resolidified, probably to the anhydride, which charred without melting. It was extremely resistant to hydrolysis. After heating in a pressure bottle with concentrated hydrochloric acid at 100°, the compound was recovered unchanged, and it was only partially hydrolyzed with cold concentrated sulfuric acid after twenty-four hours.

Anal. Calcd. for $C_6H_8NO_5SAs$: As, 26.7. Found: As, 26.3.

m-**Nitrophenylarsonic Acid.**—*m*-Nitroaniline, 138 g. (1 mole) gave 133.5 g. (54% yield) of *m*-nitrophenylarsonic acid, after one recrystallization from water.

3-Nitro-4-methylphenylarsonic Acid.—2-Nitro-4-aminotoluene gave a 40% yield of 3-nitro-4-methylphenylarsonic acid by the modified method.

m-**Carboxyphenylarsonic Acid.**—*m*-Aminobenzoic acid gave a 76% yield by the modified procedure.

Analyses of these last three substances for arsonic acid gave percentages of arsenic in close agreement with the theoretical requirements.

Attempted Preparation of *m*-Sulfophenylarsonic Acid.—When metanilic acid was subjected to the modified Bart reaction, no crystals separated from the aqueous solution. An attempt to isolate the compound by means of the barium salt yielded only *m*-phenolsulfonic acid. Similarly, 2,6-dimethyl- and 3,5-dimethylanilines gave only the corresponding xylenols when subjected to the modified Bart reaction. In the case of the 2,6- compound, this failure cannot be due to any steric factor, since 2,6-dimethylphenylarsonic acid was prepared in a 30% yield by the usual Bart procedure.

The advantage of the modified Bart procedure may be shown by the following percentage yield figures, the first figure in each case corresponding to the ordinary procedure and the second figure to the modified one: *p*-sulfamido,[1] 25, 57; *m*-sulfamido, 0, 58; *m*-nitro,[5a] 28, 54; 3-nitro-4-methyl,[5b] 15.5, 40; *m*-carboxy,[5a] 36.6, 76.

Summary

The method of Scheller for the preparation of arsonic acids by an alcoholic Bart reaction has been tried with a series of aromatic amines. With sulfamido-, carboxy-, or nitro-substituted amines the reaction gave larger yields of the arsonic acid than the usual Bart procedure, but with two dimethylanilines and metanilic acid, the modification did not prove applicable.

(5) (a) Bart, *Ann.*, **429**, 55 (1922); (b) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1580 (1918).

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The Preparation of Phenylarsenoxides in Relation to a Projected Study of their Chemotherapeutic Activity. I. Monosubstituted Derivatives

BY G. O. DOAK, HARRY EAGLE, AND H. G. STEINMAN

There is now a considerable body of evidence to show that the chemotherapeutic action of arsonic acids and arseno compounds is due to their conversion *in vivo* to the corresponding arsenoxide. Thus, Voegtlin and Smith[1] concluded that both the arsonic acids and the arseno compounds are not in themselves trypanocidal but become active only after conversion to the arsenoxides in the animal body. Further, Tatum and Cooper[2] have shown that "Mapharsen," 3-amino-4-hydroxyphenylarsenoxide, while much more toxic, actually possesses a higher therapeutic index than neoarsphenamine. More recently, Eagle[3] has shown that although the arsphenamines are directly treponemicidal *in vitro*, that activity is primarily due to their rapid oxidation in solution by molecular oxygen, and is either absent or minimal if the experiment is carried out under nitrogen.

While considerable work has been done in attempting to correlate the chemical structure and chemotherapeutic activity of arsonic acids and arseno compounds, the arsenoxides themselves have received much less attention. The present investigation was therefore undertaken in an attempt to correlate the chemical structure of the arsenoxides with their treponemicidal activity, using as the test organism *Treponema pallidum*, the causative agent of syphilis. Although the majority of investigators have hitherto used trypanosomes in testing arsenicals, compounds active against one species of trypanosome will not necessarily be active against *T. pallidum*,[4] or even against another species of trypanosome.[5] The chemical preparation and properties of the arsenoxides will be presented here; data relating to their treponemicidal activity, toxicity, and potential therapeutic utility will be published elsewhere.

The initial series consisted of the parent com-

(1) Voegtlin and Smith, *J. Pharmacol.*, **15**, 475 (1920).
(2) Tatum and Cooper, *ibid.*, **50**, 198 (1934).
(3) Eagle, *ibid.*, **66**, 423 (1939).
(4) Ehrlich and Hata, "The Experimental Chemotherapy of Spirilloses," Redman Co., New York, 1911, p. 126; Probey and McCoy, *U. S. Publ. Health Repts.*, **45**, 1716 (1930).
(5) Kuhs and Tatum, *J. Pharmacol.*, **61**, 451 (1937).

pound, phenylarsenoxide, the *o*-, *m*-, and *p*-monosubstituted methyl, carboxy, chloro, nitro, amino, and hydroxy derivatives, the *o*- and *p*-sulfophenyl arsenoxides, and *o*-iodophenyl-arsenoxide. For twelve of these compounds, work done in this Laboratory has merely confirmed previous descriptions in the literature. The *m*-chloro, *m*-amino, *m*-hydroxy, *o*-sulfo, and *o*-iodo compounds have not been previously reported. We have also obtained additional data on the three nitro arsenoxides, and slightly different results from those reported in the literature with the *o*-hydroxy and *o*-chloro compounds. The arsenoxides were prepared by reduction of the known arsonic acids in hydrochloric acid solution with sulfur dioxide and potassium iodide, followed by hydrolysis of the resulting dichloroarsine with ammonia or sodium bicarbonate. In the case of the sulfonic acids, hydrobromic acid was used in order to obtain the less soluble dibromoarsines.

There was a marked tendency for the arsenoxides to separate as sirups, particularly in the case of the meta compounds. In certain cases, these could be crystallized by the method suggested by Blicke and Smith,[6] but in other cases even this method failed to yield a crystalline compound. Except in a few cases, the arsenoxides did not melt, but charred above 250°, or softened without giving a definite melting point.

o-, *m*-, and *p*-nitrophenylarsonic acids reduced by sulfur dioxide in the usual manner gave the corresponding dichloroarsines, which yield the arsenous acids on hydrolysis with alkali.[7,8,9] It has been suggested that the presence of the nitro group prevents loss of water from the arsenous acid to form the arsenoxide. We found, however, that the *o*- and *p*-nitro compounds yielded the arsenoxides when reduced in suspension in dilute hydrochloric acid. The meta compound, however, gave only the arsenous acid. *o*-Nitro-phenylarsenoxide (or the arsenous acid) showed a curious anomaly in its pharmacological behavior, in that it dissolved in alkali to form a deep brown solution which no longer showed either the toxicity or activity of the typical arsenoxides. Unlike other arsenoxides, it could not be reprecipitated from such solutions with acid. When the alkaline solution was poured into a large excess of acetone, an oil formed which crystallized after standing for several days at −25°. Although these crystals analyzed for the composition $(NO_2C_6H_4As(ONa)_2 \cdot 2H_2O$, it seems unlikely that this is the correct formula, for when buffered with bicarbonate, the compound could not be titrated with iodine. By exposing *o*-nitrophenylarsenoxide to sunlight, Karrer[10] obtained a brown compound which he believed to be the *o*-nitrosoarsonic acid, formed by migration of one oxygen atom from the nitrogen to the arsenic. The compound we obtained, unlike Karrer's compound, did not give an insoluble magnesium salt under any conditions. It is accordingly unlikely that it is an arsonic acid. The remarkable color change on dissolving the arsenoxide in alkali suggests quinoid formation.

(6) Blicke and Smith, THIS JOURNAL, **51**, 3479 (1929).
(7) Bart, *Ann.*, **429**, 55 (1922).
(8) Kalb, *ibid.*, **423**, 39 (1921).
(9) Michaelis and Loesner, *Ber.*, **27**, 263 (1894).

Experimental Part

p-Nitrophenylarsenoxide.—*p*-Nitrophenylarsonic acid was precipitated in a finely divided state by the addition of dilute hydrochloric acid to a 10% aqueous solution of the sodium salt. When reduced with sulfur dioxide and potassium iodide, the arsenoxide was obtained as a white solid, in contrast to the yellow *p*-nitrophenylarsenous acid.

Anal. Calcd. for $C_6H_4NO_3As$: As, 35.2; N, 6.6. Found; As, 35.1; N, 6.7.

o-Nitrophenylarsenoxide.—The reduction of 10 g. of sodium *o*-nitrophenylarsonate in a similar manner gave *o*-nitrophenylarsenoxide as a light yellow powder.

Anal. Calcd. for $C_6H_4NO_3As$: As, 35.2; N, 6.6. Found: As, 35.1; N, 6.2.

The **disodium salt**, which may have a quinoid structure, was prepared by the addition of acetone to an alkaline solution of the arsenoxide. The oily precipitate crystallized after several days at −25°. These crystals tended to become oily on exposure to air, and it was difficult to wash free from alkali.

Anal. Calcd. for $C_6H_4NO_4Na_2As \cdot 2H_2O$: As, 24.2; Na, 14.8; water, 11.6. Found: As, 23.5; Na, 15.2; loss at 100°, 10.3.

The reduction of *m*-nitrophenylarsonic acid by the same method gave only *m*-nitrophenylarsenous acid,[9] which did not lose water at 100°.

Anal. Calcd. for $C_6H_6NO_4As$: As, 32.4; N, 6.1. Found: As, 32.7, N, 6.1.

m-Aminophenylarsenoxide.—The reduction of 10 g. of *m*-aminophenylarsonic acid in concentrated hydrochloric acid gave the dichloroarsine hydrochloride as a white crystalline solid. On the addition of ammonia, this gave the oxide as an amorphous solid, which was purified by dissolving in dilute hydrochloric acid and again precipitating with ammonia. Although the compound could be crystallized from alkaline solution by the addition of saturated salt solution, it was difficult to wash the crystals free from salt because of their solubility. It is soluble in acids, alkali, water, excess ammonium hydroxide, and organic solvents. It softened at 62° (cor.) without giving a definite melting point.

(10) Karrer, *ibid.*, **47**, 1783 (1914).

Anal. Calcd. for C_6H_6ONAs: As, 40.9. Found: As, 40.8.

m-**Hydroxyphenylarsenoxide.**—The *m*-dichloroarsine, obtained as a yellow oil, was dissolved in ether and neutralized with sodium carbonate solution. The ether layer was dried with anhydrous sodium sulfate and evaporated. The sirupy arsenoxide thus obtained contained two moles of water which were lost only after heating at 150° for twelve hours. The resulting compound was a brittle, pulverulent mass.

Anal. Calcd. for $C_6H_5O_2As \cdot 2H_2O$: As, 34.0. Found: As, 34.2. Calcd. for $C_6H_5O_2As$: As, 40.7. Found: As, 40.9.

o-**Hydroxyphenylarsenoxide.**—This compound, previously described by Kalb[8] as the anhydride, was obtained as the crystalline arsenoxide when the dichloroarsine was treated with ammonia. It melted at 182–184° (cor.) and gave no coloration with ferric chloride. If a drop of hydrogen peroxide was added to a solution of the oxide containing ferric chloride, a deep wine color was produced, characteristic of *o*-hydroxyphenylarsonic acid.

Anal. Calcd. for $C_6H_5O_2As$: As, 40.7. Calcd. for $C_{12}H_8O_3As_2$: As, 42.8. Found: As, 40.5.

m-**Chlorophenylarsenoxide.**—The dichloroarsine, obtained as a yellow oil, gave the oxide as a sirup on treatment with sodium bicarbonate solution. It could not be crystallized by the method of Blicke and Smith. When dissolved in alcohol and poured into ice water, the oxide separated as a white powder which again became sirupy on removal of the water.

Anal. Calcd. for C_6H_4OClAs: As, 37.0. Found: As, 36.6.

o-**Chlorophenylarsenoxide.**—This compound, recently described by Hiratuka,[11] who gives a melting point of 140–150°, was obtained by reduction of the arsonic acid in methyl alcohol and precipitation of the dichloroarsine with water. Subsequent treatment with ammonia gave the oxide as an amorphous solid, purified by dissolving in sodium hydroxide solution and reprecipitating with dilute hydrochloric acid. The resulting compound was a white powder. It softened at 208° (cor.) without giving a definite melting point.

(11) Hiratuka, *J. Chem. Soc. Japan.*, **58**, 1051 (1937); *C. A.*, **33**, 157 (1939).

Anal. Calcd. for C_6H_4OClAs: As, 37.0. Found: As, 36.8.

Sodium Salt of *o*-**Sulfophenylarsonic Acid.**—*o*-Sulfophenylarsonic acid was isolated by Barber[12] as the barium salt in 90–95% yield by treating *o*-iodophenylarsonic acid with sodium sulfite and precipitating the barium salt with barium chloride. We have prepared the disodium salt in 95% yield by refluxing the iodoarsonic acid with sodium sulfite, making the resulting solution just acid to litmus, and precipitating with alcohol. The compound was recrystallized by dissolving in water and again precipitating with alcohol.

Anal. Calcd. for $C_6H_6O_6SAsNa_2 \cdot H_2O$: As, 21.3; Na, 13.4; water, 5.2. Found: As, 21.5; Na, 12.7; loss at 100°, 5.1.

Sodium Salt of *o*-**Sulfophenylarsenoxide.**—The disodium salt described in the preceding paragraph, 10 g. in hydrobromic acid solution, was reduced, and the solution evaporated to 30 cc., when the dibromoarsine crystallized from the solution. After recrystallization, this was treated with sodium hydroxide, made acid to litmus with hydrochloric acid, and evaporated to dryness. The arsenoxide was separated from the sodium bromide by successive extractions with absolute alcohol.

Anal. Calcd. for $C_6H_4O_4SAsNa$: As, 27.7. Found: As, 27.9.

o-**Iodophenylarsenoxide.**—*o*-Iodophenylarsonic acid reduced in the usual manner and treated with sodium hydroxide gave *o*-iodophenylarsenoxide as a white powder. It softens at 263° and melts at 267°.

Anal. Calcd. for C_6H_4OIAs: As, 25.5. Found: As, 25.3.

Summary

A series of monosubstituted phenylarsenoxides has been prepared with a view to studying their action against *Treponema pallidum*. Five new compounds have been described, and additional data have been obtained on some of the known arsenoxides.

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(12) Barber, *J. Chem. Soc.*, 2047 (1930).