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

ALIPHATIC-AROMATIC ARSENO COMPOUNDS.[1] I. ARYL ARSENO-, TETRA-ARSENO- AND HEXA-ARSENO-ACETIC ACIDS

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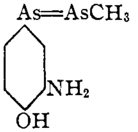
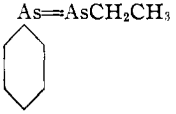
The first aliphatic-aromatic arseno compound is 3-amino-4-hydroxybenzene-arsenomethane (I). The only other compound of this type yet recorded in the literature is ethane-arsenobenzene (II). No extended study of the preparation and properties of the aliphatic-aromatic series has ever been made. Moreover, the therapeutic study of unsymmetrical aromatic arseno compounds[3] and pure aliphatic arseno compounds[4] makes desirable the availability of a combination type, RAs=AsR′, where R is a phenyl substituted by groups known to exert a favorable physiological effect, and R′ is a substituted aliphatic residue. The first step in this investigation is the synthesis of aryl arseno-acetic acids, $RAs{=}AsCH_2COOH$.



I



II

Several methods for the synthesis of unsymmetrical arseno compounds are known.[3] Compound I has been prepared by the simultaneous reduction of the respective arsine oxides or arsonic acids in equimolecular proportions by means of sodium hydrosulfite, or by reducing 3-amino-4-hydroxyphenylarsonic acid and methylarsine oxide together with stannous chloride, hydrochloric acid and hydriodic acid.[5] Compound II has been obtained by the action of phenylarsine on ethylarsine oxide in methanol solution and also by heating phenylarsine oxide and ethylarsine oxide with phosphorous acid.[6] For reasons given elsewhere,[3] the reduction of the corresponding arsonic acids by means of hypophosphorous acid or stannous chloride is preferred for the preparation of aryl arseno-acetic

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[1] A preliminary report of some of this work was made at the Ithaca meeting of the American Chemical Society, September, 1924.

[2] Research Fellow under grant from the Public Health Institute of Chicago. Certain of the compounds described below are being tested pharmacologically by Dr. A. S. Loevenhart of the University of Wisconsin with the aid of a similar grant. This article is an abstract of a portion of a thesis submitted to the Graduate School of Northwestern University, by R. Herbert Edee, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[3] Palmer and Kester, unpublished research.

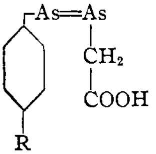
[4] Palmer, THIS JOURNAL, **45**, 3023 (1923).

[5] Ger. pat. 253,226 (1912).

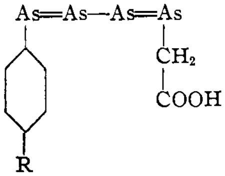
[6] Steinkopf, Schmidt and Smie, *Ber.*, **59**, 1468 (1926).

acids. Their preparation by other methods has also been investigated and will be reported in subsequent publications.

Precautions are necessary in the preparation of aryl arseno-acetic acids which are not usually required in the preparation of arseno compounds. None of the compounds can be prepared by reduction at higher than room temperature, for heating quickly decomposes them with the formation of products containing large percentages of arsenic. In many cases it is necessary to use even lower temperatures to prevent decomposition. When R is substituted by *p*-$NHCH_2COOH$, —$NHCH_2CONH_2$, —$NHCH_2CH_2OH$ and —$NHCH_2CH_2CH_2OH$, the same methods which produce aryl arseno-acetic acids in other examples give the first known unsymmetrical tetra-arseno compounds (VII, VIII, IX, X). Apparently, this is due to the fact that in acid solution arsenic is very readily split off from the benzene ring containing these substitutions even in the cold. The formation of inorganic arsenic takes place at such a rate that there is sufficient present to be reduced simultaneously with undecomposed arsonic acid to give the aryl tetra-arseno-acetic acid. The arseno compounds with these substitutions (III, IV, V, VI) can, however, be obtained by very rapid reduction with stannous chloride at low temperatures.

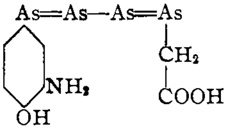


where R = —$NHCH_2CH_2OH$ (III)
= —$NHCH_2CH_2CH_2OH$ (IV)
= —$NHCH_2COOH$ (V)
= —$NHCH_2CONH_2$ (VI)

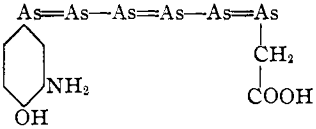


where R = —$NHCH_2CH_2OH$ (VII)
= —$NHCH_2CH_2CH_2OH$ (VIII)
= —$NHCH_2COOH$ (IX)
= —$NHCH_2CONH_2$ (X)

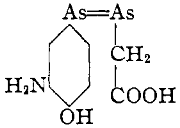
When R is 3-amino-4-hydroxyphenyl, arsenic is not split off so easily as in the four cases just mentioned, and it is necessary to add a little inorganic arsenic in the form of arsenic trichloride in order to obtain 3-amino-4-hydroxyphenyltetra-arseno-acetic acid (XI). If sufficient arsenic trichloride is used, the first known unsymmetrical hexa-arseno compound (XII) forms. 3-Amino-4-hydroxyphenylarseno-acetic acid (XIII) can be made, provided the reduction is fast enough to give the product before much arsenic has been split off from organic combination.



(XI)



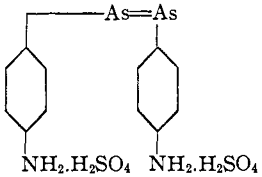
(XII)



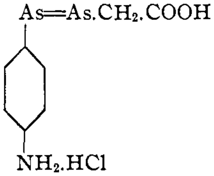
(XIII)

It is also necessary to arrange conditions so that the unsymmetrical arseno compound is the most insoluble of the possible products. The mechanism of the formation of an unsymmetrical arseno compound seems to be as follows: first, reduction of two arsonic acids to the respective arseno compounds; second, rearrangement of the two arseno compounds to give the unsymmetrical derivative; $2RAsO_3H_2 + 2R'AsO_3H_2 \xrightarrow{H} RAs{=}AsR + R'As{=}AsR' \longrightarrow 2RAs{=}AsR'$.

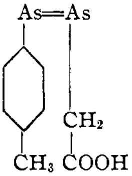
When arsanilic acid and an equimolecular amount of arsono-acetic acid are reduced in the presence of sulfuric acid, nearly all of the arsanilic acid goes to the sulfate of 4,4'-diamino-arsenobenzene (XIV), while the filtrate, on long standing, yields arseno-acetic acid. This effect is considered to be due to much more rapid reduction of arsanilic acid than of arsono-acetic acid, so that 4,4'-diamino-arsenobenzene is precipitated as its very insoluble sulfate before arseno-acetic acid can be formed to react with it. When hydrochloric acid is used instead of sulfuric acid, it is possible to get both the two symmetrical arseno compounds and also a small amount of the hydrochloride of 4-aminophenylarseno-acetic acid (XV). Finally, it is found that the addition of a small amount of pyridine to the hydrochloric acid prevents premature precipitation and gives the unsymmetrical compound as the exclusive product. In most cases it is not necessary to use this special precaution. There is also difficulty now and then with unreduced arsonic acid coming down, but it is usually put back into solution very easily.



(XIV)



(XV)



(XVI)

That the products are not mixtures follows from the observation that Compounds III to X, inclusive, and XVI, are wholly soluble in alkaline solutions, thus precluding the possibility of their containing any symmetrical aromatic arseno compounds which could not be alkali-soluble with the substitutions there present. It is also found that compounds such as XV, with amino substitution in the aromatic side and carboxyl substitution in the aliphatic side, are soluble completely either in acid or alkaline solutions. In general the arseno compounds are yellow or pale orange, the tetra-arseno compounds bright red and the hexa-arseno compound a dark red-brown. None of these products can be crystallized, but they can be dissolved in alkali and reprecipitated by acid in fractions of approximately uniform composition. They are sensitive to heat (some must be washed with ice-cold reagents or they will decompose) and oxidation and should be kept at a low temperature in ampules filled with carbon dioxide.

The preparation of other series of aliphatic-aromatic arseno compounds with various substitutions in the aliphatic side of the molecule is in progress. Formaldehyde sulfoxylate and sodium formaldehyde bisulfite derivatives are also contemplated where the aromatic side is substituted by an amino group. More exact proof of the structure of the series is being worked out in connection with a general study of the structure of arseno compounds.

Experimental Part

Aryl Arseno-acetic Acids

4-Aminophenylarseno-acetic Acid Hydrochloride, $(HCl.H_2N)C_6H_4As{=}AsCH_2COOH$, XV.—A solution was made of 4.56 g. (0.02 mole) of sodium arsono-acetate ($NaOOC.CH_2AsO_3Na_2$) and 4.34 g. (0.02 mole) of *p*-aminophenylarsonic acid in 10 cc. of hydrochloric acid (d., 1.19) and 10 cc. of water. After cooling, this was filtered and 30 cc. of pyridine and 53 cc. of 50% hypophosphorous acid were added, and the mixture was allowed to stand in an ice box. After four days a precipitate which analyzed high in arsenic was filtered off. After 12 days a bright yellow precipitate had formed. It was filtered with suction, washed with cold dil. hydrochloric acid and dried in a vacuum; yield, 2.1 g. of the second fraction, 4.5 g. of the first fraction, which was not quite pure, making a total yield of 6.6 g., or 89%. The product dissolves readily in cold, aqueous alkalies.

Anal. Subs., 0.2025, 0.1997: 44.95, 44.60 cc. of I_2 soln. (1 cc. = 0.00201 g. of As). Calcd. for $C_8H_9NO_2As_2.HCl$: As, 44.51. Found: 44.61, 44.89.

Subs., 0.100, 0.1012: AgCl, 0.0982, 0.0987. Calcd. for $C_8H_9NO_2As_2.HCl$: Cl, 10.51. Found: 9.82, 9.76.

4,4'-Diamino-arsenobenzene Sulfate and Arseno-acetic Acid from *p*-Aminophenylarsonic Acid and Arsono-acetic Acid.—One-tenth mole of sodium arsono-acetate, 21.7 g. of arsanilic acid, 106 g. of sodium hypophosphite (1 mole) and 75 g. of sulfuric acid (d., 1.84) were dissolved in 200 cc. of water, and the mixture was allowed to stand at room temperature. After 24 hours a precipitate consisting largely of inorganic salts colored by a little reduction product was filtered off. The filtrate was allowed to stand for ten days longer, during which time a beautiful lemon-yellow product gradually precipitated. It was filtered off, washed with water and dried in a vacuum over sulfuric acid; yield, 21 g. This substance contains sulfur and appears to be the disulfate of 4,4'-diamino-arsenobenzene.[7]

Anal. Subs., 0.1493, 0.1471: 8.6, 8.6 cc. of I_2 soln. (1 cc. = 0.0048 g. of As). Calcd. for $C_{12}H_{12}N_2As_2.2H_2SO_4$: As, 28.51. Found: 27.65, 27.99.

The filtrate was allowed to stand for 15 days, at the end of which time a little golden-yellow precipitate had formed. It was filtered with suction, washed repeatedly with water and dried in a vacuum over sulfuric acid; yield, 3 g. The product appears to be arseno-acetic acid with the admixture of a little tetra-arseno-acetic acid which, as shown in a previous article, is always formed by the long-continued action of an acid solution.[4]

Anal. Subs., 0.1606, 0.1217: 20.0, 15.2 cc. of I_2 soln. (1 cc. = 0.0048 g. of As). Calcd. for $C_4H_6O_4As_2$: As, 55.96. Found: 59.77, 59.95.

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[7] Ehrlich and Bertheim, *Ber.*, **44,** 1263 (1911).

Reduction of 4-Aminophenylarsonic Acid and Arsono-acetic Acid to Give Both Symmetrical and Unsymmetrical Products.—One-twentieth mole of sodium arsono-acetate, 10.8 g. of arsanilic acid, 61 g. of sodium hypophosphite and 80 cc. of hydrochloric acid (d., 1.19) were dissolved in 300 cc. of water and the mixture was allowed to stand at room temperature. Table I presents the results.

TABLE I

VARIATION OF PRODUCT WITH PERIOD OF REDUCTION

Days' standing	Color of ppt.	Wt. of ppt. dried in vacuum, g.	Wt. of sample, g.		Vol. of I_2 soln. (1 cc. = 0.0048 g. of As)		As, %	
2	Yellow	8	0.1536	0.1345	11.4	10.1	36.28	36.04
5	Yellow	4.5	.1185	.1887	10.2	16.1	41.15	40.95
8	Yellow	2	.4037	.2721	36.3	24.7	43.16	43.57
14	Yellow	2.5	.1160	.1518	12.1	16.0	50.07	50.59
28	Orange	1.5	.1692		21.4		60.71	

Calcd. for $C_8H_{10}O_2NClAs_2$: As, 44.51.
Calcd. for $C_{12}H_{14}N_2Cl_2As_2$: As, 36.85.
Calcd. for $C_4H_6O_4As_2$: As, 55.96.

From the above data it appears that Fraction 1 is the dihydrochloride of 4,4'-diamino-arsenobenzene in about 80% yield. Fraction 3 is the hydrochloride of 4-aminophenylarseno-acetic acid in small yield, while Fraction 2 is probably composed largely of 1 and 3 mixed. Fractions 4 and 5 are mainly arseno-acetic acid, in the latter case also containing a good deal of tetra-arseno-acetic acid.

4-Acetylaminophenylarseno-acetic Acid Hydrochloride, $(CH_3CONH—)C_6H_4As{=}AsCH_2COOH.HCl$.—To the cold filtered solution containing 4.56 g. of sodium arsono-acetate and 5.18 g. of 4-acetylaminophenylarsonic acid in 10 cc. of hydrochloric acid (d., 1.19) and 30 cc. of water, there was added 53 cc. of 50% hypophosphorous acid, and the mixture was allowed to stand in an ice box for 11 days. The bright yellow product which formed was filtered, washed well with water and dried in a vacuum over phosphorus pentoxide. It is slightly soluble in warm dil. hydrochloric acid and readily soluble in cold dil. alkalies; yield, 2.3 g., or 33.7%.

Anal. Subs., 0.1001, 0.1006: 23.85, 23.98 cc. of I_2 soln. (1 cc. = 0.001661 g. of As). Calcd. for $C_{10}H_{11}O_3NAs_2.HCl$: As, 39.57. Found: 39.57, 39.59.

Subs., 0.2600: AgCl, 0.0986. Calcd. for $C_{10}H_{11}O_3NAs_2.HCl$: Cl, 9.23. Found: 9.38.

4-Hydroxy-ethylaminophenylarseno-acetic Acid Hydrochloride, $(HOCH_2CH_2NH)$-$C_6H_4As{=}AsCH_2COOH.HCl$ (Free Base, III).—To an ice cold solution containing 5.22 g. of 4-hydroxy-ethylaminophenylarsonic acid and 4.56 g. of sodium arsono-acetate, in 30 cc. of hydrochloric acid (d., 1.19), 10 cc. of water and 100 cc. of methanol, was added another solution containing 25 g. of stannous chloride in 75 cc. of hydrochloric acid (d., 1.19). After thorough mixing, a solution of 2 g. of potassium iodide in a small amount of water was added in small portions with vigorous stirring, the temperature being kept below 0° for two hours. After standing at room temperature for two days, the solution was placed in a freezing mixture for an hour in order to crystallize out the highly soluble product. The orange precipitate was filtered off with suction and washed well with dil. hydrochloric acid. (Washing with water causes the residue to become gummy.) If the product is now dried and analyzed, it will be found to be low in arsenic content due to the adsorption of considerable stannous chloride and other soluble impurities. To remove these the compound is triturated several times with fresh portions of cold, dil. hydrochloric acid and finally dried in a vacuum over phosphorus pentoxide;

yield, 3.25 g., or 47.1%. The compound is light orange in color, fairly soluble in water and very soluble in dilute aqueous alkalies.

Anal. Subs., 0.1009, 0.1023: 20.40, 20.70 cc. of I_2 soln. (1 cc. = 0.001930 g. of As). Calcd. for $C_{10}H_{13}O_3NAs_2.HCl$: As, 39.36. Found: 39.02, 39.05.

4-Hydroxypropylaminophenylarseno-acetic Acid Hydrochloride, $(HOCH_2CH_2CH_2NH)C_6H_4As{=}AsCH_2COOH.HCl$ (Free Base, IV).—This compound was prepared in exactly the same manner as the corresponding hydroxy-ethyl derivative except that 5.50 g. of 4-hydroxypropylaminophenylarsonic acid was substituted for the 4-hydroxyethylaminophenylarsonic acid and the reduction was run only overnight. The red-orange product is sparingly soluble in water and readily soluble in dil. aqueous alkalies; yield, 2.34 g., or 29.7%.

Anal. Subs., 0.1018, 0.1020: 20.50, 20.50 cc. of I_2 soln. (1 cc. = 0.001904 g. of As). Calcd. for $C_{11}H_{15}O_3NAs_2.HCl$: As, 37.97. Found: As, 38.34, 38.26.

4-Glycine-phenylarseno-acetic Acid Hydrochloride, $(HOOCCH_2NH)C_6H_4As{=}AsCH_2COOH.HCl$ (Free Base, V).—The method of preparation is similar to the foregoing, using 5.50 g. of phenylglycine-*p*-arsonic acid and allowing the reduction to proceed for three days at room temperature and then for two days longer in an ice box. An orange-red precipitate comes down without the necessity of using a freezing mixture. The product was washed carefully with ice-cold dil. hydrochloric acid and dried in a vacuum over phosphorus pentoxide. It was found in this and several other cases that the acid used for washing must be cold, or it will cause partial decomposition of the compound with production of a substance in which the arsenic content is a little too high; yield, 2.38 g., or 30.2%, of an orange powder, completely soluble in aqueous alkali.

Anal. Subs., 0.1009, 0.1002: 19.42, 19.35 cc. of I_2 soln. (1 cc. = 0.001930 g. of As). Calcd. for $C_{10}H_{11}O_4NAs_2.HCl$: As, 37.97. Found: 37.14, 37.27.

4-Glycine-amide-phenylarseno-acetic Acid Hydrochloride, $(H_2NCOCH_2NH—)C_6H_4As{=}AsCH_2COOH.HCl$ (Free Base, VI).—Like the preceding compound this is prepared by stannous chloride reduction, using 5.48 g. of *p*-arsonophenylglycine amide. After allowing the reduction mixture to stand at room temperature for two hours, it was placed in an ice box for two days. At the end of this time the orange-red precipitate which had separated was filtered off and washed with cold dil. hydrochloric acid. This is not sufficient washing and one or more triturations with hydrochloric acid, which must be cold to prevent slight decomposition, are required before the product is analytically pure. It is then an orange powder, slightly soluble in water and completely soluble in dilute aqueous alkalies; yield, 2.2 g., or 31.4%.

Anal. Subs., 0.1051, 0.1004: 23.51, 22.50 cc. of I_2 soln. (1 cc. = 0.0016703 g. of As). Calcd. for $C_{10}H_{12}O_3N_2As_2.HCl$: As, 38.07. Found: 37.36, 37.43.

4-Hydroxyphenylarseno-acetic Acid, $(HO)C_6H_4As{=}AsCH_2COOH$.—A solution of 4.56 g. of sodium arsono-acetate and 4.36 g. of *p*-hydroxyphenylarsonic acid in 30 cc. of water and 10 cc. of hydrochloric acid (d., 1.19) was filtered and cooled. To this was added 53 cc. of 50% hypophosphorous acid and the mixture was allowed to stand in an ice box. After 12 days the reddish-brown, alkali-soluble compound was filtered off, washed with cold, dil. hydrochloric acid and dried in a vacuum over phosphorus pentoxide; yield, 5.14 g., or 85%.

Anal. Subs., 0.2015, 0.2014: 49.68, 49.65 cc. of I_2 soln. (1 cc. = 0.00201 g. of As). Calcd. for $C_8H_8O_3As_2$: As, 49.66. Found: 49.55, 49.55.

4-Acetoxyphenylarseno-acetic Acid, $(HOOCCH_2O—)C_6H_4As{=}AsCH_2COOH$.—The preparation of this substance is similar to that of 4-hydroxyphenylarseno-acetic acid, except that 5.52 g. of *p*-arsonophenoxy-acetic acid was used. After five days in the ice box no product had separated, so the reaction mixture was warmed to 50°, upon which treatment a yellow precipitate formed. It was filtered off, washed with cold dil. hydrochloric acid, and dried in a vacuum over phosphorus pentoxide. This gives a light yellow, alkali-soluble product; yield, 2.36 g., or 32.7%.

Anal. Subs., 0.1021, 0.1010: 24.51, 24.30 cc. of I_2 soln. (1 cc. = 0.001713 g. of As). Calcd. for $C_{10}H_{10}O_5As_2$: As, 41.66. Found: 41.12, 41.21.

3-Amino-4-hydroxyphenylarseno-acetic Acid Hydrochloride, $3(H_2N—)4(HO—)C_6H_3As{=}AsCH_2COOH.HCl$ (Free Base, XIII).—A solution of 4.38 g. of 3-amino-4-hydroxyphenylarsonic acid and 4.56 g. of sodium arsono-acetate was made in 10 cc. of water and 15 cc. of hydrochloric acid (d., 1.19). To this was added 53 cc. of 50% hypophosphorous acid and the mixture was diluted to 250 cc. After being filtered, the solution was allowed to stand at room temperature for 24 hours and then was poured into 300 cc. of cold hydrochloric acid (d., 1.19). A bright orange-yellow precipitate separated which was purified by dissolving in a small amount of cold water and pouring into hydrochloric acid as before. The final product is very soluble in water; yield, 3.76 g., or 53.25%.

Anal. Subs., 0.1000, 0.1004: 21.75, 21.85 cc. of I_2 soln. (1 cc. = 0.001958 g. of As). Calcd. for $C_8H_9NO_3As_2.HCl$: As, 42.49. Found: 42.58, 42.61.

Subs., 0.2001, 0.2004: AgCl, 0.0849, 0.0843. Calcd. for $C_8H_9NO_3As_2.HCl$: Cl, 10.04. Found: 10.49, 10.40.

Phenylarseno-acetic Acid, $C_6H_5As{=}AsCH_2COOH$.—A solution of 4.04 g. of phenylarsonic acid and 4.56 g. of sodium arsono-acetate in 10 cc. of hydrochloric acid and 30 cc. of pyridine was cooled, filtered and diluted with 53 cc. of 50% hypophosphorous acid. After eight days in the ice box there was no apparent change but, on warming the reaction mixture to 60°, a yellowish-brown product separated. It was washed with water and dried in a vacuum over phosphorus pentoxide. The compound is soluble in dilute aqueous alkalies; yield, 2.13 g., or 36%.

Anal. Subs., 0.1024, 0.1020: 32.01, 31.82 cc. of I_2 soln. (1 cc. = 0.001678 g. of As). Calcd. for $C_8H_8O_2As_2$: As, 52.44. Found: 52.45, 52.34.

***p*-Tolylarseno-acetic Acid,** $4(CH_3—)C_6H_4As{=}AsCH_2COOH$, XVI.—A process similar to that for the phenyl compound is employed, using 4.32 g. of *p*-tolylarsonic acid. After 20 days in the ice box a light yellow precipitate had separated out. It was filtered off, washed with cold water and dried in a vacuum. The compound is soluble in dilute aqueous alkalies; yield, 0.65 g., or 16.5%.

Anal. Subs., 0.1014, 0.1018: 30.20, 30.35 cc. of I_2 soln. (1 cc. = 0.001661 g. of As). Calcd. for $C_9H_{10}O_2As_2$: As, 50.00. Found: 49.47, 49.51.

***o*-Chlorophenylarseno-acetic Acid,** $2(Cl—)C_6H_4As{=}AsCH_2COOH$.—The same method was used as for the preceding compound. After seven days in the ice box a little yellow precipitate had formed which was filtered off and discarded. The filtrate was heated to boiling, whereupon a bright yellow product precipitated. It was filtered off, washed with water and dried in a vacuum. The yellow powder thus obtained is soluble in alkaline solutions; yield, 3.2 g., or 49.7%.

Anal. Subs., 0.1007, 0.1001: 28.42, 28.20 cc. of I_2 soln. (1 cc. = 0.001646 g. of As). Calcd. for $C_8H_7O_2ClAs_2$: As, 46.87. Found: 46.45, 46.37.

Aryl Tetra-arseno-acetic Acids

4-Glycine-phenyl-tetra-arseno-acetic Acid, $(HOOCCH_2NH)C_6H_4As{=}As—As{=}AsCH_2COOH$, IX.—A solution of 5.5 g. of *p*-arsonophenylglycine, 4.56 g. of sodium arsono-acetate and 53 cc. of 50% hypophosphorous acid in 10 cc. of hydrochloric acid (d., 1.19) and 30 cc. of water was filtered, and the filtrate allowed to stand in an ice box for seven days. The brick-red precipitate which separated was washed with water and dried in a vacuum over phosphorus pentoxide. It is readily soluble in alkaline solutions; yield, 3.8 g., or 37.7%.

Anal. Subs., 0.1004, 0.1004: 35.59, 35.56 cc. of I_2 soln. (1 cc. = 0.001661 g. of As). Calcd. for $C_{10}H_{11}O_4NAs_4$: As, 58.93. Found: 58.87, 58.82.

The compound can also be prepared by means of stannous chloride reduction. A solution was prepared from 5.5 g. of *p*-arsonophenylglycine, 4.56 g. of sodium arsonoacetate, 100 cc. of methanol, 10 cc. of water and 30 cc. of hydrochloric acid (d., 1.19). A second solution was prepared by dissolving 20 g. of stannous chloride in 75 cc. of hydrochloric acid (d., 1.19). Both solutions were cooled to —5° and then mixed. To this was added a solution of 2 g. of potassium iodide in a small amount of water and the whole was kept at —5° for two hours. An orange precipitate separated which was filtered off and washed with cold dil. hydrochloric acid. When dried and analyzed this precipitate was found to have a very low arsenic content. It was suspended in a second reducing bath consisting of 20 g. of stannous chloride, 75 cc. of hydrochloric acid (d., 1.19) and 10 cc. of water. After adding 1 g. of potassium iodide, the mixture was allowed to stand overnight, at the end of which time a red precipitate had formed. After being filtered, washed in water, acetone and ether, and dried in a vacuum this product weighed 2 g.

The products obtained by both methods were found to be free from halogen.

Anal. Subs., 0.1004, 0.1000: 30.70, 30.50 cc. of I_2 soln. (1 cc. = 0.001919 g. of As). Calcd. for $C_{10}H_{11}O_4NAs_4$: As, 58.93. Found: 58.67, 58.52.

4-Glycine-amide-phenyl-tetra-arseno-acetic Acid, $(H_2NCOCH_2NH—)C_6H_4As{=}As—As{=}AsCH_2COOH$, X, was prepared from 5.48 g. of *p*-arsonophenylglycine amide by the same method as described in the preceding preparation with hypophosphorous acid. After standing for one day it was necessary to add 5 cc. of hydrochloric acid (d., 1.19) and heat to 40° for five minutes in order to redissolve a little *p*-arsonophenylglycine amide which had precipitated. After standing for five days at room temperature, the bright red precipitate was filtered off, washed with water, methanol and ether and dried in a vacuum over phosphorus pentoxide. Additional material can be obtained by allowing the filtrate to stand a few days longer. The product is completely soluble in aqueous alkalies; yield, 4.56 g., or 45.1%.

Anal. Subs., 0.1002, 0.1017: 35.37, 35.81 cc. of I_2 soln. (1 cc. = 0.001713 g. of As). Calcd. for $C_{10}H_{12}O_3N_2As_4$: As, 59.05. Found: 60.46, 60.31.

The same compound can be obtained by stannous chloride reduction from 6 g. of sodium *p*-arsonophenylglycine amide by exactly the same method as that used for 4-glycine-phenyl-tetra-arseno-acetic acid; it is a red, alkali-soluble powder, free from halogen; yield, 2.15 g.

Anal. Subs., 0.1000, 0.1010: 31.51, 31.70 cc. of I_2 soln. (1 cc. = 0.001919 g. of As). Calcd. for $C_{10}H_{12}O_3N_2As_4$: As, 59.05. Found: As, 60.46, 60.22.

4-Hydroxy-ethylaminophenyl-tetra-arseno-acetic Acid, $(HOCH_2CH_2NH—)C_6H_4$-$As{=}As—As{=}AsCH_2COOH$.—In the preparation of this compound 5.22 g. of *p*-hydroxyethylaminophenylarsonic acid and 4.56 g. of sodium arsono-acetate were put into solution with 15 cc. of hydrochloric acid (d., 1.19) and 30 cc. of water. To this solution was added 53 cc. of 50% hypophosphorous acid and the mixture was warmed on the water-bath at 40° for 20 minutes. After standing at room temperature for three days, the reaction mixture was cooled to —5°. At this temperature a brick-red precipitate came down in about half an hour. It was washed with water and dried in a vacuum over phosphorus pentoxide; yield, 2 g., or 20%. It is entirely soluble in alkali and contains no chlorine.

Anal. Subs., 0.1008, 0.1004: 31.15, 31.20 cc. of I_2 soln. (1 cc. = 0.001958 g. of As). Calcd. for $C_{10}H_{13}O_3NAs_4$: As, 60.60. Found: 60.50, 60.84.

4-Hydroxypropylaminophenylarseno-acetic Acid, $(HOCH_2CH_2CH_2NH—)C_6H_4As{=}As—As{=}AsCH_2COOH$, VIII.—A solution similar to that prepared for the corresponding hydroxy-ethyl compound was prepared from 5.5 g. of *p*-hydroxypropylaminophenylarsonic acid and heated on a water-bath at 55° for 30 minutes. A red product precipitated which was filtered off, washed with water and dried in a vacuum over phosphorus pentoxide. It was entirely soluble in alkali, and free from chlorine; yield, 1 g., or 10%.

Anal. Subs., 0.1002, 0.1002: 37.62, 37.60 cc. of I_2 soln. (1 cc. = 0.001568 g. of As). Calcd. for $C_{11}H_{16}O_3NAs_4$: As, 58.93. Found: 58.86, 58.83.

3-Amino-4-hydroxyphenyl-tetra-arseno-acetic Acid, $3\text{-}(H_2N—)\text{-}4\text{-}(HO—)C_6H_3As{=}As—As{=}AsCH_2COOH$, XI.—In order to get a tetra-arseno compound with this composition it was necessary to add more arsenic in the form of arsenic trichloride, since 3-amino-4-hydroxyphenylarsonic acid does not lose arsenic rapidly enough in acid solution to permit the exclusive formation of a product with four arsenic atoms in a molecule. Thirty cc. of water, 15 cc. of hydrochloric acid (d., 1.19), 2.28 g. of sodium arsono-acetate and 2.19 g. of 3-amino-4-hydroxyphenylarsonic acid were shaken together until a homogeneous solution resulted. To this was added 0.88 g. of arsenic trichloride, drop by drop with shaking, until all dissolved. Then 26 cc. of 50% hypophosphorous acid was added and the solution cooled to 5° and kept at that temperature for 30 minutes. At the end of this time the mixture was allowed to come gradually to room temperature and an orange-brown precipitate separated. This was washed with water, alcohol and ether and dried over phosphorus pentoxide in an atmosphere of carbon dioxide. It was a red powder, soluble in alkaline solutions and free from chlorine; yield, 2 g., or 55%.

Anal. Subs., 0.1002, 0.0674: 33.5, 22.6 cc. of I_2 soln. (1 cc. = 0.001919 g. of As). Calcd. for $C_8H_9O_3NAs_4$: As, 64.24. Found: 64.15, 64.34.

Aryl Hexa-arseno-acetic Acid

3-Amino-4-hydroxyphenyl-hexa-arseno-acetic Acid, $3\text{-}(H_2N—)\text{-}4\text{-}(HO—)C_6H_3As{=}As—As{=}As—As{=}AsCH_2COOH$, XII.—This compound results when a larger amount of arsenic trichloride is used than was required for the tetra compound. To a solution of 4.38 g. of 3-amino-4-hydroxyphenylarsonic acid and 4.56 g. of sodium arsono-acetate in 15 cc. of hydrochloric acid (d., 1.19) was added 30 cc. of water and the mixture was filtered from the sodium chloride which separated. One twenty-fifth mole of arsenic trichloride (7 g.) was now added dropwise with vigorous shaking. On the addition of 53 cc. of 50% hypophosphorous acid, there was a separation of a brick-red precipitate. This was filtered off, washed with water, alcohol and ether and dried in a vacuum over phosphorus pentoxide. The red-brown powder is readily soluble in alkaline solutions; yield, 4.7 g., or 45%. The compound contains no halogen.

Anal. Subs., 0.1015, 0.1007: 38.95, 38.35 cc. of I_2 soln. (1 cc. = 0.0019127 g. of As). Calcd. for $C_8H_9O_3As_6$: As, 72.93. Found: 72.51, 72.84.

Summary

1. A series of aryl arseno-acetic acids, $RAs{=}AsCH_2COOH$, has been prepared, that are the first aliphatic-aromatic-arseno compounds in which the aliphatic part of the molecule is substituted. Unless proper conditions are observed, two symmetrical arseno compounds may be obtained instead of the aryl arseno-acetic acid.

2. A series of unsymmetrical tetra-arseno compounds, RAs=As-As=AsCH$_2$COOH, has been synthesized for the first time.

3. One member of the previously unknown series of unsymmetrical hexa-arseno compounds, RAs=As—As=As—As=AsCH$_2$COOH, has been made.

4. The properties of the three new series have been found to conform with predictions made on the basis of their relation to the previously known types of arseno compounds.

5. Similar series are being prepared in which substituted aliphatic arsonic acids other than arsono-acetic acid form the material from which the aliphatic portion of the molecule is derived.

6. More exact proof of the structure of these series is being sought in connection with a general study of the constitution of arseno compounds now in progress in this Laboratory.

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STUDIES IN VAPOR PRESSURE. III. THE TOLUIDINES

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In the previous communications[1] of this series, the method employed for the measurement of the vapor pressure and the means employed to calculate the latent heat of vaporization, the vapor-pressure equations and the entropies of vaporization are discussed in detail. This study is being pursued because of the lack of accurate vapor-pressure data for the organic compounds that enter into the manufacture of dyes and other commodities.

In this paper the measurement of the vapor pressures of the three isomeric toluidines is reported, together with some related physical properties.

In the purer toluidines that are procurable, the principal impurities, besides the isomers, are very small amounts of the nitrotoluene, aniline and complex oxidation products related to the quinones. In some commercial analyses small quantities of aminobenzylamine toluenes have been reported. An excellent separation of the *o*- and *p*-toluidines may be obtained by means of the formation of the dioxalates of these compounds.[2] The *o*-toluidine dioxalate is considerably more soluble in water and ether than the corresponding *para* compound. In fact, the *p*-toluidine dioxalate is so insoluble in ethyl ether that a practically complete quantitative separation may be acccomplished.[3] The separation of the *m*-toluidine depends

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[1] (a) Berliner and May, This Journal, **47**, 2350 (1925); (b) **48**, 2630 (1926).

[2] Rosenstiehl, *Ann. chim. phys.*, [4] **26**, 249 (1872).

[3] Wülfing, *Jahresber.*, **39**, 2066 (1886); **40**, 2570 (1887).