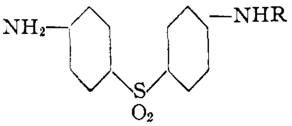
[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in the Sulfone Series. II.[1] Mono-N-Heterocyclic Derivatives of 4,4'-Diaminodiphenylsulfone

BY E. D. AMSTUTZ, E. A. FEHNEL[2] AND J. W. WOODS[3]

Although it has been known for some time that 4,4'-diaminodiphenylsulfone, like sulfanilamide, is a metabolite antagonist to *p*-aminobenzoic acid,[4] the mono-N-heterocyclic derivatives (I–III) have not been reported.



I (R = 2-pyridyl)
II (R = 2-pyrimidyl)
III (R = 2-thiazolyl)

The only N-heterocyclic derivatives of 4,4'-diaminodiphenyl sulfone which have been reported thus far are the 4,4'-bis-(N-2-pyridyl) and 4,4'-bis-(N-2-quinolyl) derivatives, and these are inactive in streptococcal and pneumococcal infections in mice.[5] It appears that the lack of activity in these compounds may be attributed to the absence of a free para-amino group, a circumstance which does not exist in the monosubstituted derivatives described in the present paper.

The following reaction outline summarizes the operations used in the synthesis of compounds (I), (II) and (III).

The 4-halo-4'-nitrodiphenylsulfides (V) were obtained in good yields by the condensation of *p*-nitrochlorobenzene with the potassium salts of *p*-bromo- and *p*-iodothiophenol in ethanol. The sulfides were oxidized in the usual way with an excess of hydrogen peroxide in acetic acid solution to yield the corresponding sulfones (VI)[6] in nearly quantitative yields.[7] Reduction of the nitrosulfones VI to the corresponding aminosulfones VII[5] was carried out in high yields by means of stannous chloride and hydrogen chloride in acetic acid solution.

The bromine atoms of VI (X = Br) and VII (X = Br) were not sufficiently reactive to permit replacement by the desired aminoheterocyclic groups. In the numerous replacement experiments which were carried out with these two compounds under various conditions only unchanged starting material or intractable tars could be isolated. The nitro derivative VI (X = Br) especially exhibited a marked tendency to form tars even under relatively mild conditions.[8] With the amino derivative VII (X = Br) tar formation did not occur as readily and the unchanged starting material was generally quantitatively recovered. Compound VII (X = Br) did, however, react with ammonia in the presence of copper powder in a sealed tube at 220°, giving an excellent yield of 4,4'-diaminodiphenyl sulfone. The more reactive 4-iodo-4'-aminodiphenyl sulfone (VII, X = I) underwent the desired replacement reaction when heated with an excess of 2-aminopyrimidine in the presence of copper powder and potassium carbonate, affording II in almost quantitative yield. The desired pyridyl derivative could not be prepared by this method because of the tendency of 2-aminopyridine to react in the tautomeric dihydroimino form under these conditions.

4-Amino-4'-(N-2-pyridyl)-aminodiphenyl sulfone (I) was readily obtained by the condensation of 2-bromopyridine with VII (X = I or Br) and subsequent amination of the resultant 4-halo-4'-(N-2-pyridyl)-aminodiphenyl sulfone (VIII).

An alternative approach was used with success in the preparation of both I and III. Here the haloheterocycle was condensed with 4-nitro-4'-aminodiphenyl sulfone after which the nitro group was reduced with stannous chloride.

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Experimental

4-Iodo-4'-nitrodiphenyl Sulfide (V, X = I).—A mixture of 28.4 g. (0.12 mole) of *p*-iodothiophenol,[9] 17.4 g. (0.11 mole) of *p*-nitrochlorobenzene, 15.0 g. (0.15 mole) of potassium bicarbonate and 250 ml. of ethanol was refluxed for twenty-three hours and about two-thirds of the solvent was then removed by distillation. The residue was diluted with 600 ml. of water and the resultant yellow

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[1] For the preceding paper in this series see Neumoyer and Amstutz, THIS JOURNAL, **69**, 1920 (1947).

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[4] (a) Marshall, Litchfield and White, *J. Pharmacol.*, **69**, 89, 166 (1940); (b) Maier and Riley, *Proc. Soc. Exptl. Biol. Med.*, **50**, 152 (1942).

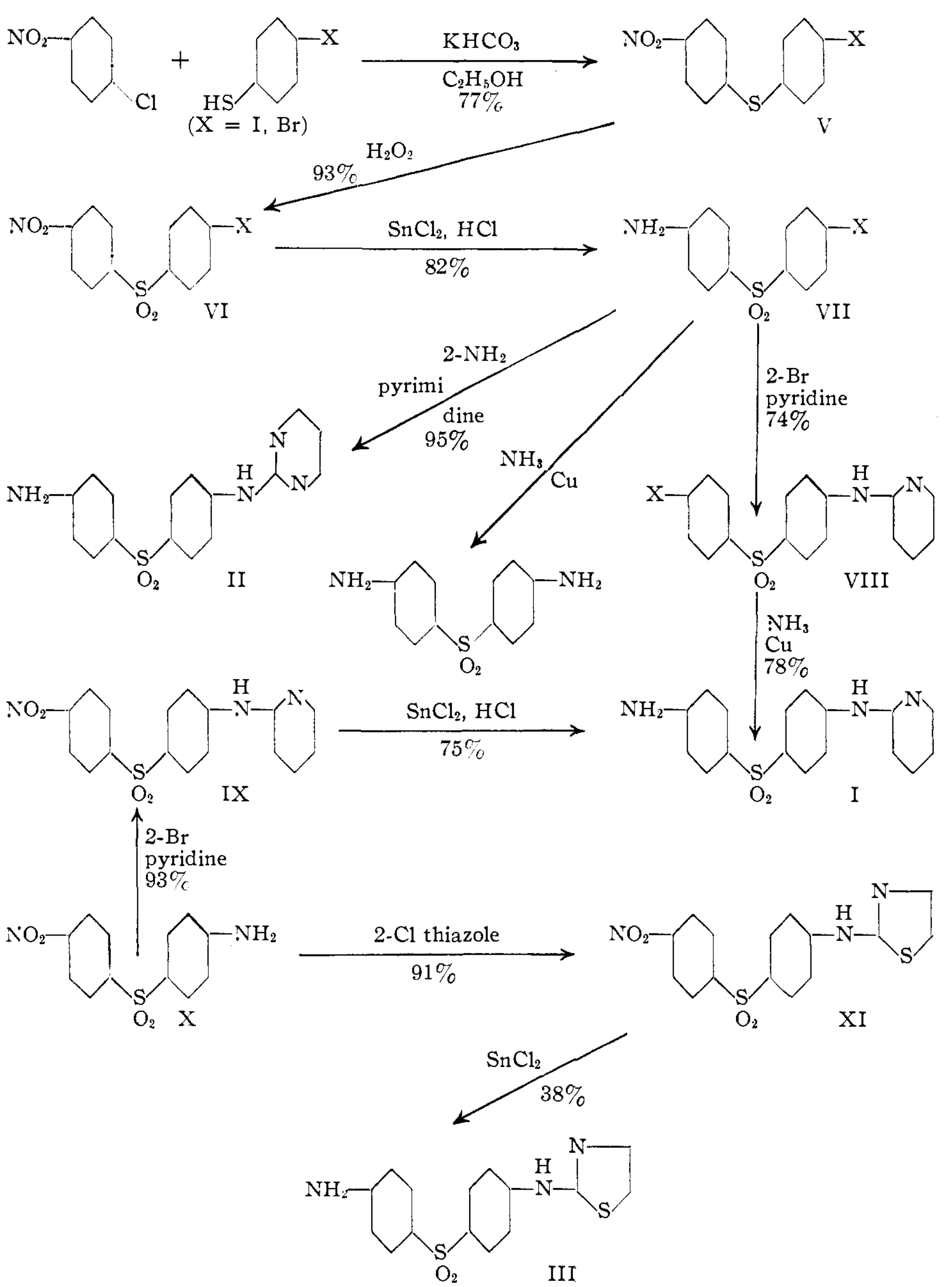
[5] Gray, *J. Chem. Soc.*, 1202 (1939).

[6] The preparation of the nitro- and amino-halosulfones by another method has been described by Ganapathi and Venkataraman, *Proc. Indian Acad. Sci.*, **21A**, 34 (1945). Notice of this paper (*C. A.*, **39**, 3524 (1945)) did not come into our hands until our final products had been obtained. Since the methods used in our work for the preparation of the halogen intermediates appear to be superior, they are given in the usual detail.

[7] In the case of the iodo compound V (X = I) these results were not consistently reproducible and there was some evidence that this compound may catalyze the decomposition of hydrogen peroxide. For this reason chromic anhydride is probably to be recommended as a more reliable oxidizing agent for this reaction.

[8] The presence of the nitro group para to the sulfonyl function may facilitate cleavage of the molecule between the nitrobenzene ring and the sulfur atom in a manner analogous to that discussed by Loudon and Robson (*J. Chem. Soc.*, 242 (1937)) for certain similarly constituted compounds.

[9] Prepared in 59% yield by the reduction of *p*-iodobenzene sulfonyl chloride with tin and hydrochloric acid; *cf.* Hubner and Alsberg, *Ann.*, **156**, 325 (1870).



precipitate was collected, washed with sodium hydroxide solution and with water, and recrystallized from ethanol to yield 30.2 g. (77%) of bright yellow crystals, m. p. 92–96°. Another recrystallization from ethanol raised the melting point to 101–102°.

Anal. Calcd. for $C_{12}H_8O_2NSI$: S, 8.98; I, 35.5. Found: S, 9.09; I, 35.7.

4-Bromo-4′-nitrodiphenyl sulfide (V, X = Br). A mixture of 18.8 g. (0.10 mole) of *p*-bromothiophenol,[10] 15.7 g. (0.099 mole) of *p*-nitrochlorobenzene, 12.0 g. (0.12 mole) of potassium bicarbonate, and 200 ml. of ethanol was treated as above. Recrystallization of the crude product from ethanol afforded 26.5 g. (86%) of bright yellow crystals, m. p. 92–94°.

Anal. Calcd. for $C_{12}H_8O_2NSBr$: S, 10.34; Br, 25.8. Found: S, 10.42, Br, 25.9.

4-Iodo-4′-nitrodiphenyl Sulfone (VI, X = I).—A mixture of 29.5 g. (0.083 mole) of V (X = I), 38 ml. (0.336 mole) of 30% hydrogen peroxide, and 180 ml. of glacial acetic acid was heated cautiously until a strongly exothermic reaction began. After this reaction, which required occasional cooling by means of a water-bath, had subsided, the mixture was refluxed for two hours, cooled to room temperature and filtered. The white crystalline product melted at 204–206° and required no further purification; yield 30.0 g. (93%).

Anal. Calcd. for $C_{12}H_8O_4NSI$: S, 8.24; I, 32.6. Found: S, 8.02, 7.98; I, 32.4, 32.9.

In at least one repetition of the above reaction evidence for the catalytic decomposition of the hydrogen peroxide was obtained and the product appeared to be a mixture

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[10] Prepared in 98% yield from *p*-bromobenzene sulfonyl chloride by an adaptation of the method for thiophenol given in "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 504 (1941).

containing considerable incompletely oxidized material; yield, *ca.* 53%; m. p. 184–194°.

4-Bromo-4′-nitrodiphenyl Sulfone (VI, X = Br).—This compound was prepared from V (X = Br) as in the case of the corresponding iodo compound above. The crude product was purified by digestion with hot ethanol, in which it is only slightly soluble. The product was obtained as white crystals, m. p. 180–182°; yield, 95%.

Anal. Calcd. for $C_{12}H_8O_4NSBr$: S, 9.37; Br, 23.3. Found: S, 9.53; Br, 23.1.

4-Iodo-4′-aminodiphenyl Sulfone (VII, X = I).—A suspension of the dihydrate (59.0 g., 0.261 mole) of stannous chloride in 250 ml. of acetic acid was treated with dry hydrogen chloride until the solution clarified. This solution was added gradually over a twenty-minute period to a mechanically stirred suspension of 29.0 g. (0.075 mole) of VI (X = I) in 90 ml. of glacial acetic acid maintained at 80–85°. Stirring was continued at this temperature for another ninety minutes and the mixture was then cooled and poured into 2 liters of water. The gelatinous white precipitate was collected, washed with 10% sodium hydroxide solution to decompose the tin complex, and dried. Recrystallization of the crude product from ethanol yielded 21.9 g. (82%) of white microcrystalline powder, m. p. 212–216°. Another recrystallization from the same solvent raised the melting point to 221.5–223°.

Anal. Calcd. for $C_{12}H_{10}O_2NSI$: S, 8.93; I, 35.3. Found: S, 9.00; I, 35.3.

4-Bromo-4′-aminodiphenyl Sulfone (VII, X = Br).—This compound was prepared by the reduction of VI (X = Br) with stannous chloride and hydrogen chloride in acetic acid as above. The product was obtained as colorless needles, m. p. 197–200°; yield 92%.

Anal. Calcd. for $C_{12}H_{10}O_2NSBr$: S, 10.28; Br, 25.6. Found: S, 10.55; Br, 25.8.

The acetyl derivative of VII (X = Br) was prepared by refluxing 6.1 g. (0.020 mole) with 10.2 g. (0.10 mole) of acetic anhydride in 100 ml. of glacial acetic acid for three hours and precipitating the product from the reaction mixture by dilution with a large volume of water. 4-Bromo-4′-acetylaminodiphenyl sulfone was obtained as a white powder, m. p. 202–204°; yield 6.4 g. (91%).[11]

Anal. Calcd. for $C_{14}H_{12}O_3NSBr$: S, 9.05; Br, 22.6. Found: S, 9.09; Br, 22.5.

4,4′-Diaminodiphenylsulfone was obtained when 0.5 g. of VII (X = Br) was heated with 5 ml. of 12 *N* ammonium hydroxide and a trace of copper powder in a sealed glass tube at 210–220° for seventeen hours. The contents of the tube were taken up in 5 *N* nitric acid and filtered, and the product was reprecipitated by the addition of excess ammonium hydroxide to the clear filtrate; yield, 0.4 g. (quantitative) of almost colorless crystals, m. p. 172–175°.

4-Amino-4′-(N-2-pyrimidyl)-aminodiphenyl Sulfone (II).—A mixture of 3.8 g. (0.0106 mole) of VII (X = I), 11.4 g. (0.120 mole) of 2-aminopyrimidine,[12] 1.5 g. (0.0108 mole) of finely powdered anhydrous potassium carbonate and a trace of copper powder was heated at 200–210° for three hours. The mixture was stirred mechanically and a nitrogen atmosphere was maintained over the melt during the reaction. After cooling to a solid vitreous mass the product was ground to a powder and extracted with water to remove the excess 2-aminopyrimidine and the inorganic salts. The insoluble residue was taken up in 6 *N* hydrochloric acid (Norit), filtered and the product was reprecipitated with ammonium hydroxide. An almost quantitative yield (3.3 g. or 95%) of white powder, m. p. 263–268° dec., was obtained. Another reprecipitation from acid solution raised the melting point to 265–268° dec.

Anal. Calcd. for $C_{16}H_{14}O_2N_4S$: S, 9.83; N, 17.2. Found: S, 9.95, 9.74; N, 17.2, 17.0.

4-Iodo-4′-(N-2-pyridyl)-aminodiphenyl Sulfone (VIII, X = I).—A mixture of 5.0 g. (0.014 mole) of VII (X = I) and 15.0 g. (0.095 mole) of 2-bromopyridine,[13] was stirred and heated on an oil-bath at 155–160° for eight hours and was then cooled and diluted with a large volume of 50% ethanol. The resultant precipitate was collected and recrystallized from aqueous ethanol (Norit), affording 4.5 g. (74%) of almost colorless powder, m. p. 178–185°. Several recrystallizations of this material from benzene gave colorless crystals melting at 184–186°.

Anal. Calcd. for $C_{17}H_{13}O_2N_2SI$: S, 7.36; I, 29.1. Found: S, 7.42; I, 28.9.

4-Bromo-4′-(N-2-pyridyl)-aminodiphenyl Sulfone (VII, X = Br).—From 3.6 g. (0.012 mole) of VII (X = Br) and 12.0 g. (0.076 mole) of 2-bromopyridine treated as above there was obtained after the first recrystallization from aqueous ethanol 2.9 g. (65%) of straw-colored plates, m. p. 178–182°. Another recrystallization from this solvent afforded colorless needles melting at 180–182°.

Anal. Calcd. for $C_{17}H_{13}O_2N_2SBr$: S, 8.24; Br, 20.6. Found: S, 8.19; Br, 20.4.

4-Amino-4′-(N-2-pyridyl)-aminodiphenyl Sulfone (I).—Two grams (0.0051 mole) of VIII (X = Br) was heated with 12 ml. of 12 *N* ammonium hydroxide and a trace of copper powder in a sealed tube at 210–220° for twenty hours. The contents of the tube were diluted with water and filtered and the insoluble portion was taken up in 5 *N* nitric acid. Reprecipitation with ammonium hydroxide afforded 1.3 g. (78%) of colorless needles, m. p. 191–194°. Repeated recrystallization raised the melting point to 206–207° with slight previous sintering. An identical product was obtained in a similar reaction with VIII (X = I); yield, 74%.

Anal. Calcd. for $C_{17}H_{15}O_2N_3S$: S, 9.86; N, 12.92. Found: S, 9.91; N, 12.85.

4-Nitro-4′-(N-2-pyridyl)-aminodiphenyl Sulfone (IX).—4-Nitro-4′-acetamidodiphenyl sulfone was prepared by the procedure of Ferry, Buck and Baltzly,[14] and immediately hydrolyzed with aqueous hydrochloric acid to 4-nitro-4′-aminodiphenyl sulfone—yield 21% (on the basis of acetanilide), m. p. 171–173°.[15]

To 10.3 g. (0.037 mole) of (X) in a 3-necked flask fitted with a mechanical stirrer, thermometer and reflux condenser, was added 11.5 g. (0.074 mole) of 2-bromopyridine. The mixture was heated with continuous agitation at 160–166° in an oil-bath for half an hour at the end of which time it solidified. The excess bromopyridine was removed with ether and the solid remaining was dissolved in hot alcohol. Upon cooling and neutralization with a 5% solution of sodium carbonate, a yellow precipitate formed, which, after recrystallization from aqueous alcohol and drying over sulfuric acid under diminished pressure, weighed 12.2 g. (93.1%) and melted at 188.5–190°.

Anal. Calcd. for $C_{17}H_{13}N_3O_4S$: S, 9.08. Found: S, 9.04.

Reduction of (IX). Preparation of (I), Alternative Procedure.—To 200 ml. of 95% ethanol in a 500-ml. 3-necked flask equipped with mechanical stirrer and reflux condenser, were added 12.5 g. (0.035 mole) of (IX) and 10 g. of activated zinc metal. Hydrochloric acid was added portion-wise to the mixture, with intermittent cooling to prevent overheating until the evolution of hydrogen became vigorous. The solution, which soon became practically colorless, was then cooled and diluted to twice its volume with water. The addition of sodium hydroxide solution precipitated a curdy white solid which was freed of zinc hydroxide by several extractions with alcohol and treatments with caustic followed by two acetone extrac-

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[11] Ganapathi and Venkataraman (ref. 5) report the melting point of this compound as 181–185°. Concerning polymorphism among diphenylsulfone derivatives, *cf.* Heymann and Heidelberger, This Journal, **67**, 1986 (1945).

[12] A generous supply of this compound was obtained from the Calco Chemical Division of the American Cyanamid Company through the courtesy of Dr. R. O. Roblin, Jr.

[13] Craig, This Journal, **56**, 231 (1934).

[14] "Organic Syntheses," **22**, 31 (1942).

[15] Buttle, *et al.*, reported m. p. 171°, *Biochem. J.*, **32**, 1101 (1938).

tions. The final product weighed 8.5 g. (75%), melted at 209–211° alone and did not depress the melting point of the same substance prepared above.

Anal. Calcd. for $C_{17}H_{15}N_3O_2S$: S, 9.86. Found: S, 9.96.

4-Nitro-4′-(N-2-thiazolyl)-aminodiphenyl Sulfone (XI).—A mixture of 27.8 g. (0.10 mole) of (X) and 20.8 g. (0.25 mole) of 2-chlorothiazole[16] was heated in an oil-bath at 100–105° until solidification occurred (about two and one-half hours). The product, after having been extracted with pyridine, treated with decolorizing charcoal and precipitated by the addition of water, was digested for three hours in 200 ml. of methanol, in which it is only slightly soluble. The suspension was cooled, and the product was collected and washed with 50 ml. of methanol and 50 ml. of water. After drying, it weighed 33 g. (91.4%) and melted at 247.5–249°.

Anal. Calcd. for $C_{15}H_{11}N_3O_4S_2$: S, 17.73. Found: S, 17.53.

4-Amino-4′-(N-2-thiazolyl)-aminodiphenyl Sulfone (III).—To a warmed (75°) suspension of 33 g. (0.091 mole) of (XI) in 500 ml. of glacial acetic acid in a one-liter 3-necked flask equipped with stirrer, thermometer and condenser was added a clarified solution of 98.5 g. (0.438 mole) of $SnCl_2 \cdot 2H_2O$ in 265 ml. of glacial acetic acid. After a three-hour period of reaction at 75–85°, the solution was cooled and neutralized below 25° by the addition of a 50% solution of sodium hydroxide. After extraction with concentrated caustic solution, decolorization with charcoal and numerous recrystallizations from aqueous acetone there was obtained 11 g. (37.8%) of colorless crystals melting at 234–237°. A small portion was recrystallized again from aqueous methanol and then melted at 235.6–240.1°.

Anal. Calcd. for $C_{15}H_{13}O_2N_3S_2$: S, 19.33. Found: S, 19.85.

Summary

4-Amino-4′-(2-pyrimidylamino)-diphenyl sulfone, 4-amino-4′-(2-pyridylamino)-diphenyl sulfone and 4-amino-4′-(2-thiazolylamino)-diphenylsulfone have been synthesized for study as possible new antibacterial agents. In the course of this work several new 4,4′-disubstituted diphenyl sulfides and sulfones have been prepared and characterized.

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(16) Obtained from 2-aminothiazole in 60% yield by the method of Ganapathi and Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 362 (1945); *C. A.*, **40**, 4059 (1946).

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

Studies in the Sulfone Series. III.[1] The Preparation and Properties of 2,8-Diaminothiaxanthone- and 2,8-Thiaxanthene-5-dioxides and Some Related Compounds

BY E. D. AMSTUTZ AND C. R. NEUMOYER[2]

In a previous paper[3] we reported the preparation of 2,8-diaminodibenzothiophene-5-dioxide which is the simplest of the *o,o′* bridged diaminodiphenyl sulfone derivatives.

The thiaxanthenes and thiaxanthones which were of primary interest to us in this investigation may be considered to be derived from 4,4′-diaminodiphenyl sulfone by joining the 2,2′ positions with methylene and carbonyl groups respectively. It was believed that one effect of methylene bridging should be to diminish the toxicity of the drug. Furthermore, it was thought that carbonyl bridging might increase the activity of the drug.

During the investigation we found it necessary to examine several possible routes to the desired 2,8-disubstituted heterocycle. These approaches all may be considered to be variants of a general process: namely, the ring-closure of substituted diphenyl sulfides and sulfones through some appropriate ortho- group. As work progressed it became abundantly clear that the state of oxidation of the sulfur has a profound effect on the ease of ring-closure. For example, we were unable in any case to bring about cyclization of sulfones although a considerable variety of ortho- substituent groups was employed.

The following reaction sequence illustrates the method of synthesis found to be most satisfactory.

The condensation of 2-chloro-5-nitrobenzaldehyde with sodium *p*-nitrothiophenoxide was performed in refluxing aqueous ethanol solution. In ionic reactions of this and related sorts, the presence of water in the reaction mixture was of decided advantage. Dissolution of the aldehydodiphenyl sulfide (I) in concentrated sulfuric acid (60°) produced a deep red colored solution which developed a green fluorescence as cyclization proceeded. The product was recovered by pouring the solution onto ice and washing the solid with water. It appears probable from the work of Loudon[4] and from the character of the product that the carbinol which might be expected is either not produced or is unstable and undergoes disproportionation to the methylene and carbonyl groups. While we were not successful in separating, in pure condition, the present mixture we were able to show, in cases to be reported later, that both species are present and in substantially equal amounts. The mixture of thiaxanthene and thiaxanthone was smoothly converted by hydrogen peroxide in acetic acid to a single product,

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(1) Paper II in this series, THIS JOURNAL, **69**, 1922 (1947).

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(3) Neumoyer and Amstutz, THIS JOURNAL, **69**, 1920 (1947).

(4) Campbell, Dick, Ferguson and Loudon, *J. Chem. Soc.*, 747 (1941).