# The Synthesis and Study of New Antibiotics in the Phenothiazine Group.

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# THE SYNTHESIS AND STUDY OF NEW ANTIBIOTICS IN THE PHENOTHIAZINE GROUP

by

Julian Getz Michels

A DISSERTATION

Presented to the Graduate Faculty

of Lehigh University

in Candidacy for the Degree of

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Professor in Charge

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H H Newell — Chairman

E D Amstutz

Warren McEwing

W Parker

## Acknowledgement

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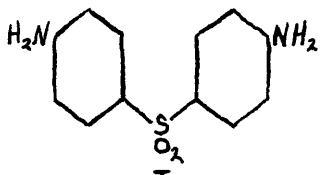
TABLE OF CONTENTS

# INTRODUCTION

For a number of years, a study of compounds related structurally to 4,4'-diaminodiphenylsulfone (I) has been conducted in this Laboratory under the direction of Dr. E. D. Amstutz. Among the compounds previously described are 2,8-diaminodibenzothiophene-5-dioxide (II) (32); 2,8-diaminothiaxanthone-5-dioxide (III) (3); 2,8-diaminothiaxanthene-5-dioxide (IV) (3) and certain of their mono-N-heterocyclic derivatives (2). Favorable results have been obtained, in some cases, on testing these compounds for antitubercular activity.

The known insecticidal (34, 37) and therapeutic value of phenothiazine and certain of its derivatives, i.e., methylene blue, made it seem desirable to prepare and study the compound in this series similar to those described above -- 2,8-diaminophenothiazine-5-dioxide (V). Its synthesis and proof of structure is the subject of this dissertation.



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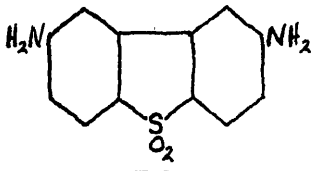

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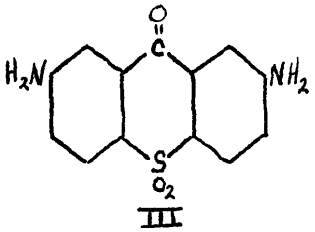

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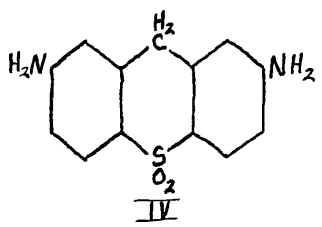

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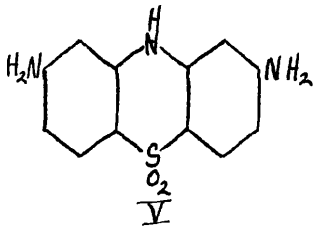
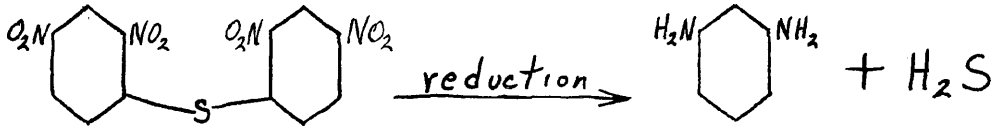
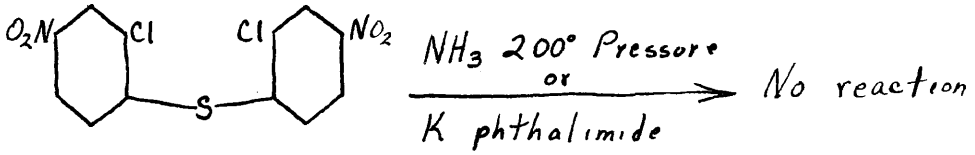
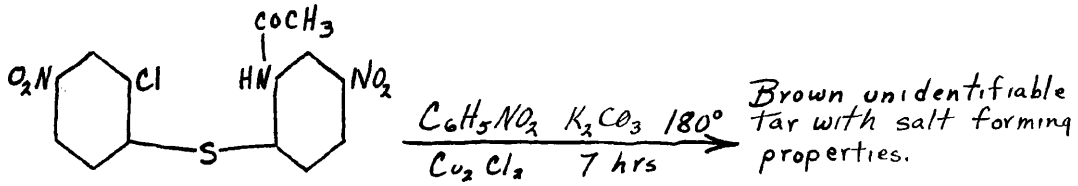


V

The only work published to date on attempts to prepare 2,8-disubstituted phenothiazines is that of Hodgson (21) who unsuccessfully tried to make 2,8-diaminophenothiazine by ring closure of a number of appropriately substituted diphenyl sulfides:

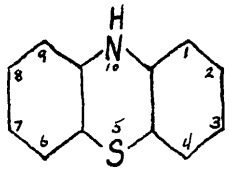



Massie (27) acetylated phenothiazine with acetic anhydride and aluminum chloride and obtained 18% of a diacetylphenothiazine (m.p. 253-254°) from which the acetyl groups could not be hydrolyzed. He did not, however, attempt to locate the acetyl groups.

Since there is to be found in the literature no summary on the general chemistry of phenothiazine, it seemed desirable to include a short outline of this subject at this point. It may be stated in passing that the literature on phenothiazine is in rather a confused state at present. The older workers in the field often used different systems of numbering the ring and did not draw structural formulas. In the present work, the newest nomenclature as given by Chemical Abstracts will be used:




In direct electrophilic substitution reactions, directive influences of the ring nitrogen overshadow those of the sulfur, in most cases. Thus, the direct nitration of phenothiazine with nitric acid leads first to 3-nitrophenothiazine-5-oxide (9, 10, 24), with stronger acid to 3,7-dinitrophenothiazine-5-oxide (9, 10) and by heating with strong acid to 1,3,7,9-tetranitrophenothiazine-5-oxide (5).

The only direct halogenation recorded is that by Unger and Hofmann (38) who passed chlorine into a chloroform solution of phenothiazine and obtained a tetrachlorophenothiazine in which the halogen is believed to occupy

positions 1, 3, 7, and 9. They also obtained this compound by treating phenothiazine with nitrous acid and warming the product with alcoholic hydrogen chloride.

There is no reference to direct sulfonation of phenothiazine in the literature.

Mercuration of phenothiazine is likewise under the control of the hetero nitrogen atom. Thus, 10-ethylphenothiazine mercurates in the 3 position (14, 39). The hetero nitrogen atom is also the predominant factor in the reaction of butyl lithium with phenothiazine itself. The first reaction is the replacement of the acidic hydrogen by lithium. The lithium, being more electropositive than hydrogen, enhances the activity of the ring nitrogen and substitution occurs in the 1 position. (16). When, however, the amino hydrogen is replaced by another group, as in 10-ethylphenothiazine, the lithium cannot increase the activity of the nitrogen, and, since hetero sulfur atoms generally have a stronger orienting influence than nitrogen in metalation, substitution in this case occurs at either the 2 or 4 position with the latter being most likely (17).

The first Friedel-Crafts reaction on phenothiazine was carried out by Scholl and Seer (36) who prepared a diphthaloyl derivative in which they believed the sub-

stituents were in the 3 and 7 positions. That their supposition was in error is indicated by a later work (4) and by the present investigation. The strongly acidic character of the aluminum chloride withdraws electrons from the basic nitrogen atom to such an extent that its influence on the system becomes secondary to that of the sulfur atom. Thus, Friedel-Crafts reactions on phenothiazine lead to the 2 monosubstituted products and the 2,8 disubstituted products.

Phenothiazines substituted in other positions cannot be made by direct replacement but many have been made by means of rearrangements. Thus, 3-chlorophenothiazine was made by Evans and Smiles (13) by rearranging 2-acetamino-2'-nitro-4'chlorodiphenyl sulfide with base. A similar rearrangement of 2,2'-di(2,4,6-trinitroanilino)-diphenyl disulfide led to 1,3-dinitrophenothiazine (23, 26). This compound was the subject of a controversy when Mitsugi, Beyschlag and Möhlau offered evidence that it was 2,4-dinitrophenothiazine (29). However, later work showed that it was actually the 1,3 compound. (25, 26). The latter compound was converted with sodium nitrite and acetic acid into 1,3,7-trinitrophenothiazine (25) and by nitration of this into Smiles' (5) known 1,3,7,9-tetranitrophenothiazine-5-oxide as a proof of structure. Recently, 2-bromo-7nitrophenothiazine was made by a rearrangement of 2-acetamino-4-bromo-

2',4'-dinitrodiphenyl sulfide (4). 1-Nitrophenothiazine has been prepared by rearrangement of the reaction product of 2,2'-diaminodiphenyl disulfide and 2,6-dinitrochlorobenzene (24).

Another type of rearrangement observed in phenothiazine compounds is that observed by Hilditch and Smiles (20) and by Kehrmann and Nossenko (24). The former authors found that by treating phenothiazine-5-oxide with acetic acid and then with zinc and acetic acid, it was converted to 3-hydroxyphenothiazine. Kehrmann and Nossenko obtained a chloro-3-nitrophenothiazine by treating 3-nitrophenothiazine-5-oxide with hydrochloric acid. The chlorine atom is probably in the 7 position.

All of the aminophenothiazines corresponding to the above mentioned nitro compounds have been prepared. By stannous chloride reduction have been prepared the 1-amino (24), 3-amino (24), 1,3-diamino (30) and 3,7-diaminophenothiazines (24). The 3-amino (9, 10) and the 3,7-diaminophenothiazines (9) have also been prepared by stannous chloride reduction of the corresponding nitro sulfoxides and by ring closure of the corresponding amino diphenylamines with sulfur.

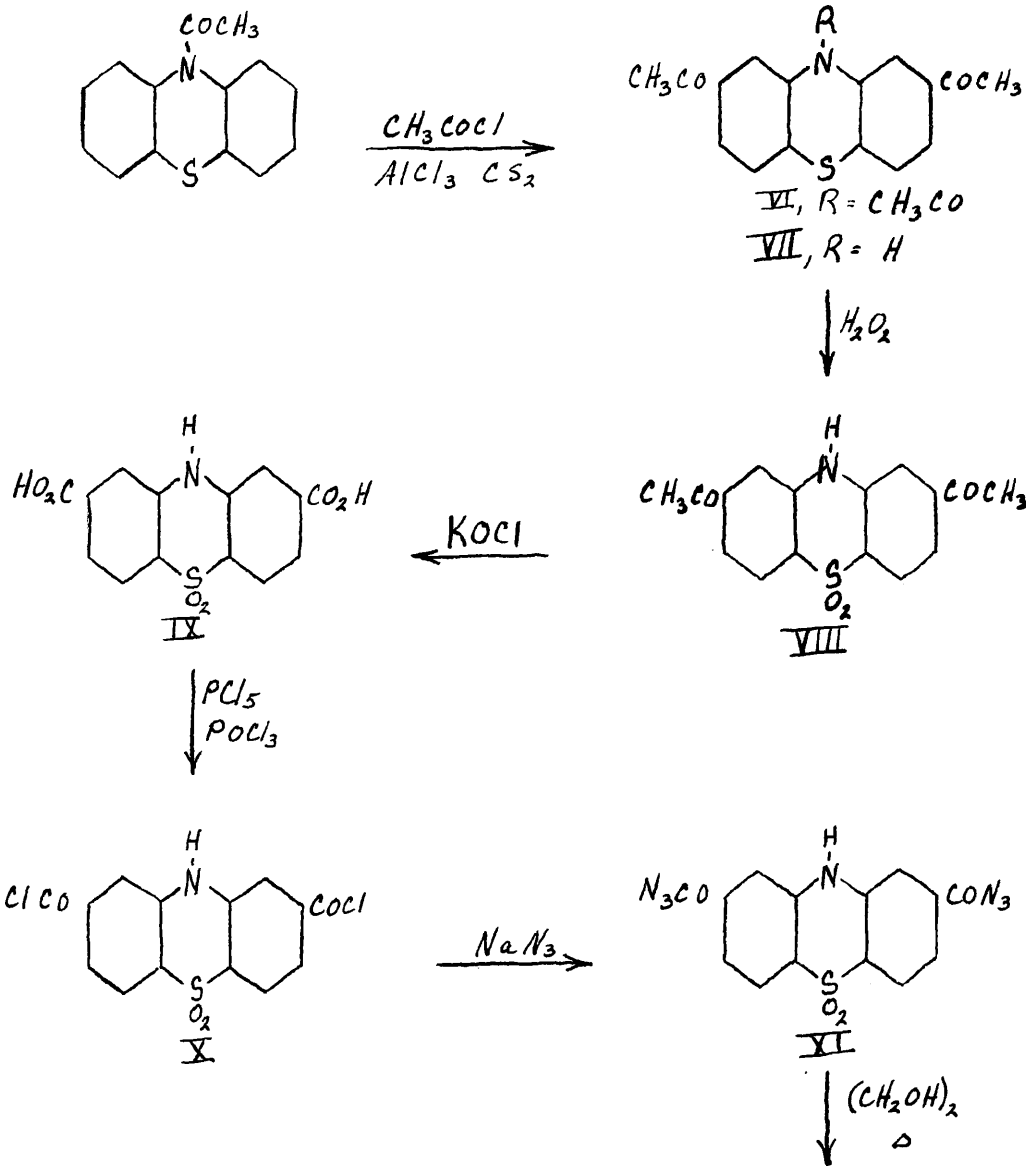
## DISCUSSION OF RESULTS

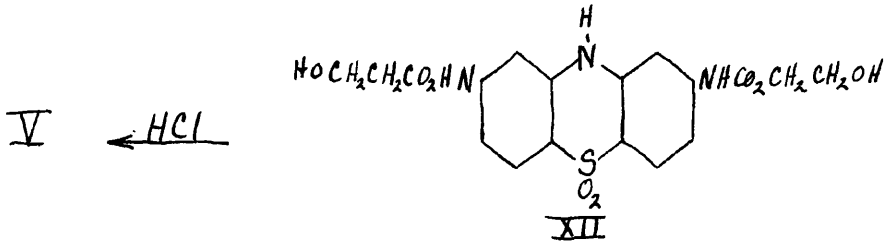
In the first attempt to prepare 2,8-disubstituted phenothiazines, it was hoped to acylate the ring nitrogen with a group that is strongly electron-withdrawing (2,4-dinitrobenzoyl and 2,4-dinitrobenzene sulfonyl) and thus transfer the directive influences in the phenothiazine nucleus from the nitrogen atom to the sulfur atom. This method was abandoned when attempts to prepare the acyl derivatives were unsuccessful.

An attempt was next made to cyclize 3,3'-dinitrodiphenylamine (15) with sulfur in order to prepare a dinitrophenothiazine but only starting material could be recovered from the reaction.

Baltzly, Harfenist and Webb (4) reported that the action of acetyl chloride on phenothiazine in the presence of aluminum chloride produced an acetyl phenothiazine in which the acetyl group was most likely in the 2 position. It thus seemed likely that by increasing the amount of acetyl chloride, two acetyl groups could be introduced into the phenothiazine nucleus. Consideration of the deactivating effect of the acetyl group also made it seem likely that the second group would assume a position symmetrical to the first, i.e., the 8 position. It was found that a second acetyl group could be introduced by this

method and the following scheme was developed for converting this acetylated phenothiazine (VI) into the desired 2,8-diaminophenothiazine-5-dioxide (V).



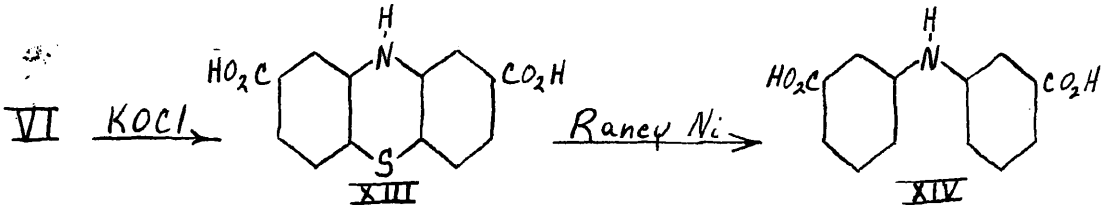



10-Acetylphenothiazine was converted into 2,8,10-triacetylphenothiazine (VI), m.p. 199.5-201.5°(dec.) in yields varying from 30 to 55%, depending on the grain size of the aluminum chloride used. Hydrolysis of VI with hydrochloric acid produced 2,8-diacetylphenothiazine (VII), m.p. 249-251°(dec.) in practically quantitative yield. 2,8-Diacetylphenothiazine-5-dioxide (VIII), m.p. 309-312°(dec.) was prepared in 85 to 95% yield by hydrogen peroxide oxidation of VI. By means of the hypohalite reaction, VIII was converted into phenothiazine-5-dioxide-2,8-dicarboxylic acid (IX), m.p. dec. above 360°, in yields of 90 to 95%. Phosphorus pentachloride and phosphorus oxychloride converted the acid IX into the acid chloride (X), m.p. dec. above 360°in 75 to 85% yield. The acid chloride X reacted with sodium azide to give 95% of the acid azide (XI), m.p. 365-375°(dec.) after first darkening at 355° (melting point block; uncorr.). The Curtius rearrangement of the azide in ethylene glycol gave pheno-

thiazine-5-dioxide-2,8-bis(B - hydroxyethyl carbamate) (XII), m.p. 270-272°(dec.) in 67% yield. Hydrolysis of this urethane with concentrated hydrochloric acid gave the desired 2,8-diaminophenothiazine-5-dioxide (V), m.p. 355-356°(dec.), with previous darkening (melting point block; uncorr.), in 60% yield.

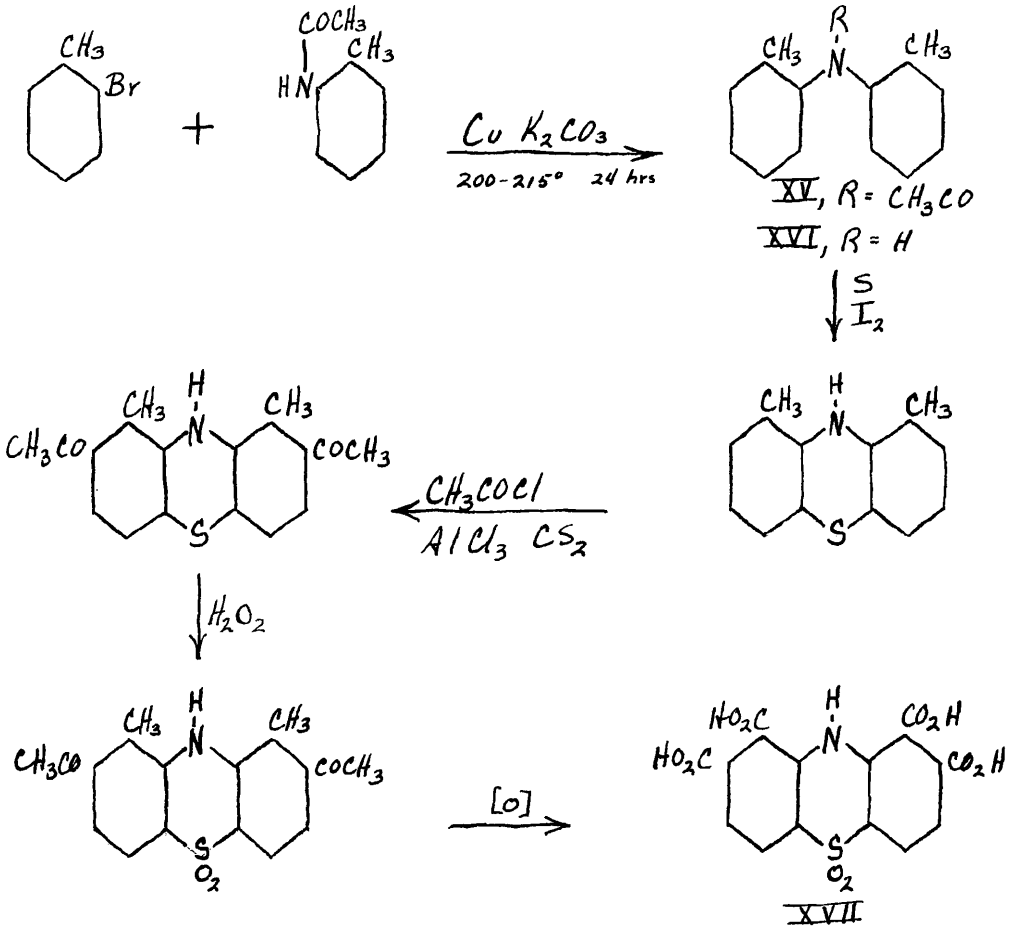
Since no definite proof was offered by Baltzly, Harfenist and Webb (4) that their acetylphenothiazine was the 2 isomer, it seemed desirable to find an unequivocal method of proving the structure of the supposed 2,8-diaminophenothiazine-5-dioxide.

An attempt was first made to convert the 2,8,10-triacetylphenothiazine (VI) into phenothiazine-2,8-dicarboxylic acid (XIII), and this acid, by desulfurization with "special" Raney nickel catalyst (31), into diphenylamine-3,3'-dicarboxylic acid (XIV). These reactions were carried out successfully, but all attempts to synthesize the unknown diphenylamine-3,3'-dicarboxylic acid failed.




A second method of proof of structure was the

attempted synthesis of phenothiazine-5-dioxide-1,2, 8,9-tetra-carboxylic acid (XVII):

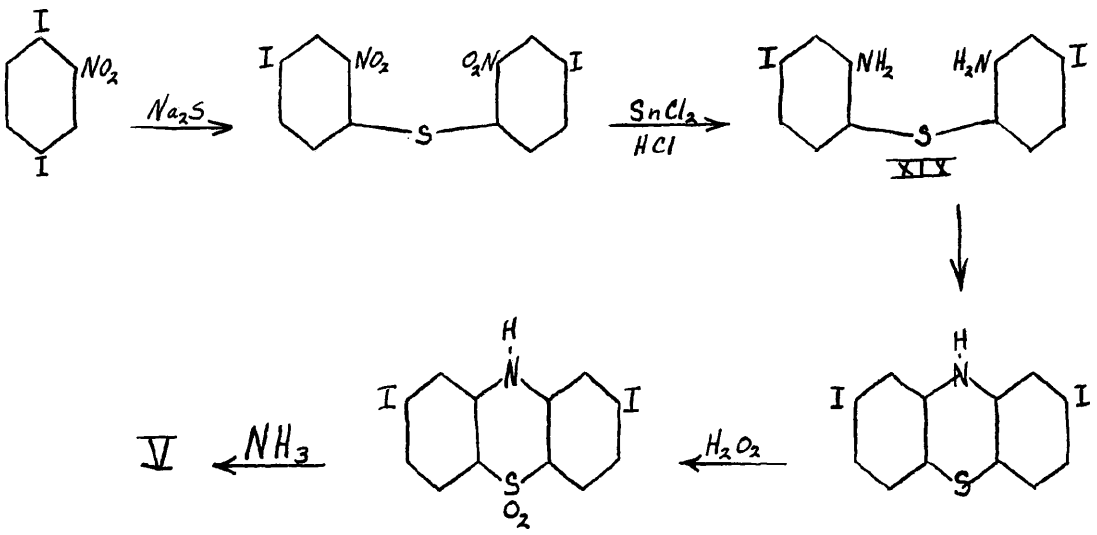



Proceeding from o,o'-ditolylamine (XVI) by the method indicated, it would be possible to obtain only one phenothiazine-5-dioxide tetracarboxylic acid capable of forming a double anhydride. Thus, if the acid obtained formed an anhydride, the entering acetyl groups would have to be ortho to the methyl groups already present, i.e., in the 2 and 8 positions. This method failed because of

the inability to remove the N-acetyl group from acetyl-o,o'-ditolylamine (XV). It is necessary that the free amine be used in the ring closure. The preparation of o,o'-ditolylamine by hydrolysis of its acetyl derivative is reported in the literature (6, 41). However, all attempts at hydrolysis by the method reported, and also with 100% phosphoric acid (8), Grignard reagent and methyl lithium, gave back only starting material with some degraded products in it. To prove that XVI was actually acetylditolylamine, analyses were run and a portion was oxidized with neutral permanganate to obtain a compound which checked in neutral equivalent with acetyldiphenylamine dicarboxylic acid. Boiling the weakly acidic solution resulting from the neutral equivalent determination gave a yellow precipitate which checked in melting point and mixed melting point with an authentic sample of diphenylamine-2,2'-dicarboxylic acid (12).

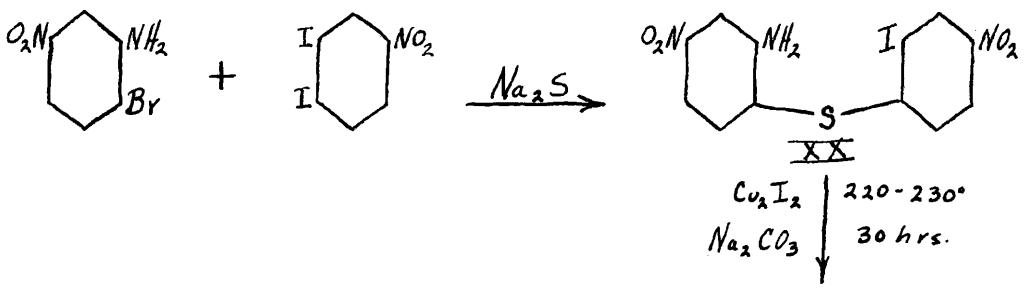
This difficulty in hydrolyzing hindered acylamine compounds is not unique. Thus, 2,6-dimethylbenzamide can be hydrolyzed only with 100% phosphoric acid (8). This is also the case with 2,6-dimethylacetanilide.

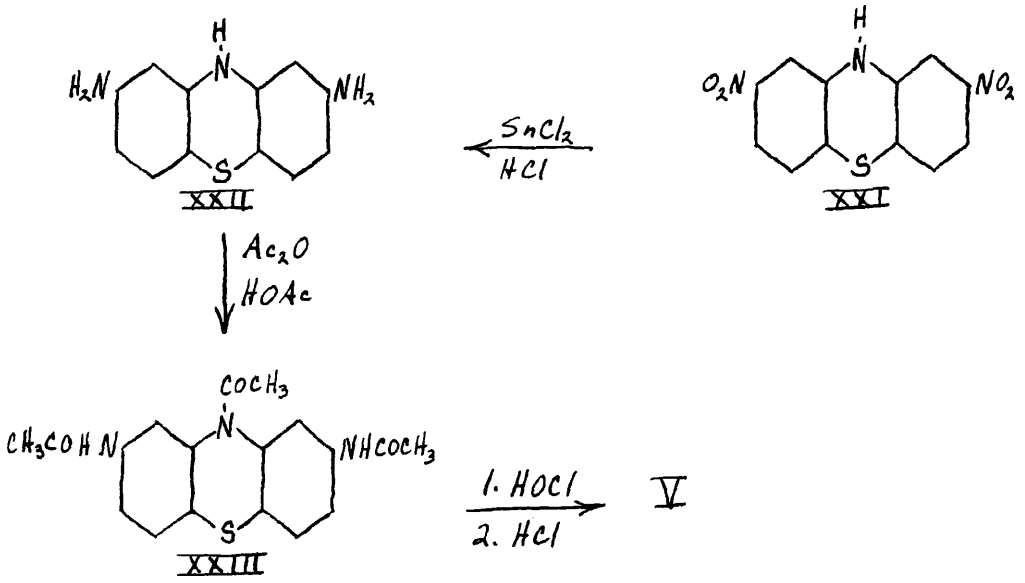
The following unequivocal synthesis of 2,8-diaminophenothiazine-5-dioxide was next postulated:




The reactions proceeded satisfactorily up to the ring closure of 2,2'-diamino-4,4'-diiododiphenyl sulfide (XIX). Ring closure of this compound by heating the monohydrochloride and by heating the tin complex (7, 22) both failed. These findings are in agreement with those of Matsumura (28) who found that 2,2',4,4'-tetraminodiphenyl ether could not be cyclized either by heating the hydrochloride alone or with zinc chloride.

The last and successful unambiguous synthesis of 2,8-diaminophenothiazine-5-dioxide was developed as follows:

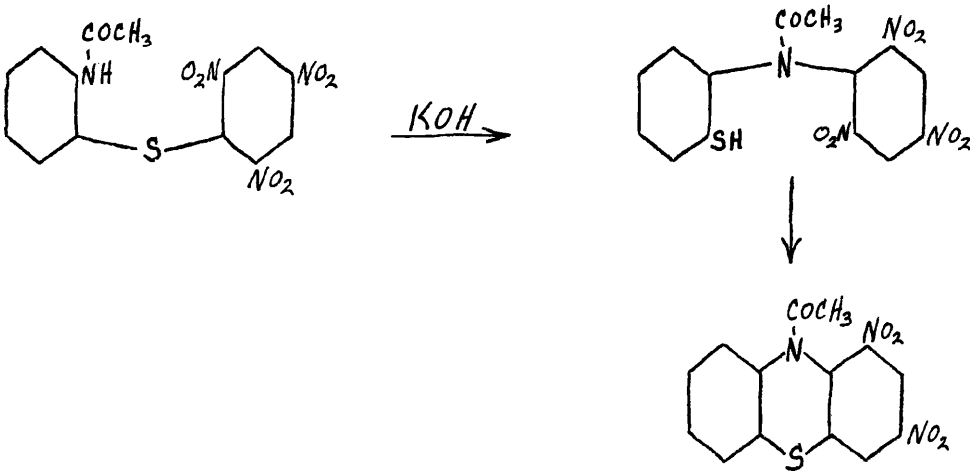





The ring closure of the 2-iodo-2'-amino-4,4'-dinitrodiphenyl sulfide (XX), m.p. 212.5-213°, was achieved in 50% yield by heating the sulfide with cuprous iodide and sodium carbonate at 220-230° for 30 hours. This form of Ullmann's reaction is in accordance with Weston and Adkins (43) who found that better yields could be obtained in this type of reaction by not using a solvent.

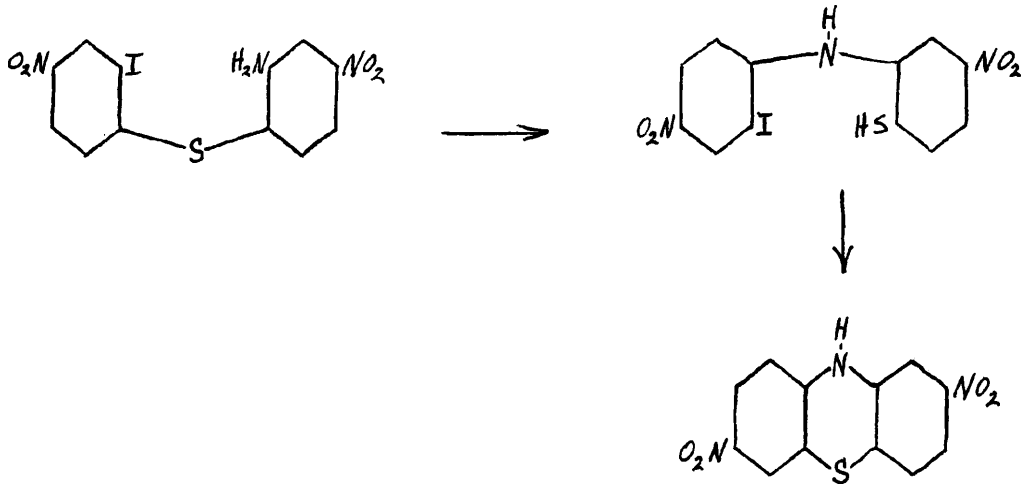
The ring closure of the aminoiododinitrodiphenyl sulfide (XX) to 2,8-dinitrophenothiazine (XXI) is the first reported closure of a phenothiazine ring from a substituted diphenyl sulfide. Besides Hodgson's (21) unsuccessful attempts which were described earlier, other workers (24, 26, 29, 30) believed that they had obtained phenothiazines by ring closure of various diphenyl sul-

fides and sulfones. However, Smiles and his co-workers (13) proved that the actual ring closure occurred on the diphenylamine thiol or sulfinic acid produced by rearrangement of the sulfide or sulfone. The following example may be used to illustrate this rearrangement:




The possibility of the Smiles rearrangement having occurred during the ring closure of the above sulfide (XX) may be ruled out for the following 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 as may be seen from the equation:



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.

The 2,8-dinitrophenothiazine (XXI), m.p. 335-340° (dec.) after first subliming at approximately 315°(melting point block; uncorr.), was reduced and acetylated in 49% yield to 2,8-diacetamino-10-acetylphenothiazine

(XXIII), m.p. 301-302°(dec.; melting point block; uncorr.). The free amino compound (XXII) was found to be unstable in air, turning purple, and was, therefore, immediately acetylated. The final step, oxidation to the sulfone and hydrolysis of the acetyl groups, was accomplished in very low yield by the action of hypochlorous acid on XXIII. Identity of the diaminophenothiazine-5-dioxide obtained from this sequence and from the Friedel-Craft series was shown by decomposition point and mixed decomposition point and analyses.

Attempted oxidations of the 2,8-dinitrophenothiazine (XXI) to its 5-dioxide were unsuccessful leading in all cases to a compound believed to be the corresponding sulfoxide. Hydrogen peroxide oxidation of the acetamino compound (XXIII) also proceeded only as far as the sulfoxide, it is believed. Both sulfoxides obtained were yellow and gave a red color with base.

## EXPERIMENTAL*

### Attempted Preparation of 10-Phenothiazine-2,4-dinitrobenzene sulfonamide.

Two grams (.01 mole) of phenothiazine and 2.7 g

* All melting points are corrected unless otherwise designated.

(.0105 mole) of 2,4-dinitrobenzene sulfonyl chloride were dissolved in 15 ml of pyridine and the solution refluxed for 1 hour. A dark tarry mass was obtained when the reaction mixture was poured into water. It was dissolved in pyridine and the clear red solution allowed to stand overnight. There was deposited a small amount of fine maroon colored crystals which were recrystallized once from dilute acetic acid and once from water. The purified product was rust in color and melted at 222-222.5°. Analyses gave the formula $C_{23}H_{16}N_4S_2O_7$ for this compound.

Anal. Calcd. for $C_{23}H_{16}N_4S_2O_7$: C, 52.65; H, 3.08; N, 10.7; S, 12.2. Found: C, 52.55; H, 3.07; N, 10.65; S, 12.0.

Further attempts at identification of this product were not made.

Attempted Preparation of 2,8-Dinitrophenothiazine:

An intimate mixture of 1 g (.00386 mole) of 3,3'-dinitrodiphenylamine (1, 19), .25 g (.00782 mole) of sulfur and one crystal of iodine were heated in an oil bath at 180-185° for 20 minutes then at 210° for 5 minutes. The reaction product was poured into a mortar and, when cool, ground and extracted with ligroin (b.p. 70-110°) for 50 hours in a Sohxlet extractor. The material extracted was recrystallized from dilute acetic acid and found by melting point and mixed melting point

to be identical with the starting material.

2,8,10-Triacetylphenothiazine (VI):

Forty-eight grams (.2 mole) of 10-acetylphenothiazine (9) and 60 ml (.8 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 15 hours. The carbon disulfide layer was decanted and the dark tarry layer 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 syrup which, on hydrolysis with hydrochloric acid, gave 25 to 27 g (52-56%) of 2-acetylphenothiazine (4). The greyish residue from the ether extraction was dissolved in alcohol and decolorized with charcoal to give 19.5 to 38 g (30-55%) of 2,8,10-triacetylphenothiazine (VI). This material is suitable for further reactions. For analysis, a sample was recrystallized twice more from alcohol to give tannish needles melting at 199-202°. A sample prepared by acetylation of pure 2,8-diacetylphenothiazine (VII) was pale yellow and melted at 199.5-201.5° (dec.).

Anal. Calcd. for $C_{18}H_{15}NSO_3$: S, 9.85; N, 4.94; C, 66.5; H, 4.65. Found: S, 9.61; N, 4.83; C, 66.5; H, 4.79.

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

Anal. Calcd. for $C_{16}H_{13}NSO_2$: S, 11.3; N, 4.31. Found: S, 11.1; N, 4.20.

2,8-Diacetylphenothiazine-5-dioxide (VIII):

To a solution of 32.5 g (.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 a 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 26.7 to 29.9 g (85-95%) of yellow needles of VIII, m.p. 309-312° (dec.).

Anal. Calcd. for $C_{16}H_{13}NSO_4$: S, 10.2; N, 4.44. Found: S, 9.94; N, 4.35.

Phenothiazine-5-dioxide-2,8-dicarboxylic acid (IX):

A suspension of 16 g (.05 mole) of 2,8-diacetyl-phenothiazine-5-dioxide in 1 liter of dioxane was stirred at room temperature while 300 ml of potassium hypochlorite, containing .112 g/ml (.367 mole), was added in 50 ml portions at such a rate that the temperature did not rise over 40°. When all the hypochlorite was in, the solution was stirred for 1 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 14.3 to 15.1 g (90-95%) and melted above 360° (dec.).

Anal. Calcd. for $C_{14}H_9NSO_6$: 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 (X):

Thirty-two grams (.1 mole) of phenothiazine-5-dioxide-2,8-dicarboxylic acid (IX), 50 g (.24 mole) of phosphorus pentachloride and 150 ml of phosphorus oxychloride were refluxed together for 17 to 20 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 oven at 100°. Due to its insolubility this product could not be further purified. It was yellow in color, weighed 26.6 to 30.2 g (75-85%) and melted above 360° (dec.).

Anal. Calcd. for $C_{14}H_7NSO_4Cl_2$: N, 3.93; Cl, 19.9. Found: N, 3.73; Cl, 19.8.

Phenothiazine-5-dioxide-2,8-dicarboxylic acid azide (XI):

A solution of 14 g (.03825 mole) of the acid chloride (X) in 600 ml of anhydrous dioxane was cooled to 20-25° and a solution of 6 g (.0927 mole) of sodium azide in 15 ml water added in one portion. After stand-for 5 minutes, water was added to the dioxane solution to precipitate the product which was collected and dried. Due to the instability of this product it could not be

further purified. It is cream in color, weighed 14 g (96.5%) and puffed violently when heated in air. Melting point ≐365-375° (dec.) after darkening at 355° (melting point block; uncorr.)

Anal. Calcd. for $C_{14}H_7N_7SO_4$: S, 8.67. Found: S, 8.43.

Phenothiazine-5-dioxide-2,8-bis-(B -hydroxyethyl carbamate) (XII):

A suspension of 14 g (.038 mole) of the acid azide (XI) 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 10 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 the desired product, melting at 270-272° (dec.)

Anal. Calcd. for $C_{18}H_{19}SN_3O_8$: S, 7.33; N, 9.38. Found: S, 7.21; N, 9.47.

2,8-Diaminophenothiazine-5-dioxide (V):

A mixture of 2.2 g (.005 mole) of the above urethane (XII) and 10 ml of concentrated hydrochloric acid was refluxed together for 6 to 8 hours, diluted

with water, heated to boiling and filtered. The red solution was decolorized with charcoal, made alkaline and cooled. There separated .75 g (60%) of colorless crystals, m.p. 355-356° (dec.), with previous darkening (melting point block; uncorr.)

Anal. Calcd. for $C_{12}H_{11}N_3SO_2$: 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 (XIII):

To a stirred suspension of 4 g (.0123 mole) of 2,8,10-triacetylphenothiazine (VI) in 300 ml of dioxane at room temperature was added in 25 ml portions 100 ml (.0937 mole) of a solution of potassium hypochlorite containing .089 g/ml. The temperature did not rise above 35°. When all of the hypochlorite was in, the solution was stirred for 1 hour more and then allowed to separate into two layers. After addition of sodium bisulfite to destroy excess hypochlorite, the product was precipitated with hydrochloric acid and collected. The green acid was re-dissolved in 10% sodium bicarbonate, 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°.

Anal. Calcd. for $C_{14}H_9NSO_4$: S, 11.1; N, 4.88.

Found: S, 10.75; N, 4.54. These analyses are low because of the hygro scopic nature of the material.

Diphenylamine-3,3'-dicarboxylic acid (XIV):

Three and seven-tenths grams (.012 mole) of phenothiazine-2,8-dicarboxylic acid (XIII) was dissolved in a minimum amount of 10% sodium bicarbonate solution and the solution diluted to about 25 ml. Approximately 25 to 30 g of special Raney nickel (30) was added and the mixture refluxed for 6 hours. The nickel was filtered off and the filtrate acidified with hydrochloric acid to obtain the product. After filtering and 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 $C_{14}H_{11}NO_4$: N, 5.44. Found: N, 5.27.

Attempted Synthesis of Diphenylamine-3,3'-dicarboxylic acid (XIV):

a. A mixture of .262 g (.001 mole) of methyl m-iodobenzoate, .151 g (.001 mole) of methyl m-aminobenzoate and a small amount of copper powder was heated in an oil bath at 160-170° for 24 hours. The dark product was boiled for 15 minutes with 10% alkali, filtered and

acidified to precipitate .07 g of a grey product which had a neutral equivalent of 151. Calculated for diphenylaminedicarboxylic acid, 129; for m-iodobenzoic acid, 138. Further work on the identification of this product was not attempted.

b. A mixture of 3.58 g (.0137 mole) of methyl m-iodobenzoate, 2.64 g (.0137 mole) of methyl m-acetaminobenzoate, .5 g of cuprous iodide and 1.65 g of sodium carbonate was heated in an oil bath at 185-190° for 17.5 hours. At the end of this time, 10 ml of water and .5 g of potassium hydroxide were added and the mixture refluxed for 1.5 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.

Acetyl-o,o'-ditolylamine (XVI):

A mixture of 76.4 g (.51 mole) of acet-o-toluide, 85 g (.50 mole) of o-bromotoluene, 55 g of potassium carbonate and 5 g of copper powder were heated in an oil bath at 200-215° for 24 hours. The resulting mixture was steam distilled to remove excess o-bromotoluene and the residue dissolved in alcohol and filtered to remove copper. Evaporation of the alcohol gave 84 g (70%) of

tan crystals. By recrystallization from a very small amount of alcohol and washing with a little ether, there was obtained colorless crystals of acetyl-o,o'-ditolylamine melting at 87.5-89°. The literature (6) gives the melting point as 89-90°.

Attempted Hydrolyses of Acetyl-o,o'-ditolylamine:

a. A solution of 2 g of acetylditolylamine and 2 g of potassium hydroxide in 7.5 ml of 95% ethanol was refluxed for 3 hours, then poured into water and extracted with ether. Evaporation of the ether and distillation of the product in vacuum gave 1.35 g of a stiff brown oil which on standing for a period of time deposited a few crystals. As much oil as possible was removed from the crystals on a porous plate. Melting point: ca. 50-85°. The literature (6, 41) records this hydrolysis as requiring only 2 hours under the above conditions.

b. A small amount of acetylditolylamine was dissolved in 3 ml of acetic acid and the solution saturated with water at the boiling point. To this solution was added 3 drops of concentrated sulfuric acid and the mixture refluxed for 2.5 hours. At the end of this time the solution was cooled, made alkaline and extracted with ether. Evaporation of the ether gave back unchanged acetylditolylamine.

c. A hydrolysis using 100% phosphoric acid was at-

tempted by dissolving 3 g of phosphorus pentoxide in 7 g of 85% phosphoric acid. To this was added 5 g of acetylditolylamine and the mixture heated at 145-150° for 8 hours. The mixture became green in color and after the period of heating had elapsed, was poured into water. The green gummy material was decomposed by heating with base and extracting with ether alternately until all the green gum had disappeared. The yellow ether solution was washed with alkali, then the ether was allowed to evaporate. There was obtained a reddish oil which could not be identified but is believed to be a mixture of unchanged acetylditolylamine and decomposition products.

d. Hydrolysis with Grignard reagent was attempted by making up .02 mole of methyl magnesium iodide in the usual manner and adding to this solution .01 mole of acetylditolylamine in ether. After refluxing for 2 hours and observing no precipitate, toluene was added and the ether replaced by distillation. The toluene solution was then refluxed for 2 hours. Evaporation of the solvent and working up in the usual manner gave back only unchanged acetylditolylamine.

e. A solution of methyl lithium in ether (.05 mole) was prepared as recorded in the literature (18) and to this was added an ether solution of .018 mole of acetylditolylamine. After refluxing for 2 hours and working up the reaction mixture only unchanged starting material

was obtained.

Attempted Preparations of o,o'-Ditolylamine:

a. A mixture of 60 g (.418 mole) of o-toluidine hydrochloride and 67 g (.627 mole) of o-toluidine was heated at 220-225° for 42 hours. The mixture was then cooled, treated with 50 ml of concentrated hydrochloric acid and poured into 1.5 liters of hot water. After cooling, the mixture was extracted with ether and the aqueous layer made alkaline and extracted with ether. The latter extract on evaporation and distillation of the product gave a 90% recovery of unchanged o-toluidine. Evaporation of the ether extract of the acidic solution gave only a very small amount of residue.

b. A mixture of 1.7 g (.01 mole) of o-bromotoluene, 15 g (.14 mole) of o-toluidine, 5 g of potassium carbonate and a small amount of copper bronze was heated at 185-190° for 25 hours. The reaction mixture was treated with water, acidified and extracted with ether. The ether solution on distillation gave .83 g of o-bromotoluene and .06 g of an oil which was not identified. There remained in the flask .15 g of residue. From the acid aqueous solution was recovered 14 g (93.5%) of o-toluidine.

c. A mixture of 145 g (1.5 moles) of o-toluidine and 127 g (1 mole) of o-toluidine hydrochloride was heated in a steel bomb for the equivalent of 30 hours - 10

hours at 260-270°, 10 hours at 270-280° and 10 hours at 280-300°. After cooling the bomb was opened and the black tarry oil removed. The tar was taken up in ether and the ether filtered to remove carbon. The ether extract was shaken with 1:3 hydrochloric acid until the aqueous layer was colorless. The ether solution was dried and hydrogen chloride passed in. Only a brown tar separated which could not be purified.

Oxidation of Acetylditolylamine:

A mixture of 2.4 g (.01 mole) of acetylditolylamine, 8 g (.05 mole) of potassium permanganate and 100 ml of water was stirred and heated slowly to reflux and refluxed for four hours. After cooling and filtering, the solution was decolorized with charcoal and acidified to precipitate 2.55 g (85%) of a colorless acid melting at 260-270° (dec.) which checked in neutral equivalent with an acetyldiphenylamine dicarboxylic acid. On boiling the weakly acidic solution resulting from the neutral equivalent, a yellow precipitate was formed which melted at 292-295°. A mixed melting of this acid with an authentic sample of diphenylamine-2,2'-dicarboxylic acid (12) (m.p. 291-295°) was unchanged.

2,5-Diiodonitrobenzene:

a. 2-Nitro-4-iodoaniline:

Chlorine gas was passed into a flask containing 25.4 g (.1 mole) of iodine until 7.1 g (.1 mole) had been taken up. The iodine monochloride was transferred to a ground glass dropping funnel by means of 25 ml of glacial acetic acid. In a 200 ml three necked ground glass flask fitted with stirrer and reflux condenser, 27.6 g (.2 mole) of recrystallized o-nitraniline was dissolved in 100 ml of glacial acetic acid with warming. The above solution of iodine monochloride was dropped in over a 20 minute period and the mixture was then heated on the steam bath for 2 hours. After this time the solution was poured into 1.5 liters of hot water and steam distilled to remove iodine and some unreacted o-nitraniline. The mixture was then cooled and the solid removed by filtration. Recrystallization from ethanol using charcoal gave 26 g (50%) of a tan product melting at 117-120° (literature gives 122°) (11, 35).

b. 2,5-Diiodonitrobenzene:

To a stirred suspension of 33.2 g (.126 mole) of 2-nitro-4-iodoaniline in 300 ml of glacial acetic acid cooled to 15° was added during 30 minutes 70 ml of nitrosylsulfuric acid (prepared by dissolving 25 g of finely powdered sodium nitrite in 140 ml of concentrated sulfuric acid held at 5 to 10°) so that the temperature did not rise above 25°. The ice bath was removed and stirring continued for 2 hours. The solution was then poured into

1.5 liters of ice and water and filtered. The clear filtrate was stirred while a solution of 30 g (.18 mole) of potassium iodide in 150 ml of water was slowly added. The resultant mixture was heated on the steam bath to 85° and then cooled. When cool, sodium bisulfite was added to destroy excess iodine and the product filtered. Two recrystallizations from methyl cellosolve gave 27.4 g of the desired product melting at 109-110.5°. From the mother liquors was obtained an additional 7 g melting at 108-109°. Total yield - 72.8%. Literature melting point - 109-110° (33).

2,2'-Dinitro-4,4'-diiododiphenyl sulfide:

To a hot solution of 3.75g (.01 mole) of 2,5-diiodonitrobenzene in 45 ml of alcohol was added a solution of 1.2 g (.005 mole) of sodium sulfide nonahydrate in 2 ml of water. During the 2 hour period of refluxing which followed, the red color first produced disappeared and a yellow precipitate formed. This was filtered from the hot alcoholic 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 materialwas recrystallized twice from glacial acetic acid with 90% recovery to give a product melting at 195.6-196.8°. Anal. Calcd. for $C_{12}H_6N_2SI_2O_4$: N, 5.31; I, 48.1. Found: N, 5.31; I, 47.9, 48.4.

2,2'-Diamino-4,4'-diiododiphenyl sulfide (XIX):

A suspension of 13.56 g (.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 (.00744 mole) of 2,2'-dinitro-4,4'-diiododiphenyl sulfide in 25 ml of acetic acid at 85-90°. By cooling and heating as necessary the temperature was held in this range for 2 hours, after which the reaction mixture was cooled and the product collected. Dilution of the acetic acid reaction solution gave a small amount of additional product. The total product 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 XIX melting at 152-153.5°. A second purification raised the melting point to 154-155.5°.

Anal. Calcd. for $C_{12}H_{10}N_2S\ I_2$: 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 .3085 g of this hydrochloride was mixed with .1595 g of the free diamino compound to give a mixture corresponding to the half hydrochloride (7.0% Cl). 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 mixture became darker and darker 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 .77 g (.001644 mole) of 2,2'-diamino-4,4'-diiododiphenyl sulfide, .78 g (.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 4 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 (XX):

To a boiling solution of 38.2 g (.176 mole) of 2-bromo-5-nitraniline (40) in 700 ml of alcohol was added in one portion a hot solution of 57.0 g (.211 mole) of sodium sulfide nonahydrate and 17.7 g (.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 5 minutes. A boiling solution of 66.0 g (.176 mole) of 3,4-diiodonitrobenzene* in 650 ml of alcohol was added and the mixture refluxed for 2 more hours. 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 crystallization 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 $C_{12}H_8N_3O_4IS$: S, 7.69; N, 10.1. Found: S, 7.66; N, 9.85.

2,8-Dinitrophenothiazine (XXI):

An intimate mixture of 33.4 g (.08 mole) of 2-iodo-2'-amino-4,4'-dinitrodiphenyl sulfide (XX), 4 g (.0105 mole) of cuprous iodide and 12 g (.113 mole) of anhydrous sodium carbonate was heated in a bath held at 220-230°

* Prepared in a manner similar to that for 2,5-diiodonitrobenzene (page 31) through 2-iodo-4-nitraniline (42).

for 30 hours. At the end of this time, the melt was removed, broken up and washed well with water. After drying, the crude material weighed 30.4 g. It was extracted continuously in a hot extractor with 300 ml of acetic acid. When solid appeared in the extractor flask, the acetic acid was changed. A total of 750 ml of acetic acid was used. 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 is 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 melting at 355-360° (dec.), after subliming at about 315° (melting point block; uncorr.)

Anal. Calcd. for $C_{12}H_7N_3O_4S$: 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 (XXIII):

A solution of 26.25 g (.138 mole) of stannous chloride dihydrate in 125 ml of glacial acetic acid was prepared by passing hydrogen chloride through the suspension until all the solid had dissolved. This solution was added in one portion to a suspension of 5 g (.0173 mole) of 2,8-

dinitrophenothiazine in 500 ml of acetic acid heated on the steam bath. After 2 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 5 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 3 to 4 hours. The dark solution was evaporated to about 100 ml and then diluted to 1 liter with water. The grey 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 recrystallization gave a product melting at 301-302° (dec.; melting point block; uncorr.).

Anal. Calcd. for $C_{18}H_{17}N_3SO_3$: S, 9.02; N, 11.8. Found: S, 8.80; N, 11.5.

2,8-Diaminophenothiazine-5-dioxide (V):

To a solution of 1.3 g (.00366 mole) of the above acetamino compound (XXIII) in 60 ml of acetic acid at 80°

was added in two portions 20 ml (.0141 mole) of potassium hypochlorite solution (made by adding 2.5 g of chlorine to a solution of 5.25 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 3.5 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 a reddish solid. This was dissolved in 1:1 hydrochloric acid and again boiled with charcoal and the clear yellow filtrate heated to boiling and made just alkaline. A reddish precipitate was formed and removed. By keeping the solution hot and adjusting the pH back and forth, practically all of this reddish material could be removed. The solution resulting was again treated with charcoal and the colorless solution made alkaline and cooled. There separated 17 mg of needles melting at 352-355° (dec.; with previous greying; melting point block; uncorr.). A mixed decomposition point with the diaminophenothiazine-5-dioxide made by the Friedel-Crafts series was unchanged.

Anal. Calcd. for $C_{12}H_{11}N_3SO_2$: N, 16.0; C, 54.8; H, 4.22. Found: N, 16.2; C, 55.15; H, 4.09.*

## SUMMARY

The preparation of 2,8-diaminophenothiazine-5-dioxide

* Analysis by Dr. Carl Tiedcke.

by means of the Friedel-Crafts reaction on phenothiazine is described.

An unambiguous proof of structure by means of a 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 preparation of phenothiazine-5-dioxide-1,2,8,9-tetracarboxylic acid which failed because of the inability to prepare o,o'-ditolylamine, a necessary starting material. Attempted ring closures of 2,2'-diamino-4,4'-diiododiphenyl sulfide also failed, as did the attempted ring closure of 3,3'-dinitrodiphenylamine with sulfur. The synthesis of diphenylamine-3,3'-dicarboxylic acid, a degradation product obtained from an intermediate in the Friedel-Crafts series, was also unsuccessful.

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# INDEX OF NEW COMPOUNDS

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# VITA

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Julian Getz Michels, the son of Ralph L. and Rose G. Michels, was born in Savannah, Ga. on July 30, 1920. He attended the local public schools and graduated in the Scientific course of studies from Savannah High School in 1937.

Having been awarded a National Youth Administration Scholarship, he entered Armstrong Junior College in Savannah in September, 1937. He completed his training there in 1939 and entered the University of Georgia in September of that year on a National Youth Administration Scholarship and a loan from the Rotary International. He received his Bachelor of Science in Chemistry in 1941.

Mr. Michels entered the Graduate School of the University of Tennessee on a teaching fellowship in September, 1941 and in March, 1943 received his Master of Science degree. From January, 1943 to June, 1944 he was employed as a research chemist with the Trojan Powder Co. of Allentown, Pa.

In August, 1944 Mr. Michels was inducted into the United States Army and served one year overseas with the 101st and 82nd Airborne Divisions. He was honora-

bly discharged in July, 1946 with the rank of Sergeant.

Immediately following his discharge, Mr. Michels enrolled in the Graduate School of Lehigh University and spent the next three years working toward his degree of Doctor of Philosophy in Chemistry. The results of this research is the subject of the foregoing dissertation. He was awarded a Research Fellowship by the Wm. S. Merrell Co. of Cincinnati, Ohio from 1946 to 1947.

Mr. Michels is the co-author of a scientific paper: "The Action of Formaldehyde on m-Hydroxybenzoic Acid. I", J. Am. Chem. Soc., 66 417 (1944) (with C.A. Buehler and T.A. Powers), which was abstracted, in part, from Mr. Michels' master's thesis.

Mr. Michels is a member of the following academic and professional organizations: Phi Beta Kappa, Phi Beta Phi, Gamma Sigma Epsilon, Pi Mu Epsilon, Sigma Pi Sigma, Sigma Xi and the American Chemical Society.

Mr. Michels was married in Allentown, Pa. to the former Mae Louisa Fetherolf on July 20, 1946.