which 3.0 g. (0.130 mole) of sodium had previously been dissolved. After three days at room temperature (25°) the solution was made neutral to phenolphthalein with 1 *N* sulfuric acid and then concentrated *in vacuo*, the residue being held at 55° and a pressure of 1.0 mm. to remove the major part of the methyl benzoate. The white, crystalline mass was then extracted with four successive 400-ml. portions of boiling ethyl acetate. The combined extracts were concentrated to a volume of approximately 80 ml. and refiltered to remove a slight turbidity. On cooling, the filtrate deposited radial masses of needles amounting to 3.63 g.; a further 0.55 g. of material was obtained on concentration of the mother liquor, giving a total yield of 90%. Recrystallized thrice from ethyl acetate and once from a mixture of 2-butanone and benzene the 1,5:3,6-dianhydro-D-galactitol formed either hair-like needles or feathery masses melting at 145–146° and showing in water a rotation of +40.2° (*c*, 2.054).

The dianhydride is readily soluble in water, alcohol, hot ethyl acetate and hot 2-butanone; insoluble in benzene and pentane. A sample was found to sublime slowly at a pressure of approximately 1 mm. and a temperature of 117°.

Anal. Calcd. for $C_6H_{10}O$: C, 49.31; H, 6.90. Found: C, 49.47; H, 7.07.

The Stability of 1,5:3,6-Dianhydro-D-galactitol toward Sodium Metaperiodate.—The technique of Jackson and Hudson[20] was employed. 1,5:3,6-Dianhydro-D-galactitol (0.2047 g.) was dissolved in a few ml. of water, treated with 5 ml. of approximately 0.45 *M* sodium metaperiodate solution and the mixture diluted with water to 25.0 ml. After seventeen hours at room temperature (27°) a 5.0-ml. aliquot was titrated for acid and oxidant; 0.07 ml. of 0.1 *N* alkali was required both for the solution and for a blank. Similarly, the aliquot required 5.84 ml. of 0.1 *N* iodine while the blank needed 5.85 ml.

2,4-Dibenzoyl-1,5:3,6-dianhydro-D-galactitol.—Benzoylation of 1.04 g. of 1,5:3,6-dianhydro-D-galactitol with benzoyl chloride in pyridine in the usual fashion furnished 2.05 g. (81%) of the dibenzoate as fine needle-like crystals. Recrystallized three times from 3 parts of 95% ethanol the substance melted at 103° and showed in chloroform a rotation of +101° (*c*, 2.04). The 2,4-dibenzoyl-1,5:3,6-dianhydro-D-galactitol is soluble in acetone and hot ethanol; insoluble in pentane, water and cold alcohol.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.85; H, 5.40.

2,4-Ditosyl-1,5:3,6-dianhydro-D-galactitol.—Pure 1,5:3,6-dianhydro-D-galactitol (0.5393 g., 0.00369 mole) was dissolved in 5 ml. of dry pyridine and treated with 2.0 g. (0.0105 mole) of pure *p*-toluenesulfonyl chloride. After standing overnight at room temperature and for one hour at 45° the excess tosyl chloride was decomposed with a chip of ice and the reaction mixture diluted with chloroform. The solution was washed successively with water, 3 *N* sulfuric acid, aqueous sodium bicarbonate and then dried over anhydrous sodium sulfate. After filtration through carbon and concentration *in vacuo* at 50° to a colorless sirup, the material was twice dissolved in absolute ethanol and concentrated *in vacuo*. Repeated cooling and scratching of a solution of the residue in 15 ml. of ethanol eventually induced the crystallization of 1.40 g. (84%) of product. Two recrystallizations from 9 parts of ethanol gave well-formed needles melting at 97% and showing in chloroform a rotation of +5.6° (*c*, 2.14). The 2,4-ditosyl-1,5:3,6-dianhydro-D-galactitol is readily soluble in ethyl acetate, acetone and hot alcohol; insoluble in cold alcohol, pentane and water.

Anal. Calcd. for $C_{20}H_{22}O_8S_2$: C, 52.85; H, 4.88. Found: C, 52.67; H, 4.98.

Summary

2,3,4 - Tribenzoyl - 6 - tosyl - 1,5 - anhydro - D-galactitol has been synthesized from 1,5-anhydro-D-galactitol and the unusual stability of its primary tosyloxy group toward sodium iodide in acetone discussed. Alkaline treatment of this ester gives 1,5:3,6-dianhydro-D-galactitol, the position of the newly introduced ring being proven by the stability of the substance to the action of periodate. 1,5:3,6-Dianhydro-D-galactitol has been further characterized through its dibenzoate and ditosylate.

BETHESDA, MARYLAND RECEIVED AUGUST 8, 1949

(20) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in the Sulfone Series. V.[1] 2,8-Diaminophenothiazine-5-dioxide

BY J. G. MICHELS AND E. D. AMSTUTZ

The investigation of compounds structurally similar to 4,4′-diaminodiphenyl sulfone has been under way in this Laboratory for several years. The compounds previously prepared and studied[1,2,3,4] include sulfones with a direct linkage between the *o,o′*-positions and several with an *o,o′*-carbonyl bridge. The present paper describes the preparation and proof of structure of another member of this series, namely, 2,8-diaminophenothiazine-5-dioxide (VIII).

Baltzly, Harfenist and Webb[5] reported that the Friedel–Crafts reaction between phenothiazine and acetyl chloride in carbon disulfide led to an acetylphenothiazine. These authors have discussed the evidence which indicates that substitution took place at the 2-position.[6]

By increasing the ratio of reactants, it has been found possible to utilize this reaction in the preparation of 2,8-diacetylphenothiazine (II). The conversion of this compound to the desired diamino compound is represented in the chart.

The yields in the Friedel–Crafts reaction varied between 35 and 50%. These variations are probably due to the grain size of the aluminum chloride used and to the gummy nature of the reaction product which always enclosed some unreacted aluminum chloride. From the crude reaction product could also be separated some of the 2-acetylphenothiazine as reported above.[1] Oxidation of the triacetylphenothiazine (I) to the di-

(1) For the preceding paper in this series see Amstutz, Fehnel and Hunsberger, THIS JOURNAL, **70**, 133 (1948).

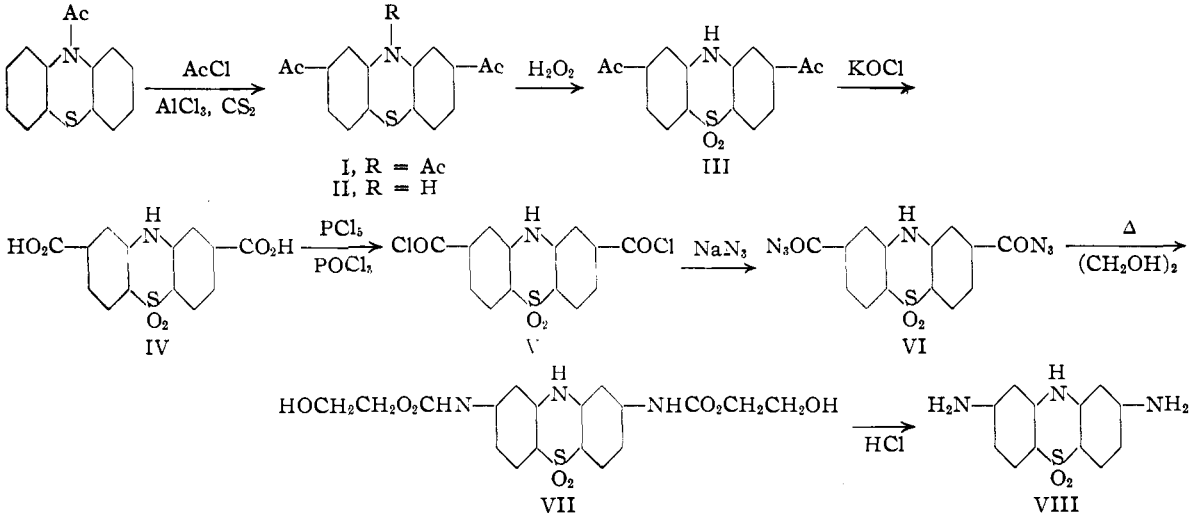
(2) Neumoyer and Amstutz, *ibid.*, **69**, 1920 (1947).

(3) Amstutz, Fehnel and Woods, *ibid.*, **69**, 1922 (1947).

(4) Amstutz and Neumoyer, *ibid.*, **69**, 1925 (1947).

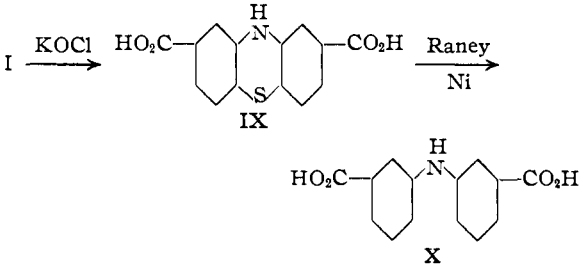
(5) Baltzly, Harfenist and Webb, *ibid.*, **68**, 2673 (1946).

(6) See also Gilman, Van Ess and Shirley, *ibid.*, **66**, 1214 (1944).



acetylphenothiazine dioxide (III) proceeded smoothly and in excellent yield by the usual method using 30% hydrogen peroxide. The haloform reaction converted III in very good yield to phenothiazine-5-dioxide-2,8-dicarboxylic acid (IV), which on treatment with phosphorus pentachloride and phosphorus oxychloride gave the acid chloride V. Treatment of V in dry dioxane with sodium azide gave the corresponding azide (VI). The Curtius rearrangement of the azide was first carried out in dry xylene to form the isocyanate, but it was not found possible to hydrolyze this compound to the free amine. The conversion of the azide to the free amine was accordingly carried out *via* the urethan (VII). The use of ethylene glycol as the rearrangement medium was found necessary when it was found that the rearrangement did not occur at the boiling point of ethanol.

Since there was no definite proof of the positions taken by the entering acetyl groups in the Friedel–Crafts reaction, it seemed desirable to develop an unambiguous proof that the final diamino compound was actually the 2,8-isomer. It was first attempted to prove that the two acetyl groups were not on the same ring by conversion of the triacetylphenothiazine (I) into phenothiazine-2,8-dicarboxylic acid (IX) and desulfurization of this acid with Raney nickel to diphenylamine-3,3′-dicarboxylic acid (X). However, attempts to synthesize this previously unreported acid were unsuccessful.



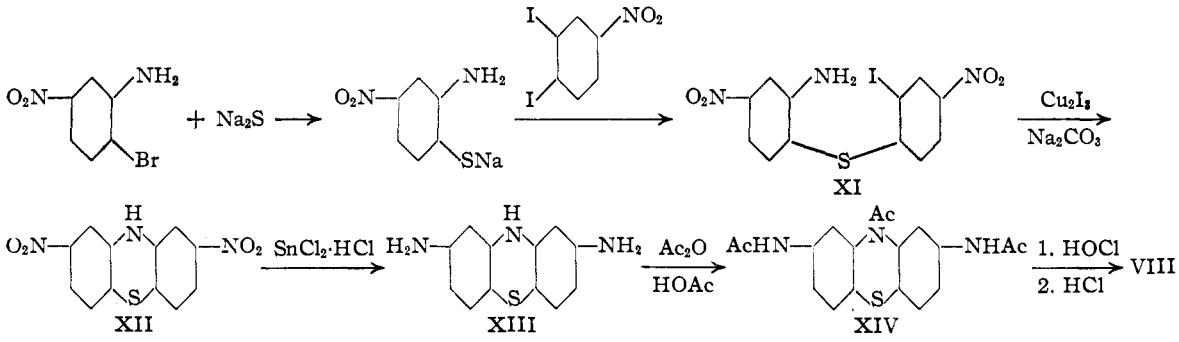
A proof of structure involving the synthesis of the diamino compound by ring closure of 2,2′-diamino-4,4′-diiododiphenyl sulfide was also attempted. This method failed when it was found that 2,8-diiodophenothiazine could not be produced by ring closure of the above sulfide either by heating its hydrochloride or its tin complex. These findings are in agreement with those of Matsumura[7] who found that 2,2′,4,4′-tetraaminodiphenyl ether could not be cyclized by heating the hydrochloride either alone or with zinc chloride. In contrast to this is the ease with which 2,2′-diaminodiphenyl[8] and 2,2′-diaminodiphenylamine[9] are cyclized to carbazole and phenazine, respectively.

The unequivocal synthesis represented in the following scheme was finally realized.

The ring closure of 2-amino-2′-iodo-4,4′-dinitrodiphenyl sulfide (XI) to 2,8-dinitrophenothiazine (XII) is the first reported closure of a phenothazine ring from a substituted diphenyl sulfide. Hodgson[10] unsuccessfully tried to make 2,8-diaminophenothiazine by ring closure of 2,2′-dichloro-4,4′-dinitrodiphenyl sulfide with ammonia and with potassium phthalimide and of 2-acetamino-2′-chloro-4,4′-dinitrodiphenyl sulfide. Earlier workers[11,12,13,14] believed they had obtained phenothiazines by ring closure of various diphenyl sulfides and sulfones, but Smiles and his co-workers[15] proved that the actual ring closure occurred on the diphenylamine thiol or sulfinic acid produced by rearrangement of the sulfide or sulfone.

The possibility of the Smiles rearrangement having occurred during the ring closure of the above sulfide (XI) may be ruled out for the fol-

(7) Matsumura, THIS JOURNAL, **52**, 3199 (1930).
(8) Tauber, *Ber.*, **24**, 197 (1891).
(9) Eckert and Steiner, *Monatsh.*, **35**, 1153 (1914).
(10) Hodgson, Dodgson and Smith, *J. Chem. Soc.*, 1104 (1948).
(11) Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913).
(12) Kehrmann and Steinberg, *ibid.*, **44**, 3011 (1911).
(13) Mitsugi, Beyschlag and Mohlau, *ibid.*, **43**, 927 (1910).
(14) Mohlau, Beyschlag and Kohres, *ibid.*, **45**, 136 (1912).
(15) Evans and Smiles, *J. Chem. Soc.*, **131**, 1263 (1935).



lowing reasons: (1) all of the rearrangements of this type known to occur take place in either aqueous or alcoholic alkali hydroxides and (2) amino sulfides such as 2-amino-2′-nitrodiphenyl sulfide and various of its substitution products do not undergo the rearrangement whereas the corresponding sulfones and/or N-acetyl derivatives do. Approaching from another viewpoint, if rearrangement of the above aminoiododinitrodiphenyl sulfide did take place, the only possible product would be 2,7-dinitrophenothiazine. The identity of the diaminophenothiazine dioxide from this ring closure with that obtained from the Friedel–Crafts series would thus indicate that the acetyl groups entering in the Friedel–Crafts reaction assumed positions, in the one case, meta to the nitrogen and, in the other, para to the nitrogen. The great improbability of such unsymmetrical substitution is evident.

Reduction of the dinitrophenothiazine (XII) to the corresponding diamino compound (XIII) was easily carried out with stannous chloride. Since the free amino compound is rapidly oxidized in air, it was immediately acetylated to 2,8-diacetamino-10-acetylphenothiazine (XIV). Attempted oxidations of the latter compound and of the dinitro compound (XII) with hydrogen peroxide led in both cases to compounds believed to be in an intermediate stage of oxidation. Finally, hypochlorous acid oxidation of XIV followed by hydrolysis of the acetyl groups afforded a small amount of 2,8-diaminophenothiazine-5-dioxide. Comparison of this compound with that obtained from the Friedel–Crafts series by decomposition point, mixed decomposition point and analyses showed them to be identical.

Acknowledgment.—The authors wish to express their appreciation to the Wm. S. Merrell Co. of Cincinnati, Ohio, for the grant which made a part of this work possible.

Experimental[16]

2,8,10-Triacetylphenothiazine (I).—Forty-eight grams (0.2 mole) of 10-acetylphenothiazine[17] and 60 ml. (0.9 mole) of acetyl chloride were placed in a two-liter ground-glass flask with 1 liter of dry carbon disulfide. In one portion was added 266 g. (2 moles) of *granular* anhydrous aluminum chloride and a condenser carrying a drying tube was fitted into place and the mixture refluxed for fifteen hours. The carbon disulfide layer was decanted and the dark tarry reaction mixture poured onto ice containing hydrochloric acid. After decomposition was complete, the product was filtered off and washed with ether until the washings were colorless. Evaporation of the ether extract gave a sirup which, on hydrolysis with hydrochloric acid, gave 25 to 27 g. (52–56%) of 2-acetylphenothiazine.[5] The grayish residue from the ether extraction was dissolved in alcohol and decolorized with charcoal to give 19 to 38 g. (30–55%) of 2,8,10-triacetylphenothiazine. This material is suitable for further reactions. For analysis, a sample was recrystallized twice from alcohol to give tannish needles melting at 199–202°. A sample prepared by acetylation of pure 2,8-diacetylphenothiazine was pale yellow and melted at 199.5–201.5° (dec.).

Anal. Calcd. for $C_{18}H_{15}O_3NS$: S, 9.85; N, 4.94; C, 66.5; H, 4.65. Found: S, 9.61; N, 4.83; C, 66.5; H, 4.51.

By refluxing an alcoholic solution of 2,8,10-triacetylphenothiazine with 5 ml. of concentrated hydrochloric acid there was obtained brick-red needles of 2,8-diacetylphenothiazine, m. p. 249–251° (dec.).

Anal. Calcd. for $C_{16}H_{13}O_2NS$: S, 11.3; N, 4.31. Found: S, 11.1; N, 4.20.

2,8-Diacetylphenothiazine-5-dioxide (III).—To a solution of 32.5 g. (0.1 mole) of 2,8,10-triacetylphenothiazine in 300 ml. of glacial acetic acid was added in one portion 100 ml. of 30% hydrogen peroxide. The dark solution was heated slowly until a steady, moderate rate of bubbling occurred. The heat was adjusted to keep the reaction at this speed until most of the bubbling was over. During this time the color became light yellow. The solution was then raised to reflux for one hour and the product obtained by pouring the solution into water. Recrystallization from alcohol gave 27 to 30 g. (85–95%) of yellow needles melting at 309–312° (dec.).

Anal. Calcd. for $C_{16}H_{13}O_4NS$: S, 10.2; N, 4.44. Found: S, 9.94; N, 4.35.

Phenothiazine-5-dioxide-2,8-dicarboxylic Acid (IV).—A suspension of 16 g. (0.05 mole) of 2,8-diacetylphenothiazine-5-dioxide in 1 liter of dioxane was stirred at room temperature while 300 ml. of potassium hypochlorite, containing 0.112 g./ml. (0.367 mole), was added in 50-ml. portions at such a rate that the temperature did not rise over 40°. When all of the hypochlorite was in, the solution was stirred for one hour more and then allowed to separate into two layers. The lower aqueous layer was drawn off, excess hypochlorite destroyed with sodium bisulfite, and acidified with hydrochloric acid. The product was collected, washed with water and redissolved in 10% sodium bicarbonate solution. After boiling with charcoal, the product was again precipitated with acid, collected and dried. It was then washed repeatedly with water until the washings gave no further test for chloride ions. Since the acid is extremely insoluble and could not be crystallized, this was the only method available for purification. The acid thus obtained was cream in color, weighed 14 to 15 g. (90–95%) and decomposed above 360°.

(16) All melting points are corrected unless otherwise designated.
(17) Bernthsen, *Ann.*, **230**, 73 (1885).

Anal. Calcd. for $C_{14}H_9O_6NS$: S, 10.0; N, 4.39; C, 52.7; H, 2.84. Found: S, 9.85; N, 4.21; C, 52.2; H, 2.85.

Phenothiazine-5-dioxide-2,8-dicarboxylic Acid Chloride (V).—Thirty-two grams (0.1 mole) of phenothiazine-5-dioxide-2,8-dicarboxylic acid, 50 g. (0.24 mole) of phosphorus pentachloride and 150 ml. of phosphorus oxychloride were refluxed together for twenty hours. After cooling, the reaction product was filtered on a sintered glass funnel with protection from moisture, washed with phosphorus oxychloride and with dry ether and immediately dried to constant weight in a vacuum desiccator over potassium hydroxide. Due to its insolubility and reactivity this product could not be further purified. It was yellow in color, weighed 27 to 30 g. (75–85%) and decomposed above 360°.

Anal. Calcd. for $C_{14}H_7O_4NSCl_2$: N, 3.93; Cl, 19.9. Found: N, 3.73; Cl, 19.8.

Phenothiazine-5-dioxide-2,8-dicarboxylic Acid Azide (VI).—A solution of 14 g. (0.03826 mole) of the acid chloride (V) in 600 ml. of anhydrous dioxane was cooled to 20–25° and a solution of 6 g. (0.0927 mole) of sodium azide in 15 ml. of water was added in one portion. After standing for five minutes, water was added to precipitate the product which was collected and dried. Due to its instability it could not be further purified. It was cream in color, weighed 14 g. (96.5%) and puffed violently when heated in air; m. p. 365–375° (dec.) after first darkening at 355° (melting point block, uncor.).

Anal. Calcd. for $C_{14}H_7O_4N_7S$: S, 8.67. Found: S, 8.43.

Phenothiazine-5-dioxide-2,8-diisocyanate.—A suspension of one-half gram of VI in 20 ml. of dry xylene was heated gradually to reflux over a period of ten hours. Bubbles were evolved at 85–90°. The product did not puff on heating and became brown with melting at 335–340°, decomposing at 340–350°. Analysis indicated a purity of about 87%.

Anal. Calcd. for $C_{14}H_7O_4N_3S$: N, 13.4. Found: N, 11.7.

Refluxing in concentrated and dilute hydrochloric acid and in acetic acid–acetic anhydride yielded little to no amine or acetamide.

Phenothiazine-5-dioxide-2,8-bis-(β-hydroxyethyl Carbamate) (VII).—A suspension of 14 g. (0.038 mole) of the acid azide (VI) in 100 ml. of ethylene glycol was heated in an oil-bath at a temperature of 110–120° until the evolution of nitrogen had ceased and then at 140–150° for ten minutes. The dark solution was filtered and poured into water to precipitate the product which was collected and used without further purification. For purification, the product was dissolved in alcohol, boiled with charcoal and the filtrate diluted with water at the boiling point. Cooling gave 11 g. (67%) of white product decomposing at 270–272°.

Anal. Calcd. for $C_{18}H_{19}O_8N_3S$: S, 7.33; N, 9.38. Found: S, 7.21; N, 9.47.

2,8-Diaminophenothiazine-5-dioxide (VIII).—A mixture of 2.2 g. (0.005 mole) of the above urethan and 10 ml. of concentrated hydrochloric acid was refluxed together for six hours, diluted with water, heated to boiling and filtered. The red solution was decolorized with charcoal, made alkaline and cooled. There separated 0.8 g. (60%) of colorless crystals, m. p. 355–356° (dec.), with previous darkening (melting point block, uncor.).

Anal. Calcd. for $C_{12}H_{11}O_2N_3S$: S, 12.2; N, 16.0; C, 54.8; H, 4.22. Found: S, 12.35; N, 15.9; C, 54.8; H, 4.12.

Phenothiazine-2,8-dicarboxylic Acid (IX).—To a stirred suspension of 4 g. (0.0123 mole) of 2,8,10-triacetylphenothiazine in 300 ml. of dioxane at room temperature was added in 25-ml. portions 100 ml. (0.0937 mole) of a solution of potassium hypochlorite containing 0.089 g./ml. The temperature did not rise above 35°. When all of the hypochlorite was in, the solution was stirred for one hour more and then allowed to separate into two layers. After addition of sodium bisulfite to the lower layer, the product was precipitated with hydrochloric acid and collected. The acid was redissolved in 10% sodium bicarbonate solution, boiled with charcoal and reprecipitated. It was dried and washed repeatedly until all the chloride ion was removed. The purified product weighed 3.3 g. (93.5%) and decomposed above 360°. On drying the tan acid in a drying pistol, the color became considerably darker. *Anal.* Calcd. for $C_{14}H_9O_4NS$: S, 11.1; N, 4.88. Found: S, 10.75; N, 4.54. These analyses are low probably because of the hygroscopic nature of the material.

Diphenylamine-3,3′-dicarboxylic Acid (X).—Three and seven-tenths grams (0.012 mole) of phenothiazine-2,8-dicarboxylic acid was dissolved in a minimum amount of 10% sodium bicarbonate and the solution diluted to about 25 ml. Approximately 25 to 30 g. of "special" Raney nickel[18] was added and the mixture refluxed for six hours. The nickel was filtered off and the filtrate acidified to obtain the product. After drying, the product was washed well with water and redried. The yield was 3 g. (93.5%) of green product decomposing above 300°.

Anal. Calcd. for $C_{14}H_{11}O_4N$: N, 5.44. Found: N, 5.27.

Attempted Syntheses of Diphenylamine-3,3′-dicarboxylic Acid. a.—A mixture of 0.262 g. (0.001 mole) of methyl *m*-iodobenzoate, 0.151 g. (0.001 mole) of methyl *m*-aminobenzoate and a small amount of copper powder was heated in an oil-bath at 160–170° for twenty-four hours. The dark product was boiled for fifteen minutes with 10% alkali, filtered and acidified to precipitate 0.07 g. of a gray product which had a neutral equivalent of 151. Calculated for diphenylaminedicarboxylic acid, 129; for *m*-iodobenzoic acid, 124; for *m*-aminobenzoic acid, 138. Further work on the identification of this product was not attempted.

b.—A mixture of 3.58 g. (0.0137 mole) of methyl *m*-iodobenzoate, 2.64 g. (0.0137 mole) of methyl *m*-acetaminobenzoate, 0.5 g. of cuprous iodide and 1.5 g. of sodium carbonate was heated in an oil-bath at 185–190° for eighteen hours. At the end of this time, 10 ml. of water and 0.5 g. of potassium hydroxide were added and the mixture refluxed for two hours. The solution was diluted, boiled with charcoal and filtered. Addition of hydrochloric acid precipitated a colorless solid which was recrystallized from 1 liter of boiling water. The white crystals thus obtained contained iodine and checked in melting point with *m*-iodobenzoic acid.

2,2′-Dinitro-4,4′-diiododiphenyl Sulfide.—To a hot solution of 3.75 g. (0.01 mole) of 2,5-diiodonitrobenzene[19,20,21] in 45 ml. of alcohol was added a solution of 1.2 g. (0.005 mole) of sodium sulfide nonahydrate in 2 ml. of water. During the two-hour period of refluxing which followed, the red color first produced disappeared and a yellow precipitate formed. This was filtered from the hot solution and washed well with hot alcohol. The yield of yellow crystals was 1.23 g. (46.6%) melting at 194.5–197°. For analysis, this material was recrystallized twice from glacial acetic acid with 90% recovery to give a product melting at 195.6–196.8°.

Anal. Calcd. for $C_{12}H_6O_4N_2SI_2$: N, 5.31; I, 48.1. Found: N, 5.31; I, 47.9, 48.4.

2,2′-Diamino-4,4′-diiododiphenyl Sulfide.—A suspension of 13.6 g. (0.06 mole) of stannous chloride dihydrate in 75 ml. of glacial acetic acid was clarified by passing hydrogen chloride through until all the solid had dissolved. This solution was added to a stirred suspension of 3.92 g. (0.00744 mole) of the above dinitro compound in 25 ml. of acetic acid at 85–90°. By cooling and heating as necessary the temperature was held in this range for two hours, after which the reaction mixture was cooled and the product collected. Dilution of the acetic acid filtrate gave a small amount of additional product. The total product

(18) Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1015 (1943).

(19) Brenans, *Compt. rend.*, **135**, 178 (1902).

(20) Sandin, Drake and Leger, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 196.

(21) Niemann and Redemann, THIS JOURNAL, **63**, 1550 (1941).

was treated with 10% potassium hydroxide to break the tin complex, then filtered and washed free of base. Purification was accomplished by dissolving the diamino compound in alcohol, decolorizing with charcoal and saturating the filtrate with water at the boiling point. There was thus obtained 1.5 g. (43.2%) of the desired product melting at 152–153.5°. A second purification raised the melting point to 154–155.5°.

Anal. Calcd. for $C_{12}H_{10}N_2SI_2$: N, 5.93; I, 54.2. Found: N, 5.99; I, 54.1, 54.6.

Attempted Ring Closures of 2,2′-Diamino-4,4′-diiododiphenyl Sulfide. a.—A small amount of the diamino compound was dissolved in anhydrous ether and hydrogen chloride passed in to precipitate the hydrochloride. Analysis showed 10.6% chlorine. A sample of 0.3095 g. of this hydrochloride was mixed with 0.1595 g. of the free amine to give a mixture corresponding to the monohydrochloride (7.0%). A small amount of this mixture was heated slowly in an oil-bath. No change occurred until 140° was reached when the mixture started to darken. On holding this temperature, the color deepened until it was all black. Hydrogen chloride was evolved simultaneously.

An attempt was made to introduce this mixture into a bath at 150° but again decomposition occurred.

b.—A mixture of 0.77 g. (0.001644 mole) of the diamino compound, 0.78 g. (0.00347 mole) of stannous chloride dihydrate, 35 ml. of concentrated hydrochloric acid and 5 ml. of water was heated in a sealed tube at 135–140° for four hours. After cooling, the mixture was made alkaline and the product collected, washed and dried. A melting point and mixed melting point showed it to be unchanged starting material.

2-Amino-2′-iodo-4,4′-dinitrodiphenyl Sulfide (XI).—To a boiling solution of 38.2 g. (0.176 mole) of 2-bromo-5-nitroaniline[22] in 700 ml. of alcohol was added in one portion a hot solution of 57.0 g. (0.211 mole) of sodium sulfide nonahydrate and 17.7 g. (0.211 mole) of sodium bicarbonate in 300 ml. of water. The red solution was refluxed on the steam-bath for one hour and then was added a hot solution of 17.7 g. of sodium bicarbonate in 150 ml. of water and refluxing was continued for five minutes. A boiling solution of 66.0 g. (0.176 mole) of 3,4-diiodonitrobenzene[21,23] in 650 ml. of alcohol was added and the mixture refluxed for two hours more. At the end of this time, the precipitated product was filtered from the hot solution and washed with 200 ml. of hot 70% alcohol, then thoroughly with water. After drying, the crude product weighed 51.5 g. and melted at 197–208°. A single recrystallization from acetic acid using charcoal gave a deep yellow product melting at 209–211° and weighing 35.8 g. From the acetic acid liquors was obtained an additional 6.4 g. giving a total yield of 57.5%. A second recrystallization gave a sample melting at 212–213.5°

Anal. Calcd. for $C_{12}H_8O_4N_3SI$: S, 7.69; N, 10.1. Found: S, 7.66; N, 9.85.

2,8-Dinitrophenothiazine (XII).—An intimate mixture of 33.4 g. (0.08 mole) of 2-amino-2′-iodo-4,4′-dinitrodiphenyl sulfide, 4 g. (0.0105 mole) of cuprous iodide and 12 g. of anhydrous sodium carbonate was heated in a bath held at 220–230° for thirty hours. At the end of this time, the melt was removed, broken up and washed with water. After drying, the crude material weighed 30.4 g. It was extracted continuously in a hot extractor with a total of 750 ml. of acetic acid in three portions. After cooling, the material insoluble in the acetic acid was filtered off and combined with the extract obtained below. Evaporation and dilution of the acetic acid gave 6.7 g. of a reddish solid which was probably incompletely reacted material. The residue from the acetic acid extraction was washed and dried and extracted in the hot with nitrobenzene. Cooling the dark red solution gave maroon platelets which weighed 11.7 g. (50.7%). For analysis, a second recrystallization from nitrobenzene gave a product decomposing at 355–360° after subliming at about 315° (melting point block, uncor.).

(22) Wheeler, *Am. Chem. J.*, **17**, 700 (1895).

(23) Willgerodt and Arnold, *Ber.*, **34**, 3343 (1901).

Anal. Calcd. for $C_{12}H_7O_4N_3S$: S, 11.1; N, 14.5; C, 49.8; H, 2.44. Found: S, 10.9; N, 14.35; C, 49.7; H, 2.79.

2,8-Diacetamino-10-acetylphenothiazine (XIV).—A solution of 26.3 g. (0.138 mole) of stannous chloride dihydrate in 125 ml. of glacial acetic acid was prepared by passing hydrogen chloride through the suspension until all of the solid had dissolved. This solution was added in one portion to a suspension of 5 g. (0.0173 mole) of 2,8-dinitrophenothiazine in 500 ml. of acetic acid heated on a steam-bath. After two hours, the mixture was cooled and the tannish product collected and washed with acetic acid. It was then dissolved in 150 ml. of water and stirred with charcoal for five minutes. The clear yellow solution obtained by filtration was placed in a centrifuge bottle and worked as much as possible under nitrogen. To the solution was added 50% potassium hydroxide until it was strongly alkaline. The precipitated 2,8-diaminophenothiazine was centrifuged, washed with alkali and then with water and finally brought upon a filter and washed. It was rapidly transferred to a flask with 200 ml. of 1:1 acetic acid: acetic anhydride and refluxed for three hours. The dark solution was evaporated to about 100 ml. and then diluted to 1 liter with water. The gray product was collected, dissolved in alcohol and treated with charcoal. The colorless solution obtained was saturated with water at the boiling point to give 2.7 g. (44%) of the desired product. A second purification gave a product decomposing at 301–302° (melting point block, uncor.).

Anal. Calcd. for $C_{18}H_{17}O_3N_3S$: S, 9.02; N, 11.8. Found: S, 8.80; N, 11.5.

2,8-Diaminophenothiazine-5-dioxide (VIII).—To a solution of 1.3 g. (0.00366 mole) of the above acetamino compound in 60 ml. of acetic acid at 80° was added in two portions 20 ml. (0.0141 mole) of potassium hypochlorite solution (made by dissolving 2.5 g. of chlorine in a solution of 5.4 g. of potassium hydroxide in 50 ml. of water). Pouring the red solution into 500 ml. of water threw down 1 g. of a brown precipitate which was refluxed with 20 ml. of 1:1 hydrochloric acid for three hours. At the end of this period, the mixture was diluted to 150 ml. and the insoluble material removed. The filtrate was boiled with charcoal and made alkaline to precipitate the reddish product. This was dissolved in 1:1 hydrochloric acid and again decolorized and the clear yellow filtrate made just alkaline. A reddish precipitate was formed and removed. By keeping the solution hot and adjusting the *p*H back and forth, practically all of this reddish material could be removed. The resulting solution was again treated with charcoal and the colorless solution made alkaline and cooled. There separated 17 mg. of needles decomposing at 352–355° with previous graying (melting point block uncor.). A mixed decomposition point with the diaminophenothiazine dioxide made by the Friedel–Crafts series was unchanged.

Anal. Calcd. for $C_{12}H_{11}O_2N_3S$: N, 16.0; C, 54.8; H, 4.22. Found: N, 16.2; C, 55.15; H, 4.09.[24]

Summary

The preparation of 2,8-diaminophenothiazine-5-dioxide by means of the Friedel–Crafts reaction of phenothiazine is described.

A proof of structure by means of ring closure of 2-amino-2′-iodo-4,4′-dinitrodiphenyl sulfide was also successfully carried out.

Several unsuccessful proofs of structure were also attempted. These included the attempted ring closure of 2,2′-diamino-4,4′-diiododiphenyl sulfide and the synthesis of diphenylamine-3,3′-dicarboxylic acid, a degradation product obtained from an intermediate in the Friedel–Crafts series.

BETHLEHEM, PENNSYLVANIA RECEIVED JUNE 29, 1949

(24) Analyses by Dr. Carl Tiedcke.