[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

MERCURATED AZO DYES DERIVED FROM BENZIDINE AND ORTHO-TOLIDINE

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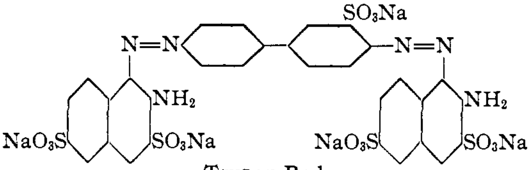
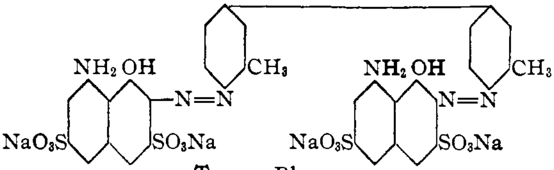
Certain azo dyes, particularly Trypan Red and Trypan Blue, have been reported[1] as having some trypanocidal action. These dyes were obtained by tetrazotizing certain benzidine derivatives and coupling with naphthalene derivatives having sulfonic acid groups in the 3- and 6-positions. The structures for these two dyes are indicated by the formulas



Trypan Red



Trypan Blue

The use of organic mercury compounds has also met with some success in the treatment of diseases which are caused by trypanosomes. Since mercury can usually be introduced into aromatic amines, it seemed worth while to prepare some mercurated benzidine derivatives and use these to obtain dyes related to Trypan Red and Trypan Blue. Such products might be expected to have very useful pharmacological properties.

Raiziss[2] has mentioned that acetoxymercuri-benzidine can be obtained as a white amorphous powder by boiling benzidine and mercuric acetate in dilute hydrochloric acid. He has never described this procedure in detail and has given no further information concerning the compound. Bernardi and Tartarini[3] have treated benzidine with mercuric acetate in glacial acetic acid and have obtained a very unstable compound which melted with decomposition at 138–140°. They say that the compound is too unstable for analysis, but suggest that it has the structure, $H_2N(p\text{-}NH_2C_6H_4)\text{-}C_6H_3HgOCOCH_3$.

In repeating this work it has been found possible to introduce one acet-

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[1] Ehrlich, *Berl. klin. Wochschr.*, **44**, 235 (1907).

[2] Raiziss in "Organic Compounds of Mercury," by F. C. Whitmore, The Chemical Catalog Company, Inc., New York, **1921**, p. 349.

[3] Bernardi and Tartarini, *Gazz. chim. ital.*, **57**, 223 (1927).

oxymercuri group into benzidine with considerable ease. The compound which was obtained melted somewhat higher (144–146°) than was recorded by Bernardi and Tartarini for their product. The product always contained acetic acid of crystallization and when this was removed by heating the sample, decomposition resulted. Only one acetoxymercuri group could be introduced even when benzidine was treated with two or three equivalents of mercuric acetate. The new mercury compound was quite unstable and lost its mercury when suspended in water. The mercury atom was attached to the benzene ring since the mercurated amine could be tetrazotized and coupled to give azo dyes which contained the expected amount of mercury.

o-Tolidine was also mercurated and the derivative was very similar to the benzidine derivative in its properties. On account of the instability of these products their exact structure has not been established. The acetoxymercuri group is presumably ortho to one of the amino groups.

In preparing the tetrazonium salts from acetoxymercuri-benzidine and acetoxymercuri-*o*-tolidine it was necessary to treat an absolute alcoholic suspension of the amine with *n*-butyl nitrite in the presence of a little aqueous hydrochloric acid. When the reaction was attempted in water suspension, the mercury was removed from the molecule. The coupling reactions were also carried out in absolute alcohol suspension. Three dyes were prepared and analyzed. Acetoxymercuri-benzidine was tetrazotized and coupled with 2-amino-8-naphthol-6-sulfonic acid and with 1-amino-8-naphthol-3,6-disulfonic acid (H-acid). Acetoxymercuri-*o*-tolidine was tetrazotized and coupled with H-acid. The dyes thus obtained separated with alcohol of crystallization. Attempts further to purify the dyes were not successful due to their instability. When dissolved in water containing sodium bicarbonate, the dyes lost metallic mercury in a few days. Heating the water solutions caused decomposition very quickly. The instability of the dyes made them unsuitable for pharmacological tests.

Experimental Part

Acetoxymercuri-benzidine.—In a liter beaker equipped with a mechanical stirrer was placed a solution of 31.8 g. (0.1 mole) of mercuric acetate in 150 cc. of glacial acetic acid. The stirrer was started and a solution of 18.4 g. (0.1 mole) of benzidine in 300 cc. of glacial acetic acid was added slowly. A precipitate began to appear at once. The mixture was stirred for about ten minutes after the solutions were mixed and was then filtered. The precipitate was washed first with glacial acetic acid, and then with ether and finally dried in the air in the dark. The yield was 55 g. of a product which melted at 144–146° with decomposition.

This compound was insoluble in water, alcohol, ether and benzene. It turned gray on standing in the light. The water suspension was acid to litmus. When this suspension was heated the compound darkened rapidly. An aqueous suspension of the product reacted in the cold with sodium sulfide solution giving mercuric sulfide. Aqueous hydrochloric acid removed the mercury from the compound very rapidly. The same product was obtained when the preparation was repeated using 63.6 g. and 95.4 g. of mercuric acetate with 18.4 g. of benzidine.

A complete analysis of this mercurated benzidine was made. Carbon and hydrogen were determined by combustion. Mercury was determined by Whitmore's gold crucible method.[4] Nitrogen was determined by the Kjeldahl method. Acetic acid was determined by drying a sample under reduced pressure over solid sodium hydroxide and by direct titration of a sample with standard alkali.

Anal. Subs., 0.1855, 0.1718: CO_2, 0.2650, 0.2440; H_2O, 0.0726, 0.0669. Subs., 0.1000, 0.1000; Hg, 0.0320, 0.0325. Subs., 1.000, 1.000: cc. of 0.102 N H_2SO_4, 32.00, 31.00. Subs., 0.5000; loss in weight on drying, 0.0535. Subs., 0.2000; cc. of 0.0980 N NaOH, 12.2. Calcd. for $C_{14}H_{14}N_2O_2Hg \cdot 3CH_3COOH$: C, 38.8; H, 4.2; Hg, 32.5; N, 4.5; CH_3COOH, 9.65; neutral equivalent, 207. Found: C, 39.0, 38.8; H, 4.3, 4.3; Hg, 32.0, 32.5; N, 4.52, 4.43; CH_3COOH, 10.07; neutral equivalent, 204.

Acetoxymercuri-*o*-tolidine.—This compound was obtained in the same manner as described for the benzidine derivative using 21.2 g. of *o*-tolidine in place of the equivalent amount of benzidine. The yield was 52 g. of a product which melted with decomposition at 120°. In all of its other properties it was very similar to the benzidine derivative.

Anal. Subs., 0.1500: Hg, 0.0500. Calcd. for $C_{16}H_{18}N_2O_2Hg \cdot 2CH_3COOH$: Hg, 33.9. Found: Hg, 33.3.

Tetrazotization of Acetoxymercuri-benzidine and Coupling with H-Acid.—To a suspension of 6.2 g. of acetoxymercuri-benzidine in 300 cc. of absolute alcohol was added 1.5 cc. of concentrated hydrochloric acid. The mixture was cooled to 0° and then with continuous stirring 2.1 g. of *n*-butyl nitrite was added. Stirring was continued for ten minutes and then this mixture was added to a cold suspension of 6.4 g. of H-acid in 300 cc. of absolute alcohol to which had been added about 0.5 cc. of concentrated hydrochloric acid. The mixture was stirred in the cold for about thirty minutes and then allowed to come to room temperature. The dye separated as a red-brown crystalline compound. The product was collected on a suction filter, washed with alcohol and ether and dried in the air out of direct light. The dye was insoluble in water. It dissolved in aqueous sodium bicarbonate to give a purple solution. The alkaline solution deposited free mercury within forty-eight hours. Since the dye was too unstable to purify, it was analyzed directly. Nitrogen was determined by the Dumas method, sulfur in the Parr bomb, mercury by the gold crucible method and sodium as the sulfate by decomposition with nitric and sulfuric acids. Ethyl alcohol was present as alcohol of crystallization. This was demonstrated by drying the sample to constant weight in a vacuum dryer over calcium chloride.

Anal. Subs., 0.1354: 9.95 cc. of N_2 at 33° and 750 mm. Subs., 0.5000, 0.5000: $BaSO_4$, 0.3752, 0.3831. Subs., 0.1500, 0.1500: Hg, 0.0245, 0.0245. Subs., 0.2965, 0.2222: Na_2SO_4, 0.0335, 0.0270. Subs., 0.2188: C_2H_5OH lost in drying, 0.0163. Calcd. for $C_{34}H_{24}O_{16}N_6S_4HgNa_2 \cdot 2C_2H_5OH$: N, 6.5; S, 10.3; Hg, 16.2; Na, 3.7; C_2H_5OH, 7.4. Found: N, 7.6; S, 10.3, 10.5; Hg, 16.3, 16.3; Na, 3.8, 3.9; C_2H_5OH, 7.6.

Tetrazotization of Acetoxymercuri-*o*-tolidine and Coupling with H-Acid.—To a suspension of 6.2 g. of acetoxymercuri-*o*-tolidine in 300 cc. of absolute ethyl alcohol was added 1.5 cc. of concentrated hydrochloric acid. The mixture was cooled to 0°; then while stirring there was added 2.1 g. of butyl nitrite. Sitrring was continued for ten minutes and then this mixture was added to a cold suspension of 6.4 g. of H-Acid in 300 cc. of absolute alcohol. The mixture was stirred in the cold for thirty minutes

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[4] Whitmore, "Organic Compounds of Mercury," The Chemical Catalog Co., Inc., New York, **1921**, p. 365.

and then allowed to come to room temperature. The orange-colored powder which separated was collected on a suction filter and washed with alcohol and ether. The product was dried in the air out of direct light. This dye was only slightly soluble in water, but in sodium bicarbonate solution it gave a deep purple solution. Mercury separated from this solution on standing for forty-eight hours.

Anal. Subs., 0.1500: Hg, 0.0217. Calcd. for $C_{36}H_{28}O_{16}N_6S_4Na_2Hg{\cdot}5C_2H_5OH$: Hg, 14.24. Found: Hg, 14.4.

Tetrazotization of Acetoxymercuri-benzidine and Coupling with 2-Amino-8-naphthol-6-sulfonic Acid.—The tetrazotization was performed with the same amount of material as described before and the tetrazonium salt was coupled with 4.8 g. of 2-amino-8-naphthol-6-sulfonic acid. The dye separated as a reddish-purple powder which was washed with alcohol and ether and dried in the air out of direct light. It was only slightly soluble in water, but gave a deep purple solution in sodium bicarbonate solution. This solution deposited mercury on standing for forty-eight hours.

Anal. Subs., 0.1500: Hg, 0.0276. Calcd. for $C_{34}H_{26}O_{10}N_6S_2Hg{\cdot}3C_2H_5OH$: Hg, 18.5. Found: Hg, 18.4.

Summary

1. Monoacetoxymercuri derivatives have been prepared by treating benzidine and *o*-tolidine in glacial acetic acid with mercuric acetate.

2. These acetoxymercuri derivatives can be tetrazotized and coupled with naphthalene derivatives to give azo dyes which are related in their structure to Trypan Red and Trypan Blue.

3. The mercurated dyes are not stable and readily lose mercury and are hence unsuitable for pharmacological testing.

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ARYL SULFONE DERIVATIVES OF DIBASIC ACIDS[1]

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It was recently shown that phthalyl chloride reacts readily with sulfonamides to give phthalimide derivatives[2] when the materials are merely heated or are boiled in toluene solution. The following study develops this and other practical methods for the preparation of aryl sulfone derivatives of dibasic acids.

Whereas certain suggested methods such as heating phthalic anhydride with *p*-tolyl sulfonamide or with its sodium salt, or heating *p*-tolyl sulfonyl chloride with phthalimide, failed to yield the desired product, it was found that heating phthalic anhydride with *p*-tolyl sulfonamide in the presence of phosphorus oxychloride readily gave the phthalimide derivative in sub-

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[1] The material presented in this paper is from part of a thesis submitted by Theodore Evans, du Pont Fellow for 1929–1930, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, **1930.**

[2] Evans and Dehn, THIS JOURNAL, **51,** 3651 (1929).