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3,5-Dichloroaniline in Sandmeyer's Isatin Synthesis. 4,6-Dichloroanthranilic Acid

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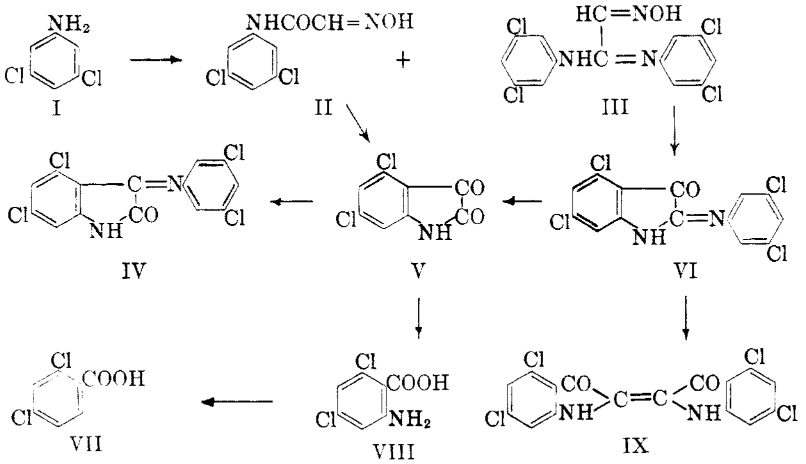
4,6-Dichloroanthranilic acid is prepared by oxidation of 4,6-dichloroisatin obtained from 3,5-dichloroaniline *via* Sandmeyer's isatin synthesis. A by-product in the preparation of the intermediate α-isonitroso-3,5-dichloroacetanilide is N,N′-bis(3,5-dichlorophenyl)isonitrosoacetamidine which is readily cyclized to 3′,4,5′,6-tetrachloroisatin-α-anil. The isomeric β-anil is obtained by fusing the isatin with the aniline. Reduction of the α-anil with hydrogen sulfide gave a blue, vat dyestuff, presumably 4,4′,6,6′-tetrachloroindigo. The anthranilic acid, the amidine, and the isomeric anils are new compounds.

Victor Villiger[1] accounted for five of the six possible dichloroanthranilic acids. The preparation of the remaining isomer, 4,6-dichloroanthranilic acid (VIII), by oxidizing 4,6-dichloroisatin (V) with alkaline hydrogen peroxide (*Cf.*[2]), is described below. Traugott Sandmeyer[3] obtained 4,6-dichloroisatin (V) from 3,5-dichloroaniline (I) by adding the intermediate α-isonitroso-3,5-dichloroacetanilide (II) to hot, concentrated sulfuric acid. On repeating Sandmeyer's synthesis of the anilide (II) by heating a suspension of 3,5-dichloroaniline (I) in an aqueous solution containing chloral hydrate, hydroxylamine hydrochloride, sodium sulfate, and hydrochloric acid, using modifications introduced by later workers,[4] it was observed that the product (II) is accompanied by a minor amount of N,N′-bis(3,5-dichlorophenyl)isonitrosoacetamidine (III) which was separated from II by utilizing the greater solubility of the latter in aqueous sodium hydroxide. The simultaneous formation of the corresponding amidine in the Sandmeyer synthesis of an isonitrosoacetanilide has not been recorded previously; indeed, except for the parent substance, $HON{:}CHC({:}NC_6H_5)NHC_6H_5$, diphenylglyoxylamidine oximes of this type, (III) do not appear to have been described. Sandmeyer's discovery[5] of N,N′-diphenylisonitrosoacetamidine antedated his classic isatin synthesis[3] by twenty years but was never used commercially, the isatin-α-anil requisite for indigo or isatin production being obtained from thiocarbanilide by a cheaper process[6] also due to Sandmeyer. Geigy & Co., however, did patent[5] his method of preparing N,N′-diphenylisonitrosoacetamidine by reacting aniline with hydroxylamine hydrochloride and chloral hydrate in water, and they also covered its cyclization to isatin-α-anil in hot sulfuric acid. The tetrachloroamidine (III), treated with hot concentrated sulfuric acid, likewise furnishes 3′,4,5′,6-tetrachloroisatin-α-anil (VI) which is readily hydrolyzed to 4,6-dichloroisatin (V) and 3,5-dichloroaniline (I) by alcoholic hydrochloric acid. The isomeric β-anil (IV) results on fusing 4,6-dichloroisatin (V) with 3,5-dichloroaniline (I).



Sandmeyer's indigo synthesis involves[6] reduction of isatin-α-anil with hydrogen sulfide in acid solution, and treatment of the resulting thioisatin with aqueous sodium carbonate. Applica-

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(1) Villiger, *Ber.*, **42**, 3534 (1909).

(2) Sumpter, *J. Am. Chem. Soc.*, **63**, 2028 (1941).

(3) Sandmeyer, *Helv. Chim. Acta*, **2**, 239 (1919).

(4) Marvel and Hiers, *Org. Syntheses*, Coll. Vol. I, 2nd Ed., p. 327 (1943).

(5) Geigy & Co., *Chem. Centr.*, **II**, 927, 929 (1900).

(6) Fierz-David and Blangey, *Fundamental Processes of Dye Chemistry*, translated by P. W. Vittum from 5th Austrian Ed., Interscience Publishers, Inc., New York, 1949, p. 329.

tions of this procedure to 3′,4,5′,6-tetrachloroisatin-α-anil (VI) produced small amounts of a dark blue substance, presumably 4,4′,6,6′-tetrachloroindigo (IX), which imparts an indigo-blue shade to wool from alkaline hydrosulfite baths.

4,6-Dichloroanthranilic acid (VIII) melts at 178° with decarboxylation (Cf.[1]), and dissolves in aqueous sodium bicarbonate solutions with effervescence. Its constitution (VIII) is confirmed by the production of 2,4-dichlorobenzoic acid (VII) on deamination.

EXPERIMENTAL

α-Isonitroso-3,5-dichloroacetanilide (II). 3,5-Dichloroaniline[7,8] (10 g.) in a 1-liter, spherical flask equipped with a stirrer and a thermometer, was covered with 50 cc. of water and 12 cc. of conc'd hydrochloric acid. To this mixture, stirred mechanically, there was added, first, a solution of 66 g. of anhydrous sodium sulfate and 10.5 g. of chloral hydrate in 224 cc. of water, and, second, a solution of 13 g. of hydroxylamine hydrochloride in 60 cc. of water. The well-stirred suspension was gradually heated to about 100° during 150 minutes; around 54° the solids turned yellow and the mixture was maintained at this temperature during ten minutes. The reaction was allowed to cool while stirring and, after standing overnight, the solids were collected, washed with water, and taken up in 750 cc. of a 1% solution of sodium hydroxide. A small amount, 1.65 g. (14%), of crude N,N′-bis(3,5-dichlorophenyl)isonitrosoacetamidine (III) remained undissolved and was removed by filtration and was washed with 250 cc. of 1% sodium hydroxide solution. The alkaline filtrate and washings were acidified with 25 cc. of concentrated hydrochloric acid diluted with 200 cc. of water, and the white, swollen precipitate was collected, pressed, washed with water, and dried. Yield 10.80 g., 75%, m.p. 190–191° dec. Shorter heating periods resulted in lower yields. Sandmeyer[3] gives m.p. 185° for the crude product.

Crystallized from benzene and recrystallized from dilute alcohol, α-isonitroso-3,5-dichloroacetanilide is a chalky, white solid, m.p. 197° corr., dec. It is very soluble in ether.

Anal. Calc'd for $C_8H_6Cl_2N_2O_2$: N, 12.02. Found: N, 11.87.

4,6-Dichloroisatin (V). To 70 cc. of concentrated sulfuric acid at 90–95° there was added, with mechanical stirring, 20.2 g. of the crude α-isonitroso-3,5-dichloroacetanilide during 30 minutes. The reaction is mildly exothermic, and the rate of addition was such that external heating was unnecessary. The mixture was finally heated at 105° for ten minutes and then was allowed to cool to 30°, stirring continuously. The clear, dark red liquid which resulted was poured into 400 cc. of cold water, and the yellow precipitate which separated was collected, washed with water, and dried. Yield 18.5 g., 98.8%, of a deep yellow powder, m.p. 253–254°. Sandmeyer[3] gives m.p. 250° for the crude isatin.

4,6-Dichloroisatin crystallizes from alcohol (1 g. to 30 cc., first crop 80%) in flat, golden yellow prisms, m.p. 260.5–261° (corr.). It is soluble in ether, sparingly soluble in chloroform, and gives the indophenine reaction. With aqueous sodium hydroxide it turns red-brown and then dissolves slowly to a yellow solution from which acids precipitate it unchanged.

Anal. Calc'd for $C_8H_3Cl_2NO_2$: N, 6.48. Found: N, 6.45.

4,6-Dichloroanthranilic acid (VIII). The crude 4,6-dichloroisatin, 21.3 g., was suspended in a solution of 21.5 g. of sodium hydroxide in 130 cc. of water, and 130 cc. of 3% hydrogen peroxide was slowly added, with gentle swirling. The dark red-brown solid dissolved rapidly with appreciable evolution of heat, and the mixture was cooled by frequently immersing the flask in cold water. After one-half hour the yellow reaction mixture containing a small amount of brown, suspended material was treated with 172 cc. of 5 *N* sulfuric acid, and the precipitate was collected, washed with water, pressed, and dissolved in a solution of 10 g. of sodium bicarbonate in 500 cc. of water. The brown, insoluble material was removed by filtration, and the filtrate was acidified with 30 cc. of 5 *N* sulfuric acid diluted with water. Collected, washed with water, pressed, and dried at 100°, the product, 16.9 g., 83.2%, was a brownish solid, m.p. 177.5–178° dec. No advantage was gained by using the purified isatin.

4,6-Dichloroanthranilic acid crystallizes from benzene (approximately 90 cc. per gram, first crop 90%) in small prisms, m.p. 178–178.5° corr., dec. It evidently decarboxylates to 3,5-dichloroaniline on fusion, for the solidified melts remelt 50–130°, and on a third heating are completely melted below 53°; cf. Villiger.[1] It is very soluble in methanol, ether, concentrated sulfuric acid, or barium hydroxide solution. It dissolves in aqueous sodium bicarbonate with effervescence and is not liberated by acetic acid. On deamination with sodium nitrite and sulfuric acid in alcohol it gave a red-brown, solid product from which boiling water extracted 9% of 2,4-dichlorobenzoic acid, m.p. 163.5–165° after successive recrystallizations from benzene and from hot water, and identical (mixture melting point) with an authentic specimen. (*3,5-Dichloroanthranilic acid dissolves* in aqueous sodium bicarbonate only on warming and is precipitated instantly by acetic acid; on deamination it gave a good yield of 3,5-dichlorobenzoic acid.)

Anal. Calc'd for $C_7H_5Cl_2NO_2$: Cl, 34.42; N, 6.80; Eq. wt., 206.0. Found: Cl, 34.02, 33.91; N, 6.86; Eq. wt., 206.9, 208.0.

In one experiment the alkaline hydrogen peroxide oxidation mixture was inadvertently acidified with dilute hydrochloric acid. The product was found to be contaminated with an appreciable amount of another acid which, judging from the composition of its barium salt, is a trichloroanthranilic acid. This acid is much less soluble in benzene than is 4,6-dichloroanthranilic acid and was separated from the latter by means of its insolubility in barium hydroxide solution. It dissolves in sodium bicarbonate with effervescence. Crystallized from benzene, hot water, or dilute alcohol, or liberated from the barium salt with hydrochloric acid and subsequently precipitated from its solution in sodium bicarbonate, the acid turned yellow with sintering at 160° and decomposed with formation of a red-brown foam at 171–176°. An aqueous solution of the acid was treated with barium chloride solution, and the white, acicular precipitate was collected, washed with water, dried at 120°, and ignited with sulfuric acid.

Anal. Calc'd for $C_{14}H_6BaCl_6N_2O_4 \cdot 2H_2O$: Ba, 21.06. Found: Ba, 21.12.

N,N′-Bis(3,5-dichlorophenyl)isonitrosoacetamidine (III). The by-product from the preparation of α-isonitroso-3,5-dichloroacetanilide (II) outlined above was a brown solid melting within the range 171–179°. It was dissolved in alcohol, filtered from insoluble material, and precipitated by diluting the solution with water. The dried precipitate was dissolved in ether, filtered, the ether removed by evaporation, and the residue stirred with hexane. The latter was decanted and the solid was crystallized thrice from benzene and twice from dilute alcohol to give a pale yellow mass of hair-like needles which melt sharply at 191° corr. to a brown liquid. The greater part of the material was retained in the aqueous alcoholic mother liquors and was recovered as gray masses of large needles, m.p. 191–192°. The substance dissolves slowly in strong, aqueous sodium hydroxide with partial decomposition. Small amounts of this compound were obtained by applying to 3,5-dichloroaniline the method of Sandmeyer[5] for preparing N,N′-diphenylisonitrosoacetamidine from aniline, but the products were very im-

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[7] Willstätter and Schudel, *Ber.*, **51**, 784 (1918). *Cf.* Carlin and Forshey, Jr., *J. Am. Chem. Soc.*, **72**, 798 (1950).

[8] Kremer and Bendich, *J. Am. Chem. Soc.*, **61**, 2660 (1939).

pure, and in some experiments α-isonitroso-3,5-dichloroacetanilide was the sole product.

Anal. Calc'd for $C_{14}H_9Cl_4N_3O$: C, 44.59; H, 2.41; Cl, 37.61; N, 11.15. Found: C, 44.87, 44.50; H, 2.14, 2.35; Cl, 37.24; N, 10.97.

3′,4,5′,6-Tetrachloroisatin-α-anil (VI). A solution of 0.5 g. of N,N′-bis(3,5-dichlorophenyl)isonitrosoacetamidine (III) in 25 cc. of concentrated sulfuric acid was heated to 100°, allowed to cool, and poured into 500 cc. of water. The red precipitate which formed was removed by filtration, washed with water, and dried, and amounted to 0.390 g. (82%) of the crude anil melting below 260°. This product was extracted with 60 cc. of benzene in a Soxhlet apparatus; the first crop, 0.277 g., m.p. 283–285° (corr.), began to crystallize before the operation was completed, and a second crop, m.p. 219–279°, obtained by inspissating the dark red benzene mother liquor, was easily purified by washing with boiling alcohol. The crude anil and the yellow, dilute sulfuric acid solution accompanying it both contain small amounts of 4,6-dichloroisatin; this is removed from the anil by washing with aqueous sodium hydroxide, and from the solution by extraction with ether.

3′,4,5′,6-Tetrachloroisatin-α-anil crystallizes from benzene (1 g. to 225 cc., recovery 90%) in dark red masses of small needles with a graphitic luster, m.p. 285.5–286° (corr.). It sublimes with slight decomposition, the colored vapor condensing to small red needles. It is sparingly soluble in boiling alcohol and practically insoluble in boiling glacial acetic acid. Dilute nitric or concentrated hydrochloric acid turns it yellow, the red color being restored on adding water. It dissolves readily in alcoholic potassium hydroxide to a dark blue solution which turns pink and then precipitates the red compound unchanged on dilution with water; this reaction is useful for detecting small amounts of the anil but it did not prove promising as a method of purification.

Anal. Calc'd for $C_{14}H_6Cl_4N_2O$: Cl, 39.39; N, 7.78. Found: Cl, 39.30; N, 7.97.

Hydrolysis of 3′,4,5′,6-tetrachloroisatin-α-anil (VI). The pure anil (0.1 g.) dissolved readily in 5 cc. of boiling alcohol containing 5 drops of concentrated hydrochloric acid. The yellow solution was evaporated to dryness and the yellow, crystalline residue was treated with aqueous sodium hydroxide solution. The solids turned dark red and then dissolved partially to a yellow solution leaving a heavy, white, granular component undissolved. The latter, collected, washed with water, and allowed to dry at room temperature, amounted to 0.0297 g., 66%, of 3,5-dichloroaniline (I), m.p. 51° corr. The yellow solution and washings, acidified with hydrochloric acid, yielded a yellow precipitate, 0.0558 g., 93%, after washing and drying, of 4,6-dichloroisatin (V), m.p. 258–259° (corr.). The identities of these products were confirmed by mixture melting points with authentic specimens.

Reduction of the anil (VI) in dilute sulfuric acid with hydrogen sulfide was effected by the method of Sandmeyer as described in Fierz-David.[6] The yields were poor and the product was separated from unreacted anil by washing it with alcoholic potassium hydroxide. The dark blue product, presumably 4,4′,6,6′-tetrachloroindigo (IX), behaved like a typical vat dye. The shades which it imparted to wool from alkaline hydrosulfite baths were lighter than those resulting from Ciba Blue 2B (5,5′,7,7′-tetrabromo-) and Brilliant Indigo B (5,5′,7,7′-tetrachloro-), and more nearly matched the blue of indigo itself.

3′,4,5′,6-Tetrachloroisatin-β-anil (IV). A mixture of 0.130 g. of 4,6-dichloroisatin and 0.117 g. of 3,5-dichloroaniline was heated in a test tube over a bare flame until it just melted and resolidified; the elimination of water was evident. Washing the solid with boiling alcohol left 0.182 g. (84%) of crude, bright red-brown product which crystallized from nitrobenzene in small needles, m.p. 311.5° (corr.), with a color like that of azobenzene. The substance is insoluble in aqueous sodium hydroxide but dissolves readily in alcoholic potassium hydroxide to orange-colored solutions. Prolonged heating of the isatin with the aniline in alcohol, alone and with iodine present,[9] yielded only negligibly small amounts of the anil.

Anal. Calc'd for $C_{14}H_6Cl_4N_2O$: N, 7.78. Found: N, 7.66.

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[9] Knoevenagel, *J. prakt. Chem.*, [2], 89, 46 (1914).