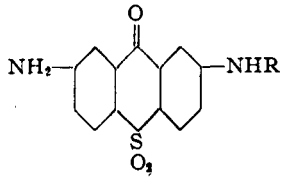
[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in the Sulfone Series. IV.[1] Certain Heterocyclic Derivatives of 2,8-Diaminothiaxanthone-5-dioxide

BY E. D. AMSTUTZ, E. A. FEHNEL[2] AND I. M. HUNSBERGER[3]

In a continuation of the work on antitubercular compounds described in the preceding paper of this series,[1] the synthesis of various monosubstituted N-heterocyclic derivatives of 2,8-diaminothiaxanthone-5-dioxide (I–IV) has been attempted to determine if these substances exhibit chemotherapeutically interesting properties in view of their relationships to the simpler materials reported earlier.[4]



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

The reactions involved in the synthesis of the desired materials are outlined in the accompanying diagram.

For the preparation of the intermediate derivatives, the older route through the 2-thiophenoxybenzoic acids (VI)[5] and the more recently described route through the corresponding aldehydes (VII)[6] both were studied, and the latter method was found to be greatly superior to the former. The condensation of the sodium salts of *p*-iodo- and *p*-bromothiophenol with 2-chloro-5-nitrobenzaldehyde took place readily and in good yields, while with 2-chloro-5-nitrobenzoic acid low yields were obtained even after prolonged refluxing. On oxidation with excess 30% hydrogen peroxide in glacial acetic acid, both the aldehyde (VII) and the acid (VI) gave the identical 5-nitro-2-(*p*-halobenzenesulfonyl)-benzoic acid (VIII).

The ring-closure of the 2-thiophenoxybenzaldehyde (VII) to an equimolecular mixture of the thiaxanthene (IX) and thiaxanthone (X) proceeded readily in cold concentrated sulfuric acid solution. In one experiment the solution was diluted with water as soon as all the aldehyde (VII, Y = I) had dissolved, and the resultant precipitate was separated into its components by repeated fractional crystallization from acetone to yield 83% of the theoretical amount of 2-iodo-8-nitrothiaxanthene (IX, Y = I) and 91% of 2-iodo-8-nitrothiaxanthone (X, Y = I). Similar results were obtained in the bromo series. The same 2-halo-8-nitrothiaxanthones (X) also were obtained by the cyclodehydration of the 5-nitro-2-(*p*-halothiophenoxy)-benzoic acids (VI) in hot concentrated sulfuric acid.

In the present investigation chromium trioxide readily oxidized both IX and X, as well as the equimolecular mixture of these compounds from the aldehyde cyclization, to the desired thiaxanthone-5-dioxide (XIII) in excellent yields.[7]

Reduction of the nitro groups to an amino group was carried out as in the previous paper.[1] Attempts to bring about the simultaneous reduction of the nitro and carbonyl groups of XIII by means of metal–acid combinations were unsuccessful, since reductive dehalogenation led to intractable mixtures which apparently contained large proportions of 2-aminothiaxanthene-5-dioxide.

At 200° 2-iodo-8-aminothiaxanthone-5-dioxide (V, Y = I)[8] reacted smoothly with excess 2-aminopyrimidine in the presence of potassium carbonate and copper powder to give good yields of II, but the reaction with 2-aminopyridine appeared to take a somewhat different course. Since this prod-

(1) For the preceding paper in this series see Amstutz and Neumoyer, THIS JOURNAL, 69, 1925 (1947).

(2) Lehigh Student Chemical Foundation Fellow, 1945–1946. Present address: Department of Chemistry, University of Pennsylvania, Philadelphia 4, Pa.

(3) A. C. S. Predoctoral Fellow, 1946–.

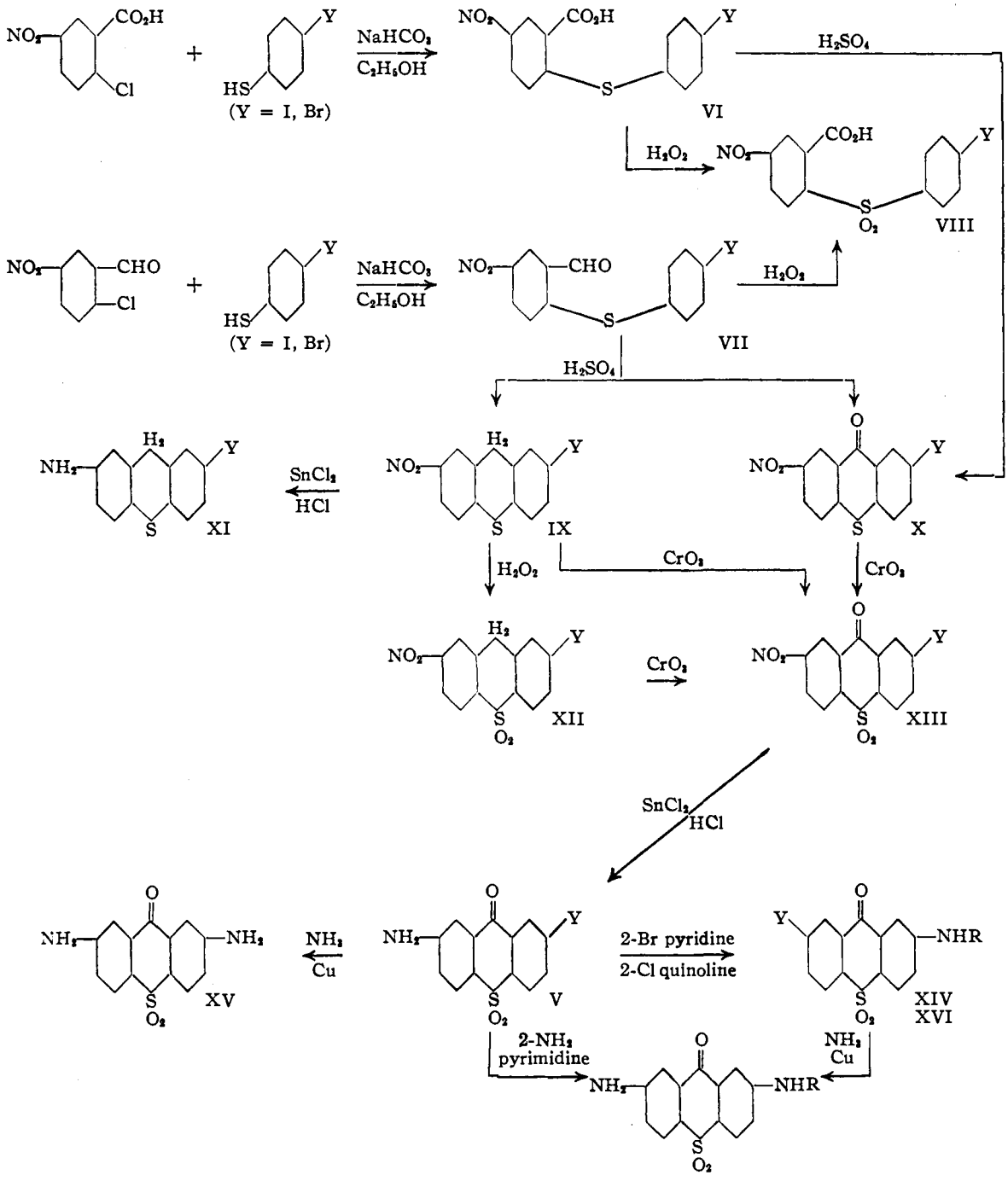
(4) Ref. (1) and Amstutz, Fehnel and Woods, THIS JOURNAL, 69, 1922 (1947).

(5) Mayer, *Ber.*, 42, 1132, 3046 (1909); 43, 584 (1910).

(6) Ref. (1) and Campbell, Dick, Ferguson and Loudon, *J. Chem. Soc.* 747 (1941).

(7) In contrast to the outstanding success reported by Campbell and his associates (6) in oxidizing the thiaxanthene–thiaxanthone mixture to the corresponding thiaxanthone-5-dioxide with 30% hydrogen peroxide, this reagent was found to be completely unsatisfactory for the oxidation of the 2-iodo-8-nitro-(thiaxanthene–thiaxanthone) mixture (IX + X, Y = I), and it gave only moderately good results with the corresponding bromo-(thiaxanthene–thiaxanthone) mixture. It was found that IX (Y = I) and X (Y = I) each rapidly catalyzed the decomposition of hydrogen peroxide and that the methylene group of IX (Y = I) remained unattacked even after repeated treatments with large excesses of fresh hydrogen peroxide in acetic acid. The only product isolated from the hydrogen peroxide oxidation of IX (Y = I) was 2-iodo-8-nitrothiaxanthene-5-dioxide (XII, Y = I), which was obtained in 92% yield. Similar but less clear-cut results were obtained with the corresponding bromo compound (IX, Y = Br), which was not so effective a catalyst for the decomposition of the peroxide. These results may be related to some peculiar observations of Hilditch and Smiles (*J. Chem. Soc.*, 99, 145 (1911)), who reported that the action of a large excess of 30% hydrogen peroxide on thiaxanthene in boiling acetic acid affords thiaxanthene-5-dioxide in good yield, while the addition of the same reagent to a cold acetic acid solution of thiaxanthene with subsequent refluxing gives thiaxanthone as the sole product.

(8) It was originally hoped that access to the mono-N-heterocyclic compounds of type I–III could be gained by condensation of 2-bromo-8-aminothiaxanthone-5-dioxide (V, Y = Br) with 2-aminoheterocycles, since the yield of the *p*-bromothiophenol intermediate greatly exceeds that of the corresponding iodo compound. Although amination to the diamino compound occurred on heating the bromo compound (V, Y = Br) with ammonia in the presence of copper powder in a sealed tube, various attempts to carry out a similar reaction with several representative amines were uniformly unsuccessful. The recovery of large amounts of unchanged V indicated that the expected activation of the bromine atom by the para sulfonyl group, ((a) Todd and Shriner, THIS JOURNAL, 56, 1382 (1934); (b) Loudon, *J. Chem. Soc.*, 902 (1939); (c) Loudon and Shulman, *ibid.*, 1618 (1938); (d) Loudon and Robson, *ibid.*, 242 (1937)), was not sufficient to permit its replacement by a substituted amino group.



uct evolved considerable ammonia on treatment with alcoholic potassium hydroxide, it was concluded that the 2-aminopyridine had reacted, at least in part, in the 2-aminopyridone form. This difficulty was circumvented by condensing 2-bromopyridine with the amino group of V (Y = I or Br), thus attaching a N-2-pyridylamino group in the desired position on the thiaxanthone dioxide nucleus.[9] The halogen atom then was replaced with an amino group by treatment of the 2-halo-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (XIV) with concentrated aqueous ammonia in the presence of copper powder in a sealed tube at 210–220°. The same product, I, was obtained from both the iodo and bromo intermediates.

(9) *Cf.* Gray, *J. Chem. Soc.*, 1202 (1939). The use of 2-chlorothiazole was attempted but with little success, a very complex mixture being obtained in every run. 2-Chloroquinoline behaved more satisfactorily, and eventually the desired product was obtained in small yield.

All of the thiaxanthone dioxide derivatives prepared in this investigation gave characteristic colors, ranging from green to violet, on treatment with zinc dust in warm aqueous-alcoholic alkali.[10] The thiaxanthene dioxides gave similar colors *directly* on treatment with cold dilute aqueous-alcoholic alkali. These colors disappear quickly on exposure to air, especially on shaking, and in the case of the thiaxanthene dioxides can be made to reappear only by the addition of a suitable reducing agent such as zinc dust. These color reactions may involve the formation of semiquinone-type free radicals, but direct evidence on this point is lacking.

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Experimental

5-Nitro-2-(*p*-iodothiophenoxy)-benzoic Acid (VI, Y = I).—To a warm (50–60°) solution of 85.0 g. (0.42 mole) of 2-chloro-5-nitrobenzoic acid[1] in 800 ml. of 95% ethanol, 400 ml. of water was added slowly followed by 103 g. (0.436 mole) of *p*-iodothiophenol[11] and 73.2 g. (0.87 mole) of sodium bicarbonate. The mixture was refluxed for twenty-two hours, and about two-thirds of the solvent then was removed by distillation. The residue was diluted with a large volume of water to precipitate the product, which was recrystallized from ethanol to yield 37.0 g. of a high-melting acid fraction and 40.0 g. (39%) of a lower-melting neutral fraction, m. p. 120–125°, which appeared to be 4,4′-diiododiphenyl disulfide. The acid fraction was purified by dissolution in hot aqueous sodium carbonate solution and reprecipitation with hydrochloric acid. Repeated crystallization from glacial acetic acid and from ethanol yielded bright yellow crystals, m. p. 244–247°.

Anal. Calcd. for $C_{13}H_8O_4NSI$: S, 7.99; I, 31.6; neut. equiv., 401. Found: S, 8.14; I, 31.6; neut. equiv., 397.

5-Nitro-2-(*p*-bromothiophenoxy)-benzoic Acid (VI, Y = Br).—A mixture of 1.7 g. (0.009 mole) of *p*-bromothiophenol,[12] 1.6 g. (0.008 mole) of 2-chloro-5-nitrobenzoic acid, 1.2 g. (0.021 mole) of potassium hydroxide, and a trace of copper powder in 90 ml. of 95% ethanol was refluxed for twenty-two hours under nitrogen. After about two-thirds of the solvent had been removed by distillation, 100 ml. of water was added to the residue, and the resultant mixture was made acid to congo red by addition of hydrochloric acid. The yellow precipitate was recrystallized from aqueous ethanol to yield 1.0 g. (36%) of yellow microcrystalline powder, m. p. 224–226°. Calcd. for $C_{13}H_8O_4NSBr$: neut. equiv., 354. Found: 357.[13]

5-Nitro-2-(*p*-iodothiophenoxy)-benzaldehyde (VII, Y = I).—A mixture of 98.4 g. (0.416 mole) of *p*-iodothiophenol, 74.2 g. (0.40 mole) of 2-chloro-5-nitrobenzaldehyde,[1] 35.0 g. (0.416 mole) of sodium bicarbonate, 850 ml. of 95% ethanol and 450 ml. of water was refluxed for two hours. The yellow curdy precipitate was washed, dried, and recrystallized from glacial acetic acid to yield 128.6 g. (84%) of yellow needles, m. p. 131–133°.

Anal.. Calcd. for $C_{13}H_8O_3NSI$: S, 8.33; I, 33.0. Found: S, 8.21; I, 33.1.

5-Nitro-2-(*p*-bromothiophenoxy)-benzaldehyde (VII, Y = Br).—This compound was prepared by condensing 28.4 g. (0.15 mole) of *p*-bromothiophenol with 26.0 g. (0.14 mole) of 2-chloro-5-nitrobenzaldehyde in the presence of 12.6 g. (0.15 mole) of sodium bicarbonate in 300 ml. of ethanol and 150 ml. of water as in the case of the corresponding iodo compound above; yield, 46.2 g. (98%) of yellow needles, m. p. 123–125°.

Anal. Calcd. for $C_{13}H_8O_3NSBr$: S, 9.49; Br, 23.7. Found: S, 9.50; Br, 23.5.

5-Nitro-2-(*p*-iodobenzenesulfonyl)-benzoic Acid (VIII, Y = I).—A solution of 1.6 g. (0.004 mole) of VI (Y = I) and 2.8 ml. (0.025 mole) of 30% hydrogen peroxide in 35 ml. of glacial acetic acid was refluxed for three hours. Addition of a large volume of water to the cooled mixture precipitated a crude product which was washed with water and recrystallized from ethanol to yield 1.4 g. (81%) of white powder, m. p. 242–246° dec.

Anal. Calcd. for $C_{13}H_8O_6NSI$: S, 7.40; I, 29.3. Found: S, 7.48; I, 29.5.

5-Nitro-2-(*p*-bromobenzenesulfonyl)-benzoic Acid (VIII, Y = Br).—A mixture of 1.0 g. (0.003 mole) of VII (Y = Br), 3.0 ml. (0.027 mole) of 30% hydrogen peroxide, and 20 ml. of glacial acetic acid was refluxed for two hours, cooled and poured into a large volume of water. The precipitate was washed with water and dried; yield, 1.0 g. (90%) of white powder, m. p. 190.5–192°.

Anal. Calcd. for $C_{13}H_8O_6NSBr$: S, 8.31; Br, 20.7; neut. equiv., 386. Found: S, 8.32; Br, 20.5; neut. equiv., 379.

2-Iodo-8-nitrothiaxanthene (IX, Y = I) and 2-Iodo-8-nitrothiaxanthone (X, Y = I).—Ten grams (0.026 mole) of VII (Y = I) was dissolved in 100 ml. of cold concentrated sulfuric acid, and the dark red solution was poured onto 150 g. of cracked ice. The yellow precipitate was washed and dried at 100°. By alternate digestion and recrystallization with hot acetone, this mixture was separated into its components, yielding 4.0 g. (83%) of 2-iodo-8-nitrothiaxanthene as yellow crystals, m. p. 155.5–157.5°, and 4.5 g. (91%) of 2-iodo-8-nitrothiaxanthone as a yellow powder, m. p. 300–303° dec.

Anal. Calcd. for $C_{13}H_8O_2NSI$ (thiaxanth*ene*): S, 8.69. Found: S, 8.54. Calcd. for $C_{13}H_6O_3NSI$ (thiaxanth*one*): S, 8.37. Found: S, 8.22.

2-Iodo-8-nitrothiaxanthone (X, Y = I) also was obtained by the following cyclodehydration of VI (Y = I). Twenty grams (0.050 mole) of VI (Y = I) was dissolved in 180 ml. of concentrated sulfuric acid at 100°. The solution was maintained at this temperature for ninety minutes, allowed to cool to room temperature, and poured onto 600 g. of cracked ice. The resultant precipitate was washed, dried, and recrystallized from acetic anhydride to yield 16.2 g. (84%) of yellow microcrystalline powder, m. p. 295–300° dec. Another recrystallization raised the melting point to 297–301° dec.; a mixed melting point with the corresponding compound obtained from the aldehyde cyclization showed no depression.

2-Bromo-8-nitrothiaxanthene (IX, Y = Br) and 2-Bromo-8-nitrothiaxanthone (X, Y = Br).—The aldehyde (VII, Y = Br) (16.2 g., 0.048 mole) was cyclized in 150 ml. of cold concentrated sulfuric acid as in the case of the corresponding iodo compound above. The yellow thiaxanthene–thiaxanthone mixture was separated into its components by alternate digestion and recrystallization with hot acetic acid, yielding 5.2 g. (67%) of 2-bromo-8-nitrothiaxanthene as yellow crystals, m. p. 162–164.5°, and 7.4 g. (92%) of 2-bromo-8-nitrothiaxanthone as a bright yellow powder, m. p. 282–285° dec.

(10) *Cf.* Graebe and Schultess, *Ann.*, **263**, 1 (1891); Ullmann and Lehner, *Ber.*, **38**, 729 (1905); Ullmann and Glenck, *ibid.*, **49**, 2487 (1916).

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

(12) Prepared in 98% yield from *p*-bromobenzenesulfonyl chloride by an adaptation of the method for thiophenol given in "Organic Syntheses," Coll. Vol. I, 2d ed., p. 504 (1941).

(13) This compound was not analyzed, but its formula may be considered established because the product obtained on ring-closure with sulfuric acid was identical with authentic 2-nitro-8-bromothiaxanthone (X, Y = Br) prepared from 5-nitro-2-(*p*-bromothiophenoxy)-benzaldehyde (VII, Y = Br).

Anal. Calcd. for $C_{13}H_8O_2NSBr$ (thiaxanth*ene*): S, 9.95. Found: S, 10.03. Calcd. for $C_{13}H_6O_3NSBr$ (thiaxanth*one*): S, 9.56. Found: S, 9.66.

The cyclodehydration of 1.0 g. (0.003 mole) of VI (Y = Br) in 9 ml. of hot concentrated sulfuric acid by the method used above for the corresponding iodo compound afforded 0.9 g. (95%) of 2-bromo-8-nitrothiaxanthone, m. p. 283–286° dec.; this material did not depress the melting point of the corresponding compound obtained from the aldehyde ring-closure.

2-Bromo-8-aminothiaxanthene (XI, Y = Br).—The solution obtained by passing dry hydrogen chloride into a suspension of 4.1 g. (0.018 mole) of stannous chloride dihydrate in 22 ml. of glacial acetic acid was added to a suspension of 1.6 g. (0.005 mole) of IX (Y = Br) in 6 ml. of glacial acetic acid heated to 80–85°, after which stirring was continued at this temperature for two hours. The white tin complex which precipitated on cooling was removed, treated with cold 10% aqueous sodium hydroxide, thoroughly washed with water, and dried at 100°; yield, 1.4 g. (96%) of yellow powder, m. p. 177–181°. Recrystallization from ethanol then afforded brownish-yellow plates, m. p. 183–184°.

Anal. Calcd. for $C_{13}H_{10}NSBr$: S, 10.99. Found: S, 11.12.

2-Iodo-8-nitrothiaxanthene-5-dioxide (XII, Y = I).—One gram (0.0027 mole) of IX (Y = I) was refluxed for three hours with 3.0 ml. of 30% hydrogen peroxide in 30 ml. of glacial acetic acid, after which the supernatant liquid gave a negative test for hydrogen peroxide (no color with aqueous potassium iodide solution). Another 8.0 ml. of 30% hydrogen peroxide was added in 2-ml. portions at intervals during the next four hours, and the mixture then was allowed to cool to room temperature. The pale yellow precipitate was crystallized from acetic anhydride to yield 1.0 g. (92%) of almost colorless needles, m. p. 229–231°, which gave a deep green color on treatment with aqueous-alcoholic alkali.

Anal. Calcd. for $C_{13}H_8O_4NSI$: S, 7.97. Found: S, 8.11.

2-Bromo-8-nitrothiaxanthene-5-dioxide (XII, Y = Br).—This compound was formed along with the corresponding thiaxanthone dioxide (XIII, Y = Br) when IX (Y = Br) was treated with a slight excess of hydrogen peroxide in boiling acetic acid. When 1.8 g. (0.0056 mole) of the thiaxanthene was refluxed for two hours with 1.5 ml. (0.015 mole) of 30% hydrogen peroxide in 30 ml. of glacial acetic acid, repeated fractional crystallization from acetic acid produced 0.5 g. (28%) of unreacted IX (Y = Br), 0.3 g. (15%) of XIII (Y = Br) melting at 265–268° with previous sintering, and 0.8 g. (41%) of pale yellow crystals of XII (Y = Br), m. p. 205–207°. The last compound gave a deep green color on treatment with aqueous-alcoholic alkali.

Anal. Calcd. for $C_{13}H_8O_4NSBr$: S, 9.07. Found: S, 9.17.

2-Iodo-8-nitrothiaxanthone-5-dioxide (XIII, Y = I).—This compound may be prepared by the chromium trioxide oxidation of the corresponding thiaxanthene (IX) or its dioxide (XII), the thiaxanthone (X), or the thiaxanthene–thiaxanthone mixture (IX + X) from the aldehyde ring-closure.

(a) **From 2-Iodo-8-nitrothiaxanthene-5-dioxide (XII, Y = I).**—A mixture of 0.8 g. of XII (Y = I), 0.5 g. of chromium trioxide, 20 ml. of glacial acetic acid, and a few drops of concentrated sulfuric acid (added as a catalyst) was refluxed for ninety minutes. Filtration of the cooled dark green solution yielded 0.8 g. of tan microcrystalline powder, m. p. 303–305° dec. Recrystallization from acetic anhydride then afforded 0.7 g. of almost colorless crystals, m. p. 303–306° dec.

Anal. Calcd. for $C_{13}H_6O_5NSI$: S, 7.73. Found: S, 7.80.

(b) **From 2-Iodo-8-nitrothiaxanthone (X, Y = I).**—This compound remained unattacked when refluxed for prolonged periods with large excesses of 30% hydrogen peroxide in acetic acid, although the oxidizing agent rapidly disappeared from the reaction mixture (potassium iodide test). Complete oxidation was effected with chromium trioxide as follows: To a suspension of 1.0 g. of X (Y = I) in refluxing glacial acetic acid enough chromium trioxide was added in small portions over a two-hour period to produce a brownish color. Filtration of the cooled mixture afforded 1.1 g. of pale yellow crystals, m. p. 296–298° dec. Recrystallization from a large volume of acetic anhydride yielded 1.0 g. (92%) of almost colorless crystals, m. p. 296–300° dec.

(c) **From the 2-Iodo-8-nitro-(thiaxanthene–thiaxanthone) Mixture (IX + X, Y = I).**—Oxidation of the thiaxanthene–thiaxanthone mixture with excess 30% hydrogen peroxide in boiling acetic acid afforded only low-melting mixtures consisting principally of partially oxidized compounds. Satisfactory results readily were obtained, however, using chromium trioxide as the oxidizing agent. The product from the ring-closure of 114 g. (0.296 mole) of VII (Y = I) with 1140 ml. of sulfuric acid according to the method previously described was sucked as dry as possible on the filter and then transferred directly to a large flask with 1500 ml. of glacial acetic acid. To this mixture was added 125 g. (1.25 moles) of chromium trioxide, and heat was applied cautiously until refluxing began. After the initially exothermic reaction had subsided, refluxing was continued for another two hours by the application of external heat. The white precipitate obtained from the cooled mixture was washed with water and dried. Since no suitable solvent for the recrystallization of this large amount of product could be found, purification was effected by digesting several times with fresh quantities of acetic anhydride. 2-Iodo-8-nitrothiaxanthone-5-dioxide was obtained as a colorless microcrystalline powder, m. p. 300–305° dec.; yield, 116 g. (95%, based on the aldehyde used).

The identity of the products obtained by these different routes was established by the method of mixed melting points. On treatment with zinc dust and warm aqueous-alcoholic alkali all these products gave a green color which was discharged on exposure to air.

2-Bromo-8-nitrothiaxanthone-5-dioxide (XIII, Y = Br).—The thiaxanthene–thiaxanthone mixture obtained from the ring-closure of 43.2 g. (0.128 mole) of VII (Y = Br) with 430 ml. of sulfuric acid was oxidized in 950 ml. of glacial acetic acid by refluxing for four hours with Superoxol (130 ml., 1.28 moles). After cooling to room temperature the mixture was filtered, and the precipitate was washed with sodium bicarbonate solution and water, and dried at 100°. The crude product melted at 244–251° with previous sintering; yield, 41.2 g. (88%). Recrystallization from acetic anhydride then afforded pale yellow crystals, m. p. 270–271° with previous sintering; over-all yield, based on the aldehyde, 79%. This compound did not depress the melting point of the analytically pure material obtained below by chromium trioxide oxidation of the aldehyde-cyclization mixture.

The same compound, m. p. 266–268°, also was obtained by the oxidation of X (Y = Br) with excess 30% hydrogen peroxide in boiling acetic acid.

The analytical sample of XIII (Y = Br) was prepared by the oxidation of a small sample of the aldehyde-cyclization mixture (IX + X, Y = Br) with excess chromium trioxide in acetic acid exactly as in the case of the corresponding iodo compound described above. Recrystallization from acetic anhydride gave almost colorless needles, m. p. 273–275° with previous sintering.

Anal. Calcd. for $C_{13}H_6O_6NSBr$: S, 8.71 Found: S, 8.70.

Like the corresponding iodo compound, XIII (Y = Br) gave a transient green color on treatment with zinc dust and aqueous-alcoholic alkali.

2-Iodo-8-aminothiaxanthone-5-dioxide (V, Y = I).—The reduction of 116 g. (0.28 mole) of XIII (Y = I) with 241 g. (1.07 moles) of stannous chloride dihydrate was effected as described for compound IX. Purification with 15% potassium hydroxide solution yielded 93.9 g

(87%) of bright yellow powder, m. p. 301–304° dec.[14]

Anal. Calcd. for $C_{13}H_8O_3NSI$: S, 8.33. Found: S, 8.26.

This compound (0.5 g.) was aminated by heating with 5 ml. of 12 *N* ammonium hydroxide and a trace of copper powder in a sealed tube for twenty-two hours at 220°. The product was taken up in 6 *N* hydrochloric acid (Darco) and reprecipitated with ammonium hydroxide to yield 0.3 g. of a bright yellow powder, m. p. 286–291° dec.; no depression when mixed with an authentic sample of 2,8-diaminothiaxanthone-5-dioxide (XV)[1] melting at 289–293° dec.

On treatment with zinc dust and aqueous-alcoholic alkali V (Y = I) gave a deep violet color which was discharged on exposure to air.

2-Bromo-8-aminothiaxanthone-5-dioxide (V, Y = Br).—The nitro compound XIII (Y = Br) was reduced as above with stannous chloride (0.076 mole) and hydrogen chloride in acetic acid. A quantitative yield (6.8 g.) of yellow-orange powder, m. p. 310–311°, was obtained. Recrystallization of a small sample from acetone caused no change in the melting point.

Anal. Calcd. for $C_{13}H_8O_3NSBr$: S, 9.49. Found: S, 9.48.

The same peculiar color reaction with zinc dust and alkali was shown by this compound as by its iodo analog.

2-Amino-8-(N-2-pyrimidyl)-aminothiaxanthone-5-dioxide (II).—A mixture of 5.0 g. (0.013 mole) of V (Y = I), 15.0 g. (0.158 mole) of 2-aminopyrimidine,[15] 2.0 g. (0.015 mole) of finely powdered anhydrous potassium carbonate, and a trace of copper powder was heated with stirring at 195–205° for eighty minutes under nitrogen. The dark-colored mixture was cooled slightly and triturated with hot water to remove excess 2-aminopyrimidine and potassium iodide. The finely ground residue was extracted repeatedly with cold 5 *N* nitric acid, treated with decolorizing charcoal, and finally reprecipitated from the combined acid extracts by addition of excess ammonium hydroxide; yield, 4.1 g. (90%) of a bright yellow powder, m. p. 327–335° dec. Digestion of a small sample with hot acetone, in which it is only very slightly soluble, raised the melting point to 335–338° dec.

Anal. Calcd. for $C_{17}H_{11}O_3N_4S$: S, 9.10; N, 15.9. Found: S, 9.04, 9.09; N, 15.7.

The diacetyl derivative of II was prepared by refluxing 1.6 g. (0.0045 mole) with 3.0 g. (0.029 mole) of acetic anhydride in 25 ml. of glacial acetic acid for three hours, cooling to room temperature and diluting with a large volume of water. The gelatinous yellow precipitate was recrystallized from aqueous acetic acid to yield 1.3 g. (66%) of yellow-orange crystals, m. p. 318–321° dec.

Anal. Calcd. for $C_{21}H_{16}O_5N_4S$: S, 7.34; N, 12.84. Found: S, 7.48; N, 12.96.

Condensation of V (Y = I) with 2-Aminopyridine.—In a typical experiment a mixture of 2.0 g. (0.0052 mole) of V (Y = I), 6.0 g. (0.064 mole) of 2-aminopyridine (Reilly Tar and Chemical Co., redistilled), 0.8 g. (0.0058 mole) of finely powdered anhydrous potassium carbonate, and a trace of copper powder was heated and stirred under nitrogen at 190–195° for ninety minutes. The dark-colored melt was cooled and the tarry mass extracted with warm water to remove the excess 2-aminopyridine and inorganic salts. After repeated extractions of the water-insoluble residue with 6 *N* hydrochloric acid, addition of excess ammonium hydroxide to the combined acid extracts precipitated 1.3 g. of yellow-orange powder, m. p. *ca.* 150–190° dec. Repeated recrystallization from aqueous ethanol (Norit) afforded 0.4 g. of orange microcrystalline powder, m. p. 233–237° dec. with previous sintering. Digestion with boiling acetone raised the melting point to 235–240° dec. with previous sintering.

Anal. Calcd for $C_{18}H_{13}O_3N_3S$: S, 9.13. Found: S, 8.97.

When this product was refluxed with aqueous-alcoholic alkali for two hours, the evolution of considerable ammonia was observed (olfactory evidence, litmus and hydrogen chloride tests). No ammonia could be detected after three hours of similar treatment of II.

2-Iodo-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (XIV, Y = I).—A mixture of 1.0 g. (0.0026 mole) of V (Y = I) and 3.0 g. (0.019 mole) of 2-bromopyridine[16] was stirred and heated on an oil-bath at 155–160° for eight hours. The cooled reaction mixture was diluted with several times its volume of ethanol, and the brownish-yellow precipitate was washed with ethanol, dissolved in a small amount of hot pyridine (Norit), and finally reprecipitated by the addition of four volumes of ethanol; yield, 1.0 g. (83%) of orange microcrystalline powder, m. p. 285–288°. Repeated reprecipitation from pyridine solution then yielded the pure product, m. p. 294–295°.

Anal. Calcd. for $C_{18}H_{11}O_3N_2SI$: S, 6.93. Found: S, 7.06.

2-Bromo-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (XIV, Y = Br).—This compound was prepared by the method described above for the corresponding iodo compound, using 3.0 g. (0.0089 mole) of V (Y = Br) and 12.0 g. (0.081 mole) of 2-bromopyridine. After one reprecipitation from pyridine the product melted at 293–297°; yield 3.4 g. (92%). Another reprecipitation afforded the pure compound as an orange microcrystalline powder, m. p. 297–298°.

Anal. Calcd. for $C_{18}H_{11}O_3N_2SBr$: S, 7.72. Found: S, 7.59.

2-Amino-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide (I).—A mixture of 2.6 g. (0.0063 mole) of XIV (Y = Br), 12 ml. of 12 *N* ammonium hydroxide and a trace of copper powder was heated at 210–220° in a sealed tube for twenty hours. The contents of the tube were diluted with water and filtered, the insoluble residue being taken up in 3 *N* hydrochloric acid, treated with Norit, and reprecipitated with ammonium hydroxide. A second reprecipitation from acid solution yielded 1.5 g. (68%) of yellow-orange powder, m. p. 245–260° dec. Pure 2-amino-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide was obtained as an orange microcrystalline powder, m. p. 280–282° dec., by recrystallization from aqueous ethanol. The same product (m. p. 279–281° dec., no depression when mixed with the above material) was obtained by the action of ammonium hydroxide on XIV (Y = I) under similar conditions.

Anal. Calcd. for $C_{18}H_{13}O_3N_3S$: S, 9.12; N, 11.97. Found: S, 9.02; N, 11.84.

2-Iodo-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide (XVI).—A mixture of 1.0 g. (0.0026 mole) of 2-iodo-8-aminothiaxanthone-5-dioxide (V, Y = I) and 2.6 g. (0.016 mole) of 2-chloroquinoline,[17] m. p. 37.5–39° (uncor.), was stirred in a test-tube (reflux condenser) for fifteen and one-half hours at 150–154° (oil-bath temperature), fifty-four hours at 155–165°, and eighteen and one-half hours at 160–170°. The temperature then gradually was raised to 185° during the last hour of heating (total reaction time, eighty-nine hours). After the first twenty-four hours white crystals appeared on the walls of the test-tube, but the main reaction mixture gave a positive test for halogen only after about sixty hours, at which time a catalytic amount of copper powder was added. The cooled mixture was diluted with ether, and from the brown solid obtained on filtration 1.0 g. (79%) of crude 2-iodo-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide, m. p. 320–321° (uncor., dec.), was obtained by reprecipitation from a pyridine solution with ethanol. This product was used for the amination despite its low sulfur content.

(14) Melting point taken in a bath heated to 295° before immersion of sample.

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

(16) Craig, THIS JOURNAL, **56**, 231 (1934).

(17) Prepared from carbostyril (Eastman Kodak Co.) in 63% yield according to the method of Friedlaender and Ostermaier, *Ber.*, **15**, 332 (1882).

Anal. Calcd. for $C_{22}H_{13}O_3N_2SI$: S, 6.26. Found: S, 5.18.

2-Amino-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide (IV).—A mixture of 0.32 g. (0.00062 mole) of XVI, 10 ml. of concentrated ammonium hydroxide, and a trace of copper powder was heated fifteen hours at 205° in a sealed tube. Water (90 ml.) was added and the insoluble dark-brown solid filtered off. Upon heating this material three times with 10 ml. of approximately 4 *N* hydrochloric acid, removing insoluble material by filtration, and reprecipitating from the cooled filtrate with ammonium hydroxide three impure brown-yellow fractions were obtained from which 8 mg. (3%) of pure 2-amino-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide was isolated by fractional extractions with boiling dioxane followed by reprecipitation from the cooled solutions with water.

Anal. Calcd. for $C_{22}H_{15}O_3N_3S$: S, 7.99. Found: S, 7.70.[18]

Summary

2-Amino-8-(N-2-pyridyl)-aminothiaxanthone-5-dioxide, 2-amino-8-(N-2-pyrimidyl)-aminothiaxanthone-5-dioxide and 2-amino-8-(N-2-quinolyl)-aminothiaxanthone-5-dioxide have been synthesized for study as possible new antibacterial agents.

(18) Analysis by Dr. Carl Tiedcke.

BETHLEHEM, PENNA. RECEIVED JUNE 21, 1947

[CONTRIBUTION FROM THE OFFICE OF DERMATOLOGY, INDUSTRIAL HYGIENE DIVISION, BUREAU OF STATE SERVICES, U. S. PUBLIC HEALTH SERVICE]

The Allergenic Principles of Poison Ivy. VII. Absorption Spectra of 3-*n*-Pentadecylcatechol and Related Compounds[1]

BY HOWARD S. MASON

In this study the absorption spectra of 3-*n*-pentadecylcatechol and a group of other substituted catechols, catechol derivatives and *o*-quinones have been determined. The feasibility of direct spectrophotometric assay of poison ivy allergens was also investigated.

Experimental

Unless otherwise noted, all substances examined were analytically pure samples previously described[1].

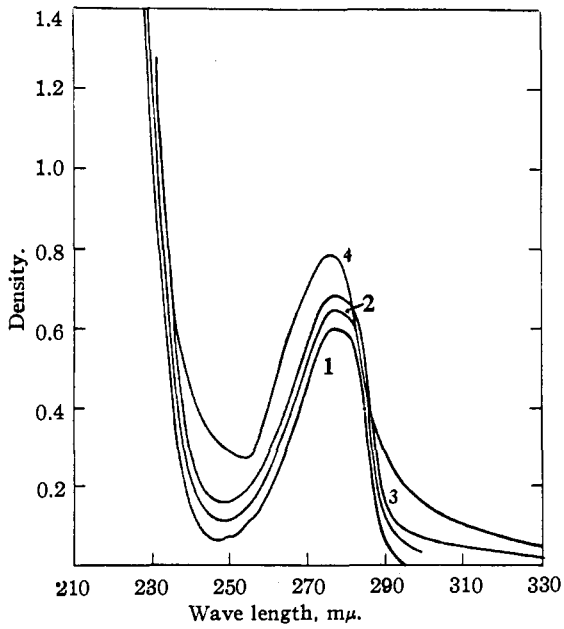

Fig. 1.—Spectrum of 3-*n*-pentadecylcatechol in ethanol. The solution contained 0.102 mg. per ml. The measurements were made at intervals of (1) zero days, (2) fourteen days, (3) thirty days and (4) ninety-one days.

(1) For the previous paper in this series, see Mason, THIS JOURNAL, 69, 2241 (1947).

3-*n*-Pentadecyl-*o*-benzoquinone.—This compound was prepared and purified by following the procedure of Willstätter[2] for the preparation of *o*-benzoquinone. It was recrystallized from a mixture of ether and hexane, from which it separated as orange rhomboids sintering and decomposing between 63–67°. The colorless modification could also be obtained by following the procedure of Willstätter and Müller[3] for the preparation of colorless *o*-benzoquinone.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 11.0.

***o*-Benzoquinone.**—This compound was readily prepared and recrystallized by the procedures of Willstätter[2] and Goldschmidt.[4] The product consisted of bright red crystals melting and decomposing between 60–70°.

3-*n*-Pentadecylcatechol Diphenylmethylene Ether.—This compound was synthesized by a general method already described[1]. It crystallized as white prisms from methanol and melted at 42°.

Anal. Calcd. for $C_{34}H_{44}O_2$: C, 84.3; H, 9.16. Found: C, 84.0; H, 9.14.

Spectral curves were determined with a Beckman quartz spectrophotometer. The solvent used was ethanol unless otherwise specified. The quartz cells employed were 10 mm. in thickness.

Results

Fresh solutions of 3-*n*-pentadecylcatechol in ethanol displayed maximum absorption at 277 mμ, log ϵ = 3.28. On standing for several months absorption became more intense, the spectral curve shifting to slightly shorter wave lengths (Fig. 1). The effect of solvent upon the rate of this process was determined by following simultaneously the absorption spectra of identical concentrations of 3-*n*-pentadecylcatechol in ethanol, acetone and hexane. Over a period of forty-five days at 21–24° the spectral changes took place most markedly in acetone and least markedly in hexane (Table I).

Crude extracts of poison ivy also displayed

(2) Willstätter and Pfannenstiel, *Ber.*, **37**, 4744 (1905).
(3) Willstätter and Müller, *ibid.*, **41**, 2580 (1908).
(4) Goldschmidt and Graef, *ibid.*, **61**, 1858 (1928).