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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quinoline. Since we desired the ethoxy compound rather than the hydroxy, we ethylated the 5-benzoyl-8-hydroxy-quinoline before converting to the oxime. Our diethylaminoethyl ester was obtained by reacting the sodium salt of the acid with diethylaminoethyl chloride. We confirmed the structure of the final compound by preparing it by the Skraup reaction, using methyl-3-amino-4-ethoxy benzoate as the starting material. A mixed melting point proved the two end products to be identical. When tested as a local anesthetic, the compound was found to be only slightly active.

EXPERIMENTAL.

Preparation of 2-Nitro-p-Propyl-Phenol (3).—Forty grams *p*-propyl-phenol were dissolved in 80 Gm. benzene, to which solution was added, dropwise, 96 Gm. of a mixture of equal volumes of concentrated nitric acid and water, stirring constantly and keeping the reaction mixture cooled to 15–20° C. The nitric acid layer was drained off, and the benzene solution was washed with water. The benzene was distilled off and the residual oil steam-distilled. The yellow oil obtained was extracted with ether, the latter distilled off and the oil fractionated.

Yield 29 Gm. of yellow oil; b. p. 110° C. at 4 mm.

Analysis: Found—N, 7.52%; calculated for $C_9H_{11}O_3N$—N, 7.74%.

The analysis by the Kjeldahl method was preceded by reduction with hydrosulphite. The 0.15-Gm. sample in a Kjeldahl flask was dissolved in 5 cc. normal sodium hydroxide and 0.5–1.0 Gm. of sodium hydrosulphite was added. After a few minutes of gentle heating the red solution was decolorized and yellowish white crystals separated. The usual Kjeldahl procedure was then followed.

Preparation of 2-Amino-p-Propyl-Phenol.—Ten grams 2-nitro-*p*-propyl-phenol were dissolved in 250 cc. of approximately normal sodium hydroxide, and while heating on a steam-bath, powdered sodium hydrosulphite was added in small portions until the red color had disappeared. The mass of silvery gray crystals which separated was filtered off and washed with water.

Yield 4.8 Gm., m. p. 140–142° C.

Analysis: Found—N, 9.17%; calculated for $C_9H_{13}ON$—N, 9.27%.

Preparation of 5-Propyl-8-Hydroxy-Quinoline.—Four and five-tenths grams 2-amino-*p*-propyl-phenol were mixed with 6.8 Gm. arsenic pentoxide and 13.5 Gm. glycerin. Thirteen and five-tenths grams of concentrated sulphuric acid were added and the mixture, heated by means of an oil-bath, was boiled under reflux for four hours. It was then cooled and diluted with water. The brown residue was filtered off and washed with water. The filtrate was neutralized with dilute sodium bicarbonate solution and 2.5 Gm. of a brown, slightly tarry substance was obtained. The original residue was boiled with three successive 100-cc. portions of 5% sulphuric acid, and these combined extracts were neutralized with sodium bicarbonate solution. Five-tenths gram of crude product was thus recovered, combined with that obtained from the original solution, and the whole dissolved in boiling alcohol. A slight insoluble residue was filtered off, and the filtrate acidified with alcoholic hydrochloric acid. The clear red solution was evaporated to dryness, the residue dissolved in water, treated with charcoal and filtered. To the bright yellow filtrate was added a solution of sodium acetate, precipitating the base.

Yield—1.5 Gm. of a grayish yellow powder; m. p. 52–52.5° C.

Analysis: The Kjeldahl method for nitrogen failed, and the Dumas method was useless since the substance exploded. Explosion followed an attempt at a carbon-hydrogen analysis. It was decided, therefore, to characterize the compound after chlorination.

Preparation of 5-Propyl-7-Chloro-8-Hydroxy-Quinoline.—Five-tenths gram 5-propyl-8-hydroxy-quinoline was dissolved in 10 cc. glacial acetic acid and mixed with 2 cc. (a large excess) of sulphuryl chloride. The mixture was heated on the steam-bath, under reflux, for one hour. It was then poured into water and the milky solution neutralized with ammonium hydroxide. The yellow substance obtained weighed 0.43 Gm. and was shown by analysis to be a mixture of the mono-chloro compound and its hydrochloride. It was dissolved in alcoholic hydrochloric acid and precipitated as the hydrochloride by means of anhydrous ether. The resulting yellow powder melted at 242° C. with decomposition.

Analysis: Found—Cl, 27.52%; calculated for $C_{12}H_{12}ONCl.HCl$—Cl, 27.52%.

The hydrochloride was hydrolyzed by boiling with water and neutralizing with sodium bicarbonate. The base so obtained was analyzed for chlorine.

Analysis: Found—Cl, 15.97%; calculated for $C_{12}H_{12}ONCl$—Cl, 16.03%.

Preparation of the Metho-Chloride of 5-Chloro-8-Hydroxy-Quinoline. Four grams 5-chloro-8-hydroxy-quinoline were dissolved in 100 cc. nitrobenzene (4) and heated on an oil-bath with 4 Gm. dimethyl sulphate for one hour at ca. 190° C. No crystals formed on cooling. The nitrobenzene was removed by steam-distillation, and the aqueous solution distilled to small volume, acidified with hydrochloric acid and saturated with sodium chloride. A precipitate appeared and was redissolved by heating. On cooling, the substance crystallized out and was filtered off, redissolved in alcohol and the solution filtered from a small insoluble residue. To the clear solution was added twice its volume of anhydrous ether, precipitating the desired compound.

Yield—2 Gm. of a brilliant yellow substance.

Analysis: Found—Cl, 27.55%; calculated for $C_{10}H_9ONCl_2$—Cl, 30.85%; for the corresponding methyl sulphate—Cl, 10.35%.

The substance was therefore judged to be a mixture of 83.9% of the metho-chloride of 5-chloro-8-hydroxy-quinoline, and 16.1% of its methyl sulphate.

Preparation of 8-Diethylaminoethoxy-Quinoline Dihydrochloride.—Forty-six hundredths gram of sodium was dissolved in 20 cc. absolute alcohol and 1.45 Gm. 8-hydroxy-quinoline added. The sodium salt which formed did not completely dissolve. Two and six-tenths grams diethylaminoethyl bromide hydrobromide, dissolved in 20 cc. absolute alcohol, were added, effecting complete solution of the sodium salt.

The mixture was refluxed for eight hours and was then filtered off from the separated sodium bromide. The alcohol was distilled off and the dark red residue dissolved in water. It was then made alkaline with dilute caustic soda solution, and an oily emulsion was obtained, which was steam distilled to remove any unreacted diethylaminoethyl bromide. The oil was extracted with ether, and dry hydrochloric acid gas was passed into the dry ether extract. A reddish oil separated out. The ether was decanted off, the oily hydrochloride washed once by decantation with ether, and dissolved in water. The aqueous solution was boiled with charcoal, filtered and evaporated to dryness. The light yellow oil which remained partially crystallized on standing over night.

Yield—1 Gm.

Analysis: Found—Cl, 22.62%; calculated for $C_{15}H_{20}ON_2.2HCl$—Cl, 22.40%.

Preparation of 5-(Diethylaminoethylamino)-8-Hydroxy-Quinoline Dihydrochloride.—Five grams 5-amino-8-hydroxy-quinoline was suspended in 20 cc. dry benzene. To this was added a solution of 4.6 Gm. diethylaminoethyl chloride in 10 cc. benzol. The mixture was refluxed on a steam-bath for seven hours. The benzene was decanted from the condensation product which had formed a dark viscous mass at the bottom of the flask. The mass was washed twice by decantation with benzol, and after expelling all benzol by heating on the steam-bath, was dissolved in water. A dark brown residue, filtered off from the red solution, was found to be unreacted 5-amino-8-hydroxy-quinoline. The aqueous solution was made alkaline with sodium carbonate, producing a dark, somewhat tarry precipitate. After steam distillation, to remove any unreacted diethylaminoethyl chloride, it was extracted with ether, the ether solution dried over anhydrous sodium sulphate and treated with charcoal. Dry hydrochloric acid gas was conducted into the light brown solution, throwing down a flocculent brown precipitate, from which the ether was decanted. The residue was washed by decantation with ether, dried and heated at 100° C. for two hours. The violet-colored substance was seen to be crystalline.

Analysis: Found—Cl, 21.58%; calculated for $C_{15}H_{21}ON_3.2HCl$—Cl, 21.38%.

Preparation of 5-Carboxy-8-Ethoxy-Quinoline by the Skraup Reaction.—Five grams methyl-3-amino-4-ethoxy benzoate were mixed with 7.5 Gm. arsenic pentoxide and 15 Gm. glycerin. Fifteen grams concentrated sulphuric acid were added and the mixture refluxed in an oil-bath for four hours at 140–150° C. The dark reaction mixture was cooled and shaken with 60 cc. water. The brown solution was filtered from a dark residue.

The filtrate was nearly neutralized with ammonia, and then treated with a solution of sodium acetate. The greenish precipitate obtained was filtered off and washed with water. It was redissolved in alcohol and treated with 0.5 cc. of concentrated sulphuric acid. On adding four volumes of ether to this solution, a brownish gray precipitate of the sulphate of 5-carboxy-8-ethoxy-

quinoline was obtained. It was filtered off and washed with ether. The dry substance weighed 1.3 Gm.

The dark residue from the original filtrate was extracted three times with 100-cc. portions of boiling 10% sulphuric acid. The three extracts were combined and evaporated to a small volume. The gray crystals which separated and were filtered have not yet been identified. The filtrate from this substance was nearly neutralized with ammonia and precipitated by the addition of sodium acetate solution. The greenish precipitate obtained was isolated, dissolved in alcohol, treated with a little sulphuric acid and precipitated as the sulphate by means of ether. It weighed 1.1 Gm.

The two crops of the sulphate of 5-carboxy-8-ethoxy-quinoline, weighing 2.4 Gm., were dissolved in water and purified by shaking with charcoal. After filtering it was treated with sodium acetate and a greenish gray substance was obtained weighing 1.5 Gm., m. p. 285° C. The melting point of the 5-carboxy-8-ethoxy-quinoline prepared previously by the method of Matsumura was 292° C. The mixed melting point of the two substances was found to be 292° C.

Preparation of the Diethylaminoethyl Ester of 5-Carboxy-8-Ethoxy-Quinoline.—The sodium salt of the acid was first prepared by dissolving 1.8 Gm. of the acid in 8.4 cc. of normal sodium hydroxide. This solution was evaporated to dryness on the steam-bath, and taken up in 70 cc. of absolute alcohol. After refluxing on the steam-bath for two hours almost all of the substance dissolved. To this boiling solution was added 3 Gm. of diethylaminoethyl chloride (a large excess) dissolved in 25 cc. of absolute alcohol. The refluxing was continued for nine hours and sodium chloride was seen to have separated out. The alcohol was distilled off, and the excess of diethylaminoethyl chloride was distilled off in high vacuo on the steam-bath. The resulting brown viscous substance was shaken vigorously with water and a silvery gray precipitate was obtained. It was filtered off, washed and dried. It weighed 1.1 Gm. and had a m. p. of 76° C. It was redissolved in alcohol, and the dark solution was shaken with charcoal. On filtering, a clear yellow solution was obtained, which on evaporation to dryness gave a grayish white substance melting at 86° C.

Analysis: Found—N, 9.44%; calculated for $C_{18}H_{24}O_3N_2$—N, 8.86%.

It is possible that not all of the diethylaminoethyl chloride had been removed from the viscous material. In view of the small amount on hand, and because of the absence of local anesthetic activity in this substance, the further purification of the compound has not been undertaken.

Preparation of Anhydro-Mercuri-5-Chloro-8-Hydroxy-Quinoline.—One and five-tenths grams 5-chloro-8-hydroxy-quinoline were dissolved, on the steam-bath, in 20 cc. of absolute alcohol. To the solution was added 2.66 Gm. of mercuric acetate dissolved in 8 cc. of water which had been slightly acidified with acetic acid. An orange precipitate appeared at once. The mixture was refluxed for five hours, at the end of which time a test for Hg^{++} with ammonium sulphide was negative. The orange compound was filtered off, and washed with water. It was then boiled with alcohol, filtered off and dried. It was almost completely insoluble in dilute alkali.

Yield—2.1 Gm. of an orange powder.

Analysis: Found—Hg, 53.7%; calculated for $C_9H_4ONHgCl$—Hg, 52.9%.

Preparation of Anhydro-Mercuri-5-Nitro-8-Hydroxy-Quinoline.- This substance was prepared in the same manner as the chloro compound above. It is also an orange powder, only slightly soluble in dilute alkali.

Analysis: Found—Hg, 49.4%; calculated for $C_9H_4O_3N_2Hg$—Hg, 51.5%.

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