[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Diarsyls. IX. Tetra-(3-amino-4-hydroxyphenyl)-diarsyl

BY F. F. BLICKE, J. F. ONETO[1] AND G. L. WEBSTER[2]

The preparation and properties of tetra-(3-amino-4-hydroxyphenyl)-diarsyl $[(H_2N)(HO)C_6H_3]_2As—As[C_6H_3(OH)(NH_2)]_2$ are of special interest because of the structural analogy of this compound with salvarsan $(H_2N)(HO)C_6H_3-As=AsC_6H_3(OH)(NH_2)$. Fargher[3] isolated and analyzed the diarsyl dihydrochloride and this substance is mentioned also by Christiansen.[4] This paper deals with a study of the diarsyl base, the preparation of the corresponding arsinic acid and several related acids.

Tetra-(3-amino-4-hydroxyphenyl)-diarsyl is insoluble in many of the common organic solvents but is soluble in alkali and acids. In the solid state the diarsyl is quite stable toward oxygen but an alkaline solution of the compound absorbs the gas quite rapidly.

Through the courtesy of Parke, Davis and Company the compounds mentioned below were tested for general toxicity by intravenous injection in white rats and for trypanocidal action against the common *T. equiperdum.*

3,3′ - Diamino - 4,4′ - dihydroxydiphenylarsinic acid (I) failed to kill rats in doses as large as 1500 mg. per kilo body weight, hence it is a relatively non-toxic substance. The corresponding oxide, tetra-(3-amino-4-hydroxyphenyl)-arsyl oxide (II), is much more toxic. Neither compound seemed to be of any value as a trypanocide.

As far as tetra-(3-amino-4-hydroxyphenyl) diarsyl tetrahydrochloride (III), methyl-3-amino-4-hydroxyphenylarsinic acid,[5] methyl-3-amino-4-hydroxyphenylchloroarsine hydrochloride[6] and dimethyl-di-(3-amino-4-hydroxyphenyl)-diarsyl dihydrochloride[7] are concerned only the first mentioned compound exhibited any appreciable activity as a curative agent against *T. equiperdum* in white rats.

The well-known therapeutic agents 3-acetylamino-4-hydroxyphenylarsonic acid (stovarsol), 3-amino-4-hydroxyphenylarsine oxide hydrochloride (mapharsen) and 3,3′-diamino-4,4′-dihydroxyarsenobenzene (salvarsan) are the *mono* aryl analogs of compounds I, II and III, respectively. In view of the data obtained it seems that no improvement is made, as far as trypanocidal action is concerned, by the attachment of a second aminohydroxyphenyl nucleus to the arsenic atom.

No thorough pharmacological study of any of the compounds was made nor were they tested against spirochetes since the preliminary investigation indicated that they would be of little practical value.

Experimental Part

4,4′-Dihydroxydiphenylarsinic Acid.—This acid, which melted at 246–247° with effervescence,[8] dissolved in hot acetic acid, is decomposed by bromine with the formation of tribromophenol; suspended in acetic acid the arsinic acid is converted quantitatively into arsenic triiodide upon the addition of hydriodic acid.

Anal. Calcd. for $C_{12}H_{11}O_4As$: As, 25.48. Found: As, 25.34.

Di-(3-nitro-4-hydroxyphenyl)-chloro- and -bromoarsine.—Two grams of 3,3′-dinitro-4,4′-dihydroxydiphenyl arsinic acid, prepared by nitration[9] of 4,4′-dihydroxydiphenylarsinic acid, was dissolved in a mixture of 10 cc. of acetic acid, 25 cc. of hydrochloric acid and a drop of hydriodic acid and treated with sulfur dioxide. The gummy precipitate soon solidified; yield 2.1 g. After recrystallization from acetic acid the yellow crystals melted at 142–143°. The product dissolved in dilute sodium hydroxide to yield a red solution.

Anal. Calcd. for $C_{12}H_8O_6N_2AsCl$: As, 19.38; Cl, 9.17. Found: As, 19.46; Cl, 8.67.

The yellow, crystalline bromoarsine, prepared from 1 g. of the arsinic acid, 5 cc. of acetic acid, 11 cc. of hydrobromic acid, a drop of hydriodic acid and sulfur dioxide, melted at 131–132° after recrystallization from acetic acid.

Anal. Calcd. for $C_{12}H_8O_6N_2AsBr$: As, 17.39; Br, 18.55. Found: As, 17.43; Br, 18.65.

3,3′-Diamino-4,4′-dihydroxydiphenylarsinic Acid.—A solution of 200 g. of flake sodium hydroxide in 300 cc. of water was added to 170 g. of ferrous sulfate, dissolved in 500 cc. of water. After the mixture had been shaken thoroughly and cooled, there was added 20 g. of 3,3′-dinitro-4,4′-dihydroxydiphenylarsinic acid, dissolved in

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[1] Parke, Davis and Company Fellow.

[2] University Fellow in the Horace H. Rackham School of Graduate Studies.

[3] Fargher, *J. Chem. Soc.*, **115**, 987 (1919).

[4] Christiansen, THIS JOURNAL, **43**, 374 (1921).

[5] Bertheim, *Ber.*, **48**, 358 (1915); Blicke and Webster, THIS JOURNAL, **59**, 535 (1937).

[6] Blicke and Webster, *ibid.*, **59**, 535 (1937).

[7] Bertheim, *Ber.*, **48**, 358 (1915); Blicke and Webster, THIS JOURNAL, **59**, 539 (1937).

[8] Benda [*Ber.*, **41**, 2371 (1908)], m. p. 239°; Fargher [*J. Chem. Soc.*, **115**, 986 (1919)], m. p. 259°, corr.; Jacobs and Heidelberger [THIS JOURNAL, **41**, 1448 (1919)], m. p. 250–251°. See also Yang and Wang, *J. Chinese Chem. Soc.*, **5**, 89 (1937).

[9] Fargher, *J. Chem. Soc.*, **115**, 986 (1919).

100 cc. of water and 9 g. of flake sodium hydroxide. The mixture was shaken again and after one hour was filtered. Hydrochloric acid (about 260 cc.) was added to the filtrate until the latter was slightly acid toward litmus, the precipitated impurities removed by filtration, the light brown filtrate treated with hydrochloric acid, drop by drop, to precipitate the last traces of colored by-products, charcoal added and the mixture filtered again. The filtrate should now be slightly yellow and if the arsinic acid does not begin to precipitate after a short time, a few more drops of acid should be added; yield 9–11 g. of light brown, glistening crystals. When heated the acid darkens about 210° and decomposes at 218°.[10] About 100 cc. of boiling water is required to recrystallize 1 g. of the arsinic acid.

Anal. Calcd. for $C_{12}H_{13}O_4N_2As$: As, 23.12. Found: As, 23.29.

Di-(3-amino-4-hydroxyphenyl)-chlorarsine Dihydrochloride.—A solution prepared from 2.5 g. of 3,3′-diamino-4,4′-dihydroxydiphenylarsinic acid, 6 cc. of water, 20 cc. of hydrochloric acid and a drop of hydriodic acid, was treated with sulfur dioxide. The precipitated chloride dihydrochloride was filtered through a Jena filter, dissolved in the least possible amount of warm water, shaken with charcoal, filtered, the colorless filtrate cooled with ice and the dihydrochloride precipitated by the addition of fuming hydrochloric acid. The pearly flakes weighed 1.9 g.; m. p. 214–215°.[11]

Anal. Calcd. for $C_{12}H_{14}O_2N_2AsCl_3$: As, 18.76; Cl, 26.62. Found: As, 18.65; Cl, 26.61.

Tetra-(3-amino-4-hydroxyphenyl)-arsyl Oxide.—To 5 g. of the above-mentioned dihydrochloride, dissolved in 35 cc. of water, there was added, slowly, 5 g. of sodium hydroxide, dissolved in 15 cc. of water. The clear, alkaline solution was then treated, gradually, with just enough acetic acid (about 3.3 cc.) to precipitate the arsyl oxide. The crystalline oxide is soluble in 0.5 *N* hydrochloric acid, 0.5 *N* sodium hydroxide, alcohol, somewhat soluble in water and insoluble in ether; m. p. 152–155° with decomposition.

Anal. Calcd. for $C_{24}H_{24}O_5N_4As_2$: As, 25.06. Found: As, 24.75.

Tetra-(3-amino-4-hydroxyphenyl)-diarsyl.—Three grams of either 3,3′-diamino-4,4′-dihydroxydiphenylarsinic acid or tetra-(3-amino-4-hydroxyphenyl)-arsyl oxide was dissolved in 30 cc. of 50% hypophosphorous acid, a drop of hydriodic acid added and the solution heated in a modified radical apparatus[12] for one hour at 60°. Upon the addition of 38 cc. of 20% sodium hydroxide solution a copious, crystalline precipitate formed; during the addition of the alkali the mixture should be allowed to become hot, otherwise the precipitate tends to separate in a flocculent state. After the addition of 100 cc. of water the product was filtered and washed three times with 100-cc. portions of water and then several times with acetone; when heated in a sealed tube filled with nitrogen the material turns brown at about 200° and melts suddenly, with decomposition, at 202°. This compound seems to be a tetrahypophosphite of the diarsyl.

Anal. Calcd. for $C_{24}H_{24}O_4N_4As_2 \cdot 4H_3PO_2$: As, 17.71. Found: As, 17.83.

In order to obtain the free diarsyl the salt mentioned above was dissolved in 15 cc. of hot, 20% sodium hydroxide solution; upon the addition of 25% acetic acid until the mixture was acidic toward phenolphthalein the diarsyl precipitated. The liquid was decanted and the diarsyl washed with acetone; yield 1.9 g.; m. p. 193–194° in a sealed tube filled with nitrogen.

Anal. Calcd. for $C_{24}H_{24}O_4N_4As_2$: As, 25.74. Found: As, 25.51.

The diarsyl is insoluble or only slightly soluble in benzene, ether, acetone, alcohol, chloroform, bromobenzene, acetophenone, ethylene bromide, nitrobenzene, tetralin and acetic acid; it is soluble in pyridine, 50% acetic acid, dilute sodium hydroxide and dilute hydrochloric acid.

The tetrahydrochloride of the diarsyl was prepared in the following manner. The diarsyl obtained from 5.0 g. of 3,3′-diamino-4,4′dihydroxydiphenylarsinic acid was dissolved, while still moist, in a mixture of 3 cc. of concd. hydrochloric acid and 5 cc. of water. After the addition of 100 cc. of alcohol the solvents were removed at 35° under diminished pressure. To the moist, gelatinous salt, dissolved in 17 cc. of absolute alcohol, there was added 40 cc. of ether whereupon the hydrochloride separated in the form of granular crystals. The alcohol and ether were removed under diminished pressure and the residue washed three times with 40 cc. of ether; after the salt had been dried and isolated in a carbon dioxide atmosphere it melted at 170–172°[13] in a sealed tube filled with nitrogen.

Anal. Calcd. for $C_{24}H_{28}O_4N_4Cl_4As_2$: As, 20.58. Found: As, 20.13.

Dissolved in 20 cc. of water 0.5884 g. of the diarsyl tetrahydrochloride absorbed little or no oxygen in ten minutes. When sufficient 0.5 *N* sodium hydroxide solution (14 cc.) was added to form the tetra salt of the diarsyl, 10 cc. (N. T. P.) of the gas was absorbed in two minutes and after thirty-five minutes 37 cc. of oxygen had been absorbed.

4,4′-Dimethoxydiphenylarsinic Acid.—To a hot, aqueous suspension of 1 g. of 4,4′-dimethoxydiphenylbromoarsine,[14] stirred vigorously, there was added an aqueous solution of potassium permanganate until the latter was no longer decolorized; any excess of permanganate was reduced with alcohol. The mixture was filtered and the filtrate acidified to congo red; yield 0.7 g. of dimethoxy acid, m. p. 190–191° after recrystallization from acetic acid or water.

Anal. Calcd. for $C_{14}H_{15}O_4As$: As, 23.26. Found: As, 23.28.

In a second procedure the bromoarsine was suspended in hot 10% sodium hydroxide solution and treated with superoxol. After some time the material all dissolved. The arsinic acid precipitated when the solution was acidified.

When 1 g. of the arsinic acid, 4 cc. of acetic acid, 8 cc. of hydrobromic acid (48%) and a drop of hydriodic acid

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(10) Fargher[3] prepared the diamino acid by reduction of the dinitroarsinic acid with sodium hyposulfite but did not report a melting point.

(11) Fargher,[3] who prepared this compound in low yield by another method, reported the melting point to be 215° (corr.).

(12) Blicke and Webster, This Journal, **59**, 538 (1937).

(13) Fargher did not report the melting point of his hydrochloride which he prepared by another method.

(14) Blicke and Smith, *ibid.*, **51**, 1565 (1929).

was treated with sulfur dioxide the bromoarsine formed melted at 63–64°[15] after recrystallization from absolute alcohol. The bromoarsine was converted into tetra-(4-methoxyphenyl)-arsyl oxide when it was warmed for a short time with ammonia water; the oxide melted at 132–134°[16] after recrystallization from petroleum ether (90–100°).

3,3′ - Dinitro - 4,4′ - dimethoxydiphenylarsinic Acid.—Twelve grams of 4,4′-dimethoxydiphenylarsinic acid was nitrated in the same manner as the corresponding dihydroxy acid; yield 12.6 g. of the dinitro acid. The compound was recrystallized from acetic acid; when heated it softened about 220° and melted at 231° with decomposition.

Anal. Calcd. for $C_{14}H_{13}O_6N_2As$: As, 18.18. Found: As, 17.73.

3,3′ - Diamino - 4,4′ - dimethoxydiphenylarsinic Acid.—Ferrous hydroxide was prepared by the addition of 9.5 g. of 70% sodium hydroxide, dissolved in 36 cc. of water, to 23 g. of ferrous sulfate, dissolved in 66 cc. of water; 2 g. of the dinitro acid, dissolved in 20 cc. of water and 1.6 g. of sodium hydroxide, was added. After several hours the mixture was filtered, the filtrate shaken with charcoal, filtered and the filtrate acidified with acetic acid; yield 1.4 g.; the glistening crystals melted at 183–184° with decomposition after recrystallization from water.

Anal. Calcd. for $C_{14}H_{17}O_4N_2As$: As, 21.28. Found: As, 21.27.

Summary

A detailed study has been made of tetra-(3-amino-4-hydroxyphenyl)-diarsyl.

The preparation of 4,4′-dimethoxydiphenylarsinic acid and of 3,3′-diamino-4,4′-dihydroxydiphenylarsinic acid and some of their derivatives has been described.

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(15) Prepared by a different method Blicke and Smith[14] found the melting point to be 60–62°.

(16) Michaelis and Weitz [*Ber.*, **20**, 50 (1887)] obtained the oxide by a different procedure and recorded the melting point as 130°.

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Quassin. I. The Preparation and Purification of Quassin and Neoquassin, with Information Concerning their Molecular Formulas

BY E. P. CLARK

The bitter and presumably the physiologically active constituent of quassia wood or Surinam wood (*Quassia amara*) is known as quassin. This material was first obtained in crystalline form by Winckler[1] in 1835. Although it has since been investigated by others, little information of value concerning its nature has emerged; in fact, instead of clarifying the problem, these investigations have tended to confuse it.

The principal contributions to the subject have been made by Wiggers,[2] Christensen,[3] Oliveri and Denaro,[4] Oliveri,[5] and Massute.[6] As Christensen and Massute give comprehensive reviews of the subject, the present discussion will present only a résumé of the essential claims concerning the material.

Wiggers, the first to analyze quassin, found it to have 65.8% carbon and 6.94% hydrogen (recalculated on the basis of present atomic weight values). Christensen, who undoubtedly had a pure material, recorded its melting point as 205°, $[\alpha]^{18}D$ as +37.8° (*C*, 4.22 in chloroform), and its analysis according to the average of three combustions as 66.9% carbon and 7.44% hydrogen. He proposed the molecular formula $C_{31}H_{42}O_9$ for the material, and showed conclusively that it was not a glucoside. Finally, by boiling quassin for twelve hours with 3% sulfuric acid, he obtained a product which melted at 237° and gave upon combustion 66.87% carbon and 6.72% hydrogen.

Oliveri and Denaro had a material that melted at 210-211°, but in view of information which will be presented later they obviously had a mixture of several crystalline substances. They proposed the molecular formula $C_{32}H_{42}O_{10}$ or $C_{16}H_{22}O_5$ for their quassin, and claimed the formation of several anhydrides as the result of the action of dilute sulfuric acid and of acetic anhydride and sodium acetate upon their material. By heating quassin with concentrated hydrochloric acid in a sealed tube, they obtained methyl chloride and a crystalline material to which they assigned the formula $C_{28}H_{38}O_6(COOH)_2$, and which they called quassic acid. On the basis

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(1) F. L. Winckler, *Repert. pharm.*, [2] **4**, 85 (1835); **15**, 74 (1838).

(2) A. Wiggers, *Ann.*, **21**, 40 (1837).

(3) A. Christensen, *Arch. Pharm.*, **220**, 481 (1882).

(4) V. Oliveri and A. Denaro, *Gazz. chim. ital.*, **14**, 1 (1884); **15**, 6 (1885).

(5) V. Oliveri, *ibid.*, **17**, 570 (1887); **18**, 169 (1888).

(6) F. Massute, *Arch. Pharm.*, **228**, 147 (1890).