[CONTRIBUTION FROM THE DEPARTMENT FOR DISEASES OF THE CHEST, JEFFERSON HOSPITAL]

MERCURY DERIVATIVES OF ACETYLAMINOCRESOLS[1]

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RECEIVED APRIL 23, 1930 PUBLISHED OCTOBER 6, 1930

Introduction

Organic compounds of mercury have gained considerable prominence during the last few years in the field of pharmaceutical chemistry as general antiseptics. In almost every field of application, they have displaced their inorganic precursor, mercuric bichloride, and have established for themselves a very important position among modern synthetic drugs. The value of the new organic mercurials in the treatment of syphilis and the importance of their use in conjunction with the well-known arsenicals are at present well recognized. Further investigation in this field, however, seemed to be especially desirable in view of the fact that comparatively few organic mercury compounds suitable for therapeutic use have been synthesized and still fewer were thoroughly studied and tried clinically. Among these, phenol derivatives and dyestuffs were given much attention and large groups of their mercury derivatives were synthesized and investigated therapeutically.

In 1906 Hantsch and Auld[2] prepared mercury derivatives of various nitrophenols. In 1919 Schamberg, Kolmer and Raiziss[3] studied the toxicity and bactericidal effect of mercurated nitrophenols and found that sodium hydroxymercury-*o*-nitrophenolate exhibited interesting therapeutic properties. Later, Raiziss and Proskouriakoff[4] synthesized a number of mercury derivatives of nitrophenols, nitroresorcinols and nitrosalicylic acids for their chemotherapeutic study, assuming that nitro groups enhance the bactericidal influence and the stability of the organic mercurials. Most of the compounds prepared were amorphous and analyses indicated that they were mixtures of mono- and di-mercury compounds and were separable only with considerable difficulty. Of the dyestuff group, mercury derivatives of phthaleins and azo dyes were more thoroughly investigated and some valuable germicidal compounds were discovered, in the first group mentioned. The di-sodium salt of dibromo-hydroxymercurifluorescein is the most successful of this group.[5] In 1925 Proskouriakoff and Raiziss[6]

[1] Financial assistance in this work has been received from the C. Mahlon Kline Fund.

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

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

[4] Raiziss and Proskouriakoff, THIS JOURNAL, **44**, 787 (1922).

[5] E. C. White, *ibid.*, **42**, 2359 (1920); Young, White and Swartz, *J. Am. Med. Assn.*, **73**, 1483 (1919).

[6] Proskouriakoff and Raiziss, THIS JOURNAL, **47**, 1974 (1925).

prepared and studied a group of azo dyestuffs and found that mercury can be detoxicated considerably by modifying the organic compound to which it is attached. Mercury derivatives of nitrocresols were studied by Raiziss, Proskouriakoff and Fisher[7] and among them the mono-mercury derivative of 6-nitro-*o*-cresol and the di-mercury derivative of 5-nitro-*o*-cresol were found to possess superior germicidal properties.

Several isomers of aminocresols were prepared and mercurated by the authors. These compounds, however, were amorphous and their sodium salts, as one would expect, were not sufficiently stable in solution, depositing on standing a fine gray powder of metallic mercury. The instability of mercurated aminocresols was probably due to the presence of the open amino groups, and the protection of these groups seemed to be desirable in order to render the compounds more stable. It would also diminish the possibility of mercury reacting directly with the amino groups, forming the complex and still more unstable compounds.

With this in mind, the authors undertook the preparation and subsequent mercuration of different isomers of acetylaminocresols. On studying the literature we were unable to find any data on properties and methods of preparation of certain amino- and acetylaminocresols. Some, apparently, never have been prepared. Most of those that have been known were prepared by reducing the corresponding nitrocresol with zinc or tin and hydrochloric acid[8] and acetylating the amino compound thus obtained by boiling it with acetic anhydride in an acetic acid solution.[9] This method of reduction was long and tedious, as it involved the precipitation of the metal and evaporation of the solution for the precipitation of the amino compounds. The yield in our hands was very poor. The acetylation of the aminocresols in glacial acetic acid medium in many cases also presented considerable difficulty, due to the ready solubility of acetylaminocresols in dilute acids, and the yields obtained were very poor, also.

Our attempts to find a better and simpler method for the preparation of aminocresols gave us very satisfactory results when we tried to reduce the nitrocresols with sodium hydrosulfite in alkaline solution. After some experimentation we have adopted the following procedure. The nitrocresol was dissolved in dilute alkali and the boiling solution was then treated with small portions of solid sodium hydrosulfite until the liquid became colorless or slightly yellow. The theoretical amount of hydrosulfite was required. The solution was then cooled and the amino compound came down in almost pure crystalline form, which, after a single

[7] Raiziss, Proskouriakoff and Fisher, paper read at the spring meeting of the American Chemical Society in Washington, D. C., 1924.

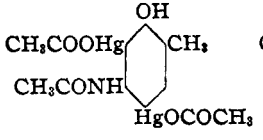
[8] (a) Nolting and Collin, *Ber.*, **17**, 270 (1884); (b) Nolting and Kohn, *ibid.*, **17**, 367 (1884).

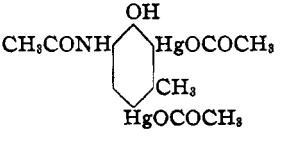
[9] Massen, *ibid.*, **17**, 609 (1884).

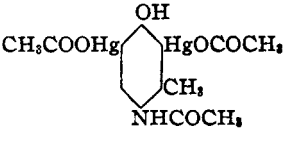
crystallization from water or dilute alcohol, was obtained as a perfectly pure compound suitable for our purposes. The method of the preparation of acetylated aminocresols was considerably improved by carrying on the reaction in aqueous medium. This is a very quick and simple method; the water medium fully protects the hydroxy groups from being involved in the reaction, even though an excess of acetic anhydride be used. The final product is pure and the yield excellent.

The aminocresol is suspended in a small amount of water and treated with a slight excess of acetic anhydride by shaking it for a few minutes in a glass-stoppered Erlenmeyer flask. The compound goes into solution and the acetyl derivative quickly crystallizes on cooling. The acetylaminocresols are thus obtained in a very pure state after the first crystallization.

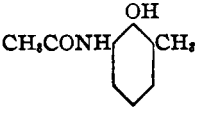
The mercuration of the aminocresols was carried out by treating an alkaline solution of acetylaminocresol with a solution of mercuric acetate in dilute acetic acid solution. The final acid concentration of the solution is in this case an important factor in obtaining uniform yields of a pure crystalline compound of definite structure. The crystalline diacetoxymercury derivatives, apparently, partly hydrolyze on heating in a neutral or insufficiently acid solution, turning into the corresponding amorphous hydroxy-mercury compounds. On boiling with water the compounds produce highly colloidal solutions, acid to litmus. All the compounds were obtained from the reaction mixtures in the form of beautifully uniform crystals of high purity. They were recrystallized once from a 10% solution of acetic acid, dried at 110° in the oven and analyzed for nitrogen and mercury. The analyses showed that in the isomers of acetylaminocresols with ortho and para positions to hydroxyl open, mercury always enters all the positions thus open, leaving the meta positions unsubstituted. Thus 5-acetylamino-*o*-cresol, 6-acetylamino-*m*-cresol and 4-acetylamino-*m*-cresol give, on mercuration, dimercurated compounds







We have attempted to mercurate, with excess of mercuric acetate, 6-acetylamino-*o*-cresol, which has only para position to hydroxyl open, both ortho positions being already occupied (A). As a result we have obtained a good yield of crystalline mono-mercury derivative identical with that



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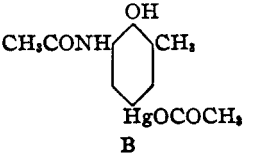

B

obtained by mercuration of this compound with the theoretical amount of mercuric acetate (one mole) (B).

All the mercurated acetylaminocresols prepared by us are soluble in dilute solutions of alkalies. The results of the investigation of their therapeutical activity will be published elsewhere.

The mercury in these compounds was determined by decomposing the compounds with sulfuric acid and potassium permanganate and estimating mercury gravimetrically as sulfide.

Experimental Part

Preparation of 5-Amino-*o*-cresol.—Thirty-four grams of 5-nitro-*o*-cresol (m. p. 117°) was dissolved in 600 cc. of a 3% solution of sodium hydroxide. The solution was brought to boiling and to the boiling solution was gradually added in small portions about 135 g. of sodium hydrosulfite. The reduction was completed when the solution was almost colorless and the addition of sodium hydroxide to a portion of it gave no red color. The solution was then filtered hot and allowed to cool for twenty-four hours. The crystalline precipitate was then filtered off, washed with a small amount of ice-cold water and dried in a desiccator. It could then be recrystallized from water, giving plates of m. p. 161°.

Preparation of 5-Acetylamino-*o*-cresol.—Eight grams of 5-amino-*o*-cresol (m. p. 161°) was suspended in 150 cc. of water in a glass-stoppered Erlenmeyer flask. To this was added 20 cc. of acetic anhydride and the flask was shaken for about a half hour. It was then cooled and allowed to stand for four hours. The precipitate was filtered off, washed with water and dried in the oven at about 70°; yield, 9.5 g. (88%). The compound was then recrystallized from 350 cc. of 50% ethyl alcohol; yield, 8 g. It can also be purified by dissolving it in dilute alkali and precipitating the compound from the filtered solution by dilute hydrochloric acid. It gives colorless crystals (prisms); melting point, 225°. It is soluble in dilute alkalies and hot water.

Preparation of 4,6-Diacetoxymercuri-5-acetylamino-*o*-cresol.—Two grams of 5-acetylamino-*o*-cresol (m. p. 225°) was dissolved in 50 cc. of water and 15 cc. of a 4% solution of sodium hydroxide. To this was added 7.8 g. of mercuric acetate dissolved in 60 cc. of warm 15% acetic acid. The whole was warmed until the precipitate dissolved. The solution was then cooled. A voluminous white precipitate formed which under the microscope appeared as colorless long needles radiating from centers.

The compound was washed with a small amount of cold water and dried in the oven at 110° for twelve hours; yield, 4.5 g. It is soluble in dilute alkali, sodium carbonate, glacial acetic acid and dilute acetic acid (on warming). It is insoluble in methyl alcohol, benzene, ether and ethyl acetate. The compound darkens and apparently begins to decompose at about 210°.

Anal. Calcd. for $C_{13}H_{15}O_6NHg_2$: Hg, 50.80; N, 2.05. Found: Hg, 59.10; N, 2.03.

Preparation of 6-Amino-*o*-cresol.—Twenty-five grams of 6-nitro-*o*-cresol was dissolved in 500 cc. of 3% solution of sodium hydroxide. The solution was heated to 90°, heating was discontinued and with rapid stirring solid sodium hydrosulfite was added in 2-g. portions at such a rate as to keep the temperature below 100°. The reduction was completed when 100 g. of sodium hydrosulfite had been added. Five grams of norit was then added and stirring was continued for a few minutes. The solution was filtered and the filtrate was cooled in ice water. The crystallized compound was filtered off and dried in the oven at 60°.

The crude dry compound was recrystallized from carbon tetrachloride. Colorless plates were obtained from water. It is soluble in methyl and ethyl alcohol, acetone, ether, chloroform, hot water, hot benzene and hot carbon tetrachloride; insoluble in petroleum ether; m. p. 89° (uncorr.). It gives a red color with ferric chloride.

Anal. Calcd. for C_7H_9ON: N, 11.38. Found: N, 11.25, 11.27.

The hydrochloride was obtained by dissolving the amino compound in dilute hydrochloric acid and precipitating the hydrochloride by adding an equal amount of concentrated hydrochloric acid (colorless crystals).

Preparation of 6-Acetylamino-*o*-cresol.—Six grams of 6-amino-*o*-cresol (m. p. 89°) was suspended in 200 cc. of water in a glass-stoppered Erlenmeyer flask. To this was added 4 cc. of acetic anhydride and the mixture was shaken vigorously. A dark solution resulted which with continued shaking quickly became lighter in color with the separation of dark semi-solid substance. This was filtered off and the filtrate was cooled in ice water. The 3-acetylamino-*o*-cresol crystallized with the help of stirring and scratching. The crystals were filtered off, washed with water and dried in the oven at 60°.

The compound recrystallized from carbon tetrachloride melted at 78–79° (uncorr.) (long prisms). It is soluble in methyl and ethyl alcohol, acetone, benzene, chloroform, ether, hot water and hot carbon tetrachloride; insoluble in petroleum ether. It gives a blue color with ferric chloride. (The corresponding amino compound gives a red color with the same reagent.)

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.49. Found: N, 8.36, 8.35.

Preparation of 4-Acetoxymercuri-6-acetylamino-*o*-cresol.—Two grams of 6-acetylamino-*o*-cresol was dissolved in 20 cc. of 3% solution of sodium hydroxide. To the warm solution was added 4 g. of mercuric acetate dissolved in 30 cc. of 15% warm acetic acid.

The mixture was heated over a low flame until the precipitate formed at first redissolved. The hot solution was filtered and then cooled in ice water. The crystalline precipitate was filtered off, washed with a little 10% acetic acid and then with water and dried in the oven at 60°; yield, 2.2 g. It can be recrystallized from 10% acetic acid. The compound is soluble in dilute alkalies, acetone, ethyl and methyl alcohol and dilute acetic acid. It is insoluble in benzene, ether and carbon tetrachloride. It melts at 122°.

Anal. Calcd. for $C_{11}H_{13}O_4NHg$: Hg, 47.34; N, 3.31. Found: Hg, 47.42, 47.68; N, 3.26.

Preparation of 6-Amino-*m*-cresol.—Ten grams of 6-nitro-*m*-cresol (m. p. 56°) was dissolved in 225 cc. of a 3% solution of sodium hydroxide and the boiling solution was treated with small portions of solid sodium hydrosulfite (about 40 g.) until the solution became almost colorless and a portion of it in a test-tube did not give a red color with sodium hydroxide. It was then allowed to cool, whereupon an amino compound crystallized out. It was filtered off and recrystallized from 50% ethyl alcohol; yield, 4.8 g.

It forms colorless long prismatic needles which melt with decomposition at 162°. An aqueous solution of the compound gives with ferric chloride a red color, while the corresponding nitrocresol and acetylaminocresol do not give this reaction.

The compound is soluble in hot water, dilute acids, methyl and ethyl alcohol, acetone, benzene and ether. It is insoluble in petroleum ether.

Anal. Calcd. for C_7H_9ON: N, 11.38. Found: N, 11.27.

Preparation of 6-Acetylamino-*m*-cresol.—Five grams of 6-amino-*m*-cresol was suspended in 75 cc. of water and treated with 7 cc. of acetic anhydride in a glass-stoppered Erlenmeyer flask. The change occurred almost immediately; all went into solution and soon after the precipitate came down. The flask was shaken for about

a half hour and then well cooled with ice water. The precipitate was then filtered off, washed with cold water and dried in the oven at about 70°; yield, 5 g.

The compound, recrystallized from 50% ethyl alcohol, forms colorless hexagonal plates. It melts at 171° (uncorr.).

The solution of 6-acetylamino-*m*-cresol gives no color with ferric chloride. (By this reaction it can be distinguished from the corresponding aminocresol.) It dissolves in alkali with a bluish-green color.

The compound can be dissolved in sodium hydroxide or sodium carbonate and precipitated from the solution by neutralizing it with acetic or hydrochloric acid. It is soluble in hot water, easily soluble in methyl and ethyl alcohol and acetone, much less so in benzene and ether. It is insoluble in petroleum ether and carbon tetrachloride.

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.49. Found: N, 8.38.

Preparation of 2,4-Diacetoxymercuri-6-acetylamino-*m*-cresol.—Ten and one-half grams of 6-acetylamino-*m*-cresol (m. p. 171°) was dissolved in 250 cc. of a 1.5% solution of sodium hydroxide. To this was added, with stirring, a hot solution of 40.2 g. (2 moles) of mercuric acetate in 210 cc. of 20% acetic acid.

The whole was then warmed until the precipitate formed went into solution. The solution was then cooled and allowed to stand for twelve hours. The precipitate was filtered off, washed with water, alcohol and ether and dried in the oven at 60°. This yellowish crystalline precipitate was recrystallized from 10% acetic acid, whereupon colorless long needles were obtained.

The compound dissolves in dilute alkalies, forming a colorless solution. It melts with decomposition at 178°. It was dried in the oven at 110° for fifteen hours and analyzed.

Anal. Calcd. for $C_{13}H_{15}O_6NHg_2$: Hg, 58.80; N, 2.05. Found: Hg, 58.70; N, 2.01.

Preparation of 4-Amino-*m*-cresol.—Sixteen grams of 4-nitro-*m*-cresol (m. p. 129°) was dissolved in 350 cc. of a 3% solution of sodium hydroxide. To the boiling solution was gradually added 65 g. of solid sodium hydrosulfite. The reduction was completed when the solution became almost colorless and the amino compound began to precipitate. The mixture was then well cooled, the precipitate filtered off and recrystallized from 100 cc. of 50% ethyl alcohol; yield, 7 g.; colorless prisms, m. p. 179°. Nolting and Kohn[8b] give the melting point for this compound as 174°.

Preparation of 4-Acetylamino-*m*-cresol.—Six grams of 4-amino-*m*-cresol (m. p. 179°) was suspended in 50 cc. of water in a glass-stoppered Erlenmeyer flask. To this was added 10 cc. of acetic anhydride and the mixture vigorously shaken. The aminocresol went into solution. On cooling a crystalline precipitate of acetylaminocresol came down. This was filtered off, washed with cold water and recrystallized from water; yield, 5 g. of needles. The compound when dried in the oven at 110° for six hours melts at 130° (incorr.). Staedel and Kolb[10] give for this compound (free from water of crystallization) m. p. 125°. It can be dissolved in dilute alkali and reprecipitated by acidifying with hydrochloric acid.

Preparation of 2,6-Diacetoxymercuri-4-acetylamino-*m*-cresol.—Two grams of 4-acetylamino-*m*-cresol (m. p. 130°) was dissolved in 20 cc. of a 3% solution of sodium hydroxide. To the warm solution was gradually added, with stirring, a solution of 7.7 g. of mercuric acetate in 30 cc. of 15% acetic acid. The mixture was allowed to stand in a cool place for twenty-four hours. The white crystalline precipitate was filtered off, washed first with cold water, then with alcohol and finally with ether and dried in the air. It was recrystallized from 10% acetic acid and dried at 110° for fifteen hours; yield, 3 g. of colorless crystals (prisms). On heating in the melting point tube,

[10] Staedal and Kolb, *Ann.*, 259, 217 (1890).

the compound darkens and gradually decomposes, but does not melt below 250°. It is soluble in dilute alkalies. The solutions are colorless.

Anal. Calcd. for $C_{18}H_{18}O_6NHg_2$: Hg, 58.80; N, 2.05. Found: Hg, 58.69; N, 2.06.

Summary

1. A simple method of preparation of aminocresols from corresponding nitrocresols by reduction with sodium hydrosulfite is described.

2. 6-Amino-*o*-cresol, 6-acetylamino-*o*-cresol, 6-amino-*m*-cresol and 6-acetylamino-*m*-cresol were prepared and studied.

3. The following mercury derivatives of acetylaminocresols were synthesized and studied: 4-acetoxymercuri-6-acetylamino-*o*-cresol, 4,6-diacetoxymercuri-5-acetylamino-*o*-cresol, 2,4-diacetoxymercuri-6-acetylamino-*m*-cresol and 2,6-diacetoxymercuri-4-acetylamino-*m*-cresol.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

BENZOHYDRYLMAGNESIUM CHLORIDE AND THE APPARENT PRIOR FORMATION OF FREE BENZOHYDRYL RADICALS

BY HENRY GILMAN AND E. A. ZOELLNER

RECEIVED JUNE 6, 1930 PUBLISHED OCTOBER 6, 1930

Introduction

In the preparation of all Grignard reagents, there are side-reactions, and chief among these is the coupling reaction to give R·R compounds.[1] The extent of this coupling reaction varies between extreme limits,[2] and until recently it was essentially impossible, for example, to prepare allylmagnesium bromide because of the unusually high yield of diallyl.[3]

Perhaps the most unusual preparation of this type is that of benzohydrylmagnesium chloride, $(C_6H_5)_2CHMgCl$. Under ordinary conditions the yield of coupling product, *sym.*-tetraphenylethane, is astonishingly high and has reached 95.5%.[4] For this reason, the application of this RMgX compound in synthesis has followed the procedure of Barbier. This involves the preparation of the benzohydrylmagnesium halide in the presence of the reactant.[5] Ordinarily this procedure has two serious disadvantages:

[1] Gilman and Fothergill, THIS JOURNAL, **50**, 3334 (1928).

[2] See Gilman, Zoellner and Dickey, *ibid.*, **51**, 1576 (1929), for the yields of some RMgX compounds. Some typical RMgX compounds like phenylmagnesium bromide and *n*-butylmagnesium bromide can be prepared in essentially quantitative yields when an excess of magnesium is used.

[3] It is now possible to prepare allylmagnesium bromide in yields greater than 93%. See Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

[4] Gilman and Kirby, THIS JOURNAL, **48**, 1733 (1926).

[5] Gomberg and Cone, *Ber.*, **39**, 1461 (1906); Bert, *Compt. rend.*, **177**, 324 (1923); Grignard and Ono, *Bull. soc. chim.*, **39**, 830, 1589 (1926); Gilman and Kirby, THIS JOURNAL, **48**, 1733 (1926); Levy and Lagrave, *Bull. soc. chim.*, **43**, 437 (1928).