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

THE CONDENSATION OF 3-NITRO-4-HALOGENO-PHENYLARSONIC ACIDS WITH ALIPHATIC AMINO COMPOUNDS AND PHENOLS

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Aromatic arsonic acid derivatives containing both primary and secondary amino groups have not been studied as extensively as those containing only a primary amino group; and arsonic acid derivatives containing more than one aromatic nucleus, the second substituted nucleus being attached to that containing the arsono group by the linkage of oxygen, have been studied hardly at all. A common method for synthesizing types of compounds such as these is through the substitution of nuclear halogen. It has long been known that this replacement could be brought about by the ordinary reagents employed in the aliphatic series, only when the attachment of the halogen was loosened by the presence of certain groups, such as nitro, cyano, carboxyl, arsono, etc. Gibson and others[2] successfully applied the method of Ullmann[3] to condensation reactions of *o*-bromophenylarsonic acid with aromatic amines. In an analogous manner Etzelmiller and Hamilton[4] condensed *o*-chlorophenylarsonic acid with aliphatic amines, aliphatic alcohols and phenol.

Boehringer and Soehne[5] showed that 3-nitro-4-chlorophenylarsonic acid and glycine reacted in an alkaline solution to give 2-nitro-4-arsonophenylglycine. King[6] condensed the same arsonic acid with piperidine in an alcoholic solution to form 3-nitro-4-piperidinophenylarsonic acid. Fourneau and Funke[7] showed that 3-nitro-4-chlorophenylarsonic acid reacted with ethylenediamine and piperazine in the presence of anhydrous sodium acetate. This reaction has been further extended by Barber,[8] who prepared a series of diphenylamine derivatives through the condensation of 3-nitro-4-chlorophenylarsonic acid with various substituted aromatic amines in aqueous alkaline solution. Thus, the reactivity of the halogen in 3-nitro-4-halogenophenylarsonic acids suggested the use of these compounds in condensation reactions with aliphatic amino compounds and substituted phenols leading to two series of arsenicals.

[1] Parke, Davis and Company Fellow.

[2] Burton and Gibson, *J. Chem. Soc.*, 247 (1927); Gibson and Johnson, *ibid.*, 2499 (1927); 2204 (1928).

[3] Ullmann, *Ann.*, **355**, 312 (1907).

[4] Etzelmiller and Hamilton, THIS JOURNAL, **53**, 3085 (1931).

[5] Boehringer and Soehne, German Patent 285,604.

[6] King, *J. Chem. Soc.*, 1053 (1927).

[7] Fourneau and Funke, *Bull. soc. chim.*, **43**, 889 (1928).

[8] Barber, *J. Chem. Soc.*, 471 (1929).

A series of condensation reactions was carried out with 3-nitro-4-halogenophenylarsonic acids and various aliphatic primary amines. The amines, iso- and *n*-amyl, iso- and *n*-butyl, *n*-propyl and ethanol, condensed with the arsonic acid in aqueous alkaline solution. The reaction worked equally well in an anhydrous mixture of potassium carbonate and *n*-amyl alcohol, but the ease of carrying out the condensation and purification of the reaction product favored the former method. Three hours at temperatures of 125–135° was found to be sufficient time for obtaining maximum yields in this type of condensation.

Glycine readily condensed with 3-nitro-4-halogenophenylarsonic acids in an anhydrous mixture of potassium carbonate, *n*-amyl alcohol and copper powder, to give good yields of 2-nitro-4-arsonophenylglycine.

The amino derivatives of the condensation products of the aliphatic primary amines with 3-nitro-4-halogenophenylarsonic acids were prepared in yields of 40–48% by the method of Jacobs, Heidelberger and Rolf.[9]

The free base, 2-amino-4-arsonophenylglycine, was not isolated when the corresponding nitro derivative was reduced. In every instance, 2-oxy-3-dihydroquinoxaline-7-arsonic acid,[10] was obtained through the elimination of water.

A series of condensation reactions was also carried out with substituted phenols. These reactions took place only in an anhydrous medium. Phenol-, *p*-chlorophenol, *o*- and *p*-cresols and *p*-nitrophenol reacted with 3-nitro-4-bromophenylarsonic acid to form the corresponding phenyl ether derivatives. Under similar conditions, salicylic acid, *o*-nitrophenol, salicylic aldehyde and *p*-hydroxybenzaldehyde failed to condense.

The amino derivatives of these phenyl ethers were prepared by means of reduction with alkaline ferrous hydroxide. When 2-amino-4-arsono-2′-carboxyphenyl ether was heated above 200°, water was eliminated, leading to the formation of the corresponding lactam.

It was considered desirable to study the reaction of 3-nitro-4-bromophenylarsonic acid with aliphatic alcohols. The alcohols, iso- and *n*-amyl, and *n*-butyl, were included in this study. The general procedure was to heat a mixture of 10 g. of 3-nitro-4-bromophenylarsonic acid, 10 g. of anhydrous potassium carbonate, 0.2 g. of copper powder and 35 cc. of the alcohol containing either potassium or sodium, in amounts varying from 1 to 2.5 g., for ten hours at refluxing temperature, with stirring. In no case was a condensation product isolated. Condensation reactions with isoamyl alcohol invariably led to tarry formations from which nothing was isolated. With *n*-butyl alcohol, although the alcohol had been carefully dried and distilled, as high as 50% of the compound was hydrolyzed to 3-nitro-4-hydroxyphenylarsonic acid. The water present was

[9] Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1581 (1918).

[10] Ewins, Newbery and Stickings, *J. Chem. Soc.*, 851 (1927).

possibly due to the formation of the double potassium salt of the arsonic acid group.

In beginning a study of the activity of the halogen in the para-position with respect to the arsonic acid group, a series of condensation reactions with aniline was carried out under varying experimental conditions. The halogenophenylarsonic acid employed in these reactions was *p*-bromophenylarsonic acid. The general procedure was to heat 10 g. of *p*-bromophenylarsonic acid, 10 g. of anhydrous potassium carbonate, 0.2 g. of catalyst and varying amounts of aniline and amyl alcohol, which was used as a solvent at different temperatures, in an Erlenmeyer flask fitted with a condenser with a ground-glass connection and mechanical stirrer. Only two catalysts, copper powder and cuprous iodide, were tried in this series of reactions while *n*-amyl alcohol was the only solvent employed. The temperatures varied from 90 to 220°, the time from ten to eighty hours and the amounts of aniline and amyl alcohol from 0 cc. to 30 cc. In some instances sealed tube reactions were employed. In no case was a substance isolated which would give the slightest qualitative test for nitrogen. In all cases from 40–80% of the original arsonic acid was recovered.

Incidentally, the halogen in *p*-bromophenylarsonic acid was not hydrolyzed when refluxed for forty-eight hours in 3 *N* sodium hydroxide solution.

Experimental[11]

General Procedure for the Preparation of 3-Nitro-4-alkylaminophenylarsonic Acids.—Twelve grams of 3-nitro-4-chlorophenylarsonic acid, 40 cc. of 2 *N* sodium hydroxide, 6 cc. of the primary alkylamine and 25 cc. of water in a 200-cc. Erlenmeyer flask, fitted with a condenser, were heated in an oil-bath at 125–135° for three hours. On acidification to Congo red paper with 6 *N* hydrochloric acid, an orange colored oil separated which on cooling solidified to a yellow crystalline mass. This was redissolved in sodium carbonate solution, acidified to litmus paper and boiled with decolorizing carbon. The arsonic acid was again precipitated with hydrochloric acid and further purified by recrystallizing from dilute acetic acid. These compounds did not melt or decompose below 250°.

TABLE I

3-NITRO-4-ALKYLAMINOPHENYLARSONIC ACIDS

-Aminophenyl-arsonic acid	Yield, %	Formula	Arsenic analyses, % Calcd.	Found	
3-Nitro-4-propyl-	68	$C_9H_{13}O_5N_2As$	24.67	24.60	24.58
3-Nitro-4-butyl-	62	$C_{10}H_{15}O_5N_2As$	23.58	23.62	23.63
3-Nitro-4-isobutyl-	60	$C_{10}H_{15}O_5N_2As$	23.58	23.57	23.48
3-Nitro-4-amyl-	85	$C_{11}H_{17}O_5N_2As$	22.59	22.70	22.70
3-Nitro-4-isoamyl-	80	$C_{11}H_{17}O_5N_2As$	22.59	22.65	22.74
3-Nitro-4-β-hydroxyethyl	74	$C_8H_{11}O_6N_2As$	24.51	24.46	24.50

2-Nitro-4-arsonophenylglycine.[12]—A mixture of 15 g. of 3-nitro-4-bromophenylarsonic acid, 12 g. of anhydrous potassium carbonate, a trace of copper powder, 6 g. of

[11] Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

[12] Boehringer and Soehne, German Patent 285,604.

glycine and 35 cc. of *n*-amyl alcohol in a 200-cc. Erlenmeyer flask fitted with a ground-glass connection was heated for seven hours in an oil-bath at 150°. The reaction mixture was agitated by means of a mechanical stirrer extending down through the condenser. The reaction mixture was cooled and the amyl alcohol removed by decantation. The mass remaining was dissolved in 75 cc. of hot water and acidified to Congo red paper with hydrochloric acid. A dark brown crystalline mass separated. This was further purified by reprecipitating from sodium carbonate solution and recrystallization from acetic acid. The arsonic acid separated from this solvent in the form of light yellow needles decomposing at 230–235°. The yield was 9.0 g. or 61% of the calculated amount.

Anal. Calcd. for $C_8H_9O_5N_2As$: As, 23.44. Found: As, 23.50, 23.55.

General Procedure for the Preparation of 3-Amino-4-alkylaminophenylarsonic Acids.—The method employed for the preparation of these compounds was that described by Jacobs, Heidelberger and Rolf,[9] an alkaline ferrous hydroxide reduction. Recrystallized from 75% methyl alcohol, the free bases separated in the form of white needles which assumed a grayish or pink color after exposure to the air for a few moments.

TABLE II

3-AMINO-4-ALKYLAMINOPHENYLARSONIC ACIDS

Aminophenyl-arsonic acid	Yield, %	Formula	Arsenic analyses, % Calcd.	Found	
3-Amino-4-propyl-	66	$C_9H_{15}O_3N_2As$	27.37	27.31	27.39
3-Amino-4-butyl-	66	$C_{10}H_{17}O_3N_2As$	26.04	25.98	25.99
3-Amino-4-isobutyl-	66	$C_{10}H_{17}O_3N_2As$	26.04	25.90	25.92
3-Amino-4-amyl-	73	$C_{11}H_{19}O_3N_2As$	24.83	24.87	24.96
3-Amino-4-isoamyl-	67	$C_{11}H_{19}O_3N_2As$	24.83	24.93	24.77
3-Amino-4-β-hydroxy-ethyl-[a]	39	$C_8H_{13}O_4N_2As$	27.17	27.15	27.15

[a] I. D. Farbenind A.-G., German Patent 530,397 (1928).

2-Oxy-3-dihydroquinoxaline-7-arsonic Acid.[10]—When 2-nitro-4-arsonophenylglycine was reduced with alkaline ferrous hydroxide, a quinoxaline derivative was formed through the loss of water. The free base was not isolated, the ring compound separating from the filtrate when it was acidified to Congo red paper. Recrystallized from 75% methyl alcohol, 2-oxy-3-dihydroquinoxaline-7-arsonic acid separated in long white needles, yield 70%.

Anal. Calcd. for $C_8H_9O_4N_2As$: As, 27.57; N, 10.28. Found: As, 27.65, 27.59; N, 10.15.

The Condensation of 3-Nitro-4-bromophenylarsonic Acid with Phenols.—A mixture of 10 g. of 3-nitro-4-bromophenylarsonic acid, 10 g. of anhydrous potassium carbonate, a trace of copper powder, a small excess of an equivalent amount of the phenol and 35 cc. of *n*-amyl alcohol in a 200-cc. Erlenmeyer flask fitted with a ground-glass connection was heated for six to eight hours in an oil-bath at 140–150°, the reaction mixture being well stirred. The excess phenol and amyl alcohol were removed by steam distillation, and the resulting solution was treated with decolorizing carbon. On acidification to Congo red paper with dilute hydrochloric acid a brownish mass separated which was further purified through crystallization from acetic acid. These phenyl ether derivatives separated from this solvent in the form of a white crystalline mass. Phenol, *p*-chlorophenol, *p*-cresol, *o*-cresol and *p*-nitrophenol were condensed with the 3-nitro-4-bromophenylarsonic acid in this manner. The carboxyl derivatives were prepared through oxidation of the corresponding methyl derivatives with alkaline permanganate. They do not melt or decompose below 250°.

TABLE III

2-NITRO-4-ARSONOPHENYL ETHER DERIVATIVES

2-Nitro-4-arsono-	Yield, %	Formula	Arsenic analyses, % Calcd.	Found	
-Phenyl ether	54	$C_{12}H_{10}O_6NAs$	22.11	22.05	21.97
-4'-Chlorophenyl ether	78	$C_{12}H_9O_6NClAs$	20.08	20.21	19.92
-4'-Methylphenyl ether	46	$C_{13}H_{12}O_6NAs$	21.25	21.35	21.27
-4'-Carboxyphenyl ether	60	$C_{13}H_{10}O_8NAs$	19.58	19.61	19.66
-2'-Methylphenyl ether	25	$C_{13}H_{12}O_6NAs$	21.25	21.35	21.27
-2'-Carboxyphenyl ether	82	$C_{13}H_{10}O_8NAs$	19.58	19.70	19.67
-4'-Nitrophenyl ether	10	$C_{12}H_9O_8N_2As$	19.53	19.74	19.67

2-Amino-4-arsonophenyl Ether Derivatives.—These compounds were prepared by reducing the corresponding nitro derivatives with alkaline ferrous hydroxide in a manner previously described.

TABLE IV

2-AMINO-4-ARSONOPHENYL ETHER DERIVATIVES

2-Amino-4-arsono-	Yield, %	Formula	Arsenic analyses, % Calcd.	Found	
-Phenyl ether	57	$C_{12}H_{12}O_4NAs$	24.27	24.29	24.34
-4'-Chlorophenyl ether	66	$C_{12}H_{11}O_4NClAs$	21.84	21.81	21.92
-4'-Carboxyphenyl ether	73	$C_{13}H_{12}O_6NAs$	21.25	21.28	21.23
-2'-Methylphenyl ether	45	$C_{13}H_{14}O_4NAs$	23.22	23.22	23.20
-2'-Carboxyphenyl ether	58	$C_{13}H_{12}O_6NAs$	21.25	21.27	21.21

2-Amino-4-arsono-2'-carboxyphenyl Ether Lactam.—Three grams of 2-amino-4-arsono-2'-carboxyphenyl ether was placed in a hard-glass test-tube fitted with a suction apparatus. The tube was placed in an oil-bath at 200–210°. At this temperature water was eliminated. Heating was continued for twenty minutes, after which the reaction mixture was dissolved in dilute sodium hydroxide and treated with decolorizing carbon. After precipitation with hydrochloric acid, the lactam was further purified by recrystallizing from 150 cc. of 75% acetic acid. It separated from this solvent in white rectangular plates; yield 2 g. or 70%. It does not melt or decompose below 250°.

Anal. Calcd. for $C_{13}H_{10}O_6NAs$: As, 22.39: N, 4.18. Found: As, 22.41, 22.44; N, 4.06, 3.97.

4-Arsono-4'-methylphenyl Ether.—Twenty grams of 4-amino-4'-methylphenyl ether was dissolved in 24 cc. of hydrochloric acid (sp. gr. 1.18) and 400 cc. of water. This solution was diazotized at 0° with a solution of 7 g. of sodium nitrite in 50 cc. of water in the usual manner. After neutralizing the diazo solution to Congo red paper with 2 *N* sodium carbonate solution, it was added to a solution of sodium arsenate at 0°, which had been prepared by dissolving 30 g. of arsenious oxide in 300 cc. of 2 *N* sodium carbonate to which had been added a solution of 1 g. of copper sulfate dissolved in 25 cc. of water. After stirring for two hours, the reaction mixture was concentrated to 400 cc. on a steam-bath, treated with decolorizing carbon and the arsonic acid precipitated with hydrochloric acid. It was further purified through recrystallization from 75% acetic acid as white plates; yield, 47%. It did not melt or decompose below 250°.

Anal. Calcd. for $C_{13}H_{13}O_4As$: As, 24.35. Found: As, 24.32, 24.28.

4-Arsono-4'-carboxyphenyl Ether.—This compound was prepared by oxidizing the corresponding methyl derivative in alkaline permanganate solution; yield, 84%. It did not melt or decompose below 250°.

Anal. Calcd. for $C_{13}H_{11}O_6As$: As, 22.19. Found: As, 22.13, 22.11.

Summary

1. Condensation reactions with 3-nitro-4-halogenophenylarsonic acids and a series of aliphatic amino compounds, namely, iso- and *n*-amyl, iso- and *n*-butyl, *n*-propyl and ethanol amines, and glycine were successfully completed.

2. The corresponding amino derivatives of the above condensation products were prepared.

3. 3-Nitro-4-bromophenylarsonic acid was condensed with phenol and a series of substituted phenols, namely, *p*-chlorophenol, *o*- and *p*-cresols and *p*-nitrophenol, leading to a series of phenyl ether derivatives. The carboxyl derivatives were also prepared through the oxidation of the methyl derivatives.

4. The corresponding amino derivatives of the substituted phenol condensation products were synthesized. The lactam of 2-amino-4-arsono-2′-carboxyphenyl ether was obtained through the elimination of water from 2-amino-4-arsono-2′-carboxyphenyl ether. This resulted in the formation of a seven-membered ring compound.

5. A study was made of the effects of experimental conditions on the reaction of *p*-bromophenylarsonic acid with aniline.

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[CONTRIBUTION FROM THE PLAUT RESEARCH LABORATORY OF LEHN & FINK, INC.]

HALOGEN DERIVATIVES OF MONOHYDROXYDIPHENYLMETHANE AND THEIR ANTIBACTERIAL ACTION

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It was shown in a recent communication that monosubstituted halogen derivatives of 2,4-dihydroxydiphenylmethane are potent bactericides for *Eberthella typhi* and *Staphylococcus pyogenes aureus*.[1] Distinct differences in antibacterial action were observed depending upon the position of the substituting halogen. Thus with both the chloro and the bromo derivatives, it was found that a greater germicidal efficacy toward both test microörganisms was obtained in the case of substitution in the nucleus bearing the two hydroxyl groups than in that of substitution in the other nucleus. While *E. typhi* appeared to be more susceptible to the action of the compounds of this group than *Staph. aureus* the differences in susceptibility were by no means indicative of bactericidal specificity.

Notes on the Preparation of Halogen Hydroxydiphenylmethane Derivatives.—In continuing our studies on related problems, we devoted

[1] Klarmann and Von Wowern, THIS JOURNAL, **51**, 605 (1929).