Anal. Calcd. for $C_{20}H_{30}O_3$: C. 75.43; H, 9.50. Found: C, 75.33; H, 9.54.

The **methyl ester** was prepared with diazomethane, and recrystallized from dilute acetone, m. p. 123.5–124.5°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H. 9.70. Found: C, 75.98; H, 9.79.

In order to make derivatives of the aldehyde, 1.3 g. of tetrahydrocafesterol acetate was distilled with zinc dust, the reaction product taken up in alcohol, and divided into two parts.

The **semicarbazone** was prepared according to the method of Shriner and Fuson.[19] Successive crystallizations from dilute methanol, dilute ethanol and finally methanol–benzene gave a compound melting at 217–218°.

Anal. Calcd. for $C_{21}H_{33}O_2N_3$: C, 70.16; H, 9.25; N, 11.69. Found: C, 70.22; H, 9.50; N, 11.75.

The *p*-**nitrophenylhydrazone**, prepared according to the method of Shriner and Fuson[19] was recrystallized from dilute alcohol, and ethyl acetate–methanol melting finally at 231–233°.

Anal. Calcd. for $C_{28}H_{35}O_3N_3$: N, 9.60. Found: N. 9.78.

Preliminary experiments showed that if the reaction with zinc dust was allowed to take place at pressures below 1.0 mm., or if the heating for distillation was too prolonged, the yield of aldehyde decreased considerably.

Ox-cafestanic acid was recovered unchanged when treated with hydrogen in acetic acid in the presence of platinum oxide catalyst and concentrated hydrochloric acid for five hours at 50 lb. and 60°.

Summary

Cafesterol contains a conjugated double-bond system as indicated by the addition of two moles of hydrogen, the facile formation of a maleic anhydride addition compound, and absorption spectra data.

The glycolic group in tetrahydrocafesterol acetate has been converted, by zinc dust distillation, into the aldehyde, ox-cafestanal; and subsequently, by oxidation, to ox-cafestanic acid.

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[19] Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2d ed., 1940.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Amidino Arsenicals. I. *p*-Amidinophenylarsonic Acid and 4,4′-Diamidinoarsenobenzene

BY FRED LINSKER[1] AND MARSTON TAYLOR BOGERT

Organic arsenicals, such as the arsphenamines (salvarsans), tryparsamide, acetarsone, mapharsen and carbarsone, have proved valuable in the treatment of syphilis, trypanosomiasis and amebiasis. Some also possess antimalarial properties. In the 1942 issue of the authoritative New and Nonofficial Remedies, of the American Medical Association, it is stated (p. 169) that "The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites. In this way they become available for combating trypanosomiasis, treponematosis, spirillosis and other protozoan infections."

As the result of the investigations of King, Yorke, Lourie, Hughes, Ewins and many others, as well as the May and Baker patents, a number of amidino derivatives have been found to possess useful curative properties for several tropical diseases, and a few are active against malaria.

The synthesis of compounds carrying both the amidino group and arsenic in their molecules, would seem to offer good possibilities of discovering within such a class some products of therapeutic value in dealing with tropical protozoal diseases. We have therefore initiated investigations in this direction because, so far as we are aware, no amidino arsenicals have as yet been described in the literature, and the present paper reports some of our experiments in this field.

As will be noted from the Flow Sheet, these first experiments follow familiar lines, paralleling syntheses and structures of well-known medicinals, but in which an amino has been replaced by an amidino group, an ethylene (—CH=CH—) by an arseno (—As=As—) union, or similar changes brought about, to yield organic amidino arsenicals as the final products.

One objection to arsphenamine (salvarsan), for example, has been always its acid reaction and consequent irritant effect when injected intravenously. It is so weak a base that its hydrochloride is easily hydrolyzed with liberation of hydrochloric acid. To protect the patient from this,

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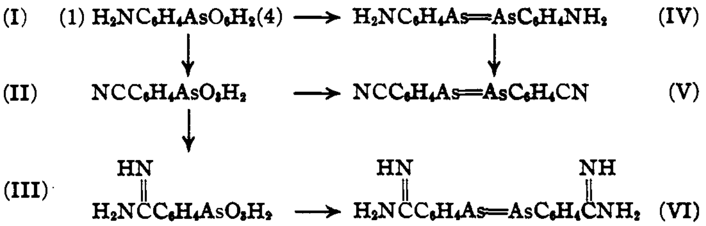
the drug is always "neutralized" with alkali before injection. Replacement of the amino in such arsenicals by the more strongly basic amidino group, would be expected to result in hydrochlorides more resistant to hydrolysis.

The *p*-amidinophenylarsonic acid (III) was selected as a pentavalent arsenical of arsanilic acid type; and the 4,4′-diamininoarsenobenzene (VI) as representing a 4,4′-diamidinostilbene with its —CH=CH— group replaced by tervalent arsenic as an —As=As— group.

These compounds are being subjected to pharmacological tests and the results will be published later. Many other amidino arsenicals are in course of preparation, and will be discussed in another contribution.

FLOW SHEET



Acknowledgments.—This investigation was made possible by the generous action of Merck & Co., Inc., Rahway, N. J., in establishing at Columbia University a research fellowship for the purpose of finding better agents in the treatment of certain tropical diseases. To Mr. Saul Gottlieb of the Columbia University Department of Chemistry, who carried out the requisite analyses, we are also under obligation.

Experimental

Unless otherwise stated, all melting points recorded have been corrected for thermometer stem exposure.

***p*-Cyanophenylarsonic Acid (II)**.—Arsanilic acid (I) was diazotized as described by Bertheim,[2] who also treated the diazo solution with cuprous cyanide solution, but failed to isolate the cyano arsonic acid.

Our process was as follows. A solution of 43 g. of *p*-arsanilic acid in 480 cc. of water and 52 cc. of hydrochloric acid (sp. gr. 1.12) was diazotized at low temperature with 67 cc. of 3 *N* sodium nitrite solution. The resulting diazonium chloride solution was poured slowly into a warm (70°) solution of 50 g. of $CuSO_4{\cdot}5H_2O$, 56 g. of potassium cyanide and 300 cc. of water. Upon completion of the reaction, the mixture was left for three hours in the refrigerator, the cuprous cyanide filtered out, and the filtrate concentrated under reduced pressure to a volume of 150 cc. After adding 20 cc. of concentrated hydrochloric acid, the *p*-cyanophenylarsonic acid was filtered out and washed with dilute hydrochloric acid. The product did not melt below 350°, was insoluble in water and dilute acids, but dissolved in alkali. When heated in strongly alkaline solution, hydrolysis occurred with evolution of ammonia and, on acidification, *p*-carboxyphenylarsonic acid precipitated. The latter was identified by its decomposition point (228°), which coincided with that recorded by LaCoste[3] for this acid. The cyanophenylarsonic acid was not further purified but was used directly for the next step. The yield was 37 g. or 82%.

***p*-Aminophenylarsonic Acid (III)**.—A suspension of 20 g. of finely pulverized dry *p*-cyanophenylarsonic acid in 40 g. of dry ether was treated with 6 cc. of absolute alcohol and the mixture then saturated with hydrogen chloride at 0°. The flask was then tightly stoppered and left for six days in the refrigerator, by which time all of the imino ether hydrochloride had precipitated. This was removed, washed with ether and dried; yield, 20 g. (74%).

The dry iminoether hydrochloride was pulverized and heated in a closed vessel with 200 cc. of 10% alcoholic ammonia for three hours at 60°. After cooling overnight, the amidine hydrochloride precipitate was collected, washed with alcohol and dried under diminished pressure; yield of *p*-amidinophenylarsonic acid hydrochloride, 15.2 g. (84%); m. p. 280° (dec.). This hydrochloride was dissolved in ammonium hydroxide solution, and the free acid precipitated by the addition of acetone. This precipitate was washed with water until free from chlorine and was then dried in an Abderhalden pistol at 50° and a pressure of 15–20 mm. The product consisted of small colorless scales, practically insoluble in water or ordinary neutral organic solvents, soluble in dilute caustic alkalies or ammonium hydroxide solution, as well as in dilute mineral acids. Its nitric acid solution gave no precipitate when a silver nitrate solution was added.

Anal. Calcd. for $C_7H_9O_3N_2As$: N, 11.5; As, 30.7. Found: N, 11.2; As, 30.6.

4,4′-Dicyanoarsenobenzene (V).—4,4′-Diaminoarsenobenzene (IV) was secured by the direct reduction of arsanilic acid with sodium hydrosulfite, as described by Ehrlich and Bertheim.[4] The yield of crude product (containing some sulfite) was 70%.

To a solution of 20 g. of sodium hydrosulfite in 100 cc. of water + 6 cc. of 10 *N* sodium hydroxide, there was added a solution of 10 g. of magnesium chloride in 20 cc. of water. The magnesium hydroxide was filtered out and the filtrate mixed with a solution of 2 g. of *p*-cyanophenylarsonic acid (II) in 2 cc. of 20% sodium hydroxide plus 40 cc. of water. The mixture was stirred vigorously for two hours at 55–60°, and a yellow precipitate separated gradually. This precipitate was collected by centrifuging, digested with water, to remove any excess of reagents, centrifuged again and dried over calcium chloride. The product formed yellow crystals, insoluble in water and in the organic solvents used, and decomposed above 260°. Heated with caustic alkali solution, ammonia was evolved. The yield from 2 g. of the arsonic acid was 0.7 g., or 43%.

Attempts to wash the compound free from sulfur proved

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(2) Bertheim, *Ber.*, **41**, 1857 (1908).

(3) LaCoste, *Ann.*, **208**, 5 (1881).

(4) Ehrlich and Bertheim, *Ber.*, **44**, 1264 (1911).

futile. It was therefore repeatedly dissolved in pyridine and precipitated by dilution with water. The precipitate was dried at 100° under diminished pressure. A sample warmed for five minutes with aqua regia, diluted with water, and treated with barium chloride solution, gave a precipitate of barium sulfate. Another sample, on analysis, showed the presence of 6.74% of nitrogen. The pure dicyanoarsenobenzene contains 7.9% of nitrogen, but a content of 2–3% of sulfur, which is stated to be the average impurity in such arsenical hydrosulfite reduction products, would bring the nitrogen content down to about 6.8%.

4-Amidino-4′-cyanoarsenobenzene, $H_2NC(=NH)C_6H_4$-As=AsC_6H_4CN.—A suspension of 0.5 g. of the dicyano compound (V) in a mixture of 5 cc. of dry ether and 0.5 cc. of absolute ethanol was saturated with dry hydrogen chloride and left for forty-eight hours in the refrigerator. Hydrogen chloride was driven off under diminished pressure and 10 cc. of alcoholic ammonia added to the residue. This mixture was heated in a closed flask for three hours at 40°, filtered, and the filtrate concentrated to a small volume. Precipitated ammonium chloride was filtered out and acetone added to the alcoholic filtrate. The pale yellow precipitate was purified by redissolving in alcohol and reprecipitating with acetone. The product then appeared in pale yellow prisms, after drying *in vacuo* at 50°, and was soluble in water or alcohol, but not appreciably in either acetone or ether. When heated, it darkened around 225°, began to decompose at 229°, and melted at about 234°. Like other arseno compounds, it crystallized with a molecule of solvent (alcohol); yield, about 40%.

Anal. Calcd. for $C_{14}H_{11}N_3As_2\cdot HCl\cdot C_2H_5OH$: N, 9.26. Found: N, 9.38.

The compound, therefore, is apparently the hydrochloride of the monoamidino derivative and not the expected diamidinoarsenobenzene. The result was the same when double the amount of absolute ethanol was used in the first stage of the reaction.

4,4′-Diamidinoarsenobenzene (VI).—Three methods suggest themselves for the preparation of this arsenical, *viz.*, (a) direct reduction of *p*-amidinophenylarsonic acid with sodium hydrosulfite ($Na_2S_2O_4$); (b) a similar reduction of *p*-cyanophenylarsonic acid to 4,4′-dicyanoarsenobenzene, followed by conversion of its cyano into amidino groups; (c) preparation of the 4,4′-dicyanoarsenobenzene from the 4,4′-diaminoarsenobenzene by the usual diazo reaction, and conversion of the cyano into the amidino compound as in (b).

(a) **By Reduction of *p*-Amidinophenylarsonic Acid.**—To a solution of 12 g. of sodium hydrosulfite in 60 cc. of water, there was added 3.6 cc. of a 10 *N* sodium hydroxide solution and 6 g. of $MgCl_2\cdot 6H_2O$ in 12 cc. of water. The precipitated magnesium hydroxide was filtered out and to the filtrate there was added slowly a suspension of 1.2 g. of *p*-amidinophenylarsonic acid in 30 cc. of water. The arsonic acid dissolved gradually and a yellow amorphous precipitate separated, whose amount increased considerably when the mixture was heated for two hours at 55–60° with vigorous stirring. When the mixture was cold, the bright yellow precipitate was filtered out and washed thoroughly with water; yield, 0.7 g.

When a portion of this yellow precipitate was dried in a desiccator over calcium chloride, it formed brown prisms, which gave a yellow powder when crushed, melted at 268° with decomposition, was chlorine-free, but contained appreciable amounts of sulfur, presumably in the form of the sulfite of the base. This sulfite was insoluble in water, dilute acids, or the organic solvents tried. It also resisted the usual treatment with methyl alcoholic hydrogen chloride, and only traces of it were dissolved by this reagent even on prolonged trituration in a mortar.

When another sample of the original yellow precipitate was rubbed up in a mortar with a sodium hydroxide (5 *N*) solution, its color changed almost immediately to a yellow-brown with a greenish cast, and was probably the free base. The alkaline filtrate from this solid contained sulfite. It was washed with water until free from alkali, and then triturated in a mortar with 10% hydrochloric acid. This restored the original bright yellow color of the precipitate, through formation of the hydrochloride, which salt was insoluble in dilute hydrochloric acid, but became soluble in water when all excess of acid was eliminated by repeated centrifuging and decantation. The acid-free compound dissolved in water to a yellow solution, from which acetone precipitated a yellow amorphous solid. Dried in a desiccator over calcium chloride, it formed small yellow plates, which melted with decomposition at 240°.

Anal. Calcd. for $C_{14}H_{14}N_4As_2\cdot 2HCl\cdot 4H_2O$: N, 10.5; As, 28.1. Found: N, 10.4; As, 27.8.

In agreement with other compounds of this type, this dihydrochloride, when precipitated from aqueous solution by acetone, crystallizes with 4 moles of water of crystallization. This is also in accord with the observation that benzamidine hydrochloride crystallizes with 2 moles of water.

Summary

1. *p*-Amidinophenylarsonic acid has been prepared from arsanilic acid, through the intermediate *p*-cyanophenylarsonic acid.

2. By hydrosulfite reduction of this arsonic acid, 4,4′-diamidinoarsenobenzene was obtained.

3. A similar reduction of *p*-cyanophenylarsonic acid, yielded 4,4′-dicyanoarsenobenzene.

4. An attempt to convert this dicyano compound into the diamidinoarsenobenzene resulted in the production of the 4-amidino-4′-cyanoarsenobenzene; *i. e.*, only one of the cyano groups of the initial compound participated in the reaction.

5. Certain of these amidino arsenicals are now being tested to determine their physiological effects.

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