fructose and mannitol were studied. Low concentrations of potassium cyanide (.0025 *M*) accelerate the rate of oxidation. Platinum has no effect. The rate of oxidation of glucose by air in this system is not influenced by insulin.

Carmel-by-the-Sea, California

[Contribution from the Chemical Laboratories of Columbia University, No. 494]

RESEARCHES ON THIAZOLES. VIII. THE CONDENSATION OF *o*-AMINOPHENYL MERCAPTAN AND *o*-AMINOPHENYL DISULFIDE WITH ACID CHLORIDES, ANHYDRIDES AND ESTERS[1]

By Marston Taylor Bogert and Arthur Stull[2]

Received September 1, 1925 Published January 8, 1926

Introductory

The work recorded in this paper was undertaken not alone for the purpose of contributing to our knowledge of the chemistry of the thiazoles, but also because we believe that there exist possibilities of discovering in this field some products of therapeutic value. Many of the compounds described beyond are derivatives of the *o*-aminophenyl disulfide first prepared by Hofmann,[3] and later recommended by McDonagh,[4] under the name of "Intramine," for use in the treatment of spirochetal infections. Several of these were converted into the corresponding benzothiazoles by reduction.

The disulfide and ethyl oxalate[5] interacted to form the ethyl oxanilate disulfide, $(\text{—}SC_6H_4NHCOCOOR)_2$ (I) and no oxalyl derivative, $\overline{SC_6H_4NHCOCONHC_6H_4S}$ (II).

By the action of ammonia and of aniline upon the oxanilate, the corresponding amide and anilide were obtained. Reduction of the oxanilate yielded benzothiazole-2-carboxylic acid, which has been prepared previously by other methods. Through the interaction of oxalyl chloride and zinc *o*-aminophenyl mercaptide, *bis*-benzothiazolyl (oxalamidothiophenol) was obtained in 60% yield, an interesting compound which has been synthesized before by other reactions.[6,7,8,9]

---

[1] An abstract of this paper was presented at the Baltimore Meeting of the American Chemical Society, April 9, 1925.

[2] Ferguson Fellow at Columbia University for the year 1924–25.

[3] Hofmann, *Ber.*, **12**, 2360 (1879).

[4] McDonagh, *Lancet*, **190**, 238 (1916); Ger. pat. 68,697 (1892).

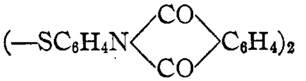
[5] Compare Meyer and Seeliger, *Ber.*, **29**, 2640 (1896).

[6] Hofmann, *Ber.*, **13**, 1227 (1880).

[7] Hofmann, *Ber.*, **20**, 2257 (1887).

[8] Lang, *Ber.*, **25**, 1902 (1892).

[9] Lauth, *Bull. soc. chim.*, [3] **15**, 82 (1896).

In the condensations of the disulfide (two molecular equivalents) with bibasic acid anhydrides (one equivalent), succinic, glutaric, camphoric and maleic, all gave an anilic acid type (III), $(-SC_6H_4NHCO(CH_2)_2COOH)_2$, whereas with phthalic anhydride the product was the imide derivative,  $(-SC_6H_4N\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle C_6H_4)_2$ (IV).

Furyl- and thienyl-benzothiazoles were obtained from the zinc aminophenyl mercaptide and the appropriate acid chloride, or by treating the aminophenyl disulfide first with the acid chloride and then reducing the product. It is interesting to note that 2-phenyl-, 2-α-furyl- and 2-α-thienyl-benzothiazoles resemble one another in many ways. All three melt within a range of about 15°, and all possess an agreeable tea rose or geranium odor, which is most pronounced in the case of the thienyl derivative.

Experimental Part

A. Oxalic Acid Derivatives

Ethyl Oxalate and *o*-Aminophenyl Disulfide, Ethyl Oxanilate *o*-Disulfide, $(-SC_6H_4NHCOCOOC_2H_5)_2$.—A solution of 3.5 g. of *o*-aminophenyl disulfide in 30 g. of ethyl oxalate was refluxed for five hours. The formation of alcohol during the refluxing was manifest. When cold, the solution was diluted with sufficient 50% alcohol to dissolve any excess of the ethyl oxalate, and the solid thus precipitated was decolorized and crystallized from 50% alcohol. It formed light yellow, lustrous plates, m. p. 104° (corr.), insoluble in water, but dissolving easily in alcohol or ethyl oxalate; yield, 3.7 g., or 68%.

Anal. Calcd. for $C_{20}H_{20}O_6N_2S_2$: C, 53.53; H, 4.45. Found: C, 53.31; H, 4.44.

Efforts to condense one molecular equivalent of ethyl oxalate with one of the disulfide under various conditions proved unavailing. This was rather surprising in view of the fact that Hofmann[6] obtained the *bis*-benzothiazolyl from *o*-aminophenyl mercaptan and ethyl oxalate.

Oxanilamide *o*-Disulfide, $(-SC_6H_4COCONH_2)_2$.—When an excess of concd. ammonium hydroxide was added to a solution of 0.5 g. of the oxanilate in 15 cc. of 95% alcohol, the amide separated immediately. Recrystallized from the same solvent, it formed colorless, lustrous, fine needles, which darkened and melted with decomposition at about 240° (corr.); yield, 0.4 g., or 93%.

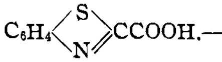
Anal. Calcd. for $C_{16}H_{14}O_4N_4S_2$: C, 49.21; H, 3.61. Found: C, 49.66; H, 3.92.

Oxanilide *o*-Disulfide, $(-SC_6H_4NHCOCONHC_6H_5)_2$.—An attempt to obtain this by the action of aniline upon an alcoholic solution of the corresponding ethyl oxanilate was unsuccessful.

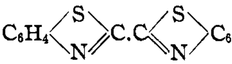
When the solvent alcohol was omitted and the disulfide (0.5 g.) was heated directly with aniline (10 g.) for two hours at 150°, then cooled and the excess of aniline diluted with 50% alcohol, a precipitate separated, which was removed, washed with alcohol and crystallized from benzene. Colorless, fine needles were thus obtained, which melted at 229–230° (corr.) with slight darkening, and were but very slightly soluble in alcohol; yield, 0.3 g., or 49%.

Anal. Calcd. for $C_{28}H_{22}O_4N_4S_2$: C, 61.99; H, 4.05. Found: C, 62.20; H, 4.12.

Reduction of Ethyl Oxanilate *o*-Disulfide, Benzothiazole-2-carboxylic Acid,

 $C_6H_4\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle CCOOH$.—Small pieces of metallic sodium were added gradually to a solution of the oxanilate in 95% alcohol. A colorless solid immediately precipitated (sodium salt), which was very soluble in water and deliquesced on standing in the air. When its aqueous solution was acidified, fine, colorless needles soon separated; *yield, 0.5 g.,* or 60%. These melted with loss of carbon dioxide at 107° (corr.), giving a yellow oil possessing the boiling point (230°) and characteristic odor of benzothiazole.

This acid has been prepared previously by other methods,[7,10] and its melting point recorded as 108°, with loss of carbon dioxide and formation of benzothiazole. Precipitated from its acetone solution by dilution, the crystalline product melted at 105°, which is also in agreement with the literature.

o-Aminophenyl Mercaptan and Oxalyl Chloride, *bis*-2,2′-Benzothiazolyl (Oxalamidothiophenol),  $C_6H_4\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle C.C\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle C_6H_4$.—A mixture of 3 g. of zinc *o*-aminophenyl mercaptide with 1.21 g. of oxalyl chloride[11] was heated at 60–80° under a reflux condenser until the reaction commenced. The heating was interrupted until the reaction moderated, when it was resumed and continued for an hour at 100°. After the finely pulverized crude product had been washed with an excess of *N* sodium hydroxide solution and repeatedly with alcohol, the *bis*-benzothiazolyl was driven out by sublimation. Fine colorless needles were thus obtained, which crystallized from toluene in colorless, glistening plates, m. p. 300.5° (uncorr.), very slightly soluble in alcohol, and dissolving in concd. sulfuric acid to give a characteristic greenish-yellow solution; yield, 1.5 g., or 60%. The melting-point has been recorded by previous investigators as 300°[6,7], 304°,[8] or 306°.[9]

B. Succinic Derivatives

***o*-Aminophenyl Disulfide and Succinic Anhydride, Succinanilic Acid *o*-Disulfide, (III).**—An intimate mixture of 1.6 g. (two molecular equivalents) of succinic anhydride and 2 g. (one equivalent) of *o*-aminophenyl disulfide was heated for an hour at 120–130°. The molten mass gradually solidified, but no separation of water was detected. The cooled melt was pulverized and extracted repeatedly with chloroform, to remove unchanged initial materials. The insoluble remainder crystallized from 60% alcohol in minute colorless needles; yield, 1 g., or 28%. From water, or from very dilute alcohol, it separated in gelatinous form resembling precipitated aluminum hydroxide. It was easily soluble in alcohol or in 10% sodium hydroxide solution, but very slightly soluble in chloroform. When heated in a melting-point tube, it turned yellow, sintered together at 155–158° and melted at 167–168° (cor.). It retained moisture very tenaciously, even when left for some time in an evacuated desiccator.

Anal. Calcd. for $C_{20}H_{20}O_6N_2S_2$: C, 53.57; H, 4.46. Found: C, 53.45; H, 4.92.

Qualitative tests showed the presence of both sulfur and nitrogen.

C. Glutaric Derivatives

***o*-Aminophenyl Disulfide and Glutaric Anhydride, Glutaranilic Acid *o*-Disulfide,** $(\text{—}SC_6H_4NHCO(CH_2)_3COOH)_2$.—An intimate mixture of 2 g. (one molecular equivalent) of the disulfide with 1.84 g. (two equivalents) of glutaric anhydride was heated for two hours at 100°. The melt solidified during this heating, but there was no evidence of the separation of any water. The cold pulverized melt was washed with a small amount of benzene, to remove any excess of the disulfide, and was then decolorized and

---

[10] Reissert, *Ber.*, **37**, 3731 (1904).

[11] Staudinger, *Ber.*, **41**, 3558 (1908).

crystallized from 80% alcohol. Minute, colorless needles were thus obtained, which melted at 155–156° (corr.), with slight darkening, and decomposed at about 160–161°; yield, 3.5 g., or 91%.

Anal. Calcd. for $C_{22}H_{24}O_6N_2S_2$: C, 55.46; H, 5.04. Found: C, 54.97; H, 4.81.

Qualitative tests showed the presence of both nitrogen and sulfur. The compound dissolved in aqueous solutions of sodium hydroxide or carbonate.

D. Camphoric Derivatives

o-Aminophenyl Disulfide and Camphoric Anhydride, Camphoranilic Acid o-Disulfide, $(—SC_6H_4NHCOC_8H_{14}COOH)_2$.—An intimate mixture of 2 g. (one molecular equivalent) of the disulfide and 2.94 g. (two equivalents) of camphoric anhydride was heated at 130–140° for two hours. The resultant solid was pulverized and extracted several times with warm benzene, to remove initial materials. It crystallized from 80% alcohol in greenish-yellow fine rhombs, which melted at 229° (corr.) with decomposition; yield, 2 g., or 40%. It was easily soluble in alcohol or chloroform, very slightly in benzene, and dissolved also in aqueous caustic alkali.

Anal. Calcd. for $C_{32}H_{40}O_6N_2S_2$: C, 62.75; H, 6.58. Found: C, 62.71; H, 6.52.

Qualitative tests showed the presence of both sulfur and nitrogen. It has not been determined which of the two possible isomers is formed in this reaction.

E. Maleic Derivatives

o-Aminophenyl Disulfide and Maleic Anhydride, Maleanilic Acid o-Disulfide, $(—SC_6H_4NHCOCH{:}CHCOOH)_2$.—When 2 g. (one molecular equivalent) of the disulfide and 1.58 g. (two equivalents) of maleic anhydride were ground together in a mortar, evolution of heat was noted and a reaction apparently took place without external heating, for when the mixture was exposed for an hour to a temperature of 100–120° no liquefaction occurred although both initial components melt below this temperature (the anhydride at 53°, and the disulfide at 93°). The product was a yellow, microcrystalline solid, difficultly soluble or insoluble in benzene, xylene, anisole, carbon disulfide, carbon tetrachloride, chloroform, ethyl alcohol (95% or absolute), *n*-butyl alcohol, ethyl or *iso*-amyl acetates, acetone, ether, petroleum ether, glacial acetic acid or water. It dissolved readily in aqueous caustic alkali, or in hot nitrobenzene. It was recrystallized from the latter, the solution being heated to only 160°; yield, 3.5 g., or 97%. The product melted at 200–201°, with some decomposition, and a few degrees above this lost water and formed a brown resin.

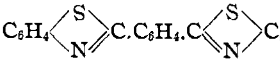
Anal. Calcd. for $C_{20}H_{16}O_6N_2S_2$: C, 54.02; H, 3.63. Found: C, 54.87; H, 3.67.

F. Phthalic Derivatives

o-Aminophenyl Disulfide and Phthalic Anhydride, o-Phthalimidophenyl o-Disulfide, (IV).—An intimate mixture of one molecular equivalent (2 g.) of the disulfide and two equivalents (2.4 g.) of phthalic anhydride was heated for an hour at 120–135°. After about 15 minutes, water was driven off and the mass solidified. This solid product was pulverized and extracted thrice with boiling 95% alcohol, to remove unaltered initial materials. The insoluble portion was dissolved in boiling benzene, the solution decolorized and the crystals obtained recrystallized from the same solvent until the melting point remained constant at 219° (corr.); yield, 3.5 g., or 85%. It formed a colorless microcrystalline solid, soluble in glacial acetic acid, but practically insoluble in water or in aqueous caustic alkali. Warmed with a 10% alcoholic potassium hydroxide solution, it dissolved with hydrolysis to phthalic acid.

Anal. Calcd. for $C_{28}H_{16}O_4N_2S_2$: C, 66.14; H, 3.17. Found: C, 66.18; H, 3.07.

Qualitative tests showed the presence of both sulfur and nitrogen.

o-Aminophenyl Mercaptan and p-Phthalyl Chloride, 2,2'(p-Phenylene)-*bis*-benzothiazole,  $C_6H_4\underset{N}{\overset{S}{\langle\rangle}}C.C_6H_4.C\underset{N}{\overset{S}{\langle\rangle}}C_6H_4$.—A mixture of 3 g. (one molecular equivalent) of zinc *o*-aminophenyl mercaptide with 1.94 g. (one equivalent) of *p*-phthalyl chloride was warmed with a small flame until the reaction began, when the flame was removed. Upon subsidence of this initial reaction, the mixture was heated at 100° for one to two hours longer. The pulverized crude product was washed with an excess of *N* sodium hydroxide solution, then with several small portions (5–10 cc.) of alcohol, after which it was decolorized and crystallized from benzene. Fine, colorless, odorless leaflets resulted, m. p. 263° (corr.), very slightly soluble in alcohol; yield, 2 g., or 62%.

Anal. Calcd. for $C_{20}H_{12}N_2S_2$: C, 69.76; H, 3.48. Found: C, 70.77; H, 3.78.

Hofmann[12] has described a similar compound (m. p., 112°) in the *o*-phthalic series.

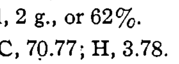
G. Pyromucic Derivatives

Pyromucyl chloride was prepared by the method of Baum.[13] From a mixture of 25 g. of pyromucic acid (m. p., 130°) and 65 g. of thionyl chloride, refluxed for two hours at 100° and then distilled, there was obtained 23 g. (79%) of pyromucyl chloride boiling at 173–174°.

o-Aminophenyl Disulfide and Pyromucyl Chloride, Pyromucylanilide o-Disulfide, $(-SC_6H_4NHCOC_4H_3O)_2$.—When 2.1 g. (two molecular equivalents) of pyromucyl chloride was added to 2 g. (one equivalent) of the disulfide, a reaction began immediately. The mixture was heated for an hour at 100°, the cooled product washed with an excess of *N* sodium hydroxide solution, and then decolorized and crystallized from 95% alcohol. Yellow prisms resulted, m. p. 160.5° (corr.), freely soluble in warm alcohol; yield, 2.3 g., or 66%.

Anal. Calcd. for $C_{22}H_{16}O_4N_2S_2$: C, 60.55; H, 3.67. Found: C, 61.18; H, 3.50.

Reduction of Pyromucylanilide o-Disulfide, 2-α-Furyl-benzothiazole,

 $C_6H_4\underset{N}{\overset{S}{\langle\rangle}}CC_4H_3O$.—

A mixture of 0.8 g. of the pyromucylanilide disulfide, 5 cc. of concd. hydrochloric acid, 45 cc. of water and 5 g. of granulated tin, when boiled for 30 minutes gave a clear solution. To this solution, 6 *N* sodium hydroxide solution was added in considerable excess, and the temperature maintained for an hour at 100°. When cold, the precipitate was removed, decolorized and crystallized from 50% alcohol. It then melted at 105° (corr.) and was identical in all respects with the 2-α-furyl-benzothiazole described in the succeeding paragraph, a mixture of the two melting sharply at 105° (corr.), and with the product obtained from *o*-aminophenyl mercaptan and fural;[14] yield, 0.6 g., or 82%.

o-Aminophenyl Mercaptan and Pyromucyl Chloride, 2-α-Furyl-benzothiazole.—A mixture of 3 g. (one molecular equivalent) of zinc aminophenyl mercaptide and 2.5 g. (two equivalents) of pyromucyl chloride was boiled for 30 minutes and the crude substance purified as described in the foregoing. The product so obtained was identical with the 2-α-furyl-benzothiazole prepared by the other methods noted; yield, 2.85 g., or 75%.

Phosphorus pentasulfide was without action upon this compound when heated with it for three hours at 195–205°, and the original furyl derivative was recovered unaltered (m. p., 105°).

---

[12] Ref. 6, p. 1233.

[13] Baum, *Ber.*, **37,** 2951 (1904).

[14] Bogert and Stull, THIS JOURNAL, **47,** 3082 (1925).

H. Thiophenic Derivatives

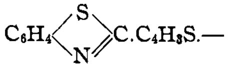
α-Thiophenic acid(thiophene α-carboxylic acid), $C_4H_3S.COOH$, was prepared by oxidizing acetothienone with alkaline potassium permanganate to thienylglyoxylic acid, as recommended by Voerman,[15] and then converting the latter into thiophenic acid by the action of 30% hydrogen dioxide, as described by Holleman.[16] The product precipitated on acidification was nearly pure. It was purified by crystallization from water, or by distillation under diminished pressure, and then melted at 124–125°; yield, 84%. The melting point for the pure acid is given in the literature as 126.2°.

α-Thenoyl chloride, $C_4H_3S.COCl$, was secured most conveniently by refluxing a mixture of thionyl chloride (50 g.) and α-thiophenic acid (19 g.), and distilling the product, following the method of Jones and Hurd;[17] yield, 19 g., or 90%; b. p., 206–208° (literature, 206°).

o-Aminophenyl Disulfide and α-Thenoyl Chloride, α-Thenoylanilide o-Disulfide, $(—SC_6H_4NHCOC_4H_3S)_2$.—When 2 g. of the disulfide was mixed with 2.35 g. of thenoyl chloride, a reaction ensued immediately. After an hour's heating at 100°, the cooled mass was washed with an excess of *N* sodium hydroxide solution, decolorized and crystallized from 95% alcohol, giving fine, pale yellow needles; m. p., 154° (corr.); yield, 2.5 g., or 67%.

Anal. Calcd. for $C_{22}H_{16}O_2N_2S_4$: C, 56.41; H, 3.41. Found: C, 57.13; H, 3.58.

Reduction of α-Thenoylanilide o-Disulfide, **2-α-Thienyl-benzothiazole,**



$C_6H_4\langle{}^{S}_{N}\rangle C.C_4H_3S.—$

A clear solution was obtained by boiling for 15–25 minutes a mixture of 0.8 g. of the disulfide, 5 cc. of concd. hydrochloric acid, 60 cc. of water and 5 g. of granulated tin. This solution was made strongly alkaline with 6 *N* sodium hydroxide solution and kept warm for an hour. The precipitate, which separated as the solution cooled, was removed and crystallized from 95% alcohol. Colorless needles resulted, m. p. 99.5° (corr.), whose tea rose or geranium odor was more pronounced than that of 2-phenyl-benzothiazole ("Rosenkoerper") itself; yield, 0.4 g., or 56%. Mixed with thienyl-benzothiazole prepared from the aminophenyl mercaptan and thenoyl chloride, the melting point remained sharp at 99.5° (corr.).

o-Aminophenyl Mercaptan and α-Thenoyl Chloride, 2-α-Thienyl-benzothiazole.—After boiling for 30 minutes a mixture of 3 g. (one molecular equivalent) of the zinc aminophenyl mercaptide and 2.8 g. (two equivalents) of α-thenoyl chloride, the product was washed with *N* sodium hydroxide solution, decolorized and crystallized from 95% alcohol. The colorless needles of thienyl-benzothiazole which separated were identical in all respects with the product obtained by reduction of α-thenoylanilide o-disulfide and melted sharply at 99.5° (corr.); yield, 2.3 g., or 56%. By slow crystallization, well formed prisms were secured, of the same melting point.

Anal. Calcd. for $C_{11}H_7NS_2$: C, 60.82; H, 3.22. Found: C, 60.93; H, 3.56.

Summary

1. By the action of esters, acid chlorides or anhydrides, upon o-aminophenyl disulfide, acyl derivatives have been obtained which upon reduction yield the corresponding benzothiazoles.

2. Many new benzothiazoles have been prepared also by the direct action of the acid chloride upon zinc o-aminophenyl mercaptide.

[15] Voerman, *Rec. trav. chim.*, **26**, 293 (1907).

[16] Holleman, *ibid.*, **23**, 169 (1904).

[17] Jones and Hurd, THIS JOURNAL, **43**, 2444 (1921).

3. An interesting similarity in aroma is shown by 2-phenyl-, 2-α-furyl-, and 2-α-thienyl-benzothiazoles.

NEW YORK, N. Y.

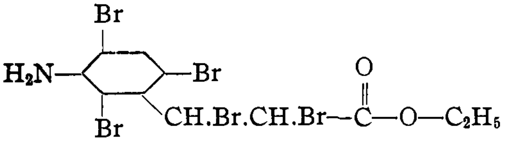
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

REACTIONS OF ETHYL AMINOCINNAMATES WITH BROMINE[1]

BY H. W. UNDERWOOD, JR., AND E. L. KOCHMANN

RECEIVED SEPTEMBER 3, 1925 PUBLISHED JANUARY 8, 1926

Since ethyl *m*-aminocinnamate contains a double bond in the side chain and one ring hydrogen atom *para* to the amino group as well as two atoms of hydrogen in *ortho* positions, treatment of this ester with an excess of bromine might yield a derivative containing three atoms of halogen in the nucleus and two in the side chain,



Possibly a study of the compound obtained by the use of bromine and the ester in molecular proportions would show whether substitution of halogen in the ring preceded addition to the ethylene linkage. The esters of *o*- and *p*-aminocinnamic acids offer analogous possibilities, except that each of these compounds contains only two sensitive aromatic hydrogen atoms. This paper is an account of results obtained in an investigation of reactions in this series. Since chloroform is not readily brominated and apparently does not cause side reactions it has been employed as a solvent and diluent.

Discussion of Experiments and Interpretation of Results[2]

Nitration of Cinnamic Acid and Esterification of the *o*- and *p*-Nitro Derivatives.—The procedure employed was essentially that given by Müller.[3] For the removal of nitrocinnamic and nitrobenzoic acids from ethyl *o*-nitrocinnamate cold, concd. sodium carbonate solution was used; crystals of the *ortho* ester were obtained from alcohol. Yields are recorded in the summary.

Ethyl *m*-Nitrocinnamate.—A 43.8% yield of *m*-nitrocinnamic acid was obtained from 100 g. of technical *m*-nitrobenzaldehyde by the usual method.[4] The average of the yields in several esterifications was 92%.

---

[1] The experimental results described in this paper are taken from a thesis submitted to the Faculty of the Massachusetts Institute of Technology by E. L. Kochmann in partial fulfilment of the requirements for the degree of Master of Science.

[2] All the temperatures given are uncorrected.

[3] Müller, *Ann.*, **212**, 124 (1882).

[4] Schiff, *Ber.*, **11**, 1782 (1878). Tiemann and Oppermann, *Ber.*, **13**, 2060 (1880).