Several attempts at replacing the amino group by hydroxyl were unsuccessful and only a reddish brown dye melting with decomposition between 260–270° was isolated but not identified.

Summary

1. 5-Phenyl-5-ethylbarbituric acid has been nitrated.

2. The following groups have been introduced into the phenyl ring through the nitro group: amino-, acetamino-, bromo-acetamino-, bromo-amino-, nitro-amino-, nitro-acetamino-, chloro-.

3. Methyl ethyl phenylethylmalonate has been nitrated and the nitro group shown to be in the para position in the benzene ring. In addition the following groups have been introduced into the phenyl ring of methyl ethyl phenylethylmalonate: 4-amino-, 4-hydroxy-, 4-acetamino-, 4-methoxy-.

4. None of the substituted phenylethylmalonates could be condensed with urea to form the corresponding barbituric acids.

5. Preliminary physiological tests which have been carried out on a majority of the 5,5-substituted phenylalkylbarbituric acids show that these compounds with the exception of the 4-chlorophenylethylbarbituric acid are inert. The sedative properties of the chloro derivative are of the same order as those of phenylethylbarbituric acid but the substance is slightly more toxic.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS, NORTHWESTERN UNIVERSITY]

CONDENSATION PRODUCTS OF AMINO-ARSANILIC AND ARSANILIC ACIDS[1]

BY P. L. CRAMER WITH W. LEE LEWIS

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This paper is a continuation of the study[2] of condensation products of amino-arsanilic acid with 1,2-diketones to yield arsenated quinoxalines and with monocarbonyl compounds to form arsenated Schiff's bases. In the present study arsanilic acid as well as amino-arsanilic acid has been employed.

Glyoxal sodium bisulfite condenses with amino-arsanilic acid to give 6-arsono-quinoxaline-2,3-sodium bisulfite. This compound when treated with hydrochloric acid gives 6-arsono-quinoxaline, parent substance of this series.

Maltosone and lactosone, prepared according to the method of Emil

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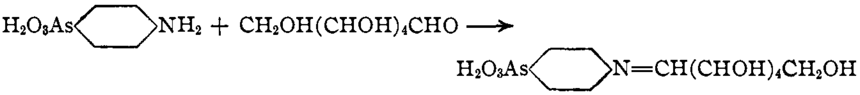
[1] This research was carried out under a grant from the Public Health Institute of Chicago. Some of the compounds are being studied for possible therapeutic value at the University of Wisconsin in the Department of Pharmacology.

[2] W. Lee Lewis, P. L. Cramer and R. S. Bly, THIS JOURNAL, **46**, 2058 (1924).

Fischer,[3] condense with amino-arsanilic acid to give substituted quinoxalines. These compounds are readily hydrolyzed by water.

Aldoses condense with arsanilic acid to form Schiff bases containing an aromatic arsonic acid group and a carbohydrate residue. The reaction of glucose is typical of these reactions.



Similar products were obtained with mannose, galactose, arabinose and xylose. These compounds are also very soluble in water and readily hydrolyzed. The rotations of the sugars are inverted by the aromatic arsonic acid group. Due to the fact that these compounds are insoluble in organic solvents and decompose rapidly in water, no definite rotation data could be obtained. The data given indicate the degree and rate of hydrolysis.

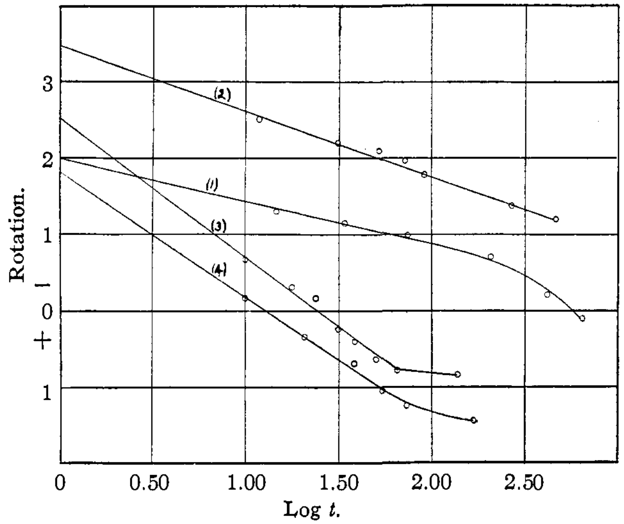


Fig. 1.—Curves showing the rate of hydrolysis and the approximate initial rotations of 4-aldo-aminophenylarsonic acids. Data from Table II.

Aromatic sulfone chlorides react with arsanilic and amino-arsanilic acids to give substituted phenylsulfone-aminophenylarsonic acids. These were prepared by the Schotten–Baumann reaction. Of this series, 4-phenylsulfone-aminophenylarsonic acid,[4] 4-*p*-tolylsulfone-aminophenylarsonic acid,[5] 4-*m*-nitrophenylsulfone-aminophenylarsonic acid[6] and 4-*m*-nitro-*p*-tolylsulfone-aminophenylarsonic acid[6] have previously been described.

[3] Fischer, "Untersuchung über Kohlenhydrate und Ferment," p. 142.

[4] Little, Cohen and Morgan, *J. Chem. Soc.*, **95**, 1482 (1909).

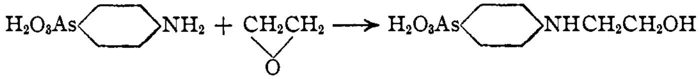
[5] Mouneyrat, French Patent 401,586 (1908); English Patent 142,947 (1919).

[6] Leslie F. Hewitt, H. King and W. O. March, *J. Chem. Soc.*, 1355–1370 (1926).

The present study includes compounds prepared from benzenesulfone chloride and *p*-tolylsulfone chloride with amino-arsanilic acid, and also *p*-bromobenzene-sulfone chloride with both arsanilic and amino-arsanilic acids. In the case of amino-arsanilic acid only one amino group is involved in the reaction. Judging from the comparative reactivities of the two groups, it is assumed that the amino group in the para position to the arsonic acid is the reactive group.

Highly colored compounds were obtained by condensing picryl chloride with both arsanilic and amino-arsanilic acids in absolute ethyl alcohol, namely, 4-(2,4,6-trinitrophenylamino)-phenylarsonic acid and 4-(2,4,6-trinitrophenylamino)-3-aminophenylarsonic acid.

p-Arsono-anilino-ethanol-2[7] is readily prepared in good yields by the reaction of ethylene oxide and arsanilic acid in the cold.



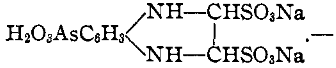
By refluxing arsanilic acid with an excess of ω-bromoacetophenone, 4-di-(phenacylamino)-phenylarsonic acid is formed.

$$H_2O_3AsC_6H_4NH_2 + 2BrCH_2COC_6H_5 \longrightarrow H_2O_3AsC_6H_4N(CH_2COC_6H_5)_2 + 2HBr$$

4-Phenacylaminophenylarsonic acid has been prepared by Jacobs and Heidelberger.[8]

Experimental Part

Preparation of 6-Arsonoquinoxaline-2,3-sodium Disulfonate,

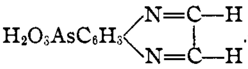


$$H_2O_3AsC_6H_3\left\langle\begin{matrix}NH—CHSO_3Na\\ |\\ NH—CHSO_3Na\end{matrix}\right.$$

.—Five grams of amino-arsanilic acid was dissolved in 25 cc. of *N* sodium hydroxide solution and 6 g. of powdered glyoxal sodium bisulfite added. The reaction mixture was heated to 60° with stirring until the bisulfite compound had dissolved. The solution was filtered and acidified slightly to congo paper with concentrated hydrochloric acid. An equal volume of ethyl alcohol was added to the solution and after standing for a few minutes in the cold a bulky mass of grayish white needles was formed. The product was purified by dissolving in a small amount of water and precipitating with ethyl alcohol as previously described. The yield was 6 g. The product is insoluble in organic solvents but very soluble in water.

Anal. Subs., 0.1583, 0.1615; 0.5631, 0.6250; 0.3861, 0.3144; 14.05, 14.35 cc. of 0.04810 *N* iodine solution; $BaSO_4$, 0.5686, 0.6470; Na_2SO_4, 0.1202, 0.0984. Calcd. for $C_8H_9O_9N_2S_2Na_2As$: As, 16.22; S, 13.88; Na, 9.95. Found: As, 16.01, 16.02; S, 13.87, 14.22; Na, 10.08, 10.13.

6-Arsonoquinoxaline,



$$H_2O_3AsC_6H_3\left\langle\begin{matrix}N{=}C—H\\ |\\ N{=}C—H\end{matrix}\right.$$

.—Five grams of 6-arsonoquinoxaline-2,3-sodium bisulfite was dissolved in 20 cc. of water. After filtering, the solution was heated to boiling and made strongly acid to congo paper with concentrated hydrochloric acid. The solution was boiled with stirring until no more sulfur dioxide was given off.

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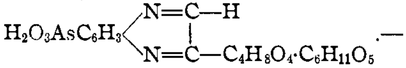
[7] Hamilton, THIS JOURNAL, **45**, 2751 (1923).

[8] Jacobs and Heidelberger, *ibid.*, **41**, 1590 (1919).

The resulting dark colored precipitate was washed with hot water and purified further by refluxing with water. The green colored product was dried to constant weight by heating at 100° under reduced pressure. The compound is slightly soluble in water and insoluble in organic solvents. It does not melt below 250°.

Anal. Subs., 0.1548, 0.1692; 24.90, 27.35 cc. of 0.04810 *N* iodine solution. Calcd. for $C_8H_7O_3N_2As$: As, 29.51. Found: As, 29.01, 29.14.

3-Glucosido-erythrityl-quinoxaline-6-arsonic Acid,

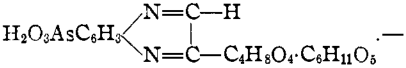


$$H_2O_3AsC_6H_3\left\langle\begin{array}{l}N{=}C{-}H\\ \quad\;\,|\\ N{=}C{-}C_4H_8O_4{\cdot}C_6H_{11}O_5\end{array}\right..\text{—}$$

Five grams of maltosone was dissolved in 159 cc. of absolute methyl alcohol and to this was added 3.5 g. of amino-arsanilic acid in 50 cc. of methyl alcohol. The solution was refluxed for three hours and the resulting purple precipitate removed and refluxed with absolute methyl alcohol for purification. The product weighed 4 g. or 60% of the theoretical and did not melt below 250°. It is quite soluble in water but is easily hydrolyzed. The red color of its aqueous solution disappears on slight warming and the solution reduces Fehling's solution in the cold, showing the presence of a free osone. The product was heated to constant weight under reduced pressure at 139°.

Anal. Subs., 0.1292, 0.1177; 9.98, 9.00 cc. of 0.04892 *N* iodine solution. Calcd. for $C_{18}H_{25}O_{12}N_2As$: As, 13.88. Found: As, 14.16, 14.02.

3-Galactosido-erythrityl-quinoxaline-6-arsonic Acid,



$$H_2O_3AsC_6H_3\left\langle\begin{array}{l}N{=}C{-}H\\ \quad\;\,|\\ N{=}C{-}C_4H_8O_4{\cdot}C_6H_{11}O_5\end{array}\right..\text{—}$$

One gram of lactosone was dissolved in 25 cc. of hot ethylene glycol and 0.8 g. of amino-arsanilic acid dissolved in 50 cc. of absolute methyl alcohol added. The solution was refluxed for five hours. A light brown substance was precipitated during the heating. The product was filtered from the hot solution and washed with methyl alcohol. The yield was 1.0 g. or 66% of the theoretical. It was purified by working and refluxing with absolute methyl alcohol. The product was dried to constant weight at 100° under reduced pressure.

Anal. Subs., 0.1240, 0.1000; 10.40, 8.40 cc. of 0.04591 *N* iodine solution. Calcd. for $C_{18}H_{25}O_{22}N_2As$: As, 13.88. Found: As, 14.43, 14.45.

Condensation Products of Certain Aldoses with Arsanilic Acid.—These reactions were carried out in absolute methyl alcohol. The sugar was dissolved in the least amount of alcohol, filtered and one molecular equivalent of arsanilic acid dissolved in methyl alcohol added. The solution was refluxed from one to four hours, during which time the condensation product was precipitated. They were worked and refluxed with small amounts of methyl alcohol for purification. These compounds are insoluble in organic solvents but quite soluble in water, in which they are readily hydrolyzed. They were dried to constant weight at 45° under reduced pressure.

TABLE I

CONDENSATION PRODUCTS OF ARSANILIC ACID AND ALDOSES

	( )-Aminophenylarsonic acid	Yield, %	Subs.	0.04869 *N* I, cc.	Arsenic, %	
					Calcd.	Found
1	4-Gluco-, $CH_2OH(CHOH)_4CH{=}NC_6H_4AsO_3H_2$	54	0.1166	12.70	19.83	19.88
2	4-Manno-, $CH_2OH(CHOH)_4CH{=}NC_6H_4AsO_3H_2$	95	.1244	13.65	19.83	20.02
3	4-Galacto-, $CH_2OH(CHOH)_4CH{=}NC_6H_4AsO_3H_2$	90	.1251	13.78	19.83	20.10
4	4-Arabino-, $CH_2OH(CHOH)_3CH{=}NC_6H_4AsO_3H_2$	65	.1018	11.82	21.48	21.19
5	4-Xylo-, $CH_2OH(CHOH)_3CH{=}NC_6H_4AsO_3H_2$	43	.1026	11.82	21.48	21.02

These compounds char below 100°. In obtaining rotation data, 1–2 g. of the substance was dissolved in 25% methyl alcohol in water and made up to 50 cc. with the same solvent. Readings were made in a 2-decimeter tube at a temperature of 22° with sodium light,

TABLE II

OPTICAL ROTATIONS OF 4-ALDO-AMINOPHENYLARSONIC ACIDS

Compounds (Table I)	Subs.	Time of reading (min.) and rotation								
1	1.239	0	15	35	55	75	210	420	640	
		—	−1.30°	−1.14°	−1.05°	−0.98°	−0.70°	−0.20°	+0.10°	
2	1.588	0	12	32	52	72	92	272	472	
		—	−2.50	−2.19	−2.08	−1.96	−1.78	−1.36	−1.19	
3	2.639	0	10	18	24	32	39	50	66	140
		—	−0.67	−0.30	−0.15	+0.25	+0.41	+0.65	+0.78	+0.85
4	1.138	0	10	21	39	55	75	166		
		—	−0.15	+0.35	+0.70	+1.06	+1.25	+1.46		
5	Compound 5 could not be read owing to instant cloudiness of the solution.									

Preparation of Substituted Phenylsulfone-aminophenylarsonic Acids.—The arsonic acids were dissolved in the theoretical amount of *N* sodium hydroxide and one molecular equivalent of the aromatic sulfone chlorides added. The reaction mixture was heated to boiling with stirring and the mixture refluxed until all of the sulfone chloride had dissolved. The solution was filtered and allowed to cool, the product crystallizing from the cold solution. These compounds were purified by dissolving in *N* sodium hydroxide and precipitating with a slight excess of hydrochloric acid to dissolve any unchanged arsonic acid. The compounds are slightly colored and melt with decomposition. The yields are poor but may be increased by carrying out the reactions in sodium carbonate solution, rather than sodium hydroxide.

TABLE III

SUBSTITUTED PHENYLSULFONE-AMINOPHENYLARSONIC ACIDS

( )-Sulfone-amino-3-aminophenylarsonic acid	Yield, %	M. p., °C. (dec.)	Analysis Subs.	0.05571 *N* I, cc.	Arsenic, % Calcd.	Found
4-Phenyl-, $C_6H_5SO_2HN(NH_2)C_6H_3AsO_3H_2$	31	205–7	0.1439	13.80	20.14	20.02
4-*p*-Tolyl-, $CH_3C_6H_4SO_2HN(NH_2)C_6H_3AsO_3H_2$	60	160–5	.1297	12.05	19.41	19.40
4-*p*-Bromophenyl-, $BrC_6H_4SO_2HN(NH_2)C_6H_3$-$AsO_3H_2$	18	180–5	.1244	9.75	16.62	16.33
(4-*p*-Bromophenylsulfone-aminophenylarsonic acid) $BrC_6H_4SO_2HNC_6H_4AsO_3H_2$	33	210–12	.1470	11.82	17.19	16.80

Preparation of 4-(2,4,6-Trinitrophenylamino)-phenylarsonic Acid, $H_2O_3AsC_6H_4$-$NHC_6H_2(NO_2)_3$.—Two grams of arsanilic acid was dissolved in 80 cc. of absolute ethyl alcohol and 3 g. of picryl chloride added. The solution was refluxed for three hours, filtered and cooled to room temperature. Beautiful yellow crystals formed on the sides of the container. The yield was 2 g. or 50% of the theoretical. The substance does not melt below 260°. The product was recrystallized from ethyl alcohol until it gave no test for chlorine.

Anal. Subs., 0.1303, 0.1364; 10.75, 11.35 cc. of 0.05571 *N* iodine solution. Calcd. for $C_{12}H_9O_9N_4As$: As, 17.59. Found: As, 17.22, 17.41.

4-(2,4,6-Trinitrophenylamino)-3-aminophenylarsonic Acid, $H_2O_3AsC_6H_3(NH_2)$-$NHC_6H_2(NO_2)_3$.—This compound was prepared from picryl chloride and amino-arsanilic acid according to the preceding method. It is a deep red colored product and chars at 165°.

Anal. Subs., 0.1040, 0.1261; 8.32, 10.02 cc. of 0.05571 *N* iodine solution. Calcd. for $C_{12}H_{10}O_9N_5As$: As, 16.91. Found: As, 16.70, 16.58.

p-Arsono-anilino-ethanol-2, $H_2O_3AsC_6H_4NHCH_2CH_2OH$.—Forty grams of arsanilic acid was dissolved in 174 cc. of *N* sodium hydroxide solution and 10 g. of ethylene oxide added. The solution was allowed to stand in a closed container for twenty-four hours at room temperature. The solution was filtered and acidified to congo paper, the white product precipitating immediately. The yield was 24 g. or 50% of the theoretical and the substance melted at 168°. The product was purified by dissolving in *N* sodium hydroxide solution and precipitating with an excess of concentrated hydrochloric acid.

Anal. Subs., 0.1081, 0.1097; 15.20, 15.30 cc. of 0.05493 *N* iodine solution. Calcd. for $C_8H_{12}O_4NAs$: As, 28.72. Found: As, 28.95, 28.72.

4-Di-(phenacylamino)-phenylarsonic Acid, $H_2O_3AsC_6H_4N(CH_2COC_6H_5)_2$.—Three grams of arsanilic acid was dissolved in the calculated amount of *N* sodium hydroxide solution and refluxed with 6 g. of bromo-acetophenone. A yellow colored mass separated after heating the solution for about fifteen minutes; a sufficient amount of *N* sodium hydroxide solution was added to dissolve the reaction product and the heating continued for ten minutes. The solution was filtered and the excess of bromo-acetophenone extracted by washing with small amounts of ether. The product was precipitated by adding an excess of concentrated hydrochloric acid. The yield was 1.5 g. and the substance melted at 162.5°.

Anal. Subs., 0.1229, 0.1674; 10.90, 14.65 cc. of 0.05240 *N* iodine solution. Calcd. for $C_{22}H_{20}O_5NAs$: As, 16.73. Found: As, 17.42, 17.20.

Summary

1. Maltosone and lactosone were condensed with amino-arsanilic acid to produce certain new types of arsenated quinoxalines. These compounds are very soluble in water but hydrolyze rapidly.

2. Aldoses condense readily with arsanilic acid to form Schiff bases containing an aromatic arsonic acid and a carbohydrate residue.

3. Further condensation products of arsanilic and amino-arsanilic acids with substituted sulfone chlorides, etc., are given.

EVANSTON, ILLINOIS