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

## Arsonium Compounds. III<sup>1</sup>

BY F. F. BLICKE AND S. R. SAFIR<sup>2</sup>

The most widely used organic arsenicals are of the arseno or arsonic acid type, although one arsenic acid (cacodylic acid) and one arsine oxide (mapharsen) have found extensive application as medicaments.

As far as we are aware no statement has appeared in the literature relative to the effectiveness of arsonium compounds as therapeutic agents. This subject deserves attention, especially because of the introduction of the quaternary nitrogen antiseptic zephiran.<sup>3</sup>

Preliminary tests<sup>4</sup> indicated that tetraphenylarsonium chloride is of little value as a germicide. However, it seemed that more active products of this type might be obtained by the introduction of nuclear hydroxyl and amino groups.

In this paper we have described the preparation of a number of hydroxy, amino and hydroxy-amino derivatives of trimethylphenyl- and dimethyldiphenylarsonium salts many of which crystallize in the form of beautiful glistening needles. The compounds obtained, and the methods of synthesis, are illustrated by schemes A, B and C in which R represents a methyl group.

Through the kind coöperation of Parke, Davis and Company we obtained the following pharmacological data from Dr. Gruhzt, who tested the

compounds on rats. In the case of trimethyl-3-aminophenylarsonium chloride the M. T. D. is 30 mg./kg.; the M. L. D. is 40 mg./kg. At a dosage level of 10 mg./kg. the compound affords no protection against *T. equiperdum* infection when administered intravenously.

For trimethyl-3-amino-4-hydroxyphenylarsonium chloride the M. T. D. is 70-80 mg./kg. There is no trypanocidal effect at 50 mg./kg. Furthermore, no germicidal action was noticed with a 1-100 concentration (pH 2.07) against *B. typhosus* or *Staph. aureus* when the pH of the solution was adjusted to 6.75.

### Experimental Part

**Trimethylphenylarsonium Nitrate (III).**—Dimethylphenylarsine (I)<sup>5</sup> was converted, by methyl iodide, into trimethylphenylarsonium iodide<sup>6</sup> (II). According to a general procedure, 5 g. (0.015 mole) of the latter, 3.6 g. (0.015 mole) of silver oxide and 75 cc. of water were shaken for twelve hours, filtered, the filtrate neutralized with the required acid (nitric) and evaporated to dryness. The colorless, crystalline nitrate was dissolved in absolute alcohol and precipitated by absolute ether; yield at least 88%.

**Trimethyl-3-nitrophenylarsonium Nitrate (IV), Iodide (V) and Chloride (VI).**—To a cold mixture of 2.5 cc. of nitric acid (sp. gr. 1.60) and 5.5 cc. of concd. sulfuric acid there was added, in portions, 5 g. of trimethylphenylarsonium nitrate. The mixture was heated on a steam-bath for ten minutes, then poured onto ice; yield 5 g.

Twenty grams of the nitrate, dissolved in 200 cc. of water, was treated with 50 g. of solid sodium iodide whereupon the arsonium iodide precipitated in quantitative yield.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by S. R. Safir in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

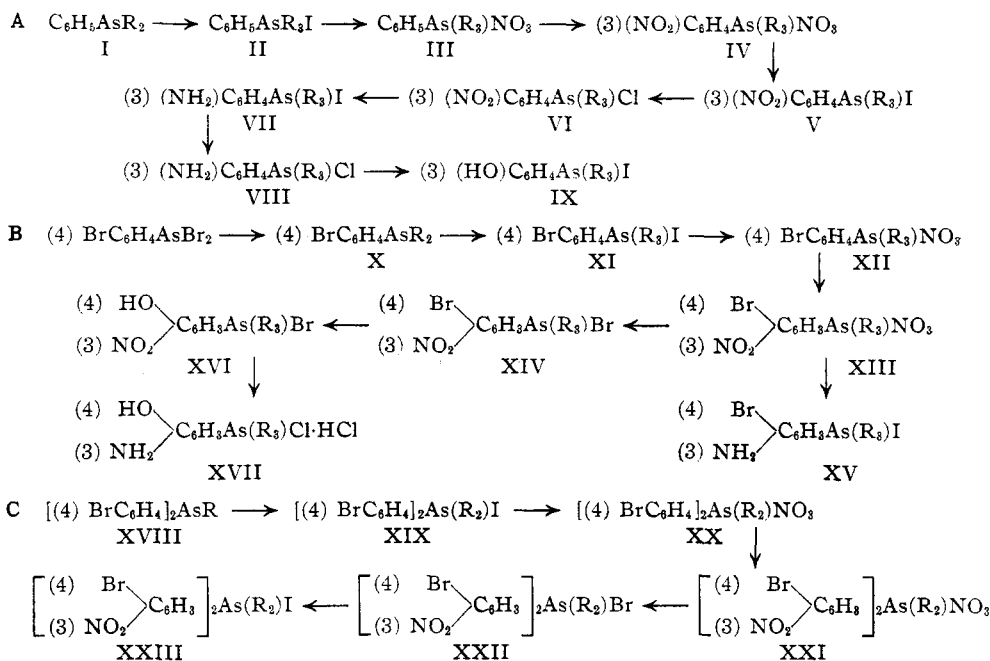
(2) Parke, Davis and Company Fellow.

(3) It is claimed (U. S. Patent 2,155,504) that certain sulfonium compounds are disinfectants.

(4) Supplied through the courtesy of Parke, Davis and Company.

(5) Winmill, *J. Chem. Soc.*, **101**, 722 (1912).

(6) Michaelis and Link, *Ann.*, **207**, 205 (1881).



The chloride was obtained from 2 g. of the iodide, 100 cc. of water, 2 g. of silver oxide and hydrochloric acid in the manner described above.

**Trimethyl-3-aminophenylarsonium Iodide (VII) and Chloride (VIII).**—To 10 g. of trimethyl-3-nitrophenylarsonium chloride, suspended in 150 cc. of acetic acid, there was added 38 g. of powdered stannous chloride dihydrate and the mixture was saturated with hydrogen chloride; the mixture became hot but the chloride did not seem to dissolve. It was cooled, the material filtered on a Jena funnel, dissolved in 100 cc. of warm water and treated with 60 cc. of 20% sodium hydroxide solution. To the clear, yellow solution there was added 20 g. of solid sodium iodide; 8 g. of the iodide precipitated.

The 3-acetylamino compound precipitated quantitatively after 1 g. of the iodide had been boiled for several minutes with 3 cc. of acetic anhydride.

The iodide was converted into the chloride and the latter into its acetylamino derivative by processes already described.

**Trimethyl-3-hydroxyphenylarsonium Iodide (IX).**—A solution of 4.2 g. of trimethyl-3-aminophenylarsonium chloride in 75 cc. of water and 2.5 cc. of concd. sulfuric acid was cooled to 0° and diazotized with 1.2 g. of sodium nitrite. After twelve hours the mixture was heated on a steam-bath until no more nitrogen was evolved, the solution neutralized with sodium hydroxide and a few drops of hydriodic acid and 20 g. of solid sodium iodide added after which 5.5 g. of the arsonium iodide precipitated.

**Trimethyl-4-bromophenylarsonium Iodide (XI) and Nitrate (XII).**—A mixture of 33 g. of dimethyl-4-bromophenylarsine (X)<sup>7</sup> and 15 cc. of methyl iodide was heated for twelve hours on a steam-bath, the excess methyl iodide removed and the residue triturated with ether; yield 49 g. (96%).

The nitrate was prepared from the iodide with the aid of silver oxide in the general manner described above.

**Trimethyl-3-nitro-4-bromophenylarsonium Nitrate (XIII) and Bromide (XIV).**—Five grams of trimethyl-4-bromophenylarsonium nitrate was added, in small portions, to a mixture of 3 cc. of nitric acid (sp. gr. 1.60) and 7 cc. of concd. sulfuric acid, the solution heated for one-half hour on a steam-bath and poured into ice water. The solution was then heated to 80° and treated with solid sodium nitrate until it became cloudy; yield of precipitated nitrate 5 g. (88%).

When 5 g. of solid sodium bromide was added to 2 g. of the nitrate, dissolved in 25 cc. of water, the bromide precipitated quantitatively.

**Trimethyl-3-amino-4-bromophenylarsonium Iodide (XV).**—To 3.0 g. of trimethyl-3-nitro-4-bromophenylarsonium bromide, suspended in 50 cc. of acetic acid, there was added 10.2 g. of stannous chloride dihydrate and the mixture saturated with hydrogen chloride. After one hour the material was filtered through a Jena filter, the product suspended in water and treated with excess 20% sodium hydroxide solution. Solid sodium iodide was added to the clear solution and the precipitated arsonium iodide washed with dilute sodium hydroxide and then with water.

**Trimethyl-3-nitro-4-hydroxyphenylarsonium Bromide (XVI) and Nitrate.**—A solution of 2.2 g. of trimethyl-3-nitro-4-bromophenylarsonium bromide in 15 cc. of water was boiled for one hour with 0.7 g. of potassium hydroxide, cooled and neutralized with hydrobromic acid whereupon the 4-hydroxy bromide precipitated; yield 1.8 g.

A solution of 1.0 g. of trimethyl-3-nitro-4-bromophenylarsonium nitrate in 6 cc. of water which contained 0.3 g. of potassium hydroxide was boiled for one hour, cooled, acidified with nitric acid, the product filtered, suspended in a small amount of hot water and sodium nitrate added; the arsonium nitrate separated from the cold solution.

(7) Blicke and Safir, *THIS JOURNAL*, **63**, 575 (1941).

TABLE I  
 SUBSTITUTED TRIMETHYLPHENYL- AND DIMETHYLDIPHENYLARSONIUM SALTS

Compound R = phenylarsonium	Recrystallized from	M. p., °C.	Formula	Analyses, %			
				Arsenic		Halogen	
				Calcd.	Found	Calcd.	Found
Trimethyl-							
R nitrate	Abs. alc. + abs. eth.	194-196 <sup>a</sup>	C <sub>9</sub> H <sub>14</sub> O <sub>3</sub> NAs	28.92	28.78		
3-Nitro-R							
Nitrate	Water	278-279 <sup>b</sup>	C <sub>9</sub> H <sub>13</sub> O <sub>6</sub> N <sub>2</sub> As	24.64	24.46		
Iodide	Water	286-290 <sup>b</sup>	C <sub>9</sub> H <sub>13</sub> O <sub>2</sub> NAsI	20.31	20.25	34.41	34.24
Chloride	Abs. alc. + abs. eth.	263-270 <sup>b</sup>	C <sub>9</sub> H <sub>13</sub> O <sub>2</sub> NAsCl	26.99	26.90	12.78	12.87
3-Amino-R							
Iodide	Abs. alc. + KOH	175-176	C <sub>9</sub> H <sub>15</sub> NAsI	22.10	21.94	37.44	37.38
Chloride	Abs. alc. + abs. eth.	243-244 <sup>b</sup>	C <sub>9</sub> H <sub>15</sub> NAsCl	30.27	30.11	14.33	14.37
3-Acetylamino-R							
Iodide	Abs. alc.	242-246 <sup>b</sup>	C <sub>11</sub> H <sub>17</sub> ONAsI	19.66	19.53	33.31	33.17
Chloride	Abs. alc.	256-258 <sup>b</sup>	C <sub>11</sub> H <sub>17</sub> ONAsCl	25.88	25.70	12.25	12.26
3-Hydroxy-R							
Iodide	Acetic acid	208-211 <sup>b</sup>	C <sub>9</sub> H <sub>14</sub> OAsI	22.04	21.90	37.34	37.36
4-Bromo-R							
Iodide	Abs. alc.	253-255 <sup>b</sup>	C <sub>9</sub> H <sub>13</sub> AsBrI			31.50	31.43
Nitrate	Abs. alc. + abs. eth.	163-165	C <sub>9</sub> H <sub>13</sub> O <sub>3</sub> NAsBr	22.17	22.20	23.65	23.54
3-Nitro-4-bromo-R							
Nitrate	Water	176-181 <sup>b</sup>	C <sub>9</sub> H <sub>12</sub> O <sub>6</sub> N <sub>2</sub> AsBr	19.56	19.61	20.87	21.07
Bromide	Water	255-275 <sup>b</sup>	C <sub>9</sub> H <sub>12</sub> O <sub>2</sub> NAsBr <sub>2</sub>	18.69	18.72	39.86	40.04
3-Amino-4-bromo-R							
Iodide	Water	235-237 <sup>b</sup>	C <sub>9</sub> H <sub>14</sub> NAsBrI			30.37	30.24
3-Nitro-4-hydroxy-R							
Bromide	Water	269-271 <sup>b</sup>	C <sub>9</sub> H <sub>13</sub> O <sub>3</sub> NAsBr	22.17	22.24	23.65	23.76
Nitrate	Water	225 <sup>b</sup>	C <sub>9</sub> H <sub>13</sub> O <sub>6</sub> N <sub>2</sub> As	23.41	23.22		
3-Amino-4-hydroxy-R							
Chloride HCl	Abs. alc. + abs. eth.	211-215 <sup>b</sup>	C <sub>9</sub> H <sub>16</sub> ONAsCl <sub>2</sub>	24.97	24.97	23.64	23.58
Dimethyl-							
Di-(4-bromophenyl)-arsonium							
Iodide	Water	221-224	C <sub>14</sub> H <sub>14</sub> AsBr <sub>2</sub> I			23.34	23.40
Nitrate	Water	195-196	C <sub>14</sub> H <sub>14</sub> O <sub>3</sub> NAsBr <sub>2</sub>	15.64	15.75	33.37	33.44
Di-(3-nitro-4-bromophenyl)-arsonium							
Nitrate	Water	206-207 <sup>b</sup>	C <sub>14</sub> H <sub>12</sub> O <sub>7</sub> N <sub>3</sub> AsBr <sub>2</sub>	13.17	13.10	28.09	28.05
Bromide	Water	183-185 <sup>b</sup>	C <sub>14</sub> H <sub>12</sub> O <sub>4</sub> N <sub>2</sub> AsBr <sub>3</sub>	12.76	12.67	40.86	40.63
Iodide	Water	169-170 <sup>b</sup>	C <sub>14</sub> H <sub>12</sub> O <sub>4</sub> N <sub>2</sub> AsBr <sub>2</sub> I			20.02	19.87

<sup>a</sup> Razuvaev, Malinovskii and Godina (*J. Gen. Chem. U. S. S. R.*, **5**, 721 (1935); *C. A.*, **30**, 1059 (1936)); found 195-196°.

<sup>b</sup> Decomposition.

**Trimethyl - 3 - amino - 4 - hydroxyphenylarsonium Chloride Hydrochloride (XVII).**—A suspension of 10.2 g. of trimethyl-3-nitro-4-hydroxyphenylarsonium bromide and 30.6 g. of stannous chloride dihydrate in 225 cc. of acetic acid was saturated with a rapid stream of hydrogen chloride. The tin double salt of the amino compound began to separate before all of the material had dissolved. The product was filtered, washed with acetic acid, suspended in 100 cc. of water and treated with hydrogen sulfide. After removal of the inorganic sulfide the clear, colorless filtrate was evaporated to dryness and the crude chloride hydrochloride, which weighed 7.5 g., dissolved in absolute alcohol and precipitated by dry ether. The product, which seemed to contain solvent of crystallization, was dried at 150° for analysis.

**Dimethyldi-(4-bromophenyl)-arsonium Iodide (XIX) and Nitrate (XX).**—A mixture of 5 g. of methyldi-(4-bromophenyl)-arsine (XVIII)<sup>7</sup> and 3 cc. of methyl iodide was heated for twelve hours on a steam-bath, the excess methyl iodide removed and the iodide recrystallized; yield 6 g.

The iodide was converted into the nitrate in 88% yield by the general procedure.

**Dimethyldi - (3 - nitro - 4 - bromophenyl) - arsonium Nitrate (XXI) and Bromide (XXII).**—Five grams of dimethyldi-(4-bromophenyl)-arsonium nitrate was added, in portions, to a cold mixture of 3.5 cc. of nitric acid (sp. gr. 1.60) and 8 cc. of concd. sulfuric acid, the mixture heated for fifteen minutes on a steam-bath, poured into ice water and the gummy precipitate heated to 50° with a small amount of water whereupon it became crystalline; yield 5.9 g.

In order to obtain the arsonium bromide 25 g. of sodium bromide was added to a boiling solution of 7 g. of the nitrate in 200 cc. of water; yield 7.2 g.

**Dimethyldi - (3 - nitro - 4 - bromophenyl) - arsonium Iodide (XXIII).**—(a) A solution of 0.5 g. of methyldi-(3-nitro-4-bromophenyl)-arsine<sup>7</sup> in 2 cc. of methyl iodide was heated on a steam-bath for four days; the arsonium iodide separated in quantitative yield.

(b) The arsonium bromide was treated with silver oxide

and the arsonium hydroxide neutralized with hydriodic acid.

### Summary

Methods for the preparation of a number of

hydroxy, amino and hydroxyamino derivatives of trimethylphenyl- and dimethyldiphenylarsonium salts have been described.

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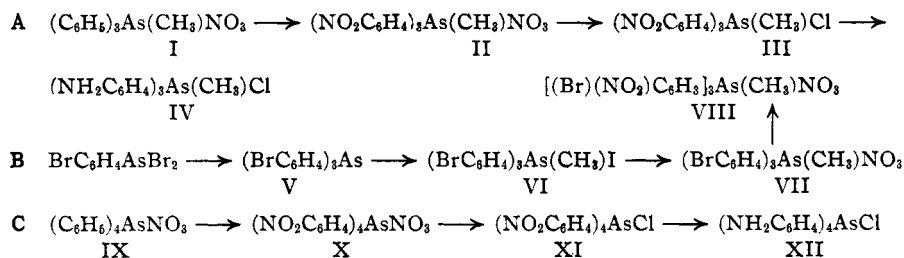
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## Arsonium Compounds. IV<sup>1</sup>

By F. F. BLICKE AND S. R. SAFIR<sup>2</sup>

A previous paper<sup>3</sup> in this series dealt with the preparation of hydroxy, amino and hydroxy-amino derivatives of trimethylphenyl- and dimethyldiphenylarsonium salts. In this article we have described amino derivatives of methyltriphenyl- and tetraphenylarsonium salts.

Some of the products and the methods by means of which they were obtained are shown by schemes A, B and C.



Through the courtesy of Parke, Davis and Company, Dr. Gruhitz supplied us with the following pharmacological data. When tetra-(4-aminophenyl)-arsonium chloride was tested on rats the M. T. D. was found to be 20 mg./kg. and the M. L. D. 30 mg./kg. At a dosage level of 10 mg./kg. there was no protection against *T. equiperdum* infection in rats when the compound was administered intravenously.

### Experimental Part

**Methyltri - (3 - nitrophenyl) - arsonium Nitrate (II) and Chloride (III).**—Methyltriphenylarsonium nitrate (I) was nitrated according to the directions of Michaelis<sup>4</sup>; however, the crude, orange, gummy nitration product was not treated with alcohol as he advised but merely heated with a small amount of water to 55° whereupon it became granular. The yield after treatment with charcoal and re-

crystallization from water was 80% of the calcd. amount. The colorless crystals melted at 197–198°.<sup>5</sup>

Seven grams of the arsonium nitrate, dissolved in 225 cc. of hot water, was treated with 50 g. of solid sodium chloride. The arsonium chloride separated from the cold solution as an oil which solidified when rubbed. The material was dissolved in 300 cc. of warm water, the solution cooled to 0°, stirred and sodium chloride added to precipitate the chloride.

**Methyltri - (3 - aminophenyl) - arsonium Chloride (IV) and Iodide.**—Sixty-three grams of powdered stannous

chloride dihydrate was added to 10 g. of methyltri-(3-nitrophenyl)-arsonium chloride, dissolved in 140 cc. of acetic acid, and the mixture saturated with a rapid stream of hydrogen chloride. All of the material dissolved and then the crystalline tin salt addition product of the amino compound precipitated. The latter was filtered on a Jena filter and treated with 60 cc. of 20% sodium hydroxide solution. The gummy product was cooled to -5° and rubbed whereupon it became crystalline. The product was dissolved in 50 cc. of absolute alcohol and an alcoholic solution of mercuric chloride added until no more material precipitated. The mercuric chloride addition product of the amino chloride was treated with charcoal and recrystallized from methyl alcohol; m. p. 191–192°. Fourteen grams of this product was suspended in 200 cc. of warm water, treated with hydrogen sulfide, the mercuric sulfide filtered and the filtrate concentrated to a small volume whereupon 5 g. of the amino chloride separated.

In order to obtain the arsonium iodide, the chloride was dissolved in water and solid sodium iodide added to the solution.

The 3-acetyl-amino compound was obtained when 2.0 g. of the arsonium chloride and 4 cc. of acetic anhydride was boiled for three minutes and then allowed to remain at room temperature for three days. The crystalline product

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by S. R. Safir in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Parke, Davis and Company Fellow.

(3) Blicke and Safir, *THIS JOURNAL*, **63**, 575 (1941).

(4) Michaelis, *Ann.*, **321**, 169 (1902).

(5) The yellow powder described by Michaelis melted at 195°.