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ORGANIC NITRO COMPOUNDS CONTAINING MERCURY

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Introduction

Up to the present day, but very few organic nitro compounds containing mercury attached to nuclear carbon have been described in the scientific literature. Dimroth[1] in 1902 prepared a mercury derivative of nitrobenzene; Hantsch and Auld[2] in 1906 described mercury derivatives of various nitrophenols; in 1911 Bayer and Co.[3] patented the mercury derivatives of 4-chloro-2-nitrophenol; in 1911 and 1912 Blumenthal[4,5,6] prepared the mercury derivative of nitrobenzoic acid. In 1919 Raiziss and Gavron[7] prepared mercury derivatives of 3-nitro-4-hydroxyphenylarsonic acid and 3,5-dinitro-4-hydroxyphenylarsonic acid. Lecher[8] in 1920 prepared mercury-*o*-nitrophenyl-mercaptide; Kharasch and Piccard[9] prepared *p,o,o'*-3-mercuric chloride-dinitro-diphenylamine and also mercury-bis-3-dinitro-mercazine.

Since 1913 one of the authors in collaboration with Drs. J. F. Schamberg and J. A. Kolmer has been engaged in the study of the toxicity and bactericidal effects of organic mercury compounds. During this time a considerable number of such compounds have been investigated by us, many of which had not previously been synthesized. Of this entire number the sodium hydroxymercuri-*o*-nitrophenolate, named by us Mercurophen, exhibited biological properties far superior to any of the others. It has since been investigated by physicians and clinicians,[10,11] and several interesting facts have been established.

The study of mercurophen suggested to us the idea that the nitro group enhances the bactericidal influence of organic mercurials. This is in direct contrast to the theory of Ehrlich who regarded the nitro group as exerting a distherapeutic influence upon organic arsenical compounds. While our experience with the latter class of compounds *in vivo* corroborates Ehrlich's findings, results of experiments *in vitro* are just the reverse.

[1] Dimroth, *Ber.*, **35,** 2036 (1902).

[2] Hantsch and Auld, *ibid.*, **39,** 1105 (1906).

[3] *Zentr.*, [I] 1769 **1911;** Ger. pat. 234851.

[4] Blumenthal, *Biochem. Z.*, **32,** 59 (1911); *Deut. Med. Wochschr.*, **38,** 543 (1912); Ger. pat. 249725.

[5] Blumenthal, *Biochem. Z.*, **39,** 50 (1912).

[6] Blumenthal and Oppenheim, *ibid.*, **57,** 261 (1913).

[7] Raiziss, Kolmer and Gavron, *J. Biol. Chem.*, **40,** 533 (1919).

[8] Lecher, *Ber.*, **53B,** 577 (1920).

[9] Kharasch and Piccard, THIS JOURNAL, **42,** 1855 (1920).

[10] DeWitt, *J. Am. Med. Assoc.*, **75,** 1422 (1920).

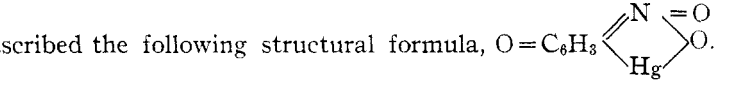
[11] Schamberg, Kolmer, Raiziss and Trist, *J. Infectious Diseases*, **24,** 547 (1919).

With these facts in mind, the authors entered upon the preparation and study of mercury derivatives of nitrophenol and its substitution products. In addition, they prepared mercury derivatives of various nitrosalicylic acids and derivatives of the same, for not only is salicylic acid itself a valuable germicide, but mercurated salicylic acid is regarded as an important factor in the treatment of syphilis.

In preparing compounds to be employed as chemotherapeutic agents, it is most desirable that they dissolve either in water, forming a neutral solution, or in just sufficient very dilute alkali to form a sodium salt. In addition, the resulting solution should be very stable. Solutions of sodium salts of organic mercury derivatives containing amino groups as a rule are unstable, the mercury splitting off from the molecule and depositing as a fine gray powder. Similar solutions of nitro compounds do not behave in this way. Alkaline solutions of the mercury derivatives of nitrophenol and nitrosalicylic acid can stand indefinitely without any mercury being deposited. Solutions of inorganic mercury salts and aromatic mercury derivatives in which the mercury is not very firmly attached, exhibit two marked characteristics. First, they precipitate the proteins in the blood, their therapeutic values thereby becoming diminished and secondly, surgical instruments immersed in them readily tarnish. Solutions of mercurophen and other mercury nitro compounds possess these qualities only to a very slight extent.

The introduction of mercury into the nucleus is effected by warming the nitrophenol or salicylic acid in water for several hours with either mercuric acetate or oxide, usually resulting in the formation of a mixture of mono- and dimercurated products.

In the case of the acetate derivatives separation of the two compounds is very difficult since they are insoluble in the usual organic solvents except glacial acetic acid. Separation by the latter, however, is incomplete. An effective method is to transform the mixture into chloromercuri derivatives by means of hydrochloric acid and subject these to fractional crystallization from methyl or ethyl alcohol. In those instances where this method fails to produce satisfactory results, separation has been effected by fractional crystallization of the sodium salts from hot water. The greater part of the dimercury compound crystallizes out upon cooling. The filtrate containing all of the monomercury derivative and still some of the dimercury is then acidulated with hydrochloric acid producing the corresponding chloromercuri derivatives which precipitate. This mixture is then subjected to fractional crystallization from hot alcohol. The monomercury derivative is usually the more soluble and by repeated recrystallizations the dimercury compound is removed. Our experiences in the mercuration of *o*-nitrophenol are not in accordance with the results claimed by Hantsch and Auld.[2] By boiling together

an alcoholic solution of sodium *o*-nitrophenolate and an aqueous solution of one mol of mercuric acetate, they obtained a yellow precipitate to which they ascribed the following structural formula,  . This product, they claimed, without any further purification, when analyzed, gave results for carbon and hydrogen remarkably close to the theoretical values.[12]

The product obtained by us was probably a mixture of the mono- and dimercury compounds from which it was impossible to separate either substance pure.

It is interesting to note that with 5-nitrosalicylic acid the dimercury derivative is obtained almost exclusively even though allowed to react with only equimolar quantities of mercuric oxide or acetate.

The mercury derivatives described in this paper belong to the series of the so-called half complex compounds in which one of the valences of the metal is attached to a nuclear carbon atom, the other to an hydroxyl, a halogen or other acid radical. The firmness of the linkage between the mercury and the nuclear carbon is not the same in the various half complex mercurials. In an earlier publication[7] one of the authors suggested an accurate method for estimating this firmness. None of the compounds described in this paper was affected by ammonium sulfide at room temperature within 30 minutes. At 80°, however, all yielded a precipitate of mercuric sulfide within the same time.

The positions of the mercury in our compounds have not been determined as yet. It is our intention to take up this question later in conjunction with other theoretical considerations. It is very possible, however, that the mercury assumes a position either *para* or *ortho* to an hydroxyl or a carboxyl group, since in several instances where the *para* and either one or both of the *ortho* positions are already occupied by a substituent, no substitution of the mercury in the ring occurred. Prolonged boiling of mercuric acetate with the following nitro compounds yielded no products of the type R-Hg.X: 2-iodo-4-nitrophenol, 2,4-dinitrophenol, 2-nitro-4-chlorophenol,2,6-dibromo-4-nitrophenol and 2-nitro-4-chlorobenzoic acid.

Experimental

4-Acetoxymercuri-2-nitrophenol.—A solution of 22.3 g. of mercuric acetate dissolved in 200 cc. of water with the aid of about 1 cc. of glacial acetic acid is added drop by drop to a warm solution of sodium *o*-nitrophenolate prepared from 10 g. of *o*-nitrophenol dissolved in 200 cc. of water and 10 cc. of 40% sodium hydroxide solution. An orange colored precipitate appears immediately. The whole is stirred mechanically for 2 hours, at the end of which time the precipitate acquires a yellow color. It is filtered

[12] Calc. for $C_8H_8NO_8Hg$: C, 21.36: H, 0.87. Found: C, 21.7: H, 0.85. Unfortunately, they give no results for mercury or nitrogen which according to their formula should be 56.34 and 4.15% respectively.

off and thoroughly washed with boiling water containing a slight amount of acetic acid. The crude product thus obtained is dissolved as completely as possible in 5% sodium hydroxide, filtered and reprecipitated by acetic acid. This precipitate is filtered off, washed with water, then methyl alcohol, and finally with ether until the last traces of nitrophenol are removed. The yield is 16.5 g. The product is easily soluble in hot glacial acetic acid and insoluble in the usual organic solvents.

Analyses for mercury and nitrogen indicate that the product is a mixture of the mono- and dimercury compounds. Four crystallizations from hot glacial acetic acid gave a product which apparently contained a larger proportion of the monomercury compound.

4-Chloromercuri-2-nitrophenol.—Our idea relative to the contamination of the corresponding acetate by the dimercuric acetate derivative is further substantiated in a study of the chloride. This is prepared from the previously described mixture of acetates by one of three methods: first, by suspending in water and transposing with 25% sodium chloride solution; second, by converting into the sodium salt by means of dil. sodium hydroxide solution, filtering off any insoluble residue and reprecipitating the filtrate by hydrochloric acid; third, by merely transposing the acetate with hydrochloric acid. In any case, the white product obtained is washed free from inorganic chlorides with water, taken up with methyl alcohol and boiled. Complete solution is not obtained. The insoluble residue is filtered off and repeatedly extracted with hot methyl alcohol. The substance remaining undissolved is dried *in vacuo* over sulfuric acid to constant weight. Mercury analyses indicate it to be a mixture of the mono- and dimercury compounds.

The original methyl alcoholic filtrate is allowed to crystallize. The product which deposits is recrystallized several times from methyl alcohol and dried to constant weight.

Analyses. Subs., 0.1983, 0.2006: HgS, 0.1384, 0.1374. Subs., 0.2000: N, 5.06 cc. of 0.1 *N* H_2SO_4. Calc. for $C_6H_4O_3NClHg$: Hg, 53.55; N, 3.75. Found: Hg, 53.18; 53.97; N, 3.57.

Sodium hydroxymercuri-*o*-nitrophenolate (Mercurophen).—This compound may be prepared from either the mercuric chloride or acetate derivative of *o*-nitrophenol by dissolving as completely as possible in dil. sodium hydroxide solution. Any insoluble residue is filtered off and the filtrate concentrated under reduced pressure. On cooling, a red solid crystallizes. This is thoroughly washed with ice-cold water and then recrystallized from hot water.

Analyses. Subs., 0.1998, 0.1998: HgS, 0.1218, 0.1230. Subs., 0.2000: N, 5.08 cc. of 0.1 *N* H_2SO_4. Calc. for $C_6H_4O_4NNaHg$: Hg, 53.05; N, 3.70. Found: Hg, 52.81; N, 3.58.

2-Acetoxymercuri-4-nitrophenol.—Aqueous solutions of equimolar quantities of sodium *p*-nitrophenolate and mercuric acetate are boiled for 2 hours. The resulting yellow precipitate is thoroughly washed with water, recrystallized thrice from hot glacial acetic acid and finally dried *in vacuo* over calcium chloride for 3 days when constant weight is obtained.

Analyses for mercury, nitrogen and carbon indicate that the product is a mixture of mono- and dimercury compounds.

2-Chloromercuri-4-nitrophenol.—The acetate mixture is converted into the monosodium salt by warming with dil. sodium hydroxide solution, filtering off any insoluble residue and allowing the filtrate to cool. An orange colored deposit is obtained, which is filtered off, dissolved in water and acidified with hydrochloric acid. A white precipitate of the chloride is obtained. This is recrystallized thrice from 50% ethyl alcohol.

Analyses. Subs., 0.1998, 0.1998: HgS, 0.1240, 0.1251. Subs., 0.2000: N, 5.26 cc.

of 0.1 *N* H_2SO_4. Calc. for $C_6H_4O_3NClHg$: Hg, 53.55; N, 3.75. Found: Hg, 53.50, 53.80; N, 3.71.

4-Acetoxymercuri-2-nitroresorcin.—Equimolar quantities of mercuric acetate and 2-nitroresorcin are heated on the water-bath for one-half hour. The orange colored precipitate obtained is filtered off, washed thoroughly with water, then ethyl alcohol, and finally with ether. It is dried *in vacuo* over calcium chloride for 48 hours. The yield is 75%. It is slightly soluble in water, ethyl alcohol, and ether.

Analysis. Subs., 0.2000: N, 4.8 cc. of 0.1 *N* H_2SO_4. Calc. for $C_8H_7O_6NHg$: N, 3.38. Found: 3.38.

4-Chloromercuri-2-nitroresorcin.—By warming together 2-nitroresorcin suspended in water and freshly precipitated mercuric oxide on the water-bath for 2 hours, an orange colored precipitate is obtained. This is filtered off, washed with water, ethyl alcohol and ether and then converted into the chloride by 10% hydrochloric acid. The precipitate is washed free from inorganic chloride and dried.

It is a pale orange colored, amorphous powder, soluble in dil. sodium hydroxide solution, methyl and ethyl alcohols, ether, benzene and chloroform. It is extremely soluble in acetone and but slightly in hot water.

Analyses. Subs., 0.2000, 0.2000: HgS, 0.1195, 0.1193. Subs., 0.2000: N, 5.12 cc. of 0.1 *N* H_2SO_4. Calc. for $C_6H_4O_4NClHg$: Hg, 51.41; N, 3.59. Found: Hg. 51.50, 51.36; N, 3.61.

5-Nitrosalicylic Acid.—Unsatisfactory results were obtained upon attempting to prepare this acid by the methods described in the literature. By the method of Deninger,[13] the reaction proceeded rather violently and the final product consisted mostly of *o*-nitrophenol and 3,5-dinitrosalicylic acid. By the methods of R. Hirsch[14] and Hübner[15] the yields of pure acid as a rule were very small.

The following method which we adopted gave satisfactory results. 100 g. of salicylic acid was dissolved in 800 g. of glacial acetic acid. This was gradually nitrated by 50 g. of nitric acid (sp. gr. 1.50), the temperature being kept at 20° and the solution stirred mechanically. The mixture was allowed to stand at ordinary temperature until it assumed a dark red color, which requires from 30 to 45 minutes, and then was poured into 2000 g. of cracked ice. A yellow crystalline precipitate was produced almost immediately. After 1 hour it was filtered off and thoroughly washed with cold water.

To obtain the pure 5-nitrosalicylic acid, the crude product was suspended in 400 cc. of water, the whole heated just to boiling, filtered while hot and the filtrate discarded. The residue as a rule is the pure product, having a sharp melting point of 228°. In some cases the impurities are not quite all removed by the above procedure. By repeating with a smaller amount of water, the last traces of impurities are removed.

3-Chloromercuri-5-nitrosalicylic acid.—Upon heating 5-nitrosalicylic acid with a suspension of 2 mols of freshly prepared mercuric oxide in water at the boiling temperature for 12 hours, an orange colored substance is obtained. After filtering, thoroughly washing with water, alcohol, ether and subsequent drying in the desiccator, it showed upon analysis 67.85% mercury and 2.54% nitrogen. When warmed for a short time with hot alkali, part of the mercury is split off forming mercuric oxide which is removed by filtration and the filtrate allowed to cool. A slight amount of a white substance deposits. This is filtered off and the filtrate acidified with hydrochloric acid. A precipitate consisting of a mixture of the mono- and dimercury derivatives of 5-nitrosalicylic acid is thrown down at once. After these two compounds are thoroughly

[13] Deninger, *J. prakt. Chem.*, [2] **42,** 550 (1890).

[14] Hirsch, *Ber.*, **33,** 3239 (1900).

[15] Hübner, *Ann.*, **195,** 45 (1879).

washed with water, separation is effected by boiling with 50% methyl alcohol, which dissolves the monomercury compound. The mixture is filtered hot and the monomercury compound crystallizes from the filtrate on cooling. It was recrystallized twice again from hot 50% methyl alcohol and dried.

Analyses. Subs., 0.0971: HgS, 0.0552. Subs., 0.2000: (Kjeldahl) 4.56 cc. of 0.1 N H_2SO_4. Subs., 0.1761: CO_2, 0.1214. Calc. for $C_7H_4O_5NClHg$: Hg, 47.96; N, 3.34; C, 20.09. Found: Hg, 47.83; N, 3.20; C, 19.38.

The fraction remaining undissolved in the hot 50% methyl alcohol is boiled with the same once more and recrystallized twice from 95% ethyl alcohol.

The product gave mercury analyses which indicated that it was a dimercury compound containing a considerable impurity of a trimercury compound.

3-Chloromercuri-5-nitrosalicylic acid is a pale yellow crystalline substance, slightly soluble in hot water, easily soluble in methyl and ethyl alcohols, ether and acetone. With dil. alkali a yellow solution is obtained. It melts with decomposition at 235°.

The dimercury derivative resembles in appearance the corresponding monomercury compound. It is insoluble in water, benzene and ether, but soluble in dilute alkali and hot ethyl alcohol. It melts with decomposition at 238°.

Di-acetoxymercuri-5-nitrosalicylic acid.—The product obtained by warming 5-nitrosalicylic acid with 2 mols of mercuric oxide is dissolved in boiling glacial acetic acid and filtered while hot. When the filtrate is cooled, a white crystalline precipitate is obtained which is recrystallized twice from boiling acetic acid. After drying *in vacuo* it assumes a pale yellow color and is insoluble in water, alcohol, ether and benzene; readily soluble in dil. sodium hydroxide solution.

Analyses. Calc. for $C_9H_7O_7NHg$: Hg, 45.35; N, 3.17; C, 24.49. Calc. for $C_{11}H_9O_9NHg_2$: Hg, 57.22; N, 2.00; C, 18.88. Found: Hg, 56.94; N, 2.91; C, 18.74.

This same substance can be prepared by boiling together 5-nitro-salicylic acid and aqueous solution of mercuric acetate.

An attempt was made to mercurize 3-bromo-5-nitrosalicylic acid[16] but the product was apparently a mixture of mono- and dimercury compounds.

3,5-Dinitrosalicylic Acid.—This acid was prepared according to the method of Hübner[15] with the following modification. Instead of purifying through the barium salt, we recrystallized from small amounts of hot water. The nitrogen analysis corresponded to the theoretical value and the melting point agreed with that found by Hübner.

Both mercuric acetate and freshly prepared mercuric oxide form mercury derivatives with 3,5-dinitrosalicylic acid which resemble each other both in appearance and physical properties. They are yellow crystalline substances, completely soluble in dil. alkali and insoluble in water, alcohol, ether, chloroform, benzene and acetone. They have no sharp melting points but begin to decompose at 230°. It was not found possible to obtain definite compounds from these products. They apparently consist of mixtures of mono- and dimercury compounds.

Summary

1. The preparation and some of the chemical properties of the following compounds have been studied: 4-chloromercuri-2-nitrophenol, sodium hydroxymercuri-*o*-nitrophenolate (mercurophen), 2-chloromercuri-4-nitrophenol, 4-acetoxymercuri-2-nitroresorcin, 4-chloromercuri-2-nitroresorcin, 3-chloromercuri-5-nitrosalicylic acid, and di-acetoxymercuri-5-nitrosalicylic acid.

[16] Lellman and Grothmann, *Ber.*, **17**, 2724 (1884).

2. The mercurization of 3-bromo-5-nitrosalicylic acid and of 3,5-dinitrosalicylic acid gave mixtures of mono- and dimercury compounds from which it was impossible to separate pure substances.

3. Modifications in the preparation of 5-nitrosalicylic acid and 3,5-dinitrosalicylic acid are described.

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[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

A STUDY OF THE NITRO-ANILINES

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The purpose of this investigation, as it developed, was twofold. It was desired, in the first place, to obtain additional information bearing upon the chemical constitution of the nitro-anilines and, second, to test the hypothesis advanced in a previous paper[4] as to the mechanism of mercurization of aromatic amines. It was pointed out in that paper that mercurization of aromatic amines proceeds probably in two stages: first, the addition of the mercury salt to the amino group forms an ammonium salt; this ammonium compound then rearranges, the most strongly positive group migrating to the *para* position or, that position being occupied, to the *ortho* position.

While this point of view seems to be generally applicable in the case of aromatic amines, it is quite conceivable that mercurization of amines capable of existing in the quinoid form, *e. g.*, the *ortho* and *para* nitro-anilines, might take place by the absorption of the mercury salt at the double bond.[5] Evidence of this type of substitution might well be obtained in the study of mercurization of the nitro-anilines and of the mono-nitro-diphenyl-amines. The present paper deals with the former phase of the problem.

As a general principle, one writes different structural formulas to indicate the tautomeric forms of a given compound. In the case of the *ortho* and *para* nitro-anilines, we might assume that, in solution, we are dealing with a mixture of the following tautomers in equilibrium,

[1] National Research Fellow in Organic Chemistry.

[2] The material presented here is used by Frederick W. M. Lommen in his dissertation presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago.

[3] Associate, Otho S. A. Sprague Memorial Institute, University of Chicago.

[4] Kharasch and Jacobsohn, THIS JOURNAL, **43**, 1894 (1921).

[5] The absorption of mercuric acetate by quinone, and also the behavior of the mercury salts of unsaturated aliphatic acids containing the double bond in the α-β, β-γ and γ-δ positions will be discussed in a subsequent paper by Kharasch.