[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF WISCONSIN]

ARSENATED N-ARYLAMINO ALCOHOLS[1]

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The action of ethylene chlorohydrin on aromatic amines was first studied by Knorr.[2] He found that when equivalent amounts of aniline and ethylene chlorohydrin were heated together in a closed tube at 110° for one hour, 2-anilino-ethanol was the chief product. More recently Rindfusz and Harnack[3] have shown that N-arylamino alcohols can be prepared by boiling aniline with ethylene chlorohydrin or with trimethylene chlorohydrin in the presence of sodium carbonate.

This investigation was undertaken in order to study the action of chlorohydrins on aromatic arsonic acids, containing an amino group in the ring. The condensation took place in the case of *p*-arsanilic acid. With *m*-arsanilic acid, 3-amino-4-methyl-phenylarsonic acid and 3-amino-4-hydroxy-phenylarsonic acid,—that is, compounds containing the amino group in the *meta* position with respect to the arsenic,—negative results were obtained.

The arsonated N-arylamino alcohols were prepared by heating the amino-aryl arsonic acid, dissolved in sodium hydroxide solution, with an excess of the chlorohydrin. They are beautiful crystalline compounds and have definite melting points. By dissolving the arsonic acids in the calculated amount of 2 *N* sodium hydroxide solution and filtering into alcohol, sodium salts were obtained as colorless crystalline compounds, containing various amounts of water of hydration, depending upon the concentration of the alcohol used. Treatment of the arsonated N-arylamino alcohols with sodium hydrosulfite gave the yellow, highly insoluble arseno compounds.

Pharmacological experiments have been carried out with the mono-sodium salt of 2-*p*-arsono-anilino-ethanol and 3-*p*-arsono-anilino-propanol. As was expected, the latter, having the longer side chain, was the more toxic. From preliminary experiments, 3-*p*-arsono-anilino-propanol appears to have the higher trypanocidal action.

Experimental Part

Preparation of Arsono Compounds

One molecular equivalent of the amino-aryl arsonic acid was dissolved in the calculated amount of *N* sodium hydroxide solution to form a mono-sodium salt; 1.5 molecular equivalents of the chlorohydrin was then added

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[1] This work was made possible by a grant from the Public Health Institute, Chicago. Some of the products are being studied pharmacologically in this Laboratory under the direction of Dr. A. S. Loevenhart.

[2] Knorr, *Ber.*, **22**, 2092 (1889).

[3] Rindfusz and Harnack, THIS JOURNAL, **42**, 1720 (1920).

and the mixture boiled under a reflux condenser for 4 to 5 hours. The solution deposited almost colorless crystals on cooling. Concd. hydrochloric acid was added to the cold mixture to hold any unchanged *p*-arsanilic acid in solution and the product was filtered off and washed carefully with water. It was purified by recrystallization from hot water.

2-*p*-Arsono-anilino-ethanol, $CH_2OHCH_2NHC_6H_4AsO_3H_2$.—This compound prepared from *p*-arsanilic acid and ethylene chlorohydrin was obtained in 35–40% yields. The colorless needles, which melt at 167–168° (uncorr.), are soluble in hot water and dil. alkalies, but are insoluble in ether and benzene.

Analyses. Subs., 0.1989, 0.1994: 32.40, 32.60 cc. of 0.0464 *N* iodine soln. Subs., 0.4011, 0.4005: 14.95, 15.05 cc. of 0.1 *N* HCl soln. Calc. for $C_8H_{12}O_4NAs$: N, 5.36; As, 28.73. Found: N, 5.22, 5.26; As, 28.37, 28.47.

MONOSODIUM SALT.—Ten g. of 2-*p*-arsono-anilino-ethanol was dissolved in 19 cc. of 2 *N* sodium hydroxide solution and the solution was filtered in a fine stream into 95% alcohol. Colorless crystals were deposited immediately. The yield was almost quantitative.

Analyses. Sample dried at 105°. Subs., 0.1992, 0.1998: 30.20, 30.35 cc. of 0.0464 *N* iodine soln. Subs., 0.4001, 0.3992: 14.50, 14.20 cc. of 0.1 *N* HCl. Calc. for $C_8H_{11}O_4NAsNa$; N, 4.94; As, 26.50. Found: N, 5.07, 4.98; As, 26.41, 26.46.

MONO-AMMONIUM SALT.—Using ammonium hydroxide in place of sodium hydroxide solution, this compound was prepared by the method outlined under the sodium salt, as colorless needles, readily soluble in cold water.

Analyses. Sample dried at 105°. Subs., 0.1991, 0.2003: 32.40, 32.70 cc. of 0.0436 *N* iodine soln. Subs., 0.3012, 0.2996: 21.42, 21.38 cc. of 0.1 *N* HCl. Calc. for $C_8H_{14}O_4N_2As$: N, 10.07; As, 26.97. Found: N, 9.96, 9.99; As, 26.65, 26.74.

BARIUM SALT.—This compound was prepared by dissolving the arsonic acid in hot water and adding the calculated amount of a barium hydroxide solution. A white precipitate formed on standing that was insoluble in alcohol, but somewhat soluble in water.

Analyses. Sample dried at 105°. Subs., 0.2002, 0.1999: 27.10, 27.50 cc. of 0.0436 *N* iodine soln. Calc. for $C_{16}H_{22}O_8N_2As_2Ba$: As, 22.88. Found: 22.17, 22.53.

3-*p*-Arsono-anilino-propanol, $CH_2OH(CH_2)_2NHC_6H_4HsO_3H_2$.—Following the general procedure for the preparation of arsono compounds, 21.7 g. of *p*-arsanilic acid when treated with 14 g. of trimethylene chlorohydrin, gave 8 g. of product. Recrystallization from hot water gave colorless crystals; m. p., 160–161° (uncorr.).

Analyses. Subs., 0.2016, 0.2004: 32.50, 32.40 cc. of 0.0452 *N* iodine soln. Subs., 0.4052, 0.4041: 14.30, 14.42 cc. of 0.1 *N* HCl. Calc. for $C_9H_{14}O_4NAs$: N, 5.09; As, 27.27. Found: N, 4.94, 4.99; As, 27.42, 27.40.

SODIUM SALT.—Four g. of the corresponding arsonic acid gave 3.9 g. of the sodium salt as colorless crystals from 95% alcohol, on standing.

Analyses. Subs. (dried in oven at 105°), 0.1987, 0.1991: 30.60, 30.60 cc. of 0.0443 *N* iodine soln. Subs., 0.3991, 0.3980: 13.61, 13.52 cc. of 0.1 *N* HCl. Calc. for $C_9H_{13}O_4NAsNa$: As, 25.25; N, 4.71. Found: N, 4.77, 4.75; As, 25.60, 25.55.

AMMONIUM SALT.—By dissolving the arsonic acid in ammonium hydroxide and filtering the solution into alcohol, colorless needles were obtained in good yields.

Analyses. Subs. (dried in oven at 105°), 0.1898, 0.1901: 30.00, 29.90 cc. of 0.0436 *N* iodine soln. Subs., 0.3008, 0.3006: 20.48, 20.51 cc. of 0.1 *N* HCl. Calc. for $C_9H_{16}O_4N_2As$: N, 958; As, 25.68. Found: N, 9.54, 9.55; As, 25.89, 25.76.

Barium Salt.—A white powder, prepared as was the barium salt of 2-*p*-arsono-anilino-ethanol, was obtained.

Analyses. Subs. (dried in oven at 105°), 0.2017, 0.2003: 26.40, 26.20 cc. of 0.0436 *N* iodine soln. Calc. for $C_{17}H_{24}O_8N_2As_2Ba$: As, 21.89. Found: 21.43, 21.42.

Preparation of Arseno Compounds[4]

One molecular equivalent of the arsonated N-arylamino alcohol was dissolved in hot water. This solution was added with shaking to a solution of 10 equivalents of sodium hydrosulfite in 550 equivalents of water, after the latter solution had been previously treated successively with 6 equivalents of 10 *N* sodium hydroxide solution and 10 equivalents of crystalline magnesium chloride and filtered from the magnesium hydroxide formed. After this mixture had been heated on a water-bath and frequently shaken for 1/2 hour, the yellow precipitate which formed was filtered off, washed with water, alcohol, and ether and dried in a vacuum.

2-*p*-Arseno-anilino-ethanol, $CH_2OHCH_2NHC_6H_4As{=}AsC_6H_4NHCH_2CH_2OH$.—Five g. of 2-*p*-arsono-anilino-ethanol upon reduction, as outlined above, gave a 30% yield of the yellow arseno compound. It is insoluble in common organic solvents and does not melt below 250°.

Analyses. Subs., 0.1779, 0.1783: 38.70, 38.60 cc. of 0.0440 *N* iodine soln. Calc. for $C_{16}H_{20}O_2N_2As_2$: As, 35.57. Found: 35.93, 35.77.

3-*p*-Arseno-anilino-propanol, $CH_2OH(CH_2)_2NHC_6H_4As{=}AsC_6H_4NH(CH_2)_2CH_2OH$.—The reduction of 10 g. of 3-*p*-arsono-anilino-ethanol gave 4.5 g. of the arseno product. It does not melt below 250° and has the usual properties of arseno derivatives.

Analyses. Subs., 0.1984, 0.1990: 39.80, 39.90 cc. of 0.0440 *N* iodine soln. Calc. for $C_{18}H_{24}O_2N_2As_2$: As, 33.33. Found: 33.14, 33.12.

Arsonated *s*-Di-anilino Ethane

***s*-Bis(*p*-arsono-anilino)ethane,** $H_2O_3AsC_6H_4NH(CH_2)_2NHC_6H_4AsO_3H_2$.—To a solution of 21.7 g. of *p*-arsanilic acid in 100 cc. of *N* sodium hydroxide solution was added 12 g. of ethylene dibromide and the mixture was boiled under a reflux condenser. The ethylene dibromide gradually dissolved, and a white solid began to form. After the mixture had been boiled for two hours, it was cooled, 10 cc. of concd. hydrochloric acid was added to hold the unchanged arsanilic acid in solution, and the product was separated by filtration. It was purified by dissolving it in 10% sodium hydroxide solution, filtering and acidifying the filtrate with concd. hydrochloric acid; yield, 7 g.

The product is readily soluble in dil. alkalies, two molecular equivalents of sodium hydroxide being required for the neutral salt. It does not melt below 250°.

Analyses. Subs., 0.1888, 0.1992: 33.10, 34.80 cc. of 0.0494 *N* iodine soln. Subs., 0.3871, 0.3992; 16.65, 17.05 cc. of 0.1 *N* HCl. Calc. for $C_{14}H_{18}O_6N_2As_2$: N, 6.08; As, 32.60. Found: N, 6.02, 5.98; As, 32.52, 32.41.

Monosodium Salt: Five g. of the above arsonic acid was dissolved in the calculated amount of 2 *N* sodium hydroxide solution to form the neutral salt, and the solution was filtered in a fine stream into 95% alcohol; 3.8 g. of colorless crystals was deposited.

Analyses. Subs. (dried in oven at 105°), 0.2009, 0.2016: 33.40, 33.45 cc. of 0.0474 *N* iodine soln. Calc. for $C_{14}H_{16}O_6N_2As_2Na_2$: As, 29.76. Found: 29.59, 29.53.

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[4] Meister, Lucius and Bruning, Ger. pat. 206,057.

Summary

1. The action of chlorohydrins on amino-aryl arsonic acids has been investigated, and the properties of the resulting compounds and some of their derivatives have been described.

2. The condensation of ethylene dibromide with *p*-arsanilic acid has been studied, and the neutral sodium salt prepared.

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ANALYSIS OF THE JERUSALEM ARTICHOKE[1]

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The Jerusalem artichoke, *helianthus tuberosus*, has long been known and used as an article of food. The common books on food analysis and food values do not, however, list it.

There is an analysis by Strauss[2] and one by Langworthy[3] to which the reader is referred for a further description of the occurrence, habits and methods of preparing the Jerusalem artichoke for table use.

This investigation was undertaken with the idea of establishing the importance of the Jerusalem artichoke in the treatment of diabetics, but suitable clinical material has not been available. The following analysis is published in the hope of suggesting such use to others.

It is well known that this tuber contains large amounts of inulin, a carbohydrate which on hydrolysis yields levulose. Inulin in the form of "Topinambur" (Jerusalem artichoke) was used in the treatment of diabetes as early as 1851 by Bouchardat.[4] Külz[4] in 1874 showed that inulin was burned in the body, since diabetics excreted none in the feces. Inulin has fallen into disuse since Sandmeyer,[4] 1894, showed that dogs with partial removal of the pancreas could not utilize inulin and Mendel,[4] 1908, objected to its use because there are no enzymes in the body to split it. Inulin is, however, hydrolyzed by dil. acids. That there is enough acid in the gastric juice to split it has been shown by Chittenden,[5] Lewis[6] and Okey.[7]

Strauss[8] has reopened the question and found that inulin was well

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[1] Read at the Rochester meeting of the American Chemical Society, 1921.

[2] Strauss, *Ther. Gegen.*, **52**, 347 (1911).

[3] Langworthy, *U. S. Dept. Agr. Bull.*, **468** (1917).

[4] Cited by Goudberg, Ref. 9.

[5] Chittenden, *Am. J. Physiol.*, **2**, xvii (1898).

[6] Lewis, *J. Am. Med. Assoc.*, **58**, 1176 (1912).

[7] Okey, *J. Biol. Chem.*, **39**, 149 (1919).

[8] Strauss, *Berl. klin. Wochschr.*, **49**, 1213 (1912).