[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, PURDUE UNIVERSITY]

SYNTHESIS OF IODOSULFOPHENYLAZO AND IODOCARBOXYPHENYLAZO DERIVATIVES OF NAPHTHOL AND NAPHTHYLAMINE SULFONIC ACIDS[1]

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Received February 14, 1944

As there is still a need for better radiographic opaques, this work on a new class of iodinated organic compounds was undertaken. Azonaphthalene sulfonic acid compounds have been found to be excreted from the liver and concentrated in the gall bladder (1); therefore, they were selected as a nucleus from which to begin. In this work, azo derivatives of naphthol and naphthylamine sulfonic acids were prepared from 3,5-diiodosulfanilic acid and 3,5-diiodo-*p*-aminobenzoic acid.

I. *Iodinated sulfophenylazonaphthalene sulfonic acids.* In this series 3,5-diiodosulfanilic acid was diazotized and coupled with the following naphthalene sulfonic acids: (A) 1-naphthol-4-sulfonic acid to give the disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthol-4-sulfonic acid; (B) 1-naphthylamine-4-sulfonic acid to give the disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4-sulfonic acid; (C) 1-naphthylamine-4,8-disulfonic acid to give the trisodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4,8-disulfonic acid.

II. *Iodinated carboxyphenylazonaphthalene sulfonic acids.* 3,5–Diiodo-4-aminobenzoic acid was diazotized and coupled with the naphthalene sulfonic acids listed under I to yield: (D) the disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthol-4-sulfonic acid; (E) the disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4-sulfonic acid; (F) the trisodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4,8-disulfonic acid.

Sodium chloride is generally a contaminating substance in these preparations since it is extremely difficult to get a complete separation of it from the dyes. Therefore, the percentages of iodine and chlorine were determined by electrometric titration with *N*/10 silver nitrate solution, using a silver electrode and a mercurous sulfate half-cell according to the method used by Klemme and Hunter (2).

EXPERIMENTAL

3,5-Diiodosulfanilic acid. This compound was prepared by a modification of the method proposed by Boyle (3). One hundred four and six-tenths grams of reagent sulfanilic acid was dissolved with heating and stirring in 3 liters of 10% hydrochloric acid. When solution was complete, 60 cc. (200 g.) of iodine monochloride was added and the mixture kept at 80° for two hours with mechanical stirring.

After standing overnight, the mixture was filtered and the moist, crude acid dissolved in boiling distilled water, activated charcoal added, and boiling continued for a few minutes.

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[1] From a portion of a thesis submitted by Haakon Bang in partial fulfilment for the degree of Doctor of Philosophy, December, 1941.

Filtration yielded a reddish filtrate which was made slightly alkaline by the addition of 30 g. of potassium hydroxide dissolved in 300 cc. of distilled water. After a few minutes, a precipitate of potassium 3,5-diiodosulfanilate appeared. The solution was cooled; the crystals were filtered off and washed with water. A second crop of crystals was obtained by concentration of the mother liquor. The yield at this point was 199.2 g. of the dried salt.

The product obtained above was dissolved in 1500 cc. of boiling water containing 50 cc. of 37% hydrochloric acid. When solution was complete, activated charcoal was added and the solution filtered. The filtrate was cooled and the white crystals of 3,5-diiodosulfanilic acid filtered off and dried at 105°; yield, 149.4 g. (64.2%).

2-(2,6-Diiodo-4-sulfophenylazo)-1-naphthol-4-sulfonic acid. Forty-two and five-tenths grams of 3,5-diiodosulfanilic acid was suspended in 185 cc. of 10% hydrochloric acid and the mixture cooled to 0°. Six and nine-tenths grams of pure sodium nitrite, dissolved in about 4 cc. of ice-cold distilled water, was added gradually to the cold mixture of the 3,5-diiodosulfanilic acid, and stirred for 30 minutes, maintaining the temperature at 0°. The mixture was tested with starch iodide paper and when the test was positive, 0.1 g. of 3,5-diiodosulfanilic acid was added to decompose the excess nitrous acid.

The cold mixture containing the 3,5-diiodo-4-diazobenzene-1-sulfonic acid was poured, a small quantity at a time, into a solution containing 23.6 g. of recrystallized Eastman technical 1-naphthol-4-sulfonic acid and 40 g. of anhydrous sodium carbonate, allowing the effervescence and the foam to subside before each subsequent addition of the diazo mixture. The deep red solution was heated to boiling, cooled, and filtered. The filtrate was evaporated to about 200 cc., 50 g. of sodium chloride was dissolved in the hot solution which was then cooled, and the precipitated dye collected and dried overnight at 105°.

The dry salt cake was powdered and extracted several times with 95% methanol, using 1 liter for the first extraction and 500-cc. portions for three further extractions. The combined alcoholic extracts were evaporated to dryness on a steam-bath and the dried, powdered residue again extracted with 1500 cc. of 99.5% methanol. This alcoholic extract was evaporated, and the powdered residue dried at 105°. This powder was washed twice with a mixture of 200 cc. of ether and 100 cc. of 99.5% methanol. The insoluble dye was filtered off and again dried and powdered; yield, 29.9 g. (40.3%, corrected for sodium chloride content).

A small quantity of the dye was dissolved in distilled water, treated with a few drops of chlorine water and shaken with chloroform. The chloroform layer remained perfectly colorless, indicating the absence of free iodine or iodides.

Anal. Calc'd for $C_{16}H_8I_2N_2Na_2O_7S_2$: I, 36.05. Found: I, 35.76, 35.84.

Sodium chloride content 5.1%.

The compound when dry is a dark brownish-red powder, but on exposure to air it takes up moisture and becomes light red. It is insoluble in ether, chloroform, and acetone; soluble in ethanol and methanol. When added to water, there is an evolution of heat as the dye goes into solution. Solubility: 27.2 g. per 100 g. of water.

Disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4-sulfonic acid. The uniodinated dye was first prepared by Griess (4). Forty-two and five-tenths grams of 3,5-diiodosulfanilic acid was suspended in 185 cc. of 10% hydrochloric acid and the mixture cooled to 0°. A cold solution containing 6.9 g. of pure sodium nitrite in 5 cc. of distilled water was added in portions. After one-half hour of continuous stirring, during which the solution was kept at 0° the diazo mixture was tested for excess nitrous acid as before.

The mixture containing the yellow 3,5-diiodo-4-diazobenzene-1-sulfonic acid was poured, in small quantities, into a solution containing 25.7 g. of Eastman sodium naphthionate and 50 g. of anhydrous sodium carbonate. A slight excess of the sodium naphthionate was found to give better results since, when just the theoretical amount was used, the product obtained gave results high in per cent of iodine. It is believed that this may be due to the formation of 3,5-diiodo-4-hydroxybenzene-1-sulfonic acid. No attempt was made to isolate this substance. It was also found that the coupling reaction yielded better results when carried out cold. Again it was necessary to use care in adding the diazo mixture to the sodium naphthionate solution to prevent excessive foaming. Constant and vigorous stirring was employed.

The deep red solution resulting from the coupling reaction was heated to boiling, cooled, and filtered. The filtrate was evaporated to complete dryness on a steam-bath, since this dye could not be salted out readily. The dried residue was extracted with 1 liter of 95% methanol and then with three 500-cc. portions. The combined extracts were evaporated to dryness and again extracted with 1 liter of 99.5% methanol. The dark red powder was then washed with an ether-methanol mixture as before; yield, 38.6 g. (54.9%, corrected for sodium chloride content.) The test for free iodine and iodides was negative.

Anal. Calc'd for $C_{16}H_9I_2N_3Na_2O_6S_2$: I, 36.10. Found: I, 35.16, 35.90.

Sodium chloride: 13.1%.

The disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4-sulfonic acid is a fine red powder which is insoluble in chloroform, ether, and acetone. It is soluble in methanol and ethanol, the former being the better solvent. Solubility: 33.1 g. per 100 g. water.

Trisodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4,8-disulfonic acid. Forty-two and five-tenths grams of 3,5-diiodosulfanilic acid was suspended in 185 cc. of 10% hydrochloric acid and the mixture cooled to 0° and diazotized as before.

Thirty and five-tenths grams of recrystallized Eastman technical 1-naphthylamine-4,8-disulfonic acid was dissolved with 40 g. of anhydrous sodium carbonate in 200 cc. of distilled water and the 3,5-diiodo-4-diazobenzene-1-sulfonic acid was added in small quantities with continuous and vigorous stirring, allowing the foaming to subside before each subsequent addition. The deep red solution was then heated to boiling, cooled, filtered, and the filtrate evaporated on a steam-bath to complete dryness. As in the previous experiment, it was not possible to salt out the dye with sodium chloride.

The residue was extracted with 1500 cc. of 95% methanol and a second portion of 800 cc. of methanol of the same strength. The 99.5 g. of residue obtained from the evaporation of the combined extracts was again extracted with 1500 cc. of 99.5% methanol. The filtrate from the latter extraction was evaporated to dryness on a steam-bath and the residue dried and powdered. The powder was washed twice with a mixture of 250 cc. of ether and 75 cc. of 99.5% methanol and dried at 105°; yield, 50.1 g. (62.2%, corrected for sodium chloride content.)

The dye was found to be free from iodine or inorganic iodides when tested with chloroform and fresh chlorine water.

Anal. Calc'd for $C_{16}H_8I_2N_3Na_3O_9S_3$: I, 31.52. Found: I, 31.99, 32.22.

Sodium chloride content: 15.5%.

The trisodium salt of 2-(2,6-diiodo-4-sulfonphenylazo)-1-naphthylamine-4,8-disulfonic acid is a dark red powder which is insoluble in chloroform, ether and acetone. Solubility: 48.8 g. per 100 g. of water.

4-Amino-3,5-diiodobenzoic acid. This compound was first prepared by Michael and Norton (5) and again by Wheeler and Liddle (6), who also determined the structure of the compound. The method used for the preparation of this compound was similar to that employed by Klemme and Hunter (2).

One hundred thirty-seven grams of Eastman practical *p*-aminobenzoic acid was suspended in three and a half liters of 10% hydrochloric acid and dissolved with the aid of heat. When the temperature reached 80°, 110 cc. of iodine monochloride (10% excess) was added. Stirring was continued and the mixture was kept hot for two hours then allowed to cool. After standing overnight the brown precipitate was filtered off.

The residue was suspended in boiling distilled water and dissolved by adding 25% sodium hydroxide until the mixture was slightly alkaline to litmus. The solution was boiled with activated charcoal, filtered, and while hot, precipitated with hydrochloric acid. When cool, the fine, white precipitate of 4-amino-3,5-diiodobenzoic acid was filtered off, dried at 105° and finely powdered; yield, 320.6 g. (84%).

Disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthol-4-sulfonic acid. A method for the diazotization of 4-amino-3,5-diiodobenzoic acid is described by Wheeler and Liddle (7) and used by Klemme and Hunter (8).

Thirty-eight and eight-tenths grams of 4-amino-3,5-diiodobenzoic acid was diazotized in 150 cc. of concentrated sulfuric acid at 0° by the gradual addition of 6.9 g. of pure dry sodium nitrite. Fifteen or twenty minutes after the last addition of the sodium nitrite, a drop or two of the acid solution was added to 1 cc. of distilled water and tested with starch iodide paper. Small quantities of the 3,5-diiodo-4-aminobenzoic acid were added until the test for free nitrous acid was just negative.

The acid solution was then poured into about 1 kg. of cracked ice, whereupon a yellow precipitate of 3,5-diiodo-4-diazobenzoic acid settled out. It was necessary to keep an excess of ice present to prevent decomposition of the diazo compound.

A solution was prepared by dissolving 28 g. of recrystallized Eastman technical 1-naphthol-4-sulfonic acid and 220 g. of sodium hydroxide in 500 cc. of distilled water. When this solution was cool, the diazo mixture was added slowly with stirring. The solution was allowed to stand overnight and filtered. The deep red filtrate was concentrated on a hot-plate at low heat to about 1 liter and made acid with 37% hydrochloric acid. The red precipitate which formed was filtered off and redissolved in about 300 cc. of 2% of sodium hydroxide solution. The resulting solution was filtered and the acid reprecipitated with 37% hydrochloric acid. The precipitate was filtered off, and washed with cold distilled water. The powder was dried, but upon analysis it was found necessary to repeat the purification a third time; yield, 38.5 g. (61.7%, corrected for sodium chloride content). The compound gave no test for free iodine or iodides.

Anal. Calc'd for $C_{17}H_{10}I_2N_2O_6S$: I, 40.68. Found: I, 41.36, 40.28.

Sodium chloride content: 0.6%.

To form the disodium salt of the compound, 20 g. of the acid was dissolved with 2.7 g. of anhydrous sodium carbonate, the theoretical quantity, in about 100 cc. of distilled water. The resulting solution was evaporated to dryness on a water-bath and the residue dissolved in 99.5% methanol and filtered. The methanol filtrate was evaporated and the residue dried at 105° overnight.

The disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthol-4-sulfonic acid is a fine, dark red powder. It is insoluble in chloroform, ether, and acetone, but is soluble in methanol and ethanol, the former being the better solvent. Solubility: 30.8 g. per 100 g. water.

Disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4-sulfonic acid. Thirty-eight and eight-tenths grams of 4-amino-3,5-diiodobenzoic acid was diazotized in 150 cc. of concentrated sulfuric acid at 0° as described in the previous experiment. The diazotized mixture was poured with vigorous stirring into 1 kg. of cracked ice, and this cold solution was poured slowly with stirring into 500 cc. of an aqueous solution containing 25 g. of Eastman sodium naphthionate and 220 g. of sodium hydroxide. Again it was found best to keep the reaction mixture cold.

The cool solution resulting from the coupling reaction was filtered and made acid with 37% hydrochloric acid. The precipitated acid dye was collected and redissolved in 300 cc. of distilled water containing 5 g. of sodium hydroxide (a slight excess). The deep red solution was filtered and the acid reprecipitated with 37% hydrochloric acid. The precipitate was collected, washed with distilled water, dried, and powdered; yield, 51.1 g. (81.9%, corrected for sodium chloride content.) The test for free iodine and iodides was negative.

Anal. Calc'd for $C_{17}H_{11}I_2N_3O_5S$: I, 40.49. Found: I, 40.03, 40.57.

Sodium chloride content: 5.3%.

Fifteen grams of the acid dye was mixed with the theoretical quantity of sodium carbonate and dissolved in the smallest possible quantity of water. The solution was then evaporated to dryness on a steam-bath and the residue powdered and dissolved in 99.5% methanol, filtered, and the filtrate evaporated. The residue was powdered and dried at 105°.

The disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4-sulfonic acid is a fine red powder which when heated strongly gives off iodine vapors and finally burns to a white ash. It is insoluble in chloroform, ether, and acetone, but is soluble in methanol and ethanol. Solubility: 24 g. per 100 g. water.

Trisodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4,8-disulfonic acid. Thirty-eight and eight-tenths grams of 4-amino-3,5-diiodobenzoic acid was dissolved in 150 cc. of concentrated sulfuric acid and the solution was cooled to 0° in an ice and salt mixture. The diazotization was carried out by adding 6.9 g. of pure, dry sodium nitrite in small quantities while the mixture was stirred as prescribed before. After the reaction was complete and there was a negative test for nitrous acid, the reaction mixture was added to 1 kg. of cracked ice with vigorous stirring.

Thirty and three-tenths grams of recrystallized Eastman technical 1-naphthylamine-4,8-disulfonic acid was dissolved with 300 g. of anhydrous sodium carbonate in about 1 liter of distilled water.

The diazotized solution of the 4-amino-3,5-diiodobenzoic acid was added, in small quantities and with continuous stirring, to the solution containing the 1-naphthylamine-4,8-disulfonic acid. The coupling reaction was kept cool in an ice-bath. There was considerable effervescence and foaming. When the coupling was complete, the deep red solution was heated to the boiling point, cooled, and filtered. The filtrate was evaporated to about 700 cc. and made acid with concentrated hydrochloric acid, precipitating the acid dye. The dye was filtered off and added to a slight excess of anhydrous sodium carbonate and enough distilled water to form a solution. This solution was then filtered and evaporated to dryness. The resulting red powder was dissolved in 1700 cc. of 99.5% methanol and filtered. The filtrate was evaporated to dryness on a steam-bath, and the dark brownish-red residue was powdered and dried at 105°; yield, 28.9 g. (37.1%, corrected for sodium chloride content).

Anal. Calc'd for $C_{17}H_8I_2N_3Na_3O_8S_2$: I, 32.5. Found: I, 32.82, 33.05.

Sodium chloride content: 3.4%.

The trisodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4,8-disulfonic acid is a dark red powder which, when heated strongly, gives off iodine vapors and finally burns to a white ash. It is insoluble in chloroform, but slightly soluble in ether. It is very soluble in methanol and ethanol. Solubility: 37.8 g. per 100 g. water.

SUMMARY

By coupling various naphthol and naphthylamine sulfonic acids with diazotized 3,5-diiodosulfanilic and 3,5-diiodo-*p*-aminobenzoic acids, iodinated azo dyestuffs have been synthesized for testing as radiographic opaques. Several of the sodium salts of these dyestuffs are highly soluble in water.

Lafayette, Ind.

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