

very small compared with that necessary in the regular density test which involves distillation of a 100cc. sample.

Summary

1. In general, hypochlorous acid reacts with monohydric alcohols to form esters. The hypochlorites of dihydric or trihydric alcohols could not be prepared.

2. Tertiary alcohols were found to give more stable esters than either primary or secondary alcohols.

3. The constitution of ethyl hypochlorite has been proved to be that of a true ester.

4. Ethyl hypochlorite readily hydrolyzes in water, even in its saturated solution, to the extent of 69%.

5. A simple method of preparing solvent solutions of alkyl hypochlorites has been described.

6. A new method for the approximate determination of alcohols has been described.

NIAGARA FALLS, NEW YORK

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF HAWAII]

SYNTHESIS OF THE ANHYDRIDE OF HYDROXYMERCURI-ETHOXY-CHAULMOOGRIC ACID AND ETHYL ACETOXYMERCURI-ETHOXY-CHAULMOOGRATE

By A. L. DEAN, R. WRENSHALL AND G. FUJIMOTO

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While the administration of the mixed ethyl esters of the fatty acids from chaulmoogra oil in the treatment of leprosy has produced highly gratifying results,¹ and derivatives of the acids of the chaulmoogric series have been shown, both *in vitro*² and *in vivo*³ to possess unique therapeutic value against the lepra bacillus, these products should by no means be considered an absolute specific against the disease.

While practically all the patients who have received this treatment at the United States Leprosy Investigation Station, Honolulu, Hawaii, have shown marked improvement, a considerable number of them have come to a standstill after a few months, and even in the cases where apparent cures have been effected, the treatment is a slow one, usually requiring from one to two or more years.

To improve the present method for treating leprosy, compounds of higher therapeutic value than these chaulmoogra esters will be required. For

¹ McDonald, *J. Am. Med. Assoc.*, **75**, 1483 (1920).

² Walker and Sweeney, *J. Infectious Diseases*, **26**, 238 (1920).

³ McDonald and Dean, *J. Am. Med. Assoc.*, **76**, 1470 (1921) and *Pub. Health Repts.*, Aug. 20, 1920, 1959.

this purpose the incorporation of mercury or arsenic in the chaulmoogric acid molecule seemed logical, because such compounds might be expected to combine the specific action of the fatty acid with the bactericidal action of the metals.

Mercuration of unsaturated compounds, in which category chaulmoogric acid belongs, has been studied by a number of investigators. The general reaction of this type of compound with mercuric salts in alcoholic solution probably consists in the addition of HgX to one end of the double bond, and an alkoxy group to the other.⁴ Fraenkel reports that a process for mercurating chaulmoogra oil and its esters has been patented.⁵ In 1921 Kharasch⁶ mercurated chaulmoogric acid by allowing molecular proportions of the acid and mercuric acetate to react over a period of 24 hours in a solution in absolute alcohol and glacial acetic acid and investigated the viscous product which he obtained on pouring this solution into water.

The results of an attempt to prepare and analyze Kharasch's viscous product in this Laboratory indicated that it was an unstable substance of indefinite composition. The product is more stable in its original solution than after being precipitated by water. When the solution is allowed to stand for about two weeks in the ice chest, a granular precipitate forms which can be purified by several crystallizations from 95% alcohol. The pure product consists of very minute, colorless needles melting sharply at 112–113° to give a colorless liquid.

Quantitative tests for hydroxyl groups by both the acetic anhydride and Grignard reagent methods⁷ gave negative results. The entire absence of effervescence with the latter reagent indicated the absence of a free carboxyl group. Treatment with hydrochloric acid readily forms inorganic mercury compounds and regenerates chaulmoogric acid. A solution of the substance in hot 95% alcohol neutralizes a considerable quantity of potassium hydroxide; but when the hot neutral solution cools, the original product separates and the supernatant liquid becomes strongly alkaline. This behavior indicates an equilibrium between the alkali, the potassium salt and the less soluble anhydride or inner salt.

The iodine value, determined by both the Hanus and the Hübl methods, indicates that each molecule of the mercurated product reacts with two atoms of iodine, as is usual with carbon-mercury compounds.⁸

The approximate molecular weight of 574, determined by the depression of the freezing point of naphthalene, precludes the possibility of this being a polymerization product of chaulmoogric acid, or of its having more than

⁴ Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., New York, 1921, p. 31.

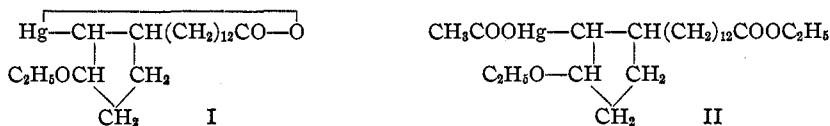
⁵ Fraenkel, "Arzneimittelsynthese," 5th ed., 1921, p. 681; Ger. pat. 245, 571.

⁶ Kharasch, private communication.

⁷ Hibbert and Sudborough, *J. Chem. Soc.*, **85**, 933 (1904).

⁸ Ref. 4, p. 40.

one atom of mercury in the molecule. All lines of evidence, including analyses for carbon, hydrogen and mercury, indicate that the product is the anhydride or inner salt of hydroxymercuri-ethoxy-chaulmoogric acid. If chaulmoogric acid is assumed to react as a cyclopentene,⁹ Formula I can be assigned to the product.



Of course the positions of the mercury and the ethoxy group may be reversed.

One objectionable feature of this anhydride, from the standpoint of clinical use, is its great insolubility. It has been found, however, that when ethyl chaulmoograte is used instead of the free acid and the synthetic method slightly modified, a mercurated ethyl chaulmoograte can be obtained which is soluble in all the common organic solvents.

This substance crystallizes from alcohol in minute, colorless needles that melt sharply at 67–68° to form a colorless liquid. It gives the usual reactions of mercury compounds obtained from unsaturated esters. Quantitative determinations show the presence of one acetoxy group and two ethoxy groups, indicating that the substance is the ethyl ester of acetoxymercuri-ethoxy-chaulmoogric acid. A possible formula would be that shown in II. The ethoxy group and the acetoxymercuri group may occupy the reverse positions. It should also be borne in mind that chaulmoogric acid may exist or react in more than one form.⁹

Experimental Part

Anhydride of Hydroxymercuri-ethoxy-chaulmoogric Acid.—One mole of mercuric acetate was dissolved in a mixture of 2000cc. of hot, absolute ethyl alcohol and 400cc. of glacial acetic acid, which was then cooled to room temperature. To this was added, in small portions, one mole of chaulmoogric acid and the mixture was constantly stirred until a fairly clear solution was obtained. About six hours after preparing this solution a flocculent precipitate began to form. After 24 hours, as no more appeared, it was filtered off and found to be an infusible substance, containing mercury and weighing less than 3 g. The clear filtrate was then placed in a stoppered flask and allowed to stand in the ice chest. At the end of ten days a white granular precipitate began to develop in clusters on the sides and bottom of the flask. The deposition of this material was fairly rapid during the next five days, then continued over a period of three months, finally coming to a standstill. The total yield was 50 g. and the crude material melted at 80–95°.

After four crystallizations from 95% alcohol it separated as a beautiful, silvery-white mass of minute needles, melting sharply at 112–113° to form a clear liquid. Further crystallization did not alter this melting point. Purification by crystallization from alcohol was found rather difficult, on account of the low degree of solubility in the hot

⁹ Barrowcliff and Power, *J. Chem. Soc.*, **91**, 562 (1910).

solvent. Success in obtaining a fair yield of the pure material was had by dissolving the crystallized material melting at 108–110° at a slow rate in a large volume of boiling alcohol, rapidly filtering the solution by suction to remove the impurities (which are less soluble than the compound itself), then allowing the filtrate to stand in the ice chest for two hours to crystallize and again filtering rapidly by suction.

The purified product is readily soluble in chloroform and glacial acetic acid, less so in hot alcohol, hot ethyl acetate and hot acetone and practically insoluble in cold alcohol, cold ethyl acetate, cold ether and cold petroleum ether. The best solvent for recrystallization is 95% alcohol.

Anal. Subs., 0.2679, 0.1803, 0.2085, 0.2482: Hg, 0.1019, 0.0695, 0.0794, 0.0956 (gold crucible method).¹⁰ Subs., 0.6151, 0.5677, 0.5454, 0.5255: HgS, 0.2726, 0.2256, 0.2419, 0.2331. Calcd. for $C_{20}H_{30}O_3Hg$: Hg, 38.21. Found: 38.04, 38.54, 38.08, 38.52; 38.21, 38.91, 38.24, 38.25.

Subs., 0.2920, 0.2447: CO_2 , 0.4870, 0.4091; H_2O , 0.1843, 0.1509. Calcd. for $C_{20}H_{30}O_3Hg$: C, 45.73; H, 6.91. Found: C, 45.49, 45.60; H, 7.06, 6.90.

The method used by Hewitt and Moore,¹¹ in which hydriodic acid is used to liberate ethyl iodide which is passed into silver nitrate and the silver iodide then determined, showed that one ethoxy group was present.

Anal. Subs., 0.3563, 0.3033; AgI, 0.1536, 0.1309. Calcd. for $C_{20}H_{30}O_3Hg$ containing one ethoxy group: C_2H_5O , 8.58. Found: 8.27, 8.28.

The approximate molecular weight was determined through the depression of the freezing point of naphthalene.

Mol. wt. Calcd. for $C_{20}H_{30}O_3Hg$: 524.99. Found: 574.0. Calcd. for $C_{20}H_{30}O_3Hg$, if two atoms of iodine react: I, 48.35. Found (Hübl method): 48.95, 48.95.

Subs., 1.0629, 1.0587: KOH, 0.11037, 0.10700. Calcd. for $C_{20}H_{30}O_3Hg$, if the anhydride is hydrolyzed and saponified: KOH, 106.97 mg. Found: 103.8 mg., 101.0 mg.

The distillation method with sirupy phosphoric acid¹² showed no acetoxy groups present; Perkin's method showed no acetyl groups present; the acetic anhydride method and the Grignard reagent method showed no hydroxyl groups present and the latter indicated that there was no free carboxyl group (no effervescence took place). The compound $C_{20}H_{30}O_3$ requires the presence on none of these groups.

Ethyl Acetoxymercuri-ethoxy-chaulmoograte.—One mole of freshly distilled ethyl chaulmoograte and 1.25 mole of mercuric acetate (crystallized from glacial acetic acid) were dissolved, at ordinary temperature, in a mixture of 1000 cc. of absolute alcohol and 100 cc. of glacial acetic acid. The solution was kept in a tightly stoppered flask in the ice chest for ten days, then filtered to remove a small amount of impurity and poured into a large volume of water. The viscous oil which separated was washed by stirring and decanting until the washings were only slightly acid to litmus. The water was removed, as far as practicable and the viscous oil allowed to stand in an open dish overnight to crystallize. The resulting product, which was semi-solid, was filtered by suction and the solid portion crystallized several times from petroleum ether, then thrice from absolute alcohol. The yield was 15 g., and consisted of minute, colorless needles, melting sharply at 67–68° to form a clear liquid.

The product is stable in the air, but inorganic acids form soluble inorganic mercury compounds, and an oily layer of ethyl chaulmoograte (as shown by its conversion to

¹⁰ Ref. 4, p. 365.

¹¹ Hewitt and Moore, *J. Chem. Soc.*, **81**, 318 (1902).

¹² White, *THIS JOURNAL*, **42**, 2359 (1920).

chaulmoogric acid by saponification with alcoholic potassium hydroxide and treatment with mineral acids).

Anal. Subs., 0.5095, 0.5119: HgS, 0.1936, 0.1945. Calcd. for $C_{24}H_{44}O_5Hg$: Hg, 32.72. Found: 32.76, 32.76.

Subs., 0.4810, 0.3747: AgI, 0.3548, 0.2907. Calcd. for $C_{24}H_{44}O_5Hg$ (two ethoxy groups): C_2H_5O , 14.67. Found: 14.15, 14.88.

Subs., 0.4947, 0.4670: KOH to neutralize CH_3COOH evolved, 0.04664, 0.04265. Calcd. for $C_{24}H_{44}O_5Hg$ (one acetoxy group): CH_3COO , 9.63. Found: 9.91, 9.60.

Summary

From mercuric acetate and chaulmoogric acid a crystalline compound can be prepared which is shown to be the anhydride or inner salt of hydroxymercuri-ethoxy-chaulmoogric acid.

Under similar conditions, mercuric acetate and ethyl chaulmoograte give a crystalline ethyl acetoxymercuri-ethoxy-chaulmoograte.

These compounds are being used experimentally in the treatment of leprosy.

HONOLULU, HAWAII

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

CERTAIN SUBSTITUTED BIURETS

BY ELIZABETH STUART GATEWOOD¹

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Because biurets have recently been obtained as oxidation and decomposition products of certain purines, it becomes increasingly necessary to know more about the chemistry of these substances. The preparation and the exact determination of the structures of the phenyl- and methyl-phenyl-biurets are of immediate interest in connection with the mechanism of the oxidation of certain phenyl-substituted uric acids by hydrogen peroxide.²

The phenyl-biuret melting at 165° has now been synthesized in a way that shows definitely its unsymmetrical structure. It is formed when ethyl *N*^ω-phenyl-allophanate, prepared by the action of chloro-formanilide on urethan, is heated with a concentrated aqueous ammonia solution for an hour at 100°: $C_6H_5NHCOC_2H_5 + NH_2COOC_2H_5 = C_6H_5NHCONHCOOC_2H_5 + HCl$; $C_6H_5NHCONHCOOC_2H_5 + NH_3 = C_6H_5NHCONHCONH_2 + C_2H_5OH$.

ω-Phenyl-biuret can be directly methylated with dimethyl sulfate. A monomethyl-phenyl-biuret, m. p. 183°, is obtained. The method of formation gives no indication as to the position of the methyl group.

When ethyl *N*^ω-phenyl-allophanate is heated with an aqueous 33% methylamine solution at 100°, a beautifully crystalline substance is formed

¹ National Research Fellow in Chemistry.

² Moore and Gatewood, *THIS JOURNAL*, **45**, 135 (1923).