[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, NO. 491]

RESEARCHES ON THIAZOLES. VII. THE BEHAVIOR OF *o*-AMINOPHENYL MERCAPTAN WITH ALDEHYDES, KETONES AND *gem*-DIHALIDES. THE SYNTHESIS OF BENZOTHIAZOLES[1]

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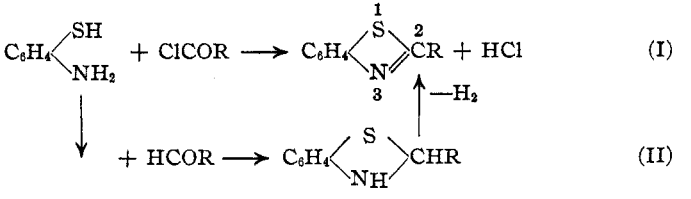
RECEIVED AUGUST 31, 1925 PUBLISHED DECEMBER 12, 1925

Introductory

Hofmann,[3] in his original investigations upon the benzothiazoles, reported that they were produced when *o*-aminophenyl mercaptan and aldehydes interacted. Green and Perkin[4] also found that *p*-phenylenediamine-2,5-di(thiosulfonic acid) gave the same benzobisthiazoles with aldehydes as with acid anhydrides. Later, Claasz[5,6] claimed the formation of benzothiazolines from *o*-aminophenyl mercaptan hydrochloride and aldehydes. It seemed desirable, therefore, to investigate these apparently conflicting statements. Our results agree entirely with those of Hofmann and are at variance with those of Claasz.

Inasmuch as the benzothiazoles (I) are formed readily by the condensation of *o*-aminophenyl mercaptans and acyl halides or anhydrides,[7,8] it was natural to assume that the use of the aldehyde in place of the acid should yield benzothiazolines (II), an assumption which seemed supported by the difficulty in detecting either the evolution or the fate of the hydrogen which should be the by-product if the thiazole and not the thiazoline is formed.



We have repeated the work of Claasz, following his directions as carefully as we could, in the condensation of *o*-aminophenyl mercaptan hydrochloride with formaldehyde, benzaldehyde and vanillin, and obtained products corresponding to the description of his supposititious thiazolines.

[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.*, **13**, 1236 (1880).

[4] Green and Perkin, *J. Chem. Soc.*, **83**, 1204 (1903).

[5] Claasz, *Ber.*, **45**, 1031 (1912).

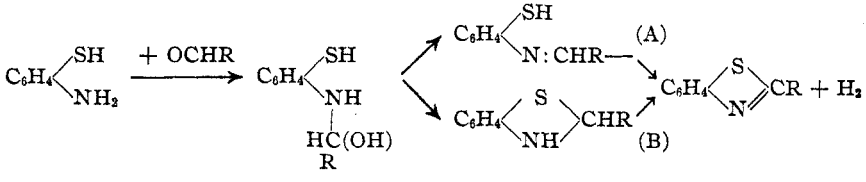
[6] Claasz, *Ber.*, **49**, 1141 (1916).

[7] Hofmann, *Ber.*, **12**, 2362, 2365 (1879).

[8] Hofmann, *Ber.*, **13**, 21 (1880).

All of these, however, were simply crude impure thiazoles, as might have been inferred from their ragged melting points, and on recrystallization readily yielded pure thiazoles of sharp and constant melting point, identical with the thiazoles prepared from the acid chlorides. Further, we found that the thiazole prepared from fural is identical with that from pyromucyl chloride, and that piperonal also yields only a thiazole. The characteristic geranium-like odor of 2-phenyl-benzothiazole could be detected instantly upon bringing benzaldehyde into contact with *o*-aminophenyl mercaptan hydrochloride. Various tests were carried out in connection with the repetition of Claasz' work, to detect the presence of any thiazoline in the products, but the results were consistently negative. When benzal chloride was condensed with *o*-aminophenyl mercaptan, the product was likewise the thiazole.

On the other hand, neither the ketones nor their corresponding dichlorides could be condensed with *o*- aminophenyl mercaptan, an observation which may be urged as an argument in favor of representing the mechanism of the reaction with aldehydes by (A) rather than by (B).



Experimental Part

***o*-Nitrophenyl Disulfide,** $(O_2NC_6H_4)_2S_2$.—In the preparation of this compound from *o*-nitrochlorobenzene, by the method of Blanksma,[9] as developed by Wohlfahrt,[10] it was found that a good commercial grade of nitrochlorobenzene (m. p., 31°) gave 50% yields of the disulfide (m. p., 195°, corr.), as against 60% from a pure initial material.

***o*-Aminophenyl Mercaptan** (*o*-Aminothiophenol).—The zinc salt was prepared by reducing a warm glacial acetic acid solution of the nitrophenyl disulfide with zinc dust, as described by Bogert and Snell;[11] yield, 90%. By saturating with hydrogen sulfide a hot glacial acetic acid solution of this zinc salt and filtering from the zinc sulfide, an acetic acid solution of the free aminophenyl mercaptan was obtained conveniently, containing sufficient hydrogen sulfide to protect it from rapid oxidation.

The *hydrochloride*, prepared by the method of Claasz,[5] melted at 217° (corr.), with previous darkening, as recorded by him.

***o*-Aminophenyl Disulfide,** $(H_2NC_6H_4)_2S_2$, was prepared from zinc *o*-aminophenyl mercaptide by suspending the latter in dil. ammonium

[9] Blanksma, *Rec. trav. chim.*, **20**, 121 (1901).

[10] Wohlfahrt, *J. prakt. Chem.*, [2] **66**, 553 (1902).

[11] Bogert and Snell, THIS JOURNAL, **46**, 1309 (1924).

hydroxide and passing a current of air through the mixture, as described by Bogert and Snell;[11] it formed lustrous, light yellow plates; m. p., 93°; yield, 57%.

o-Aminophenyl Mercaptan and Formaldehyde, Benzothiazole.—As described by Claasz, *o*-aminophenyl mercaptan hydrochloride and formaldehyde were condensed, and the crude product was distilled, first under diminished pressure and then at ordinary pressure, when practically all came over at 230–235°. The boiling point, as determined by the method of Siwoloboff,[12] was 230–231°, which agrees with that recorded by Hofmann[13] for benzothiazole, in addition to which it agreed with the latter in its nitrogen-base odor and in its solubility in alcohol and carbon disulfide. Claasz regarded the product as the benzothiazoline, and gave its boiling point at 270°.

o-Aminophenyl Mercaptan and Benzaldehyde, 2-Phenyl-benzothiazole.—To a hot solution of 1 g. of zinc *o*-aminophenyl mercaptide in 50 cc. of glacial acetic acid was added a like amount of benzaldehyde, and a rapid stream of hydrogen sulfide was passed in until zinc sulfide no longer precipitated. Experiments showed that there was no advantage in precipitating the zinc sulfide before adding the benzaldehyde. When the clear yellow filtrate from the sulfide was diluted with 4–5 volumes of water, a curdy, yellow precipitate separated, which crystallized from 50% alcohol in colorless, lustrous needles, m. p. 114° (corr.), possessing the characteristic odor of 2-phenyl-benzothiazole; yield, 61.5%.

Anal. Calcd. for $C_{13}H_9NS$: C, 73.93; H, 4.26; for $C_{13}H_{11}NS$: C, 73.24; H, 5.16. Found: C, 73.70; H, 4.06.

This product, in appearance, odor, melting point and percentage composition, was indistinguishable from the well-known 2-phenyl-benzothiazole, and did not agree with Claasz' description of 2-phenyl-benzothiazoline. No evolution of hydrogen was observed during the reaction.

In an attempt to detect any thiazoline present, the warm filtrate from the zinc sulfide (as noted above) was cooled and treated with an excess of acetic anhydride. There was no evidence of any reaction and on dilution with water and crystallization of the precipitate from 50% alcohol, the same product (m. p., 114°) as before was obtained. The precipitate secured by diluting the zinc sulfide filtrate was also treated with acetic anhydride, but no acetylation occurred and 2-phenyl-benzothiazole was the sole product isolated.

When benzaldehyde and *o*-aminophenyl mercaptan hydrochloride were condensed, as set forth by Claasz,[6] the purified product formed colorless needles, whose odor was identical with that of 2-phenyl-benzothiazole. It melted sharply at 114° (corr.), and a mixture with some pure 2-phenyl-

[12] Siwoloboff, *Ber.*, **19**, 795 (1886).

[13] Hofmann, *Ber.*, **13**, 19 (1880).

benzothiazole of different origin melted at the same point. Claasz reported that his benzothiazoline softened at 105° and melted at 108–109°.

o-Aminophenyl Mercaptan and Benzal Chloride, 2-Phenyl-benzothiazole.—To a solution of 2 g. of the zinc *o*-aminophenyl mercaptide and 5 g. of fused sodium acetate in 100 cc. of warm glacial acetic acid was added 2 g. of benzal chloride, and the solution was refluxed for about 30 minutes. As no action was evident, a rapid current of hydrogen sulfide was passed through the solution. Some hydrogen chloride was evolved and zinc sulfide precipitated. The clear brown filtrate from the sulfide was diluted with 4–5 volumes of water and the curdy precipitate obtained was crystallized from 50% alcohol. Fine colorless needles resulted; m. p., 114° (corr.). The yield was low, due partly to losses in crystallization. An intimate mixture of this product with 2-phenyl-benzothiazole of different origin likewise melted sharply at 114° (corr.).

When a mixture of the zinc mercaptide (one mole) and benzal chloride (two moles), in the absence of any solvent, was boiled for 30 minutes, then treated with *N* sodium hydroxide solution and filtered, tarry products insoluble in 50% alcohol were formed in considerable amount, together with some 2-phenyl-benzothiazole, but no thiazoline was found.

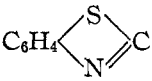
o-Aminophenyl Mercaptan and Vanillin, 2-(*m*-Methoxy-*p*-hydroxyphenyl)benzothiazole.—To a solution of 2 g. (one molecular equivalent) of zinc aminophenyl mercaptide in 100 cc. of warm glacial acetic acid, 2 g. (two equivalents) of vanillin was added, and the same operations carried out as described for benzaldehyde. The crude product was crystallized from 95% alcohol until the melting point remained constant at 175.5° (corr.). It then formed pale yellowish, lustrous prisms, of faint but sweet odor; yield, 1.5 g., or 46.8%. Its solution in alcoholic alkali exhibited a purplish fluorescence.

Anal. Calcd. for $C_{14}H_{11}O_2SN$: C, 65.32; H, 4.31. Found: C, 65.40; H, 4.24.

Following the procedure of Claasz,[6] vanillin and *o*-aminophenyl mercaptan hydrochloride yielded a crude product which was removed, decolorized and crystallized from 95% alcohol until the melting point remained constant at 175.5° (corr.). When this material was mixed with the product obtained in the previous experiment, the melting point was unaltered. Claasz reported his benzothiazoline as forming yellow flakes, melting at 163–165°.

o-Aminophenyl Mercaptan and Piperonal, 2-(*m,p*-Methylenedioxyphenyl)benzothiazole.—The condensation was carried out in a manner entirely similar to that in which benzaldehyde was used. The crude product crystallized from 95% alcohol in colorless scales, m. p. 125° (corr.), of faint, sweet odor; yield, 62.5%.

Anal. Calcd. for $C_{14}H_9O_2SN$: C, 65.88; H, 3.53. Found: C, 65.46; H, 3.60.

o-Aminophenyl Mercaptan and Fural, 2-α-Furyl-benzothiazole, 

C_6H_4 ring $C.C_4H_3O$.—A rapid stream of hydrogen sulfide was passed through a boiling solution of 2 g. (one molecular equivalent) of zinc aminophenyl mercaptide in 100 cc. of glacial acetic acid as long as zinc sulfide precipitated. The mixture was allowed to cool, the sulfide removed, 1.22 g. (two equivalents) of fural added to the filtrate, the flask corked and left overnight at room temperature, after which the liquid was diluted with 4–5 volumes of water. A crystalline precipitate soon separated. This was collected, decolorized and crystallized from 60% alcohol until the melting point remained constant at 105° (corr.). It then appeared in colorless, lustrous, flaky crystals, of a geranium-like odor, quite similar to that of 2-phenyl-benzothiazole; yield, 0.9 g., or 36%. Addition of the fural to the cold acid solution gave better results than when the addition was made to a hot one.

Anal. Calcd. for $C_{11}H_7ONS$: C, 65.67; H, 3.50. Found: C, 66.17; H, 3.70.

o-Aminophenyl Mercaptan and Acetone.—From a warm solution of 1 g. of zinc aminophenyl mercaptide in 50 cc. of glacial acetic acid, the zinc was removed as sulfide and 2 g. of acetone added to the cool filtrate. Dilution and neutralization of this caused the separation of a small amount of heavy oil, which congealed to a colorless, crystalline solid, soluble in acid or caustic alkali, but not in alkaline carbonate, and of low melting point. This was manifestly unaltered *o*-aminophenyl mercaptan (m. p., 26°), as it rapidly oxidized in the air to the *o*-aminophenyl disulfide.

o-Aminophenyl Mercaptan and Michler's Ketone.—The experiment was conducted in exactly the same way as described for acetone, using 1 g. of the zinc mercaptide, 50 cc. of glacial acetic acid and 1 g. of the ketone. The filtrate from the zinc sulfide was dark red. When this solution was diluted, the original ketone was recovered and was identified by a mixed melting point and by its conversion into Crystal Violet with dimethylaniline. There was no evidence of any condensation between the amino mercaptan and the ketone.

o-Aminophenyl Mercaptan and Benzophenone Chloride.—The condensation of zinc *o*-aminophenyl mercaptide with benzophenone chloride was attempted under various conditions, but the products isolated were only unchanged initial materials and tars.

Summary

1. *o*-Aminophenyl mercaptan condenses with aldehydes to form thiazoles, as stated by Hofmann, and not thiazolines as claimed by Claasz. Benzal chloride likewise yields the thiazole.

2. Neither ketones nor ketone chlorides could be condensed with the *o*-aminophenyl mercaptan under the conditions of our experiments.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE FELLOWSHIP OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH, AND COLLEGE OF PHARMACY, UNIVERSITY OF PITTSBURGH]

THE SYNTHESIS OF 5-β-HYDROXYETHYL-BARBITURIC ACID AND ITS ALKYL DERIVATIVES

BY LEONARD H. CRETCHER, JULIUS A. KOCH AND W. H. PITTENGER

RECEIVED SEPTEMBER 2, 1925 PUBLISHED DECEMBER 12, 1925

Continuing the study of the effect of the introduction of an hydroxyl group on the toxicity and pharmacological action of medicinal substances[1] a number of β-hydroxyethyl derivatives of barbituric acid have been synthesized.

The parent substance, 5-β-hydroxyethyl-barbituric acid, has been prepared by Johnson and Shepard[2] by hydrolysis of 5-β-phthalimidobarbituric acid with concd. hydrochloric acid. So far as the authors are aware, no other members of this series are known.

The synthesis of these substances was first undertaken by the senior author in conjunction with Dr. Ivan P. Lambrette.[3] Sodium diethylmalonate was converted into β-hydroxyethyl-diethyl malonate by a reaction with ethylene oxide.[4] This substance was condensed with urea and with thio-urea in the presence of sodium ethylate. In this manner 5-β-hydroxyethyl-barbituric acid and 2-thio-5-β-hydroxyethyl-barbituric acid, described below, were prepared. Owing to decomposition on distillation, it was impossible to obtain hydroxyethyl-malonic ester and its alkyl derivatives of sufficient purity for our work. Furthermore, the yield of product obtained on condensation with urea was low. Because of these difficulties, this method was abandoned in favor of a procedure mentioned in a previous paper from this Laboratory.[5]

It has been found that β-chloro-ethyl-vinyl ether readily reacts with sodium diethylmalonate and mono-alkyl substituted malonic esters to form diethyl-vinyloxyethyl-malonate and its corresponding alkyl-substitution products. These esters are stable and can be purified by distillation. They condense smoothly with urea and with thio-urea, forming 5-vinyloxyethyl-barbituric acids; these compounds, on treatment with dilute

[1] (a) Cretcher and Pittenger, THIS JOURNAL, **46**, 1504 (1924); (b) **47**, 2560 (1925).

[2] Johnson and Shepard, THIS JOURNAL, **35**, 1003 (1913).

[3] Belgian American Foundation Student, whose untimely death occurred in Brussels, Belgium, in 1924.

[4] Traube and Lehmann, *Ber.*, **32**, 720 (1899).

[5] Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1176 (1925).