[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS, NORTHWESTERN UNIVERSITY, AND THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF WISCONSIN]

ARSENATED BENZANILIDE AND ITS DERIVATIVES[1]

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This study was undertaken with a view to the synthesis of new organic compounds of arsenic, especially those containing a $-C(O)-N=$ linkage. The very reactive dichloro-*p*-arsinobenzoyl chloride, $Cl_2AsC_6H_4COCl$, was chosen as a starting point and was condensed with various aromatic primary and secondary amines, such as aniline, ethyl aniline, anthranilic acid, anisidine, phenetidine, and arsanilic acid to give compounds of the general type, $H_2O_3AsC_6H_4CONRR'$. The arseno and halogen derivatives of these compounds were also prepared. An entirely new type of arsenical was obtained by condensing gluconic acid with arsanilic acid and aminoarsanilic acid.

Hugounenq and Morel[2] condensed dichloro-*p*-arsinobenzoyl chloride with certain of the degradation products of protein, such as hippuric acid, alanine, phenyl-alanine, tyrosine, leucine, aspartic acid and glutamic acid. The arsenated benzanilides described in this paper were prepared by adding, drop by drop with much shaking, a benzene solution of dichloro-*p*-arsinobenzoyl chloride to twice the calculated amount of the aromatic amine dissolved in benzene or xylene. The impure condensation product thus obtained still contained chlorine on the arsenic and could be isolated in pure form as the arsonic acid only after oxidation in glacial acetic acid with 3% hydrogen peroxide solution. The addition of sodium halide to the acetic acid solution gives the corresponding dihalide, while the arseno derivatives were best prepared by the usual reduction in alcoholic solution with phosphorous or hypophosphorous acid.

For the most part these compounds are readily hydrolyzed by boiling 10% aqueous sodium hydroxide, but are quite stable in water solution even on prolonged boiling. The free acids are insoluble in water but freely soluble in alcohol or acetone, while the arseno derivatives are insoluble in all common organic solvents. The arsonic acids and chloro- and bromo-arsines form colorless crystals while the arseno and iodo derivatives are a beautiful yellow.

Experimental Part

The Preparation of Benzarsonic Acid.—As a result of a previous

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[1] This work was done under a grant from the U. S. Interdepartmental Social Hygiene Board, Washington, D. C. Some of the water-soluble compounds are being studied pharmacologically under the direction of Dr. A. S. Loevenhart of the University of Wisconsin.

[2] Hugounenq and Morel, *J. Pharm. Chem.*, 7, 383 (1913).

comparative study[3] of available methods of obtaining benzarsonic acid, this compound was prepared in two steps from *p*-nitrobenzoic acid.

1. **Reduction of *p*-Nitrobenzoic Acid.**[4]—Twenty-five g. of *p*-nitrobenzoic acid was dissolved in 50 cc. of warm dil. ammonium hydroxide, and added, with shaking, to a boiling solution of 300 g. of commercial ferrous sulfate in 400 cc. of water. One hundred cc. of conc. ammonium hydroxide was then cautiously added and the boiling continued for 5 minutes. An additional 75 cc. of conc. ammonium hydroxide was added and the mixture filtered hot. When the filtrate was acidified with acetic acid, *p*-aminobenzoic acid separated in yellow needles; yield, 85%.

2. **Conversion of *p*-Aminobenzoic Acid to Benzarsonic Acid.**[5]—Fifty g. of *p*-aminobenzoic acid was dissolved in a mixture of 750 cc. of water and 75 cc. of conc. hydrochloric acid, and diazotized with 26 g. of sodium nitrite. The arsenite solution was prepared by dissolving 460 g. of arsenic trioxide in a solution of 54 g. of sodium hydroxide in 400 cc. of water. After the arsenic trioxide had dissolved, 20 cc. of 6 *N* copper sulfate solution was added as a catalyst. The diazo solution was added to the arsenite solution with stirring, the temperature being allowed to rise to 20°. After mixing, the solution was held at 60° for $^1/_2$ hour or until the evolution of nitrogen had ceased, and was then acidified with hydrochloric acid. The flocculent precipitate was separated and, on concentrating the filtrate to 500 cc. and cooling, colorless crystals of benzarsonic acid were deposited; yield, 50–60%.

Dichloro-*p*-arsinobenzoyl Chloride,[6] $Cl_2AsC_6H_4COCl$.—Twenty cc. of phosphorus trichloride was added drop by drop to 25 g. of benzarsonic acid, suspended in 100 cc. of dry chloroform. Twenty g. of phosphorus pentachloride was then added in one portion, and the reaction completed by warming the mixture on a water-bath. The chloroform was distilled under reduced pressure, and the resulting product used directly for the condensations.

Preparation of Arsono Compounds.—One-tenth mole of crude dichloro-*p*-arsinobenzoyl chloride, dissolved in 50 cc. of dry benzene, was added in small portions with vigorous shaking to 0.2 moles of the primary amine in 200–300 cc. of dry benzene. A precipitate immediately deposited. After standing for several hours the product was separated and washed repeatedly with benzene and finally with ether. It was then triturated with water in order to remove the hydrochloride formed in the reaction. The crude product, which consisted chiefly of the substituted amide of dichloro-*p*-arsenobenzoic acid was dissolved in hot glacial acetic acid and an excess of the calculated amount of 3% hydrogen peroxide added. On cooling, the arsonic acid was deposited. Recrystallization from glacial acetic acid gave colorless crystals.

***p*-Arsonobenzoyl-anilide,** $C_6H_5NHCOC_6H_4AsO_3H_2$.—This compound is insoluble in cold water, benzene and xylene, soluble in cold alkali and ethyl alcohol, decomposed by heating with dil. alkalies, and does not melt below 250°.

Analyses. Subs., 0.2061, 0.1995: 22.90 cc., 22.30 cc. of 0.0554 *N* iodine soln. Subs., 0.3110, 0.3105: 9.65 cc., 9.47 cc. of 0.100 *N* HCl. Calc. for $C_{13}H_{12}O_4NAs$: As, 23.33; N, 4.36. Found: As, 23.23; N, 4.33; 4.27.

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[3] Lewis and Cheetham, THIS JOURNAL, **43**, 2118 (1921).

[4] Jacobs and Heidelberger, *ibid.*, **39**, 1437 (1917).

[5] Bart, Ger. pat., 250,264, and 254,345.

[6] Poulenc, French pat., 441,215.

***p*-Arsonobenzoyl-anthranilide,** $CO_2HC_6H_4NHCOC_6H_4AsO_3H_2$.—The yield of colorless crystals was 35–40%. The product is insoluble in water and benzene, but soluble in alcohol and dil. alkali, and does not melt below 250°.

Analyses. Subs., 0.2010, 0.1919: 20.80, 19.70 cc. of 0.0525 *N* iodine soln. Calc. for $C_{14}H_{12}O_6NAs$: As, 20.54. Found: 20.38, 20.22.

***p*-Arsonobenzoyl-*p*-anisidide,** $CH_3OC_6H_4NHCOC_6H_4AsO_3H_2$.—Following the general procedure a 53% yield of the arsonic acid was obtained. It is insoluble in cold water and xylene, soluble in dil. alkali and ethyl alcohol, and does not melt below 250°.

Analyses. Subs., 0.1998, 0.2004: 21.80, 21.90 cc. of 0.0525 *N* iodine soln. Subs., 0.3126, 0.3137: 44.10, 43.00 cc. of 0.02 *N* HCl soln. Calc. for $C_{14}H_{14}O_5NAs$: As, 21.36; N, 3.99. Found: As, 21.16, 21.20; N, 3.93, 3.84.

***p*-Arsonobenzoyl-*p*-phenetidide,** $C_2H_5OC_6H_4NHCOC_6H_4AsO_3H_2$.—The solubilities of this compound are similar to those of the corresponding anisidide. It does not melt below 270°; yield 50%.

Analyses. Subs., 0.1969, 0.2017: 21.10, 21.50 cc. of 0.0525 *N* iodine soln. Subs., 0.2775, 0.2954: 37.30, 38.10 cc. of 0.02 *N* HCl soln. Calc. for $C_{15}H_{16}O_5NAs$: As, 20.55; N, 3.83. Found: As, 20.18, 20.67; N, 3.75, 3.62.

***p*-Arsonobenzoyl-*o*-anisidide,** $CH_3OC_6H_4NHCOC_6H_4AsO_3H_2$.—The crude product when recrystallized from glacial acetic acid gave colorless needles. It does not melt below 250°, and its solubilities are similar to those of the *p*-anisidide.

Analyses. Subs., 0.1931, 0.1994: 23.01, 23.80 cc. of 0.0418 *N* iodine soln. Calc. for $C_{14}H_{14}O_5NAs$: As, 21.36. Found: 21.08, 21.12.

Hydrated *p*-Arsonosobenzoyl-arsanilide, $H_2O_3AsC_6H_4NHCOC_6H_4As(OH)_2$.[7]—This compound is of peculiar interest since it contains arsenic in both of the aromatic nuclei connected by the C-N linkage.

Fifty-four g. of arsanilic acid was dissolved in a solution of 35 g. of sodium bicarbonate and 300 cc. of water. Fifteen g. of dichloro-*p*-arsinobenzoyl chloride was added drop by drop with shaking to the alkaline solution of arsanilic acid. A pure white precipitate at once separated. It was collected on a filter, extracted with 150 cc. of water and acidified with hydrochloric acid. The resulting white precipitate was purified by shaking and washing it with dil. hydrochloric acid to remove the arsanilic acid, and with a large amount of boiling water to remove the hydrochloric acid and sodium chloride. The product was then refluxed twice with 25 cc. of ether to remove any benzarsenious oxide; yield, 5 g. The product is insoluble in ether and chloroform, but soluble in alcohol and dil. alkali.

Analyses. Subs., 0.2437, 0.2242: 44.15, 40.50 cc. of 0.0520 *N* iodine soln. Subs., 1.0002: 20.55 cc. of 0.1154 *N* HCl soln. Calc. for $C_{13}H_{13}O_6NAs_2$: As, 34.9; N, 3.26. Found: As, 35.4, 35.2; N, 3.32.

***p*-Arsonobenzoyl-arsanilide,** $H_2O_3AsC_6H_4NHCOC_6H_4AsO_3H_2$.—To a solution of 4.4 g. of hydrated *p*-arsonosobenzoyl-arsanilide in 365 cc. of 0.1 *N* sodium hydroxide was added a large excess of hydrogen peroxide and the whole was heated for 15 minutes under a reflux condenser. After the mixture had cooled, 350 cc. of 0.1154 *N* hydrochloric acid was added and after several hours a white powder separated; yield, 2.5 g. The compound is soluble in dil. alkali and alcohol, but is insoluble in benzene, chloroform or ether.

Analyses. Subs., 0.2162, 0.2066: 37.00, 35.30 cc. of 0.0525 *N* iodine soln. Calc. for $C_{13}H_{13}O_7NAs_2$: As, 33.7. Found: 33.9, 33.4.

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[7] First prepared in this Laboratory by F. H. Bergeim.

Preparation of Arseno Compounds.—The crude reaction products obtained as outlined under the preparation of arsono compounds were dissolved in the minimum of hot alcohol. An excess of the calculated amount of phosphorous or hypophosphorous acid was then added, and the solution heated for 30 minutes under a reflux condenser. The resulting yellow precipitate was filtered hot, and washed repeatedly with alcohol. All of the arseno compounds are yellow in color, insoluble in common organic solvents and do not melt below 250°. On standing they are slowly converted into the corresponding oxides.

_p_-Arsenobenzoyl-anilide, $C_6H_5NHCOC_6H_4As = AsC_6H_4CONHC_6H_5$.

Analyses. Subs., 0.2991, 0.1929: 30.30, 29.20 cc. of 0.0486 *N* iodine soln. Subs., 0.3026, 0.2994: 11.45, 11.42 cc. of 0.1 *N* HCl soln. Calc. for $C_{26}H_{22}O_2N_2As_2$: As, 27.57; N, 5.15. Found: 27.72, 27.60; N, 5.30, 5.34.

_p_-Arsenobenzoyl-anthranilide, $CO_2HC_6H_4NHCOC_6H_4As = AsC_6H_4CONHC_6H_4CO_2H$.

Analyses. Subs., 0.1983, 0.1959: 25.90, 25.40 cc. of 0.0486 *N* iodine soln. Calc. for $C_{28}H_{20}O_6N_2As_2$: As, 23.82, Found: 23.79, 23.62.

_p_-Arsenobenzoyl-_p_-anisidide, $CH_3OC_6H_4NHCOC_6H_4As = AsC_6H_4CONHC_6H_4OCH_3$.

Analyses. Subs., 0.1833, 0.1864: 23.30, 23.80, 0.0525 cc. of *N* iodine soln. Subs., 0.2144, 0.2252: 35.20, 36.20 cc. of 0.020 *N* HCl soln. Calc. for $C_{28}H_{24}O_4N_2As_2$: As, 24.92; N, 4.65. Found: As, 24.65, 24.77; N, 4.59, 4.50.

_p_-Arsenobenzoyl-_p_-phenetidide, $C_2H_5OC_6H_4NHCOC_6H_4As = AsC_6H_4CONHC_6H_4OC_2H_5$.

Analyses. Subs., 0.1774, 0.1891: 21.60, 22.90 cc. of 0.0525 *N* iodine soln. Subs., 0.2180, 0.2262: 33.15, 34.20 cc. of 0.020 *N* HCl soln. Calc. for $C_{30}H_{28}O_4N_2As_2$: As, 23.80; N, 4.44. Found: 23.63, 23.49; N, 4.27, 4,23.

_p_-Arsenobenzoyl-_p_-xylidide, $(CH_3)_2C_6H_3NHCOC_6H_4As = AsC_6H_4CONHC_6H_3(CH_3)_2$.

Analyses. Subs., 0.1903, 0.2004: 27.20, 28.30 cc. of 0.0471 *N* iodine soln. Subs., 0.3574, 11.51 cc. of 0.100 *N* HCl soln. Calc. for $C_{30}H_{28}O_2N_2As_2$: As, 25.08; N, 4.68. Found: 25.24, 24.93; N, 4.51.

_p_-Arsenobenzoyl-α-naphthylamide, $C_{10}H_7NHCOC_6H_4As = AsC_6H_4CONHC_{10}H_7$.

Analyses. Subs., 0.1998, 0.1994: 26.10, 26.20 cc. of 0.0471 *N* iodine soln. Subs., 0.3538: 10.73 cc. of 0.100 *N* HCl soln. Calc. for $C_{34}H_{24}O_2N_2As_2$: As, 23.37; N, 4.36. Found: 23.09, 23.20; N, 4.25.

Preparation of Di-iodo, Dibromo and Dichloro Compounds.—The various di-iodo, dibromo and dichloro compounds listed below were prepared as follows.

The crude reaction product, obtained as outlined under the preparation of arsono compounds, was dissolved in hot glacial acetic acid and an excess of the desired sodium halide added in solid form. The mixture was heated under a reflux condenser for 5 minutes and the excess sodium halide removed by filtration. On cooling the hot filtrate, a crystalline product was obtained in almost a quantitative yield.

Di-iodo-*p*-arsinobenzoyl-*p*-anisidide, $CH_3OC_6H_4NHC_6H_4AsI_2$.—Upon recrystallization from glacial acetic acid the product separates as beautiful yellow needles, which melt at 209–210° (uncorr.). The compound is insoluble in water and dil. alkalies, but soluble in benzene. It has a slightly irritating effect on the mucous membrane of the nose and throat.

Analyses. Subs., 0.1896, 0.1914: AgI, 0.1610, 0.1589. Calc. for $C_{14}H_{12}O_2NAsI_2$: I, 45.76. Found: 45.26, 45.41.

Di-iodo-*p*-arsinobenzoyl-*p*-phenetidide, $C_2H_5OC_6NHCOC_6H_4AsI_2$.—These yellow needles melt at 227–228° (uncorr.). They are insoluble in water and alkali, but soluble in glacial acetic acid and benzene.

Analyses. Subs., 0.1988, 0.1951: AgI, 0.1634, 0.1601. Calc. for $C_{15}H_{14}O_2NAsI_2$: I, 44.64. Found: 44.42, 44.30.

Di-iodo-*p*-arsinobenzoyl-ethylanilide, $C_6H_5N(C_2H_5)COC_6H_4AsI_2$.—Recrystallization from glacial acetic acid gave canary-yellow needles which melt at 115–116° (uncorr.).

Analyses. Subs., 0.2043, 0.2331: AgI, 0.1733, 0.2004. Calc. for $C_{15}H_{14}ONAsI_2$: I, 4593. Found: 45.81, 46.42.

Di-iodo-*p*-arsinobenzoyl-*o*-anisidide, $CH_3OC_6H_4NHCOC_6H_4AsI_2$.—The compound melts at 148–149° (uncorr.) and may be recrystallized from glacial acetic acid. It is insoluble in benzene and xylene.

Analyses. Subs., 0.2147, 0.2104: AgI, 0.1920, 0.1786. Calc. for $C_{14}H_{12}O_2NAsI_2$: I, 45.76. Found: 45.86, 45.83.

Dibromo-*p*-arsinobenzoyl-*o*-anisidide, $CH_3OC_6H_4NHCOC_6H_4AsBr_2$.—Slightly yellow crystals were obtained by recrystallization of the crude product from glacial acetic acid. The compound melts at 167–168° (uncorr.).

Analyses. Subs., 0.2069, 0.2016: AgBr, 0.1679, 0.1640. Calc. for $C_{14}H_{12}O_2NAsBr_2$: Br, 34.70. Found: 34.49, 34.57.

Dichloro-*p*-arsinobenzoyl-*o*-anisidide, $CH_3OC_6H_4NHCOC_6H_4AsCl_2$.—The product separates as slightly yellow crystals. It melts at 164–165° (uncorr.).

Analyses. Subs., 0.2090, 0.1803: AgCl, 0.1578, 0.1374. Calc. for $C_{14}H_{12}O_2NAsCl_2$: Cl, 19.08. Found: 18.65, 18.82.

Dichloro-*p*-arsinobenzoyl Ethyl Anilide, $C_6H_3N(C_2H_5)COC_4H_6AsCl_2$.—This compound is obtained as colorless cubes from glacial acetic acid. It is insoluble in water, but soluble in benzene or ethyl alcohol. It melts at 147–148° (uncorr.).

Analyses. Subs., 0.2026, 0.2119: AgCl, 0.1568, 0.1618. Calc. for $C_{15}H_{14}ONAsCl_2$: Cl, 19.16. Found: 19.11, 18.86.

Gluconyl-*p*-arsanilic Acid, $CH_2OH(CHOH)_4CONHC_6H_4AsO_3H_2$.—Eleven g. of gluconic acid in 50 cc. of absolute methyl alcohol was added drop by drop with shaking to a solution of 10.8 g. of *p*-arsanilic acid dissolved in 100 cc. of hot absolute methyl alcohol. After heating under a reflux condenser for 5 minutes, a slightly pink precipitate formed. This was filtered while hot and washed repeatedly with absolute methyl alcohol to remove any unchanged gluconic acid; yield, 13 g. The product is slightly soluble in cold methyl alcohol and insoluble in glacial acetic acid. It is readily hydrolyzed by heating with dil. alkalies.

Analyses. Subs., 0.1926, 0.2002: 20.60, 21.10 cc. of 0.0418 *N* iodine soln. Calc. for $C_{12}H_{18}O_9NAs$: As, 18.98. Found: 18.93, 18.65.

3,4-Digluconyl-3,4-diamino-phenylarsonic Acid, $[CH_2OH(CHOH)_4CONH]_2C_6H_3AsO_3H_2$.—To a solution of 23.2 g. (0.1 mole) of almost colorless 3,4-diamino-phenylarsonic acid in 400 cc. of absolute methyl alcohol a solution of 33.6 g. (0.2 mole) of gluconic acid in 75 cc. of absolute methyl alcohol, was added in small portions with vigorous shaking, and the mixture allowed to stand for several hours. The 3,4-digluconyl-3,4-diamino-phenylarsonic acid, which separated immediately was freed from any unchanged 3,4-diamino-phenylarsonic acid and from free gluconic acid, by shaking it at intervals over a period of several hours with absolute methyl alcohol warmed to 40°. The cream-colored compound is soluble in cold water and dil. alkalies, and is readily hydrolyzed by hot water; yield, 70%.

Analyses. Subs., 0.1989, 0.2002: 16.40, 16.65 cc. of 0.0416 N iodine soln. Calc. for $C_{18}H_{29}O_{16}N_2As$: As, 12.75. Found: 12.86, 12.97.

Summary

1. The reaction of dichloro-*p*-arsinobenzoyl chloride with primary and secondary amines has been studied and the resulting compounds described.

2. Gluconic acid has been condensed with *p*-arsanilic acid and *o*-amino-arsanilic acid to form a new type of arsenical containing a solubilizing carbohydrate grouping.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ADDITION REACTIONS OF THE PHOSPHORUS HALIDES. VII. THE ADDITION OF ALKOXY AND AROXY CHLOROPHOSPHINES TO CARBONYL COMPOUNDS

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Introduction

The previous papers of this series[1] have dealt with the 1,2 and 1,4 addition of phosphorus trichloride and its aryl derivatives, phosphenylchloride ($C_6H_5PCl_2$) and diphenylchlorophosphine. As a continuation of this work we have investigated the action of substances of the general type $ROPCl_2$ and $(RO)_2PCl$ on simple ketones and aldehydes and on an α,β unsaturated ketone. By carrying out the reaction in the usual manner in the presence of acetic acid or acetic anhydride we have prepared the mono- and di-esters of the phosphonic acids which are formed by the reaction of phosphorus trichloride with the corresponding aldehyde or ketone. This investigation completes the study of the various types of chlorophosphines in regard to their addition reactions with aldehydes, ketones and α,β unsaturated ketones. In general it may be said that phosphorus halides of the type $APCl_2$ and A_2PCl, where $A = R$ or RO, combine with carbonyl compounds in the same manner as phosphorus trichloride. As would be expected, compounds of the type A_3P do not

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[1] THIS JOURNAL, (a) **39,** 2679 (1917); (b) **42,** 830, (c) 2337 (1920); (d) **43,** 1665, (e) 1677, (f) 1928 (1921); (g) **44,** 165 (1922).