[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NEBRASKA]

N-PHENYL-BETA-AMINOPROPIONAMIDE-4-ARSONIC ACID AND RELATED COMPOUNDS

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The comparatively recent preparation of "tryparsamide," N-phenylglycine-amide-4-arsonic acid[1] and its growing use in trypanosomiasis and neuro-syphilis stimulated an interest in the preparation and study of other arsenicals of a similar structure which might be more efficient. Those which merited special interest were the two compounds corresponding to tryparsamide, one having an additional methylene group in the side chain and the other having a shorter side chain.

The method employed in the preparation of "tryparsamide" involved the condensation of *p*-arsanilic acid with chloro-acetamide and subsequent conversion into the monosodium salt. N-Phenyl-β-aminopropionamide-4-arsonic acid was prepared by refluxing a neutral solution of sodium *p*-arsanilate with either β-bromopropionamide or with β-iodopropionamide. The monosodium salt was obtained by dissolving the acid in a sodium hydroxide solution and filtering into absolute alcohol. Attempts to prepare 4-carbamido-phenylarsonic acid by the action of carbamyl chloride on *p*-arsanilic acid were unsuccessful. However, N-4-methylcarbamido-phenylarsonic acid[2] was prepared by the action of methylcarbamyl chloride on *p*-arsanilic acid. This compound was first prepared from methyl isocyanate and *p*-arsanilic acid. β-iodopropionamide was also condensed with several other amino-arylarsonic acids.

It was of interest also to make a study of an unsymmetrical arseno compound, composed of a half molecule of arsphenamine, used in the treatment of primary syphilis, and a group somewhat similar to tryparsamide, of benefit in neuro-syphilis. 3-Amino-4-hydroxy-4′-propionamide-amino-arsenobenzene resulted when molecular equivalents of 3-amino-4-hydroxyphenylarsonic and N-phenyl-β-aminopropionamide-4-arsonic acid were condensed, using hypophosphorous acid as the reducing agent.

A detailed study of the pharmacological action of N-phenyl-β-aminopropionamide-4-arsonic acid is now being carried out in the Department of Pharmacology, University of Wisconsin. Preliminary results indicate that it may be useful in trypanosomal infections.

Experimental Part

β-Bromopropionyl Chloride.—Twenty g. of β-bromopropionic acid and 10 cc. of phosphorus trichloride were heated under a reflux condenser on a water-bath for five hours. The pale straw-colored liquid was collected at 65–70° at 25–30 mm.; yield, 19.6 g.

[1] Jacobs and Heidelberger, THIS JOURNAL, **41**, 1589 (1919).

[2] Farb. Meister, Lucius and Bruning, German Patent 213,155.

Anal. Subs., 0.2001, 0.2004. Calcd., 0.3865, 0.3871 g. of silver halide. Found: 0.3854, 0.3862.

β-Iodopropionyl Chloride.—This was obtained in 80% yields, being collected at 85–90° and 30 mm.

β-Bromopropionamide.—Sixteen g. of β-bromopropionyl chloride was admitted drop by drop with rapid stirring to a solution of 21 cc. of concentrated ammonium hydroxide diluted to 35 cc. and kept at −10°. The white crystalline amide separated and after stirring the mixture for a short time it was filtered and washed with a small amount of ice water to remove ammonium chloride; yield, 11.2 g.; m. p. 110–111°. For analysis the product was recrystallized twice from hot water.

Anal. Subs., 0.4005, 0.4011: 26.1, 26.3 cc. of 0.1 *N* HCl. Calcd.: N, 9.21. Found: N, 9.13, 9.17.

β-Iodopropionamide.—This compound was prepared in 80% yields by following the method of Jacobs and Heidelberger.[3]

N-Aryl-β-aminopropionamide-arsonic Acids

General Method of Preparation.—One molecular equivalent of the amino-arylarsonic acid was dissolved in the calculated amount of normal sodium hydroxide solution to form a monosodium salt; one and one-half molecular equivalents of the halopropionamide was then added and the mixture boiled under a reflux condenser for five hours. Sufficient concentrated hydrochloric acid was added to the hot solution to hold any unchanged arsanilic acid in solution. The solution deposited almost colorless crystals on cooling. The product was filtered, washed with a little cold water and purified by dissolving in 2 *N* sodium hydroxide solution, filtering and reprecipitating by the addition of concentrated hydrochloric acid. This purification was repeated until the product gave a negative R-salt test.

β-Bromopropionamide and β-iodopropionamide were the two halopropionamides used in the preparation of the N-aryl-β-aminopropionamide-arsonic acids. Of these the β-bromo compound was found to give the better results, the crude products being whiter and the yields just as high as when β-iodopropionamide was used.

TABLE I

N-ARYL-β-AMINOPROPIONAMIDE-ARSONIC ACIDS

N-Phenyl-β-aminopropionamide-( )-arsonic acid	Formula	Yield, %	Subs., g.	Analysis 0.0497 *N* I_2, cc.	Analysis Arsenic, % Calcd.	Found
-4-	$NH_2CO(CH_2)_2NHC_6H_4AsO_3H_2$	35–40	0.2060	28.52	26.04	26.00
-2-Methyl-5-	$NH_2CO(CH_2)_2NHC_6H_3(CH_3)AsO_3H_2$	15–20	.2016	26.6	24.73	24.60
-2-Methyl-4-	$NH_2CO(CH_2)_2NHC_6H_3(CH_3)AsO_3H_2$	25–30	.2034	26.8	24.73	24.54

Monosodium Salt of N-Phenyl-β-aminopropionamide-4-arsonic Acid.—This was prepared by dissolving N-phenyl-β-aminopropionamide-4-arsonic acid in the calculated amount of 2 *N* sodium hydroxide solution to give a neutral solution and filtering in a fine stream into 10 volumes of absolute alcohol, previously cooled to 0°. The mixture was allowed to stand for several hours in a freezing bath to insure complete precipitation. The sodium salt separated in fine white needles containing approximately two moles of water of hydration. The yield was almost quantitative.

Anal. (Sample dried at 110°) Subs., 0.2245; 29.33 cc. of 0.0497 *N* I_2. Calcd. for $C_9H_{12}O_4N_2AsNa$: As, 24.19. Found: As, 24.20. (Sample air dried) Subs., 0.2016:

[3] Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 145 (1915).

23.90 cc. of 0.0497 *N* I_2. Calcd. for $C_9H_{12}O_4N_2AsNa2H_2O$: As, 21.68. Found: As, 21.90.

N-Phenyl-β-aminopropionic Acid-4-arsonic Acid.—Five g. of N-phenyl-β-aminopropionamide-4-arsonic acid was gently boiled under a reflux condenser with 50 cc. of 2 *N* sodium hydroxide solution for three hours, or until ammonia ceased to be evolved. The solution deposited flake-like crystals when made acid to Congo Red paper with concentrated hydrochloric acid and cooled in a freezing mixture; yield 4.5 g. It did not melt below 250°.

Anal. Subs., 0.2019, 0.2012; 28.1, 27.9 cc. of 0.0497 *N* I_2. Calcd. for $C_9H_{11}O_4NAs$: As, 26.04. Found: As, 25.92, 25.83.

N-4-Methyl-carbamido-phenylarsonic Acid.—Five g. of methylcarbamyl chloride, prepared by treating methylamine hydrochloride with phosgene at 250–300°, was dissolved in 30 cc. of dry benzene and cooled to 5°. Five g. of finely powdered sodium *p*-arsanilate was then added in small portions with shaking. In order to complete the reaction the temperature of the mixture was allowed to rise slowly to 20°. The resulting product was then filtered, washed repeatedly with benzene and finally with ether. It was then triturated with water to remove the hydrochloride formed in the reaction and recrystallized from hot water; yield, 25%.

Anal. Subs., 0.2004: 29.50 cc. of 0.0497 *N* I_2. Calcd. for $C_8H_{11}O_4N_2As$: As, 27.37. Found: As, 27.44.

Arseno Compounds

3-Amino-4-hydroxy-4′-propionamidamino-arsenobenzene Dihydrochloride.—A mixture of 4.7 g. of 3-amino-4-hydroxyphenylarsonic acid and 5.8 g. of N-phenyl-β-aminopropionamide-4-arsonic acid was dissolved in a solution of 50 cc. of concd. hydrochloric acid and 30 cc. of water. Fifty cc. of 50% hypophosphorous acid was then added and the solution kept in a refrigerator for twenty-four hours. The yellow precipitate was filtered, washed with alcohol, then with ether and dried in a vacuum; yield, 4.2 g. The compound was soluble in water.

Anal. Subs., 0.2012, 0.2005: 32.0, 31.9 cc. of 0.0501 *N* I_2. Calcd. for $C_{15}H_{19}O_2N_3Cl_2As_2$: As, 30.36. Found: As, 29.88, 29.89.

In order to prepare the free base, the dihydrochloride was dissolved in water and 3-amino-4-hydroxy-4′-propionamidamino-arsenobenzene precipitated by the careful addition of a sodium hydroxide solution. The free base was also prepared as follows: one hundred g. of sodium hydrosulfite was added with stirring to a solution of 21.2 g. of magnesium chloride hexahydrate in 500 cc. of water. To this was then added 3.6 g. of 3-amino-4-hydroxyphenylarsonic acid and 4.6 g. of N-phenyl-β-aminopropionamide-4-arsonic acid, dissolved in 160 cc. of water containing 20 cc. of a saturated sodium carbonate solution. The mixture was filtered as quickly as possible and warmed at 50° for one hour. The free base separated as a yellow, insoluble powder, which was filtered, washed with water and immediately dried in a vacuum; yield, 5.5 g. It decomposed at 120–125° and contained a small amount of sulfur as an impurity.

Anal. Subs., 0.2006: 38.44 cc. of 0.0497 *N* I_2. Calcd. for $C_{15}H_{17}O_2N_3As_2$: As, 35.63. Found: As, 35.01.

Summary

1. N-Phenyl-β-aminopropionamide-4-arsonic acid and its sodium salt have been prepared. Preliminary pharmacological tests indicate that it may be useful in treatment of trypanosomal infections.

2. β-Bromopropionyl chloride, β-bromopropionamide, N-phenyl-β-

aminopropionamide-2-methyl-5-arsonic acid and N-phenyl-β-propionamide-2-methyl-4-arsonic acid have been described for the first time.

3. 3-Amino-4-hydroxy-4′-propionamido-arsenobenzene and its hydrochloride have been prepared.

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NEW CONDITIONS FOR THE FORMATION OF GLUCOSAZONE

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Hydrazine derivatives of recently described compounds in which uronic acids are conjugated with sugars[1] have not yet been studied. We desired to prepare such derivatives of the aldobionic acid isolated from gum arabic[1b] in order further to characterize it. While a number of hydrazine derivatives of glucuronic acid have been prepared, the lack of agreement in the results of various investigators in this field seems to indicate that the reaction is not a simple one.[2]

A preliminary investigation of the action of phenylhydrazine on the simpler sugars, glucose, mannose and fructose was therefore made. The chemistry of glucose phenylhydrazone[3] is complicated by the existence of at least two isomeric forms. Although we have spent a considerable amount of time attempting to prepare the pure isomers, our results indicated that these are not readily produced by any of the published methods. Since our results were not conclusive, further discussion in this paper will be confined to a description of the formation of glucosazone from glucose and fructose, and from their phenylhydrazones under conditions not ordinarily considered favorable to osazone formation, and of the behavior of mannose phenylhydrazone under similar conditions.

The precipitation of glucosazone from a cold dilute acetic acid solution of 1 equivalent of glucose and 1.5 equivalents of phenylhydrazine was observed by Jacobi.[3c] This investigator did not examine the reaction further. It was found in the present work that when glucose is treated under

[1] (a) Heidelberger and Goebel, *J. Biol. Chem.*, **74**, 613, 619 (1927); (b) Butler and Cretcher, THIS JOURNAL, **51**, 1519 (1929); (c) see also Anderson and Sands, *ibid.*, **48**, 3172 (1926).

[2] References to the literature of this subject may be found in (a) Van der Haar, "Anleitung zum Nachweis, zur Trennung und Bestimmung der Monosaccharide und Aldehydesäuren," Gebrüder Borntraeger, Berlin, **1920**, Chapter VI, and in (b) Tollens, "Kurzes Handbuch der Kohlenhydrate," Barth, Leipzig, **1914**, pp. 766–767.

[3] (a) Fischer, *Ber.*, **20**, 824 (1887); (b) Skraup, *Monatsh.*, **10**, 406 (1889); (c) Jacobi, *Ann.*, **272**, 172 (1892); (d) Simon and Benard, *Compt. rend.*, **132**, 564 (1901); (e) Behrend, *Ann.*, **353**, 106 (1907); (f) Behrend and Lohr, *ibid.*, **362**, 78 (1908); (g) Behrend and Reinsberg, *ibid.*, **377**, 189 (1911).