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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[Contribution from the College of Pharmacy, University of Michigan]

Arsonium Compounds. IV[1]

By F. F. Blicke and S. R. Safir[2]

A previous paper[3] in this series dealt with the preparation of hydroxy, amino and hydroxyamino 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.

$$\begin{tikzcd}[column sep=small]
\mathbf{A} & \underset{\text{I}}{(C_6H_5)_3As(CH_3)NO_3} \arrow[r] & \underset{\text{II}}{(NO_2C_6H_4)_3As(CH_3)NO_3} \arrow[r] & \underset{\text{III}}{(NO_2C_6H_4)_3As(CH_3)Cl} \arrow[r] & {} \\
 & \underset{\text{IV}}{(NH_2C_6H_4)_3As(CH_3)Cl} & & & \underset{\text{VIII}}{[(Br)(NO_2)C_6H_3]_3As(CH_3)NO_3} \\
\mathbf{B} & BrC_6H_4AsBr_2 \arrow[r] & \underset{\text{V}}{(BrC_6H_4)_3As} \arrow[r] & \underset{\text{VI}}{(BrC_6H_4)_3As(CH_3)I} \arrow[r] & \underset{\text{VII}}{(BrC_6H_4)_3As(CH_3)NO_3} \arrow[u] \\
\mathbf{C} & \underset{\text{IX}}{(C_6H_5)_4AsNO_3} \arrow[r] & \underset{\text{X}}{(NO_2C_6H_4)_4AsNO_3} \arrow[r] & \underset{\text{XI}}{(NO_2C_6H_4)_4AsCl} \arrow[r] & \underset{\text{XII}}{(NH_2C_6H_4)_4AsCl}
\end{tikzcd}$$

Through the courtesy of Parke, Davis and Company, Dr. Gruhzit 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[4]; 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 recrystallization from water was 80% of the calcd. amount. The colorless crystals melted at 197–198°.[5]

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-acetylamino 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

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[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°.

TABLE I

SUBSTITUTED METHYLTRIPHENYL- AND TETRAPHENYLARSONIUM SALTS

Compound, A = arsonium	Recrystn. solvent	M. p., °C.	Formula	Analyses, % Arsenic Calcd.	Arsenic Found	Halogen Calcd.	Halogen Found
Methyltri-(3-nitrophenyl)-A chloride	Water	130[a]	$C_{19}H_{15}O_6N_3AsCl$	15.24	15.23	7.21	6.92
(3-Aminophenyl)-A chloride	Water	198–200	$C_{19}H_{21}N_3AsCl$	18.65	18.57	8.83	8.74
(3-Aminophenyl)-A iodide	Water	167–169	$C_{19}H_{21}N_3AsI$	15.19	15.12	25.74	25.80
(3-Acetylaminophenyl)-A chloride	Water	181–190[b]	$C_{25}H_{27}O_3N_3AsCl$	14.20	14.18	6.72	6.65
(3-Methoxyphenyl)-iodide	Abs. alc. + abs. eth.	120–121	$C_{22}H_{24}O_3AsI$	13.93	13.83	23.59	23.61
(4-Bromophenyl)-A iodide	Abs. alc. + KOH	178–180	$C_{19}H_{15}AsBr_3I$			18.53	18.40
Nitrate	Water	187–195[c]	$C_{19}H_{15}O_3NAsBr_3 \cdot H_2O$	11.74	11.59	37.60	37.50
(3-Nitro-4-bromophenyl)-A nitrate	50% acetone	175–177[b]	$C_{19}H_{12}O_9N_4AsBr_3$	9.92	9.84	31.77	31.50
Tetra-(3-nitrophenyl)-A							
nitrate	Water + $NaNO_3$	248–256[b]	$C_{24}H_{16}O_{11}N_5As$	11.99	12.12		
Chloride[d]	Abs. alc. + abs. eth.	235–239[b]	$C_{24}H_{16}O_8N_4AsCl$	12.52	12.47	5.92	5.92
Bromide	Water + NaBr	252–258[b]	$C_{24}H_{16}O_8N_4AsBr$	11.65	11.86	12.43	12.24
Iodide	Acetone–water	235–237[b]	$C_{24}H_{16}O_8N_4AsI$	10.86	10.81	18.39	18.32
(3-Aminophenyl)-A							
chloride	Water	>325	$C_{24}H_{24}N_4AsCl$	15.66	15.64	7.41	7.45
Bromide	Water	>325	$C_{24}H_{24}N_4AsBr$	14.33	14.29	15.28	15.32
(3-Acetylaminophenyl)-A chloride	Abs. alc.	172–220[b]	$C_{32}H_{32}O_4N_4AsCl$	11.59	11.33	5.48	5.38

[a] Softens at 80°, foams at 100°, all decomposed at 130°. [b] Decomposition. [c] The compound softens and apparently loses water of crystallization between 91 and 105°. [d] Dried at 160° to remove what was apparently alcohol of crystallization.

which had separated was filtered and ether added to the filtrate to precipitate dissolved material; yield 2.0 g.

Methyltri-(3-methoxyphenyl)-arsonium Iodide.—Three grams of tri-(3-methoxyphenyl)-arsine[6] and 5 cc. of methyl iodide was heated on a steam-bath for fourteen hours, the excess methyl iodide removed and the oily residue cooled and rubbed whereupon it became crystalline.

Methyltri-(4-bromophenyl)-arsonium Iodide (VI) and Nitrate (VII).—A mixture of 10.8 g. of tri-(4-bromophenyl)-arsine (V)[7] and 5 cc. of methyl iodide was heated for twenty-four hours on a steam-bath. The arsonium iodide was washed with ether and recrystallized from absolute alcohol which contained a small amount of potassium hydroxide; yield 13.6 g.

In order to obtain the arsonium nitrate, a mixture of 25 g. of the arsonium iodide, 400 cc. of water and 8.5 g. of silver oxide was shaken for twenty-four hours, filtered and the filtrate acidified with nitric acid; part of the nitrate precipitated and the remainder was obtained by concentration of the solution. The product, recrystallized from water, seems to contain water of crystallization.

Methyltri-(3-nitro-4-bromophenyl)-arsonium Nitrate (VIII).—Five grams of methyltri-(4-bromophenyl)-arsonium nitrate was added, in small portions, to a cold mixture of 3 cc. of nitric acid (sp. gr. 1.60) and 7 cc. of concd. sulfuric acid. After the material had been heated on a steam-bath for fifteen minutes it was poured into ice water and the gummy precipitate, which became crystalline after trituration with water, recrystallized from 50% acetone; yield practically quantitative.

Tetra-(3-nitrophenyl)-arsonium Nitrate (X), Chloride (XI), Bromide and Iodide.—To a mixture of 16.8 cc. of concd. sulfuric acid and 7.8 cc. of nitric acid (sp. gr. 1.60) there was added, in two portions, 5.4 g. of tetraphenylarsonium nitrate (IX)[8]; the mixture was cooled after each addition of the nitrate. After fifteen minutes the material was heated for one-half hour on a steam-bath. The green, gummy mass was triturated with water until most of the acid had been removed and then warmed with water on a steam-bath whereupon the product turned into an orange granular material. The latter was washed with 10% sodium bicarbonate solution, then with water, dried and suspended in 60 cc. of hot acetone. About 20 cc. of water was added and the mixture heated and stirred until a solution was obtained.[9] Charcoal was added, the mixture filtered and water was added to the boiling filtrate until a very slight turbidity was produced. The mixture was treated again with charcoal, filtered, water added to the hot filtrate. The process mentioned in the last three lines was repeated three more times and, finally, the solution was evaporated to dryness. The pale yellow, crystalline residue was dissolved in water; about 130 cc. of solvent is

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(6) Blicke and Cataline, THIS JOURNAL, **60**, 421 (1938). By the use of the same procedure we obtained approximately twice the yield reported.

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

(8) Blicke, Willard and Taras, *ibid.*, **61**, 89 (1939).

(9) The material is insoluble in either water or acetone alone.

required for each gram of material. The solution was treated with charcoal, filtered and 0.5 g. of sodium nitrate added to the colorless filtrate; yield 69%.

Ten grams of the arsonium nitrate was dissolved in 1300 cc. of boiling water and sodium chloride added until the solution became cloudy. When the mixture was cooled and the sides of the container rubbed, the colorless crystalline chloride separated. The product was dissolved in absolute alcohol and precipitated by ether. The chloride, which seemed to contain alcohol of crystallization, was dried at 160°.

When 3.0 g. of the nitrate, dissolved in 400 cc. of hot water, was treated with 20 g. of solid sodium bromide, the arsonium bromide precipitated in practically quantitative yield. The compound was dissolved in hot water, treated with charcoal, filtered and 0.5 g. of sodium bromide added to the filtrate. The compound precipitated when the sides of the container were scratched.

The arsonium iodide was obtained by the process described except that sodium iodide was added to the aqueous solution. The crude iodide was suspended in hot acetone and just enough hot water added to bring it into solution. After addition of charcoal the mixture was filtered; the iodide precipitated, in practically quantitative yield, in the form of sparkling brown crystals.

Tetra-(3-aminophenyl)-arsonium Chloride (XII) and Bromide.—A right angle tube, about one-half inch in diameter, was fused onto the side of a wide mouth Erlenmeyer flask very near the bottom; this served as an inlet tube. A short outlet tube was fused onto the flask just below the neck. The flask was fitted with a stirrer which passed through a mercury seal.

A solution of 10 g. of tetra-(3-nitrophenyl)-arsonium chloride in 95 cc. of acetic acid was poured into the flask and 70 g. of powdered stannous chloride dihydrate added. The mixture was stirred and a rapid stream of hydrogen chloride passed into it. A clear solution was obtained and the crystalline tin double salt of the amino compound separated rapidly. When hydrogen chloride began to escape through the side arm, the mixture was cooled and filtered on a Jena funnel. The product was dissolved in water and treated with 20% sodium hydroxide solution until strongly alkaline, the precipitated arsonium chloride (6 g.) filtered, washed with sodium hydroxide solution, then with water.

The acetylamino compound was obtained when 1.5 g. of the amine and 5 cc. of acetic anhydride were boiled for several minutes. After twenty-four hours the precipitated product was filtered; yield 1.5 g.

To obtain the arsonium bromide in practically quantitative yield, the arsonium chloride was dissolved in the smallest possible amount of hot water and three times the calcd. amount of solid sodium bromide added.

Summary

Amino derivatives of methyltriphenyl- and tetraphenylarsonium salts have been described.

Based on preliminary pharmacological tests of a representative compound it seems that these products are ineffective as germicides.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Diaryl- and Dicycloalkylethanolamines

BY JOSEPH B. NIEDERL AND ROBERT LAY[1]

In the course of the investigation of physiological properties of certain types of aromatic, particularly phenolic amino compounds,[2] it became desirable to prepare a series of diaryl- and dicyloalkylethanolamines. Structurally related diaryl- and dialkylethanolamines had been prepared previously by other workers, for instance, Paal and Weidenkaff[3] and Krabbe and co-workers.[4]

The substances listed in the table were prepared by the action of the appropriate Grignard reagents upon glycine ethyl ester hydrochloride.

Experimental

The general method of procedure was to add small amounts of dry glycine ethyl ester hydrochloride (1 mole) to the ether solution of a Grignard reagent prepared as usual from the corresponding halide (10 moles) and magnesium (10 moles), the solution being kept cold during the addition. After all the hydrochloride had been added the cooling was stopped and the reaction proceeded of its own accord with gentle boiling of the ether. After about fifteen minutes the reaction had moderated and the flask was then placed on the water-bath and boiled for several hours. The ether solution was cooled, two layers usually being formed, and poured on ice and hydrochloric acid mixture to decompose the Grignard complex. After the decomposition, the mixture was allowed to stand for a day or two. The hydrochloride of the aminoalcohol, which formed a layer between the ether and water layers, was filtered and dried on porous tile. The ether and water layers were separated, the aqueous solution cooled and made alkaline with concentrated ammonium hydroxide, added slowly

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[1] Abstracted from Part I of the thesis presented by Robert Lay to the Faculty of the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] J. B. Niederl and M. I. Dexter, THIS JOURNAL, **63**, 1475 (1941).

[3] Paal and Weidenkaff, *Ber.*, **38**, 1686 (1905).

[4] Krabbe and co-workers, *ibid.*, **69**, 1569 (1936); **71**, 64 (1938); **72**, 381 (1939).