[Contribution from the Research Laboratories of the School of Pharmacy, Purdue University]

IODINATED DERIVATIVES OF SOME SULFONAMIDO COMPOUNDS[1]

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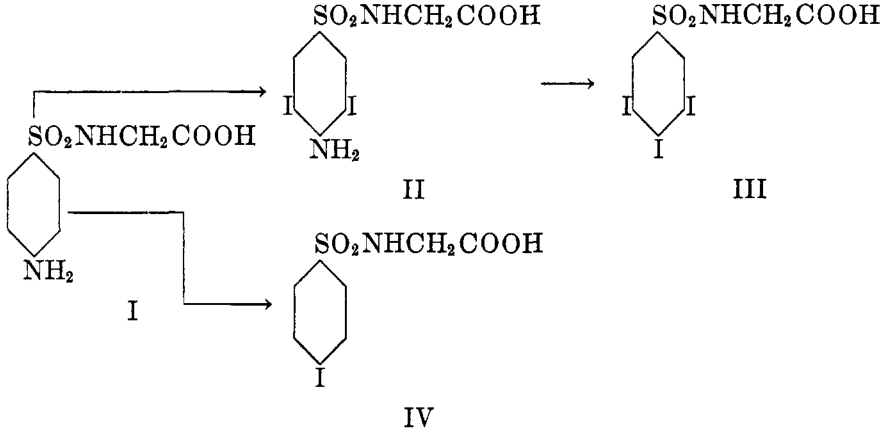
The synthesis of certain iodinated sulfonamido derivatives was undertaken with the object of obtaining compounds of high iodine content and containing solubilizing groups which might prove of value as contrast media for radiographic practice.

This report deals with the syntheses of a few of the above mentioned iodinated compounds. The investigations of the alkali salts as to solubility, toxicity, and suitability as contrast media are problems for subsequent study.

I. *Iodinated sulfanilylglycines.* N-Acetylsulfanilylchloride was coupled with glycine to give the starting material, N-acetylsulfanilylglycine. From this were prepared 3,5-diiodosulfanilylglycine, 3,4,5-triiodobenzenesulfonylglycine, and 4-iodibenzenesulfonylglycine as indicated in formulas I–IV.



II. *Iodinated N-sulfanilylsulfanilic acids.* Synthesis of the precursors and the scope of the study of these iodinated derivatives are shown in formulas V–VIII.

N-3,5-diiodosulfanilylsulfanilic acid. The treatment of N-sulfanilylsulfanilic acid with iodine monochloride might be expected to yield a tetraiodo acid with substitution in the 3,5, 3′,5′ positions. However, no indication of the entrance of more than two atoms of iodine was obtained, even when a large excess of iodine monochloride was used. It appears probable that steric hindrance prevents the entrance of iodine at positions 3 and 5. Scudi (1) found that 3,5-diiodosulfanilamide could not be acetylated under a variety of conditions, the failure being attributed to spatial configuration. Conversely, it would be expected that iodination of N-sulfanilylsulfanilic acid in the 3,5 positions would likewise

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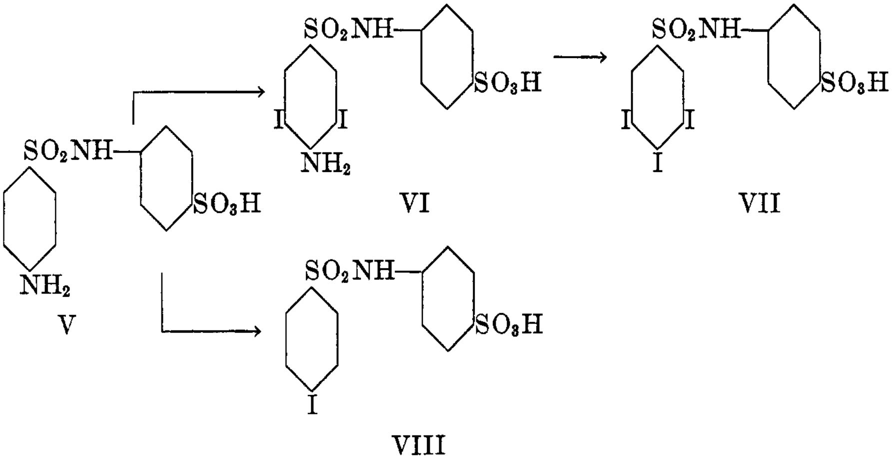
[1] From a portion of a thesis submitted by Ernest L. Beals in partial fulfillment for the degree of Doctor of Philosophy, June 1940.

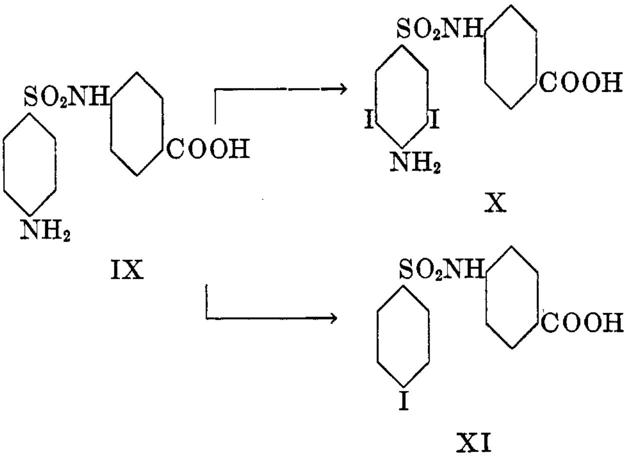
fail, because of the large substituent attached at position 4. It might be mentioned that unsuccessful attempts were made to acetylate the sodium salt of 3,5-diiodosulfanilic acid, although sodium sulfanilate reacts readily with acetic anhydride (2). From these facts it was concluded that the action of iodine monochloride on N-sulfanilylsulfanilic acid yielded the N-3,5-diiodosulfanilylsulfanilic acid.



N-3,4,5-triiodobenzenesulfonylsulfanilic acid. Attempts to prepare this acid led to a compound slightly deficient in iodine content, indicating either incomplete replacement of the amino group, or a tendency for the third iodine atom to be expelled. The relatively high solubility of the free acid in water makes a further study of this compound desirable.

N-4-iodobenzenesulfonylsulfanilic acid. Diazotization of N-sulfanilylsulfanilic acid and treatment with potassium iodide yielded only free iodine and the desired iodinated acid could not be isolated.

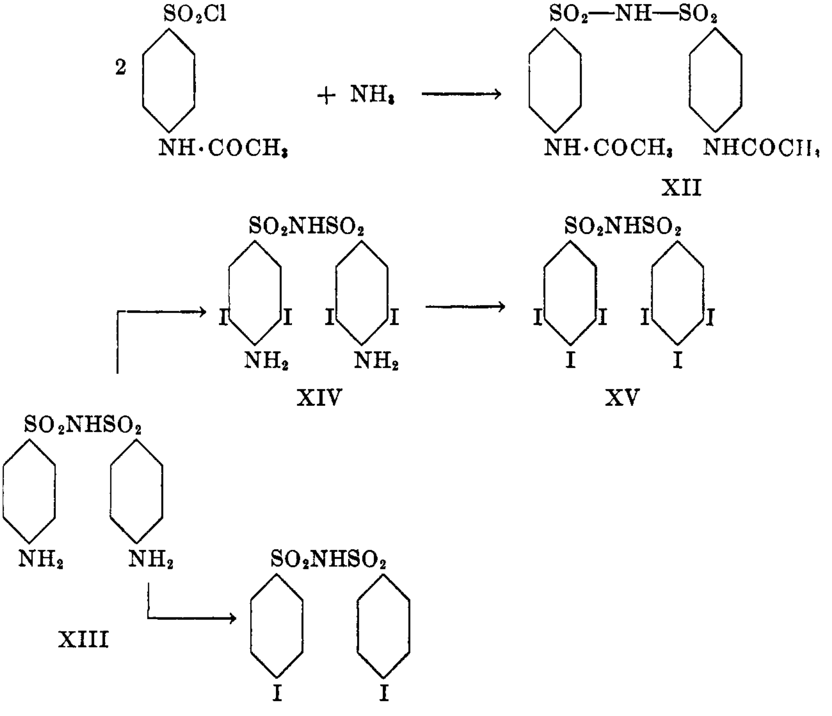
III. *Iodinated N-sulfanilyl-*p*-aminobenzoic acids.* This group of iodinated compounds and their precursor are shown in formulas IX–XI.



*N-3,5(?)-diiodosulfanilyl-*p*-aminobenzoic acid.* From a consideration of the spatial configuration of the parent acid, and the experimental results obtained on the iodination of N-sulfanilylsulfanilic acid, it was expected that a tetraiodo derivative would not be realized. This was confirmed by the experimental findings, only the diiodo acid being obtained. Attempts at hydrolysis of the sulfonamido linkage for the purpose of identification of the products were vitiated by decomposition of the acid with loss of iodine. However, it was concluded that iodination probably took place in the 3,5-sulfanilyl positions to give N-3,5-diiodosulfanilyl-*p*-aminobenzoic acid.

*N-3,4,5-triiodobenzenesulfonyl-*p*-aminobenzoic acid.* A limited yield of the necessary precursor (X) did not permit the synthesis of this acid which remains a problem for future investigation.

IV. *Iodinated disulfanilamides.* The precursors and iodinated derivatives of disulfanilamide were prepared as indicated in formulas XII–XVI.



3,3′,5-Triiododisulfanilamide was the unexpected product obtained upon direct iodination of disulfanilamide with iodine monochloride. Variation of acid strength, concentration of iodine monochloride used, and temperature failed to yield a tetraiodo derivative.

3,3′,5,5′-Tetraiododisulfanilamide. A mixture of the tetra- and tri-iododisulfanilamides was obtained by a reversed iodination process in which an acid solution of disulfanilamide was added dropwise to an excess of iodine monochloride contained in hot, dilute hydrochloric acid. Separation of the two was accomplished by taking advantage of the lower water solubility of the ammonium salt of the tetraiodo variety.

3,3′,4,4′,5,5′-Hexaiododibenzenesulfonamide. This derivative was not prepared due to the difficulty of separation of the tetraiodo precursor with very low yields of the pure compound. Work will be continued in an attempt to obtain this compound.

V. *Iodinated sulfapyridines.* The study of this group of iodinated sulfapyridines involved experimental difficulties such that only *3,5-diiodosulfanilyl-2-aminopyridine* was obtained in a pure state. *4-Iodobenzenesulfonyl-2-aminopyridine(?)* Diazotization of sulfapyridine and treatment with potassium iodide yielded a complex, iodinated, brick-red product the true identity of which has not been determined. *3,4,5-Triiodobenzenesulfonyl-2-aminopyridine.* Work is to be continued in an attempt to prepare this triiodo derivative of sulfapyridine.

Iodine was determined by electrical ignition in a Parr sulfur bomb. Silver iodate in the fusion filtrate was reduced with hydrazine sulfate and then precipitated as silver iodide. Sulfur was determined by the standard procedure using a Parr sulfur bomb.

EXPERIMENTAL

All melting points are corrected.

3,5-Diiodosulfanilylglycine. N-acetylsulfanilyl chloride was prepared according to Organic Syntheses (3). The crude, moist product was coupled at once with glycine by the method of Kolloff (4) giving a 70% yield of N-acetylsulfanilylglycine melting at 237.7° (Kolloff 237.5–238.5°). For removal of the acetyl group five grams of N-acetylsulfanilylglycine was gently refluxed with 50 cc. of 5 *N* hydrochloric acid for 45 minutes and then added dropwise, with mechanical stirring, to a hot solution of 10 g. of iodine monochloride in 50 cc. of 5 *N* hydrochloric acid. The mixture was heated on a water-bath for one and a half hours, precipitation of the iodo compound commencing within 10 minutes. The crude product was suspended in 4 liters of boiling water, made slightly alkaline with 5% sodium hydroxide, treated with charcoal, and filtered. The hot filtrate was acidified with dilute hydrochloric acid and allowed to stand overnight. (Note: Precipitation from more concentrated solutions yielded an amorphous, colloidal product.) The fine, white crystals were collected, washed with water, and dried. Yield: 6.73 g. (76%), melting with decomposition at 249.5°.

Anal. Calc'd for $C_8H_8I_2N_2O_4S$: I, 52.67. Found: I, 52.87.

3,4,5-Triiodobenzenesulfonylglycine. Two grams of 3,5-diiodosulfanilylglycine was suspended in 100 cc. of water and dissolved by the addition of 5% sodium hydroxide. After the addition of 6 cc. of 5% sodium nitrite the solution was chilled to 3° and added dropwise, over a period of 45 minutes, to 100 cc. of cold, 5 *N* hydrochloric acid. The resulting bright yellow solution gradually darkened and finally threw down a slight precipitate. A few minutes additional stirring caused the sudden appearance of a heavy bright yellow precipitate. The addition of an excess of cold potassium iodide solution caused an immediate evolution of nitrogen, the reaction being completed by warming to 50°. In order to obtain a crystalline product, an alkaline solution of the tan precipitate was diluted to 800 cc. with water, heated to boiling, and then acidified with 5 *N* hydrochloric acid. After slow cooling the pale yellow crystals were collected, washed with water, and again precipitated from a hot, dilute, alkaline solution with acid. The pale greenish-yellow, crystalline product weighed 1.05 g. (42.7%) and melted with decomposition at 279–280°.

Anal. Calc'd for $C_8H_6I_3NO_4S$: I, 64.22. Found: I, 64.09.

4-Iodobenzenesulfonylglycine. Two grams of N-acetylsulfanilylglycine was deacetylated by refluxing gently for one hour with 25 cc. of 5 *N* hydrochloric acid. The solution was diluted with 25 cc. of water, chilled to 3°, and diazotized by the addition of 10 cc. of 5% sodium nitrite over a period of 30 minutes. An excess of cold potassium iodide solution was then added and allowed to warm slowly to room temperature, nitrogen being evolved at about 5°. After warming to 50°, the mixture was cooled, the reddish-tan precipitate collected and repeatedly washed with water. The murky, yellow solution, obtained by dissolving the product in 100 cc. of water with the aid of 5 cc. of 10% potassium hydroxide, was treated with charcoal and filtered. Acidification of the solution with 5 *N* hydrochloric acid and chilling, yielded 1.52 g. of a buff colored powder (61%) melting with decomposition at 189–191°. Alkaline solutions of 4-iodobenzenesulfonylglycine exhibit a canary-yellow color.

Anal. Calc'd for $C_8H_8INO_4S$: I, 37.21. Found: I, 36.97.

Potassium N-3,5(?)-diiodosulfanilylsulfanilate. The starting material, N-sulfanilylsulfanilic acid was prepared in 83.5% yield according to the method of Crossley (5). Five grams of the acid was suspended in 50 cc. of 10% hydrochloric acid, warmed to 40–50° and 2 cc. of iodine monochloride added dropwise with mechanical stirring. At the end of two hours the mixture was chilled in ice, yielding a tan colored paste surmounted by a gelatinous layer. The insoluble product was filtered off and dissolved in a little warm water. Chilling of this solution in ice gave a clear jell which, when made slightly basic with 10% potassium hydroxide and warmed, was replaced by a mass of fine crystals on cooling. The potassium salt was recrystallized five times from hot water, yielding 2.0 g. of the anhydrous salt (21.4%). Potassium N-3,5(?)-diiodosulfanilylsulfanilate crystallized with two molecules of water and was rendered anhydrous when dried over sulfuric acid or heated to 100°.

Anal. Calc'd for $C_{12}H_9I_2KN_2O_5S_2$: I, 41.07; S, 10.37.
Found: I, 41.01; S, 10.44.

N-3,4,5-triiodobenzenesulfonylsulfanilic acid. One and sixty-nine hundredths grams of potassium N-3,5-diiodosulfanilylsulfanilate was suspended in 100 cc. of water. The addition of 5 cc. of hydrochloric acid gave a stiff jell which was thinned by the addition of 50 cc. of water. When chilled to 5° the gelatinous material consisted in part of fine, needle crystals. The addition of the theoretical amount of sodium nitrite solution over a period of 2.5 hours replaced the gelatinous material with a bright yellow precipitate. To this was added 1.0 g. of potassium iodide in 10 cc. of water, the yellow precipitate giving way to a clear, red solution which was allowed to warm slowly to room temperature and then heated to 50°. It was found necessary to evaporate the solution to a small volume on the steam-bath and chill in ice to obtain a paste of pale yellow material which was twice recrystallized from small volumes of water. The final product (0.93 g.) was in the form of extremely long crystals appearing as masses of microscopic hair. The material did not melt nor show signs of decomposition when heated to 310°.

Anal. Calc'd for $C_{12}H_8I_3NO_5S_2$: I, 55.11. Found: I, 51.40.

N-sulfanilyl-p-aminobenzoic acid. N-acetylsulfanilyl-*p*-aminobenzoic acid was prepared in 52% yield by the method of Kolloff (4). Kolloff found that deacetylation of the acid by boiling with a mixture of 4.9 *N* hydrochloric acid and ethyl alcohol resulted in partial esterification. To avoid this, hydrolysis was accomplished by refluxing with 5 *N* hydrochloric acid in the absence of alcohol.

The crude, powdered N-acetylsulfanilyl-*p*-aminobenzoic acid (41 g.) was refluxed with 400 cc. of 5 *N* hydrochloric acid. After five minutes most of the material had dissolved, when suddenly the solution set to an almost solid mass of crystals. The heat was withdrawn and 200 cc. more of the acid added to increase the fluidity of the mass. The mixture was then refluxed for one hour, cooled, chilled in ice, and the precipitate collected. The filter cake was dissolved in 200 cc. of 10% sodium carbonate, treated with charcoal, filtered, and the free acid precipitated by the careful addition of 10% hydrochloric acid. Final purification consisted of two crystallizations from 25% alcohol, yielding 23.2 g. (64.5%) of the crystalline acid melting at 201°. Kolloff (4) reports the melting point as 202°, while Crossley (5) lists it as 198–200.5°.

*N-3,5(?)-diiodosulfanilyl-*p*-aminobenzoic acid.* The addition of iodine monochloride contained in 10% hydrochloric acid to N-sulfanilyl-*p*-aminobenzoic acid dissolved in a large volume of hot 10% hydrochloric acid gave a product deficient in iodine content (35–37%). Reversing the order of mixing and using 5 *N* acid increased the iodine content to 44.0% (theory 46.66%). The desired derivative was obtained as follows: Five grams of N-sulfanilyl-*p*-aminobenzoic acid was dissolved in 100 cc. of glacial acetic acid by gently warming. The clear solution was added dropwise over a period of 1.5 hours to 10 cc. of iodine monochloride in 100 cc. of 10% hydrochloric acid maintained at 80–90°. The solution was stirred mechanically and heated for a total of 3 hours, precipitation being noted within 20 minutes. After standing overnight the mixture was again heated and stirred for 2 hours, the volume being maintained by the addition of more dilute hydrochloric acid. After cooling, the insoluble material was filtered off, washed with water, and dried, yielding 8.9 g. (93%) of a rose colored, sandy product. Repeated crystallization from hot alcohol failed to yield a pure compound. However, treatment with hot, dry acetone gave the desired product as the acetone-insoluble fraction. The white crystalline product melted with decomposition at 261.1°.

The acetone-soluble portion was reclaimed and recrystallized from water as the ammonium salt. Conversion to the free acid gave an additional yield of the diiodo derivative melting at 261.1°.

Anal. Calc'd for $C_{13}H_{10}I_2N_2O_4S$: I, 46.66. Found: I, 46.50.

*N-4-iodobenzenesulfonyl-*p*-aminobenzoic acid.* Two grams of N-sulfanilyl-*p*-aminobenzoic acid was suspended in 50 cc. of water and dissolved with the least amount of 10% potassium hydroxide. To this was added 0.53 g. of sodium nitrite, the solution chilled to 0°, and added, over a period of one hour, to 100 cc. of ice-cold, 2.5 *N* hydrochloric acid. An excess of cold potassium iodide solution was then added and, after warming slowly to room temperature, the mixture was heated to 50°, yielding 2.83 g. of a tan product. Partial purification resulted when the acid was twice precipitated from alkaline aqueous solution with dilute hydrochloric acid. The material was then dissolved in hot alcohol, treated with charcoal, and filtered. The filtrate was heated to boiling under reflux and sufficient hot water added to produce a distinct cloudiness. The precipitate which formed as the solution cooled was collected and the process repeated three times, yielding 1.5 g. (54%) of a buff colored powder melting with decomposition at 265–267°.

Anal. Calc'd for $C_{13}H_{10}INO_4S$: I, 31.49. Found: I, 31.40.

3,3',5-Triiododisulfanilamide. Using Crossley's method (6), $N^4,N^{4'}$-diacetyldisulfanilamide was prepared (78%) and deacetylated to N^1-sodium disulfanilamide in 90% yield.

Five grams of N^1-sodium $N^4,N^{4'}$-diacetyldisulfanilamide was boiled for 3 hours with 40 cc. of 10% sodium hydroxide, the volume being maintained by the addition of water. The solution was cooled, the deacetylated product filtered off and heated to 80° with 60 cc. of 25% hydrochloric acid. In an attempt to obtain complete solution, 5 cc. more acid was added, causing the separation of fine, needle crystals. To this suspension was added a solution of 4 cc. of iodine monochloride in 15 cc. of 25% hydrochloric acid. The mixture was stirred mechanically and maintained at 80° for two hours. At the end of this time 1 cc. of iodine monochloride was added directly and the stirring continued for one hour. The heavy white precipitate was washed several times by decantation with 25-cc. portions of 25% hydrochloric acid, collected on a filter, and washed with water; yield: 7.6 g.

The crude material was converted to the sodium salt by warming with 3 cc. of 10% sodium hydroxide in 15 cc. of water, digested with charcoal, and filtered hot. Well-defined crystals were obtained when the filtrate was chilled in the ice-box overnight. The crystalline material was collected and recrystallized three times from small volumes of hot water. When dried for one hour at 110° the crystals effloresced and became opaque; yield: 4.1 g. (50%).

Anal. Calc'd for $C_{12}H_9I_3N_3NaO_4S$: I, 52.38; S, 8.22.
Found: I, 52.67; S, 8.63.

A small amount of the sodium salt of triiododisulfanilamide was dissolved in water and converted to an insoluble, amorphous substance by the addition of 10% hydrochloric acid.

The triiododisulfanilamide was filtered off, washed thoroughly with water and dried. Melting point 249.2°, with decomposition.

3,3′,5,5′-Tetraiododisulfanilamide. Two grams of N^1-sodium disulfanilamide (99.92% by nitrite assay) was treated with 50 cc. of water. A trace of insoluble material dissolved only on boiling and reappeared on cooling. The insoluble fraction was filtered out in the belief it might be unhydrolyzed diacetyldisulfanilamide. Sufficient hydrochloric acid was then added to give a final acid strength of 10%, and the clear, cold solution added dropwise over a period of one hour to 5 cc. of iodine monochloride contained in 50 cc. of hot 10% hydrochloric acid. The mixture was cooled, the precipitate collected and washed with 10% hydrochloric acid and with water; yield: 4.0 g. of lavender powder (84.5%).

The powder was suspended in 200 cc. of water and made alkaline with 28% ammonium hydroxide. The reddish solution obtained on boiling was treated with charcoal and filtered hot, the lavender filtrate throwing down fine needle crystals on cooling. These were collected and twice recrystallized from 100-cc. portions of boiling water, yielding 0.75 g. of N^1-ammonium 3,3′,5,5′-tetraiododisulfanilamide.

Anal. Calc'd for $C_{12}H_{12}I_4N_4O_4S_2$: I, 59.87. Found: I, 59.70.

A small amount of ammonium tetraiododisulfanilamide was dissolved in boiling water, precipitated with 10% hydrochloric acid, washed with water, and dried. Tetraiododisulfanilamide darkened gradually at 230° and melted with decomposition at 259–260°.

The mother liquor from the crystallization of ammonium tetraiododisulfanilamide gave a bulky precipitate upon acidification with hydrochloric acid. This material was repeatedly recrystallized from hot water as the ammonium salt, decomposed with dilute hydrochloric acid, collected, washed with water, and dried. About 0.1 g. of amorphous material was obtained which assayed 54.05% iodine, and melted with decomposition at 248.6–249.6°, values in good agreement with those found for triiododisulfanilamide.

N^1-potassium $4,4^1$-diiododibenzenesulfonamide. Two grams of N^1-sodium $N^4,N^{4'}$-diacetyldisulfanilamide was boiled into solution with 50 cc. of 5 *N* hydrochloric acid, requiring 1.5 hours. The solution was treated with charcoal and filtered, the clear filtrate cooled to 0°, and a slight excess of sodium nitrite solution added dropwise, yielding a water-white solution. The addition of an excess of potassium iodide solution gave a greenish-black precipitate which changed to yellow on warming to 50°. After standing overnight the yellow, insoluble material was filtered off, washed with water, and dissolved in 25% alcohol. The hot solution was treated with charcoal, filtered, and made alkaline with 10% potassium hydroxide. On cooling, the potassium salt separated as a pale yellow precipitate which was twice recrystallized from 300-cc. portions of boiling water. The nearly white product weighed 0.5 g. (18.5%).

Anal. Calc'd for $C_{12}H_8I_2KNO_4S_2$: I, 41.95. Found: I, 41.45.

3,5-Diiodosulfanilyl-2-aminopyridine. Two grams of sulfapyridine (Calco) dissolved in 10 cc. of 10% hydrochloric acid was added dropwise over a period of 45 minutes to 2 cc. of iodine monochloride contained in 50 cc. of 10% hydrochloric acid. The mixture was stirred mechanically and kept at a temperature of 80–90°. At the end of one hour the mixture was chilled, the tan precipitate filtered off and washed with water. The product was purified by precipitation from hot alkaline 50% alcohol solution by the addition of dilute hydrochloric acid. This process was repeated twice, the hot alkaline solutions being digested with charcoal and filtered. A yield of 2.7 g. (78%) of white, crystalline product was obtained which melted with decomposition at 269–272°.

Anal. Calc'd for $C_{11}H_9I_2N_3O_2S$: I, 50.67. Found: I, 50.57.

SUMMARY

1. Three new iodinated derivatives of sulfanilylglycine, *viz.*, 3,5-diiodosulfanilylglycine, 3,4,5-triiodobenzenesulfonylglycine, and 4-iodobenzenesulfonylglycine have been prepared.

2. N-3,5(?)-diiodosulfanilylsulfanilic acid has been prepared and described as its potassium salt.

3. N-3,5(?)-diiodosulfanilyl-*p*-aminobenzoic acid and N-4-iodobenzenesulfonyl-*p*-aminobenzoic acid, iodinated derivatives of N-sulfanilyl-*p*-aminobenzoic acid have been prepared and described.

4. A study of the action of iodine monochloride upon disulfanilamide has been made. 3,3′,5-Triiododisulfanilamide has been obtained by the addition of an acid solution of iodine monochloride to disulfanilamide dissolved in hot dilute hydrochloric acid. A reverse iodination process yielded both the triiodo- and 3,3′,5,5′-tetraiodo-disulfanilamide, which were separated and identified as their ammonium salts.

A method for the preparation of the potassium salt of 4,4′-diiododibenzenesulfonamide has been given.

5. 3,5-Diiodosulfanilyl-2-aminopyridine, a diiodo derivative of sulfapyridine, has been obtained in good yield.

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