[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

THE PREPARATION AND STUDY OF SYMMETRICAL BIS-ARSONO-ARYL-BENZAMIDO-UREAS[1]

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"Bayer 205" has recently received considerable attention[2] as a remedy for African sleeping sickness. The formula has not been disclosed by the discoverer except to state that the drug contains no arsenic. For some time there has been evidence to indicate that it is a symmetrical substituted urea. Quite recently Fourneau has developed a compound which he finds to have properties similar to those of the German drug. This compound is the urea of *m*-aminobenzoyl-*p*-methyl-*m*-aminobenzoyl-1-aminonaphthalene-4,6,8-sodium-trisulfonate.[3]

Due to the great importance of organic arsenicals in the treatment of sleeping sickness and similar diseases it was thought that compounds structurally related to "Fourneau's 309" but which contained arsenic might be of value in the treatment of these diseases. Accordingly, several *sym.-bis*-arsono-aryl-benzamido-ureas have been prepared. Intermediate in the preparation of these ureas it was necessary to make a number of new nitro- and amino-benzoyl-amino-arylarsonic acids.

A study of the physiological properties of these compounds has not been completed.

Benzoyl-*p*-amino-phenylarsonic acid[4] was prepared by condensing benzoyl chloride with atoxyl in alkaline solution. Meyer[5] prepared *o*-nitrobenzoyl-anthranilic acid by shaking together equal volumes of an aqueous solution of potassium anthranilate and an ethereal solution of *o*-nitrobenzoyl chloride. *m*-Nitro-benzoyl-*m*-aminobenzamide[6] was made by heating a mixture of *m*-nitrobenzoyl chloride and *m*-aminobenzamide to a temperature of 210° and also by refluxing the two substances with xylene. The nitrobenzoyl-amino-arylarsonic acids described in this paper were prepared by refluxing and stirring for two hours, molecular equivalents of the nitrobenzoyl chloride, dissolved in dry toluene or xylene, and the sodium salt of the amino-arylarsonic acid. A few of them were

[1] Constructed from a thesis submitted to the Graduate College of the University of Nebraska by Randolph T. Major in partial fulfilment of the requirements for the degree of Master of Science.

[2] Haendel and Joetten, *Berl. klin. Wochschr.*, **57**, II, 821 (1920); *C. A.*, **16**, II, 3128 (1922). Mayer and Zeiss, *Arch. Schiffs-Trop. Hyg.*, **24**, 257 (1920). Hirschfelder, *Ind. Eng. Chem.*, **15**, 458 (1923).

[3] *Science*, **59**, April 18, 1924.

[4] Kuratorium der Georg and Franziska Speyerschen Studienstiftung, Ger. pat. 191,548; *Chem. Zentr.*, **1908**, I, 780.

[5] Meyer, *Ann.*, **351**, 273 (1907).

[6] Schulze, *Ann.*, **251**, 167 (1889).

also prepared by heating on the water-bath intimate mixtures of the acid chloride with the sodium salt of the amino-arylarsonic acid. The nitrobenzoyl-amino-arylarsonic acids were then reduced to amino-benzoyl-amino-arylarsonic acids with ferrous chloride in alkaline solution.[7] Due to their great ease of oxidation, these amino acids were all precipitated in a vacuum and filtered in an inert gas. *Sym.*-diphenylurea-4,4′-diarsonic acid[4] was produced by shaking together a cold aqueous solution of atoxyl with a 20% solution of phosgene in toluene. Similarly the *sym.-bis*-arsono-aryl-benzamido-ureas were prepared by bubbling phosgene through an aqueous solution of the aminobenzoyl-amino-arylarsonic acid dissolved in the calculated amount of sodium hydroxide in solution. The amino acid solution was kept in a container cooled by an ice-bath from which air was excluded, both before and during the reaction.

All of these compounds are white or cream-colored solids that are only very slightly soluble in water, are insoluble in all common organic solvents but readily soluble in alkalies, alkali carbonates or bicarbonates.

Experimental Part

Preparation of Amino-arylarsonic Acids

***p*-Arsanilic Acid.**—This compound was prepared according to the method of Cheetham and Schmidt,[8] somewhat modified.

3-Methyl-4-amino-phenylarsonic Acid.—This intermediate was prepared by an adaptation of the method of Cheetham and Schmidt[8] for the preparation of *p*-arsanilic acid, the reaction being carried out at 170–175°; yield, 14%.

***m*-Arsanilic Acid.**—*m*-Arsanilic acid was prepared by the reduction of *m*-nitrophenylarsonic acid,[9] which in turn was made by nitrating phenylarsonic acid.

Nitrobenzoyl-amino-arylarsonic Acids

Forty millimoles of the finely divided monosodium salt of the amino-phenylarsonic acid, thoroughly dried at 110°, was added to 150 cc. of dry toluene.[10] To this suspension forty millimoles of the nitrobenzoyl chloride was added, and the mixture was heated under a reflux condenser and constantly stirred for two hours.[11] The hot mixture was filtered and washed with toluene, and alcohol, transferred to a flask containing 125 cc. of water and made just acid to congo-red with concd. hydrochloric acid. An additional 4.5 cc. of concd. hydrochloric acid was then added to hold in solution any unchanged amino-arylarsonic acid, and after it had been shaken for

[7] Benda, *Ber.*, **44**, 3302 (1911); **47**, 1006, 1316 (1914). Johnson and Adams, THIS JOURNAL, **45**, 1307 (1923).

[8] Cheetham and Schmidt, THIS JOURNAL, **42**, 828 (1920).

[9] Michaelis, *Ann.*, **320**, 294 (1902). Palmer and Adams, THIS JOURNAL, **44**, 1361 (1922).

[10] In the case of the *p*-amino-arylarsonic acids, xylene was used.

[11] In order to keep out moisture the top of the condenser was fitted with a one-holed rubber stopper bearing a short piece of glass tubing, the bore of which was just large enough to permit the stirring rod through it to revolve easily.

five minutes, it was filtered, washed with water containing a small amount of hydrochloric acid, then with alcohol and finally with ether. In order to remove any of the unchanged nitrobenzoyl chloride, the product was shaken for five minutes with 150 cc. of ether, the solution filtered and washed with ether. For final purification the product was dissolved in the calculated amount of 0.75 *N* sodium hydroxide, the solution filtered and reprecipitated by the addition of concd. hydrochloric acid. The compounds obtained ranged in color from a cream white to pure white. With one exception these compounds melted above 250°, but all decomposed somewhat explosively at higher temperatures. All were soluble in sodium hydroxide, carbonate and bicarbonate solutions, concd. sulfuric acid, and ammonium hydroxide, the *ortho* isomers being somewhat more soluble in the latter than the *meta* and *para* compounds. For the most part they were insoluble in ether, cold ethyl or methyl alcohol, chloroform, glacial acetic acid, acetone, cold toluene or xylene, and but very slightly soluble in water, hot ethyl or methyl alcohol and hot toluene or xylene. Two of them, namely, 3-nitrobenzoyl-4′-amino-phenylarsonic acid and 3-nitrobenzoyl-3′-amino-phenylarsonic acid, were also prepared by adding little by little the sodium salt of the amino-phenylarsonic acid to the stirred molten mass of the nitrobenzoyl chloride heated on a water-bath. The resulting crude product was then treated as outlined in the first method. The first method, however, was found preferable.

TABLE I

NITRO-BENZOYL-AMINO-ARYLARSONIC ACIDS

Amino-phenylarsonic acid	Yield %	M. p. °C.	Analysis: Subs. G.	0.0319 *N* I_2 Cc.	Calcd. % As	Found %
4-NB[a]-4′-$NO_2C_6H_4CONHC_6H_4AsO_3H_2$	50	>250	0.1870	19.91	20.48	20.65
3-NB-4′-$NO_2C_6H_4CONHC_6H_4AsO_3H_2$	90	>250	.1920	20.05	20.48	20.38
2-NB-4′-$NO_2C_6H_4CONHC_6H_4AsO_3H_2$	65	>250	.1984	21.01	20.48	20.58
4-NB-3′-methyl-4′-$NO_2C_6H_4CONHC_6H_3(CH_3)AsO_3H_2$	65	>250	.2001	20.38	19.73	19.78
3-NB-3′-methyl-4′-$NO_2C_6H_4CONHC_6H_3(CH_3)AsO_3H_2$	63	>250	.1983	20.25	19.73	19.90
2-NB-3′-methyl-4′-$NO_2C_6H_4CONHC_6H_3(CH_3)AsO_3H_2$	63	>250	.1920	19.80	19.73	20.02
3-NB-3′-$NO_2C_6H_4CONHC_6H_4AsO_3H_2$	38	>250	.1926	20.28	20.48	20.53
2-NB-3′-$NO_2C_6H_4CONHC_6H_4AsO_3H_2$	11	249–250[b]	.1997	20.97	20.48	20.46

[a] NB = nitrobenzoyl.

[b] Melts and decomposes at 249–250°.

Aminobenzoyl-amino-arylarsonic Acids

Twenty-five millimoles of the nitrobenzoyl-amino-arylarsonic acid was dissolved in the calculated amount of *N* sodium hydroxide solution cooled in an ice-bath. A solution of 225 millimoles of anhydrous ferrous chloride in 80 cc. of water in a 250cc. flask was made strongly alkaline to

litmus with 25% sodium hydroxide solution, and after the ferrous hydroxide mud had been thoroughly cooled, the solution of the nitrobenzoyl-amino-arylarsonic acid was added in small portions, and finally the contents of the flask were vigorously shaken for ten minutes. The mass was then filtered with suction, and washed well with water, care being taken to keep enough water on the precipitate to prevent air from being drawn in on the filtrate. The filtrate was then poured into a 500cc. Erlenmeyer flask, fitted with a two-holed rubber stopper, through one hole of which a 250cc. dropping funnel was passed and through the other a glass tube with a stopcock. The flask was at once evacuated and cooled by immersion in an ice-bath. The aminobenzoyl-amino-arylarsonic acid was then precipitated by the addition of concd. hydrochloric acid through the dropping funnel, care being taken to prevent the entrance of air. Sufficient hydrochloric acid was added to turn congo red to blue, then an additional 3 cc. to dissolve any amino-arylarsonic acid formed by hydrolysis during the reaction. The precipitate was filtered by means of an apparatus constructed as follows.[12] A 250cc. Büchner funnel (diameter 125 mm.), Fig. 1, was fitted into a liter filter flask. Over the funnel was placed a bell jar with a small opening at the top. The diameter of the lower opening was equal to that of the funnel; a rubber connection tube between the two was made from an automobile inner tube. A two-holed rubber stopper was inserted in the opening at the top of the bell jar, through one hole of which a 250cc. dropping funnel was passed and through the other the stem of a three-way stopcock, one opening of which led to a source of carbon dioxide (which was washed by being bubbled through water), and the other to one arm of a Y-tube. One other arm of the Y-tube was connected by suction tubing to the filter flask and the third arm to the suction pump. By the use of this apparatus it was possible to filter the compounds in an atmosphere of inert gas; this was found necessary due to their tendency to oxidize readily in the air.

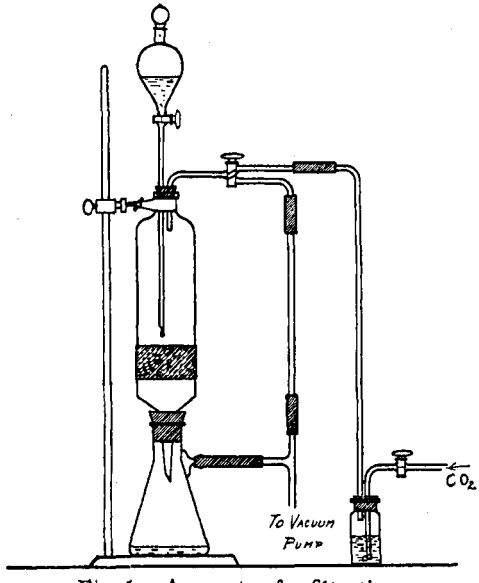

Fig. 1.—Apparatus for filtration.

[12] An apparatus somewhat similar to this was constructed by Reddelien [*Chem.-Ztg.*, **41**, 580 (1917); *Chem. Zentr.*, [2] **1917**, 262] for a like purpose.

In order to filter the compound a piece of filter paper the diameter of which was somewhat greater than that of the Büchner funnel was fitted into place, dampened and the funnel then fixed in place under the bell jar, being connected to it by the rubber tube. The lower part of the funnel was connected to the filter flask and then by proper adjustment of the three-way stopcock, suction was produced above and below the funnel. When a vacuum had been established in the apparatus the three-way stopcock was closed, and the aqueous suspension of the aminobenzoyl-amino-aryl-arsonic acid, which up to this time had been kept in the evacuated Erlenmeyer flask, was poured into the dropping funnel, and at once admitted onto the filter by opening the stopcock in the dropping funnel. The three-way stopcock was then so turned as to admit carbon dioxide gas to the bell jar, causing rapid filtration. The precipitate was washed with slightly acidulated water admitted through the dropping funnel. Carbon dioxide was then turned off and a vacuum again produced in the bell jar. The precipitate under these conditions was washed well, first with alcohol and later with ether, both of which were introduced through the dropping funnel. Due to the vacuum both above and below the precipitate the washing fluids passed through more slowly, giving them a better chance to wash out impurities. Carbon dioxide was again introduced at the end of this washing in order to remove the last traces of ether. After this, all suction was removed, the filter flask emptied, washed out with water, replaced, and a vacuum established again both above and below the precipitate. Sufficient water was then introduced through the dropping funnel to wet the precipitate thoroughly. Then concd. ammonium hydroxide was admitted sufficient to dissolve the aminobenzoyl-amino-aryl-arsonic acid, which was finally completely washed through by the introduction of carbon dioxide. This solution in the filter flask was poured into the above-mentioned 500cc. Erlenmeyer flask, air withdrawn from the flask, and the compound precipitated as previously described except that in this case glacial acetic acid was used. The precipitate was similarly filtered, washed well with water and dried in a vacuum. The compounds obtained were light cream-colored, darkening on exposure to the air, especially when moist. The alkaline solution was found to be especially readily attacked by oxygen. These oxidation products on analysis were found to have lower percentages of arsenic than the corresponding aminobenzoyl-amino-aryl-arsonic acids. None of these compounds was found to melt below 250° but they decomposed, not explosively, at higher temperatures. All were soluble in sodium hydroxide, carbonate and bicarbonate solutions, concd. sulfuric acid and ammonium hydroxide. They were insoluble in ether, ethyl or methyl alcohol, glacial acetic acid, acetone, toluene, but very slightly soluble in water and chloroform and very difficultly soluble in concd. hydrochloric acid. All were quite deliques-

cent. For analysis, they were dried, first in a vacuum and then in the oven.

TABLE II

AMINOBENZOYL-AMINO-ARYLARSONIC ACIDS

Amino-phenylarsonic acid	Yield %	M. p. °C.	Analysis: Subs. G.	0.0509 *N* I_2 Cc.	Calcd. % As	Found %
4-AB[a]-4′-$NH_2C_6H_4CONHC_6H_4AsO_3H_2$	70	>250	0.1913	22.36	22.35	22.25
3-AB-4′-$NH_2C_6H_4CONHC_6H_4AsO_3H_2$	28	>250	.1861	21.40	22.35	21.91
2-AB-4′-$NH_2C_6H_4CONHC_6H_4AsO_3H_2$	25	>250	.1831	21.43	22.35	22.30
4-AB-3′-methyl-4′-$NH_2C_6H_4CONHC_6H_3(CH_3)AsO_3H_2$	60	>250	.2043	22.63	21.42	21.20
3-AB-3′-methyl-4′-$NH_2C_6H_4CONHC_6H_3(CH_3)AsO_3H_2$	25	>250	.1870	21.18	21.42	21.52
3-AB-3′-$NH_2C_6H_4CONHC_6H_4AsO_3H_2$	55	160[b]	.1995	23.05	22.35	22.50

[a] AB = aminobenzoyl.

[b] Decomposed.

Sym.-Bis-Arsono-aryl-benzamido-ureas

Six millimoles of the aminobenzoyl-amino-arylarsonic acid in a 250cc. distilling flask was dissolved in 12 millimoles of sodium hydroxide in 100 cc. of water cooled in an ice-bath. The flask was evacuated by suction. With the flask still in the ice-bath, phosgene was slowly bubbled through the solution until the mixture turned acid to congo red paper. The precipitate which separated was filtered off, washed well with water, followed by alcohol and then ether. It was dried at first over sodium hydroxide in a vacuum then in the oven. The compounds obtained are cream colored, and do not darken on exposure to the air. With one exception, all of them melted above 250°, but they decomposed, not explosively, at higher temperatures. All were soluble in sodium hydroxide, carbonate and bicarbonate solutions, concd. sulfuric acid and ammonium hydroxide, but insoluble in ether, ethyl or methyl alcohol, glacial acetic acid, acetone, toluene and water.

TABLE III

SYM.-BIS-ARSONO-ARYL-BENZAMIDO-UREAS

Urea	Yield %	M. p. °C.	Analysis: Subs. G.	0.0514 *N* I_2 Cc.	Calcd. % As	Found %
Sym.-bis-3-methyl-4-APB[a]-4′-$(H_2O_3AsC_6H_3(CH_3)NHCOC_6H_4NH)_2CO$	95	>250	0.1922	20.72	20.65	20.75
Sym.-bis-4-APB-4′-$(H_2O_3AsC_6H_4NHCOC_6H_4NH)_2CO$	35	>250	.1943	22.05	21.50	21.55
Sym.-bis-3-APB-3′-$(H_2O_3AsC_6H_4NHCOC_6H_4NH)_2CO$	30	249–250[b]	.2026	22.43	21.50	21.32
Sym.-bis-4-APB-3′-$(H_2O_3AsC_6H_4NHCOC_6H_4NH)_2CO$	30	>250	.1070	11.88	21.50	21.35
Sym.-bis-4-APB-2′-$(H_3O_2AsC_6H_4NHCOC_6H_4NH)_2CO$	90	>250	.1914	21.28	21.50	21.41

[a] APB = arsonophenylbenzamido.

[b] Melted and decomposed.

Summary

1. The sodium salts of *m*-arsanilic, *p*-arsanilic and 3-methyl-4-amino-phenylarsonic acids were condensed with the three isomeric nitrobenzoyl chlorides.

2. By reduction with ferrous hydroxide the nitrobenzoyl-amino-phenylarsonic acids were converted into aminobenzoyl-amino-phenyl-arsonic acids.

3. *Sym.-bis*-arsono-aryl-benzamido-ureas were obtained by condensing various aminobenzoyl-amino-phenylarsonic acids with phosgene.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF MIAMI UNIVERSITY]

THE PROPERTIES OF ARYL ESTERS AND ETHERS OF N- PIPERIDINO ALKYL COMPOUNDS

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In the preparation of synthetic bodies with anesthetic properties similar to those of cocaine, the attention of the investigators has usually been focused on the relative positions of the basic and the carboxyl groups.[1]

The application of this principle has resulted in the preparation of a considerable number of excellent compounds which function as substitutes for cocaine and tropacocaine for anesthetic purposes.

The presence of the piperidine residuum in cocaine and tropacocaine and its possible part in the production of the desirable properties of these two alkaloids have more generally been ignored in the synthesis of new cocaine substitutes. J. v. Braun[2] has prepared a substance, in his eccaine, of a constitution that departs from that of cocaine and tropacocaine in that the alkylbenzoate is attached to the nitrogen of the ecgonine portion instead of to a carbon as in cocaine. This compound has anesthetic properties similar to those of cocaine.[3] Pyman[4] has used piperidine itself without the substituting groups in the preparation of the hydrochloride of β-N-piperidino-ethyl benzoate. This compound he found to possess anesthetic properties but to be irritating. The properties of these two substances indicate that the piperidine residuum can take the place of the alkylamine group in the preparation of Procaine-like compounds. In order to test this relationship somewhat more thoroughly, the salts of γ-N-piperidino-propyl benzoate, γ-N-piperidino-propyl phenyl ether, and β-N-piperidino-ethyl phenyl ether were prepared, and their properties studied.

[1] Kamm, THIS JOURNAL, **42**, 1030 (1920).

[2] J. v. Braun and Müller, *Ber.*, **51**, 235 (1918).

[3] Fraenkel, "Die Arzneimittel Synthese," Julius Springer, Berlin, 5th ed., **1921**, p. 355.

[4] Pyman, *J. Chem. Soc.*, **93**, 1793 (1908).