbon disulfide is placed in the separatory funnel. After the solution

had cooled sufficiently, the bromine - carbon disulfide mixture was slowly added, the addition being spread out over the entire period of six hours required for the reaction. The flask was covered with a heavy towel during the reaction to keep out any sunlight, since the absence of sunlight has a directing influence towards substitution in the ring. (16)

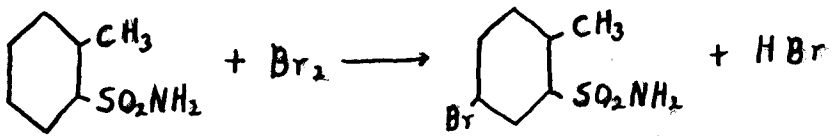
After completing the addition of the bromine, the reaction was permitted to run for 30 minutes to complete the reaction.

The apparatus was then set up for fractional distillation and distillate was collected in a closed container, and all the joints of the apparatus were carefully closed to insure no leakage of carbon disulfide fumes. The heat for the distillation was supplied by a water bath. The mixture was distilled to dryness, leaving the impure bromo - toluene - ortho - sulphonamide in the flask.

The product was then washed with cold water. Then 500 mls. of water was added and the solution evaporated to 100 mls. permitting the product to crystallize.

40.5 grams (0.162 moles) of bromo - toluene - ortho - sodium sulphonate was obtained representing a yield of 65 percent of the theoretical yield. The crystals were leaf shaped. This compares favorably with the data given in the literature for 4 - bromo - toluene - 2 - sodium sulphonate. (14)

2. Bromination of toluene - ortho - sulphonamide.

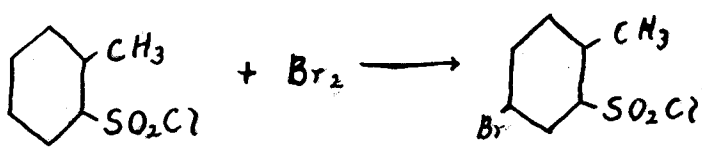


This bromination was carried out in exactly the same manner as the preceding one. 42 grams (0.242 moles) of toluene ortho sulphonamide was dissolved in 250 mls. of carbon disulfide and treated with 39 grams (0.243 moles) of bromine dissolved in 125 mls. of carbon disulfide.

The mixture, after completion of the distillation, was washed with cold water. This was dissolved in 500 mls. of water, the solution evaporated to 100 mls. and allowed to set over night for crystallization. 39 grams (0.156 moles) of the brome toluene - ortho-sulphonamide was obtained. The crystals were needle shaped, having a melting point between 164° - 165° C. This data checking with that given by Beilstein for 4 - brome - toluene - 2 - sulphonamide. (14)

The filtrate from a sodium fusion gave a positive test with silver nitrate, indicating the presence of bromine.

3. Bromination of toluene - ortho - sulphonchloride.



This bromination was carried out in the same manner as the preceding ones. 46.1 grams (0.242 mole) of toulene - ortho - sulphonchloride was dissolved in 250 mls. of carbon disulfide and treated with 39 grams (0.243 moles) of bromine dissolved in 125 mls. of carbon disulfide. The mixture, after completion of the distillation, was washed with cold water to remove all excess bromine and carbon disulfide. 40.5 grams (0.15 moles) of brome - toluene - 2 - sulphonchloride was obtained.

The filtrate from a sodium fusion imparted a brown color to carbon tetrachloride when treated with chlorine water, indicating the presence of bromine. The crystals were very fine, having a melting point of 35°- 36° C. This data checked with that given in the literature for 4 - brome - toluene - 2 - sulphonchloride. (17).

C. Preparation of 4 - iodo - 2 - sulphimide benzoic acid ("p - iodo - saccharin").

On the basis of the successful preparation of 4 - bromo - 2 - sulphimide benzoic acid from para bromo toluene, it was decided to follow the general outline of that procedure. The procedure was divided into the following steps.

1. Preparation and Purification of 4 - iodo - toluene.
2. Preparation and Purification of 4 - iodo - toluene - 2 - sulphonic acid.
3. Preparation and Purification of 4 - iodo - toluene - 2 - sulphonechloride.
4. Preparation and Purification of 4 - iodo - toluene - 2 - sulphonamide
5. Oxidation of 4 - iodo - toluene - 2 - sulphonamide to 4 - iodo - 2 - sulphimide - benzoic acid.

1. Preparation and Purification of 4 - iodo - toluene.

The replacement of hydrogen by iodine in the nucleus of aromatic compounds has always presented an interesting problem. The iodo - derivatives may be obtained by the action of iodine, iodic acid being added to oxidize the hydriodic acid which is formed. They are, however, usually obtained by boiling with KI the diazo - compounds obtained from the corresponding nitro - or amino compounds.

$$C_6H_5N{:}NCl + KI \longrightarrow C_6H_5I + KCl + N_2$$

(18)

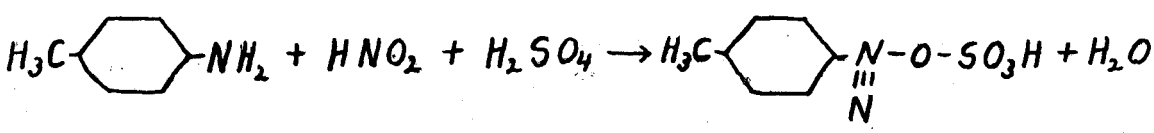
In the preparation of bromides and iodides, the sulphate of amine is commonly used:

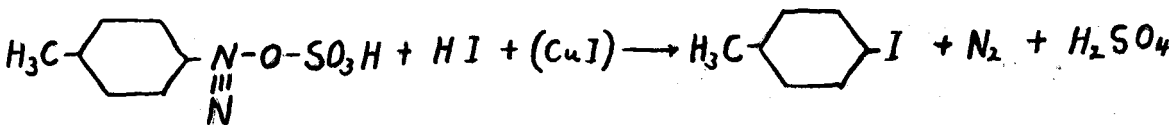
$$C_6H_5N_2 \cdot SO_4H + HI \longrightarrow C_6H_5I + N_2 + H_2SO_4$$

(19)

With this in mind, it was decided that it would be best to prepare p - iodo - toluene from p - toluidine by preparing its diazonium sulphate and then replacing the diazonium group with iodine.

The procedure followed is that given in Organic Syntheses (20) for the preparation of p - bromtoluene with the exception that KI was substituted for Na Br in order to obtain the iodine derivative. The equations for the reaction being as follows:





A mixture of 31.5 grams (0.125 moles) of crystallised $CuSO_4 \cdot 5H_2O$, 10.0 grams (0.155 Moles) of copper turnings, 9 1.315 (0.55 moles) of KI, 15 gr. (0.14 moles) of conc. H_2SO_4 (sp. g. 1.84), and 500 Ml. of H_2O was refluxed over a flame for two hours.

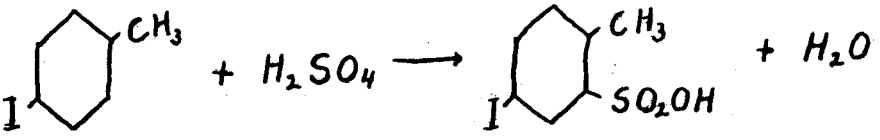
When the above hydriodic acid - cuprous iodide solution was ready for use, the diazonium solution was prepared. A solution of 53.5 grams (0.5 moles) of p - toluidine and 98.0 grams (0.92 moles) of conc. H_2SO_4 (sp. g. 1.84) in 500 ml. of H_2O was cooled below 20° C. and diazotized with a solution of 35 grams (0.5 moles) of Na NO_2 in 62.5 ml. of H_2O. This required about 25 minutes, with the temperature maintained between 15° and 20°C.

A 3 - l round bottomed flask containing the hydriodic acid - cuprous iodide solution was then arranged for steam distillation. After the copper solution was heated to boiling, the diazonium salt was added gradually from a separatory funnel and a vigorous current of steam passed through the mixture at the same time. This addition required about four hours. Only the small amounts (10 ml.) of the diazonium salt were placed in the separatory funnel at a time, the remainder being kept cool in an ice bath.

The aqueous distillate obtained was made alkaline with Na O H sol. and the p - iodotoluene separated from the H_2O layer with a separatory funnel. The crude product was purified by washing once with conc. H SO and then with water.

The Crystalline product was dried over night in a dessicator over $CaCl_2$. A yield of 69 grams (0.316 moles) wasobtained, representing a yield of 63.2% of the theoretical. The crystals were small, leaf-like, and had a light yellowish-brown color.

2. Preparation and Purification of 4 - iodo - toluene - 2 - sulphonic acid. (21)



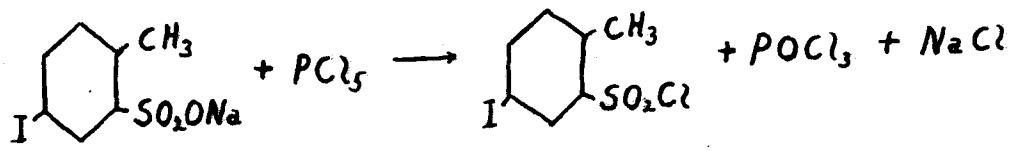
The 4 - iodo - 2 - sulphonic acid was prepared by treating para - iodo - toluene dissolved in chloroform with 30 percent fuming sulphuric acid dissolved in chloroform at 0° to 5° C. 114 grams (sp. g. of 1.9)fo 30 percent fuming sulphuric acid was employed to 69 grams (0.316 mole) of p - iodo toluene. The sulphuric acid was dissolved in 150 ml. of chloroform, while 200 ml. of chloroform was used to dissolve the p - iodo - toluene.

The para - iodo - toluene mixture was placed in a 1000 ml. 3 holed roundbottomed flask equipped with a mechanical stirrer and placed in an ice bath after the temperature of the mixture had been

lowered to 0° to 5° C., the fuming sulphuric acid mixture was slowly added by means of a separatory funnel, the outlet tube of the funnel being placed below the level of the mixture in the flask. The mixture was stirred constantly throughout the addition of the acid and continued throughout the reaction. The reaction was permitted to run for nine hours.

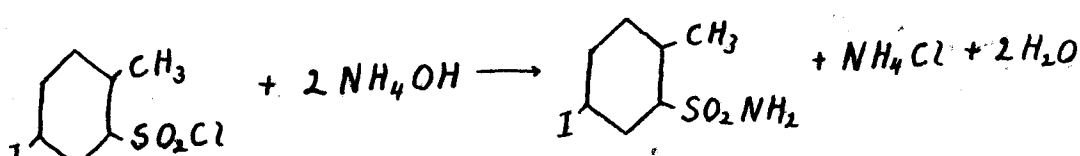
The sulphonation mixture was then pured into 750 ml. of iced water and stirred vigorously. The upper aqueous layer was then decanted and the remaining portion further separated by means of a separatory funnel. The aqueous portion was then neutralised with 340 grams (1.72 mole) of barium carbonate. The precipitated barium sulphate was then removed by filtration. The filtrate contained the barium salts of 4 - iodo - toluene - 2 - sulphonic acids and 4 - iodo - toluene - 3 - sulphonic acid. These isomers were separated by the differences in solubility of their barium salts. The ortho salt is much less soluble than the meta salt, therefore, crystallizing from the solution first.(21) The filtrate was placed in a large evaporating dish and heated on a waterbath. The solution was evaporated to 100 ml. and allowed to cool to permit crystallisation. 187.41 grams (0.256 mole) of the barium salt of 4 - iodo - toluene - 2 - sulphonic acid was obtained. 750 ml. of water was then added to this salt and it was then treated with 13.568 grams (0.128 mole) of sodium carbonate. The precipitated barium carbonate was removed by filtration and the filtrate evaporated to dryness. 82 gr. (0.256 mole) of the sodium being obtained, giving a yield of 83.3 percent.

3. Preparation and Purification of 4 - iodo - toluene - 2 - sulphonchloride. (13) (21)



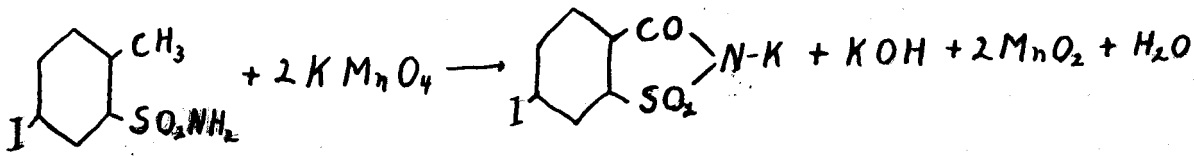
The 82 grams (0.256 moles) of dry 4 - iodo - toluene - 2 - sodium sulphonate was treated with 62.1 grams (0.298 mole) of phosphorous pentachloride in a 3 liter round bottomed flask under a hood. The phosphorous pentachloride was first ground finely in a morter and then slowly added to the 4 - iodo - toluene - 2 - sodium sulphonate. Two silicate marbles were added to facilitate mixing and the flask shaken by hand with a rotating motion. The mixture was cooled during the reaction by the use of an ice bath, the temperature being kept below room temperature. After the completion of the reaction, which took about thirty minutes, two liters of iced water was added and the mixture shaken vigorously and filtered. The residue consisted of the 4 - iodo - toluene - 2 - sulphonchloride, while the filtrate contained the phosphorus oxychloride and sodium chloride.

4. Preparation and Purification of 4 - iodo - toluene - 2 - sulphonamide. (13) (21)



1240 ml. of 27 percent ammonium hydroxide was then poured into a 3 liter flask containing the 4 - iodo - toluene - 2 - sulphonchloride. This mixture was allowed to set over night, the reaction being completed by boiling gently for about thirty minutes. Upon cooling, the 4 - iodo - toluene - 2 - sulphonamide crystallised and was removed by filtration. The product was purified by repeated washing with iced water. A yield of 26 grams (0.0876 mole) was obtained. The product had a m. p. of 179°- 180°C., which is close to that given (178°- 179°C) in the literature for this compound. (21)

5. Oxidation of 4 - iodo - toluene - 2 - sulphonamide to 4 - iodo - 2 - sulphimide - benzoic acid.



The oxidation of the 4 - iodo - toluene - 2 - sulphonamide to 4 - iodo - 2 - sulphimide benzoic acid was carried out by the use of potassium permanganate. 26 grams (0.0876 mole) of 4 - iodo - toluene - 2 - sulphonamide was dissolved in 3.51 grams (0.0876 mole) of sodium hydroxide and 230 ml. (12.8 moles) of water contained in a 1000 ml. 3 holed round bottomed flask. The mixture was heated to 40°- 50°C. by means of a water bath and 23.4 grams (0.148 mole) of potassium permanganate added with stirring and in small quantities at a time. The addition of the permanganate was spread out over the entire period of eight hours required for the oxidation. The excess permanganate was destroyed by the addition of sodium hydrogen sulphite. The solution was then

filtered from the precipitated manganese dioxide, which was washed with water until the addition of conc. hydrochloric acid to the filtrate no longer produced a precipitate of "iodosaccharin".

The combined filtrate and washings were cooled to 15°- 18° C. and made neutral to methyl orange with conc. hydrochloric acid. The excess of 4 - iodo - toluene - 2 - sulphonamide was thereby precipitated and filtered off. Conc. hydrochloric acid was then added to the filtrate until a precipitate was no longer obtained. The solution was then filtered and the residue retained for examination.

The residue was then dissolved in 50 ml. of ether and allowed to crystallize. The product had a m. p. of 230°- 231°C. The filtrate from a sodium fusion, imparted a violet color to carbon tetrachloride when treated with chlorine water indicating the presence of iodine.

The molecular weight of the compound was determined by Smith and Young's method (22) using the formula.

$$M.W. = \frac{1000 \times 39.7 \times w}{\Delta t \times W}$$

Where W. is the weight of the unknown substance or solution used, W is the weight of camphor or solvent used and Δt is the depression in melting point observed.

The following data was obtained:

Wt. of camphor used - - - -	-0.031 Grams
Wt. of Unknown used - - - -	-0.003 "

Melting point of last crystal - - -	-168° C.
Melting point of last crystal - - -	-168° C.
Melting point of last crystal - - -	-168° C.
Mean	168° C.

Temperation for formation of 1st crystal -	-164° C.
Temperation for formation of 1st crystal -	-164° C.
Temperation for formation of 1st crystal -	-164° C.
Mean	164° C.

The average giving the melting point of the mixture is 166° C.

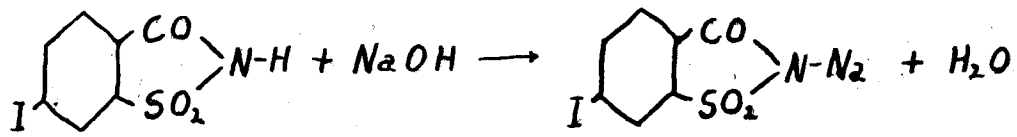
Melting point of camphor used - -	-178.5° C.
Melting point of mixture - - - -	-166.0° C.
Lowering of melting point of (camphor	12.5° C.

Substituting in the equation we get

$$M.W. = \frac{1000 \times 39.7 \times 0.003}{12.5 \times 0.031} = 307.35$$

The molecular weight as calculated from the emperical formula $NH \cdot SO_2 C_6 H_4 I CO$ is 309.036.

The compound was found to have a bitter taste exceeding that of saccharin but not as great as that of 4 - bromo - 2 - sulphimide benzoic acid. It is insoluble in water and in hydrochloric acid. It is soluble in ether, but its degree of solubility has not been established as yet. It is also soluble in the Na O H solution, probably with the formation of the sodium salt.



(The temperatures as given in the experimental work of this paper are all uncorrected)

IV. Conclusion.

A. Brominations.

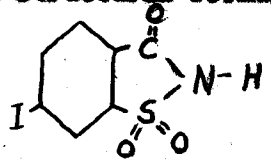
The results obtained indicate that no particular steric hindrance is noted in the bromination of the above compounds. The yields in the three cases in which the investigation has been completed being practically the same, represented a yield of 65 percent and 63 percent and 62 percent, respectively, of the calculated values. The melting point in each case indicates that substitution took place predominately in the p - position. Little, if any, of the other possible isomers being formed. It is concluded that no particular advantage of the one compound over the other can be noted as a point for the introduction of the halogen into the nucleus of the compound. However, it might be noted that the use of p - halogen derivative of toluene as a starting point in the preparation of halogen derivatives of o - sulphimide benzoic acid would remove the objection of separating the isomeric halogen derivatives formed, giving a more uniform product.

B. Preparation of 4 - iodo - 2 - sulphimide benzoic acid ("p - iodo saccharin")

The molecular weight of 307.35 as determined experimentally compares favorably with the calculated molecular weight of 309.036 for 4 - iodo - 2 - sulphimide benzoic acid; giving an experimental error of 0.55 percent.

On the basis of the method of preparation, which closely parallels the successful preparation of 4 - bromo - 2 - sulphimide benzoic acid and of the molecular weight determination given above, it is

concluded that the compound formed is 4 - iodo - 2 - sulphimide benzoic acid, having a structural formula of



Its properties seem to parallel those of saccharin and "p - bromo - saccharin" being insoluble in water and H Cl and soluble in ether and Na OH.

In the early part of this paper it was stated that saccharin in the blood, in proportion to its concentration passes into the lymph, cerebro-spinal fluid, saliva, tears and mammary secretion. It was also stated that saccharin was eliminated from the body unchanged. In view of these reports, it would be interesting to note the physiological action of the iodo - derivative of saccharin to determine its therapeutic value in those cases where iodine is indicated as a treatment.

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