cent Bi. However, when this product was redissolved in water, reprecipitated with alcohol and dried to constant weight in a vacuum desiccator, it was found to contain only 6.97 per cent moisture removable by drying at 100°. The product dried at 100° analyzed 71.1 per cent Bi and was found to be insoluble in water. Thus our attempts to obtain a water-soluble tetra-bismuthyl gluconate corresponding to Kober's tetra-bismuthyl tartrate were unsuccessful.

Toxicity of the Bismuthyl Gluconates.—These preparations were dissolved in water so that each cc. contained 12 mg. of metallic bismuth and injected intravenously in rats. This route of administration is not used clinically but has been employed by a number of laboratory workers for rapidly estimating the systemic toxicity of various water-soluble bismuth compounds.

Preliminary experiments seemed to indicate that the tri-bismuthyl gluconate was somewhat less toxic than the di-bismuthyl gluconate. However, more complete studies using a large number of rats indicated that all these gluconates are approximately equally toxic. The minimum fatal dose was found to be approximately 7 mg. of bismuth metal per kilo and death occurred on the second to fifth day after injection. Parallel injections of water-soluble citrates and tartrates gave results indicating a similar toxicity.

These results indicate that these various water-soluble bismuth preparations when injected intravenously in rats in equivalent doses of metallic bismuth are approximately equally toxic. The wide differences in the intramuscular toxicities of numerous water-soluble bismuth preparations reported from the literature by Hanzlik, Seidenfeld and Johnson (3) are probably due in large part to differences in rates of absorption from the muscle. When such preparations are injected intravenously the factor of absorption is not introduced and the toxicities are greater and show lesser individual variation.

SUMMARY.

A mono-sodium-di-bismuthyl gluconate and a mono-sodium-tri-bismuthyl gluconate have been prepared containing 59.6 per cent and 67.6 per cent bismuth, respectively. When injected intravenously in aqueous solution into rats these compounds show a minimum fatal dose of approximately 7 mg. of metallic bismuth per Kg. which agrees with a similar toxicity observed for some water-soluble tartrates and citrates which were injected in parallel groups of rats.

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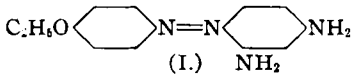
MERCURY DERIVATIVES OF AZO DYES.*[1]

BY W. BRAKER AND W. G. CHRISTIANSEN.

Azo dyes such as the hydrochloride of 2,4-diamino-4′-ethoxy azobenzene (compound I)

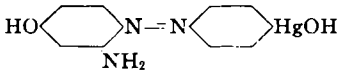
* Scientific Section, A. PH. A., Portland meeting, 1935.

[1] Research Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, N. Y.

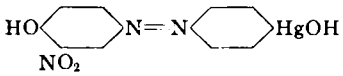


(I.)

are used as antiseptics in the treatment of infections of the urinary tract. While investigating dyes more or less closely related to the above it was considered of interest to prepare several examples having an hydroxy-mercuri group attached to one of the benzene nuclei. It was realized that such compounds might be unsuitable for use owing to low solubility and that the only ones which could be expected to be suitable for practical use would have salt-forming groups such as phenolic hydroxyls. Since nitro phenols are more acidic than the unnitrated phenols, a compound containing a nitro group as well as an hydroxyl group was included. Two compounds of this type were prepared; they were, however, insoluble even in excess alkali hydroxide and therefore of no practical interest. The substances were:



4-Hydroxymercuri-2'-amino-4'-hydroxy azobenzene.



4-Hydroxymercuri-3'-nitro-4'-hydroxy azobenzene.

Attempts to prepare compounds with still more acidic substituents such as carboxyl and sulphonic acid groups resulted in numerous difficulties such as internal salt formation.

EXPERIMENTAL.

Preparation of Para-Amino Phenyl Mercury Acetate.—This substance was prepared according to the method described by Whitmore.[1] A white crystalline material of melting point 166–167° C. was obtained.

Preparation of 4-Hydroxymercuri-2'-Amino-4'-Hydroxy Azobenzene.—10.2 Gm. of para-amino phenyl mercury acetate was dissolved in 25 cc. of concentrated hydrochloric acid contained in 125 cc. of water. The substance was diazotized with 2.0 Gm. of sodium nitrite. The excess nitrous acid was eliminated by the addition of 0.5 Gm. of urea. A solution of 3.1 Gm. of meta-amino phenol in 100 cc. of 15% sodium hydroxide was added at 0° C. The mixture was stirred at 0° C. for one hour and at 26° C. for three hours. The mixture was then acidified with dilute acetic acid and the dark red flocculent precipitate was filtered off, washed with water and dried *in vacuo*.

Yield, 3.75 Gm. of a dark red powder.

Assay.—Mercury: Found, 47.07%; calculated for $C_{12}H_{11}N_3O_2Hg$, 46.69%.

Preparation of 4-Hydroxymercuri-3'-Nitro-4'-Hydroxy Azobenzene.—10.5 Gm. of para-amino phenyl mercury acetate contained in dilute hydrochloric acid was diazotized with 2.5 Gm. of sodium nitrite. The excess nitrous acid was destroyed by the addition of 1.0 Gm. of urea. 4.5 Gm. of ortho-nitrophenol dissolved in 100 cc. of 10% sodium hydroxide solution was then added at 0° C. The mixture was further stirred for two hours at 0° C. and allowed to remain over night at 25° C. A yellow crystalline material insoluble in this alkaline medium was filtered off, washed with water and dried *in vacuo*. This material was shown by assay to be 4-hydroxymercuri-3'-nitro-4'-hydroxy azobenzene. The filtrate of the latter was made slightly acid with hydrochloric acid and the brown precipitate thus obtained was filtered off, washed with water and dried *in vacuo*.

[1] Whitmore, "Organic Compounds of Mercury," 210 (1921).

This material was identified by assay as *p*-hydroxymercury aniline. Evidently the diazotization had been only partially completed prior to the coupling reaction.

Yield, 2.1 Gm. of a yellow crystalline material.

Assay.—Mercury: Found, 43.25%; calculated for $C_{12}H_9O_4N_3Hg$, 43.65%.

SUMMARY.

Hydroxymercury derivatives of azo dyes frequently used as urinary antiseptics have been prepared but have been found to be too insoluble for biological testing.

MISCELLANEOUS DERIVATIVES OF 8-HYDROXY-QUINOLINE.*

BY E. MONESS AND W. G. CHRISTIANSEN.[1]

The alkylation of phenolic germicides frequently increases the activity of the compound. We therefore introduced the propyl group into chloro-8-hydroxy-quinoline. To this end we prepared 5-propyl-8-hydroxy-quinoline and chlorinated it to form 5-propyl-7-chloro-8-hydroxy-quinoline. This compound was incorporated into an oily medium and evaluated by the agar cup-plate method (1). It was found to be less active than the non-alkylated compound, giving a clear zone of only 1–2 mm., whereas chloro-8-hydroxy-quinoline, tested simultaneously with it, showed a 5-mm. clear zone. It is reasonable to believe that a lowered water-solubility, brought about by alkylation, is the reason for its lesser activity.

While 5-chloro-8-hydroxy-quinoline is soluble in oily vehicles, and in such media is a valuable germicide, its usefulness is limited by its insolubility in aqueous solutions. An attempt was therefore made to render it water-soluble by preparing its metho-chloride. When prepared, this compound (analogous to the metho-chloride of acridine) was readily soluble in water, but its activity was found to be considerably less than that of the original chlorohydroxy quinoline.

Two mercury derivatives of 8-hydroxy-quinoline: anhydro-mercuri-5-chloro-8-hydroxy-quinoline and anhydro-mercuri-5-nitro-8-hydroxy-quinoline, were prepared for evaluation as germicides. They were obtained as orange-colored, microcrystalline powders, but were found to be insoluble in dilute alkali, and therefore were not tested for activity.

Since the quinoline nucleus is present in certain parasiticides of the quinoline type, we used hydroxy-quinoline as an intermediate in the preparation of two compounds which seemed to offer possibilities of such activity. 5-(Diethylaminoethylamino)-8-hydroxy-quinoline and 8-diethylaminoethoxy-quinoline were prepared and tested as trypanocides. The former showed practically no activity, and the latter, while definitely active, was inferior to other well-known trypanocidal agents.

It was thought possible to obtain derivatives of hydroxy-quinoline which would possess local anesthetic properties, and as an example we prepared the diethylaminoethyl ester of 5-carboxy-8-ethoxy-quinoline. In this synthesis we followed the method used by Matsumura (2) in the preparation of 5-carboxy-8-hydroxy-

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