

of the two by the use of a single absorbing agent, a solution of silver nitrate, is at once apparent.

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MENTHOL STUDIES. II. MENTHYL ESTERS OF THE 2-NITRO-4-CARBOXYPHENYLARSONIC AND PHENYLARSENIOUS ACIDS

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The first report¹ on the synthesis of aromatic terpene compounds to be used in chemotherapeutic studies in experimental tuberculosis included menthyl esters of the nitro- and aminocinnamic acids. Due to the great insolubility in water caused by the menthol, the menthyl esters of the aminocinnamic acids could not be made water-soluble through their hydrochlorides. Since a water-soluble product is desirable, the introduction of arsenic into the aromatic terpene group was thought to be desirable for two reasons; first, to increase the solubility in water and second, to confer probably greater therapeutic properties.

A few organic arsenicals have been used in experimental studies in tuberculosis therapy, and arsenic in the form of arsenic acid was tried early in the treatment of tuberculosis. Sodium cacodylate, atoxyl, arsacetin and neosalvarsan have no tuberculocidal properties, according to Arkin and Corper,² but earlier investigators (Buchner, Weismayr, Pokhorow)³ comment favorably upon the worth of arsenic in the treatment of tuberculosis because of its favorable influence on metabolism, although they conclude that it is not a true chemotherapeutic agent with a specific action on human tubercle bacilli.

The new menthol arsenicals described here were made with the hope that they might possess some favorable pharmacological action.

Experimental

2-Nitro-4-methylphenylarsonic Acid.—This compound was first prepared by Jacobs, Heidelberger and Rolf⁴ using a different technique in the arsonation process from that described here. 3-Nitro-4-toluidine (110 g.) is stirred by means of a mechanical stirrer in 20% hydrochloric acid (500 cc.) until the hydrochloride is formed, and then diazotized at 0° with sodium nitrite (55 g.) dissolved in water (250 cc.). The diazo solu-

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¹ McCluskey and Sher, *THIS JOURNAL*, **49**, 452 (1927).

² Arkin and Corper, *J. Infectious Diseases*, **18**, 333 (1916).

³ Quoted by Weismayr in Ott's, "Chem. Path. der Tuberc.," **1903**, p. 480-481.

⁴ Jacobs, Heidelberger and Rolf, *THIS JOURNAL*, **40**, 1585 (1918).

tion is filtered from a small amount of undissolved substance. Solutions of hydrated copper sulfate (25 g. in 375 cc. of water), sodium hypophosphite (35 g. in 500 cc. of water) and sodium arsenite (135 g. in 1 liter) are heated separately to 60 to 70°, and then poured into a large flask. At this temperature the cold filtered diazo solution is added slowly with vigorous stirring. Nitrogen is evolved copiously and in a short time a stormy reaction sets in and the arsonic acid is immediately precipitated. Very little tarry material is formed. After the evolution of nitrogen has subsided the substance is collected and washed well with water; yield, 130 g. The arsonic acid is purified by solution in 4% potassium hydroxide, treatment with charcoal and precipitation with hydrochloric acid. Further purification from alcohol gives a substance melting in a closed tube at 253–255°. It is insoluble in benzene and acetone, slightly soluble in hot ethyl alcohol and quite soluble in hot methyl alcohol.

Anal. Subs., 0.2082: 29.99 cc. of I₂ soln. (1 cc. = 0.001967 g. of As). Calcd. for C₇H₅O₅NAs: As, 28.74. Found: 28.34.

2-Nitro-4-carboxyphenylarsonic Acid.—Maschmann⁵ prepared this compound through the oxidation of the corresponding methyl compound with potassium permanganate. A convenient method for the preparation in rather large quantities is as follows. Crude 2-nitro-4-methylphenylarsonic acid (390 g.) is dissolved in potassium hydroxide solution (390 g. in 7.5 liters of water) treated with charcoal and filtered. Mechanical stirring facilitates the process. To the clear filtrate is added a solution of potassium permanganate (390 g. in 12.5 liters of water) and the reaction mixture placed on a water-bath until the permanganate color is lost through oxidation. The manganese oxides are removed by filtration and the green colored filtrate is acidified with hydrochloric acid until acid to congo red. The green color changes to pink and finally disappears. The acid solution is evaporated to dryness on the water-bath and the desired arsonic acid extracted with hot ethyl alcohol. The alcohol is removed by evaporation and the nitrocarboxyphenylarsonic acid is purified by crystallization from boiling water after treatment with charcoal; yield, 80 to 90%. The glistening needle-like crystals contain one molecule of water of crystallization and melt with decomposition at 226–227°, which confirms Maschmann's findings.

Anal. Subs., 0.2484, 0.1987: 30.84, 24.67 cc. of I₂ (1 cc. = 0.001933 g. of As). Calcd. for C₇H₆O₇NAs·H₂O: As, 24.27. Found: As, 24.01, 24.00.

The water of crystallization is lost at 115° and the following analysis is obtained.

Anal. Subs., 0.2126, 0.2030: 28.25, 26.93 cc. of I₂ soln. (1 cc. = 0.001967 g. of As). Calcd. for C₇H₆O₇NAs: As, 25.77. Found: As, 26.14, 26.10.

Sodium Salt.—This salt is prepared by titrating an alcoholic solution of 2-nitro-4-carboxyphenylarsonic acid with an alcoholic solution of sodium hydroxide. The sodium salt is very soluble in water.

Anal. Subs., 0.2076: 22.41 cc. of I₂ soln. (1 cc. = 0.001967 g. of As). Calcd. for C₇H₅O₇NAsNa₃: As, 21.01. Found: As, 21.23.

2-Nitro-4-carboxyphenyldichloro-arsine.—The phenyldichloro-arsine compound can be obtained by reduction of the corresponding arsonic acid in concentrated hydrochloric acid with either hypophosphorous acid, sulfur dioxide, hydroquinone or camelite. 2-Nitro-4-carboxyphenylarsonic acid (20 g.) is dissolved in concentrated hydrochloric acid (150 cc.) and after the addition of 10% potassium iodide (10 drops) sulfur dioxide is passed into the solution until precipitation is complete. The dichloro-arsine compound is collected under suction on hardened filter paper, washed first with concentrated hydrochloric acid and then with dilute hydrochloric acid. Partial drying is obtained

⁵ Maschmann, *Ber.*, **57B**, 1759–1766 (1924).

by pressing the preparation on a porous plate, after which it is transferred to a vacuum desiccator and dried over sulfuric acid and sodium hydroxide sticks; amount of crude product, 20 g. For purification the crude dried material is dissolved in hot chloroform and precipitated by cooling. Twelve grams of a light yellow, fluffy product melting at 173–174° is obtained. Petroleum ether added to the filtrate gives an additional quantity of less pure material.

Anal. Subs., 0.1740: 21.80 cc. of I₂ soln. (1 cc. = 0.001936 g. of As). Calcd. for C₇H₄O₄NAsCl₂: As, 24.04. Found: As, 24.26.

To a solution of 2-nitro-4-carboxyphenylarsonic acid (10 g.) in concentrated hydrochloric acid (400 cc.), 50% hypophosphorous acid (20 cc.) and 10% potassium iodide (10 drops) are added. The reaction mixture is gradually warmed to 37–40° and shortly the solution becomes turbid, the iodine color gradually disappears and the dichloro-arsine separates. The precipitate is collected and treated as described above; yield of crude product, 9 g.

2-Nitro-4-carboxyphenyldihydroxyarsine (2-Nitro-4-carboxyphenylarsenious Acid).—This compound can be prepared either by the hydrolysis of the corresponding dichloro-arsine or by reduction of the corresponding arsonic acid in water by means of sulfur dioxide in presence of potassium iodide as catalyst.

2-Nitro-4-carboxyphenylarsonic acid (10 g.) is dissolved in hot water (225 cc.) and after the addition of 10% potassium iodide (20 drops) sulfur dioxide is passed into the solution until complete precipitation of the arsenious acid; yield, 7.5 g. or 85%. 2-Nitro-4-carboxyphenylarsenious acid is a light yellow substance which does not melt or decompose below 290°.

Anal. Subs., 0.1718: 24.19 cc. of I₂ soln. (1 cc. = 0.001936 g. of As). Calcd. for C₇H₆O₆NAs: As, 27.28. Found: 27.26.

2-Nitro-4-carboxyphenyldichloro-arsine (3 g.) is suspended in water (100 cc.) and the mixture shaken for an hour. A change in structure is visible. The dihydroxyarsine is collected and washed free from chlorides. The filtrate becomes strongly acid and silver chloride is precipitated upon the addition of silver nitrate.

Menthyl Ester of 2-Nitro-4-carboxyphenylarsenious Acid.—2-Nitro-4-carboxyphenyldichloro-arsine (42 g.) is refluxed with thionyl chloride (100 cc.) on a water-bath for one hour. Complete solution results after fifteen minutes. The excess of thionyl chloride is removed by distillation under reduced pressure. To the crude acid chloride, menthol (54.6 g.) is added and the reaction mass is heated under a reflux condenser on a water-bath for one to one and a half hours. The excess menthol is removed by distillation under reduced pressure (outside bath 140°) and petroleum ether is added to the residue, which dissolves the menthyl ester and separates it from an insoluble, tarry by-product. The petroleum ether is removed by evaporation and the sticky semi-liquid mass is macerated with 4 *N* sodium carbonate, whereupon a semi-solid mass is obtained which is dissolved in ether and shaken with more 4 *N* sodium carbonate until the carbonate solution is chloride free. The ether solution is washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The sticky mass soon crystallizes on stirring. The amount obtained at this point is 50 g. which still contains a small amount of free menthol. This ester, like menthol, is very soluble in organic solvents and is separated only with difficulty from small amounts of menthol through fractional crystallization. The last traces of menthol were best removed by steam distillation. The menthyl ester is a light yellow, crystalline substance which does not have a sharp melting point but gradually evolves a gas above 100°.

Anal. Subs., 0.2882, 0.3060: 28.38, 29.92 cc. of I₂ soln. (1 cc. = 0.001843 g. of As). Calcd. for C₁₇H₂₄O₆NAs: As, 18.16. Found: As, 18.14, 18.02.

Menthyl Ester of 2-Nitro-4-carboxyphenylarsonic Acid.—The menthyl ester of this acid could not be made directly from the acid itself with thionyl chloride and menthol, as the thionyl chloride reduced the arsonic group. The menthyl ester of 2-nitro-4-carboxyphenylarsenious acid (10 g.) is dissolved in acetone (200 cc.) and 3% hydrogen peroxide (105 cc.) is added in small portions at room temperature. The heat of reaction raises the temperature to 27–29°. After reaction is complete and the temperature subsides, the solution is filtered if necessary and allowed to stand in an evaporating dish at room temperature. The solid which separates after the evaporation of the acetone is collected and sucked dry. The ester is a white, crystalline substance which decomposes at 210–211° and is soluble in alcohol and chloroform, not so soluble in ether when pure and insoluble in petroleum ether. Purification from chloroform and petroleum ether gave a product of the following analysis.

Anal. Subs., 0.3012: 28.46 cc. of I₂ soln. (1 cc. = 0.001843 g. of As). Calcd. for C₁₇H₂₄O₇NAs: As, 17.48. Found: As, 17.41.

Sodium Salt.—The pure menthyl ester of 2-nitro-4-carboxyphenylarsonic acid is dissolved in warm ethyl alcohol and titrated to the pink point of phenolphthalein with an ethyl alcoholic solution of sodium hydroxide. The salt begins to separate as soon as the alkali is added but comes down at first in a gummy form. The solvent is removed through slow evaporation in a warm place and the salt is obtained as a white, fluffy substance. It is suspended in ethyl alcohol and macerated well to remove any excess either of free acid or free alkali, then collected and washed with ether. Thus obtained, the salt crystallizes with 4 molecules of water of crystallization.

Anal. Subs., 0.3336: 24.42 cc. of I₂ soln. (1 cc. = 0.001843 g. of As). Calcd. for C₁₇H₂₂O₇NAsNa₂·4H₂O: As, 13.76. Found: As, 13.50.

After drying at 110°, the following analysis is obtained.

Anal. Subs., 0.2863: 24.45 cc. of I₂ soln. (1 cc. = 0.001843 g. of As). Calcd. for C₁₇H₂₂O₇NAsNa₂: As, 15.85. Found: As, 15.72.

The hydrated salt is a pure white substance while the anhydrous form is a very light yellow. Both forms are very soluble in water.

Summary

The preparation of the following new compounds is reported: 2-nitro-4-carboxyphenyldichloro-arsine, 2-nitro-4-carboxyphenylarsenious acid, menthyl ester of 2-nitro-4-carboxyphenylarsenious acid, menthyl ester of 2-nitro-4-carboxyphenylarsonic acid, together with some of the sodium salts. The presence of the nitro and the carboxy groups favors the arsenious acid form rather than the arsenious oxide form.

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