Ethyl Ester.—Liquid boiling at 141–2° and 3 mm.

Anal. Calcd. for $C_{13}H_{18}S_2$: S, 26.97; C, 65.5; H, 7.57. Found: S, 26.88; C, 65.1; H, 7.53.

Action of Phenylhydrazine.—An unexpected reaction took place between phenylhydrazine and the carbithioic acid. Small, white plates were obtained, melting sharply at 112°. The substance was insoluble in most organic solvents and evolved hydrogen sulfide when heated with any such solvent. It contains 6.79% N and 16.18% S.

Acid Chloride.—The action of phosphorus pentachloride on the carbithioic acid gave a liquid boiling at 141° and 8 mm. Though its odor was somewhat sharp it gave no typical reaction with ammonia or aniline so doubt remains as to its nature.

Summary

1. *p*-Cymyl-2-carbithioic acid is obtained by the action of carbon disulfide on cymyl-2-magnesium bromide.

2. Its zinc salt was prepared.

3. Complex salts of metals with acetic acid and carbithioic acid were obtained. Zinc, copper, mercury and cadmium gave such salts.

4. The methyl and ethyl esters of carbithioic acid were prepared.

5. Reactions (undetermined) took place between the carbithioic acid and phenylhydrazine, also phosphorus pentachloride.

CHAPEL HILL, NORTH CAROLINA

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

UNSYMMETRICAL ARSENO COMPOUNDS DERIVED FROM PARA-ARSONOPHENYLAMINO-ETHANOL AND PARA-ARSONOPHENYLGLYCINE-AMIDE[1]

BY CHARLES SHATTUCK PALMER AND ERNEST B. KESTER[2]

RECEIVED JUNE 6, 1928 PUBLISHED NOVEMBER 6, 1928

During recent years there has been considerable interest in the attempts to apply *p*-arsonophenylglycine-amide in the form of its monosodium salt, "tryparsamide" (1), to the treatment of diseases of protozoal origin. Especial success has attended its introduction into the treatment of trypanosomiasis,[3] and it has also shown promise in paresis.[4] To a lesser

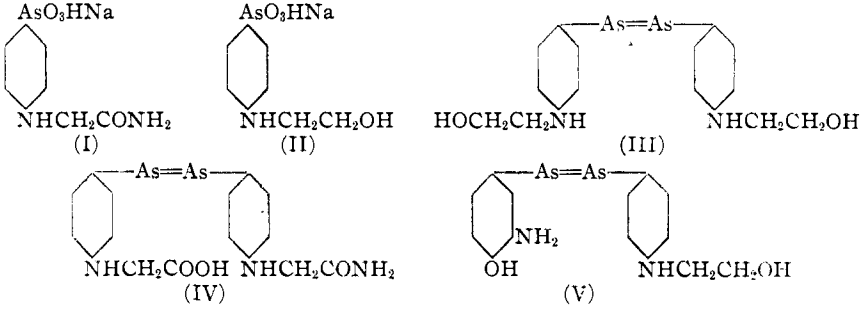
[1] An abstract of Part I of a thesis submitted to the Graduate School of Northwestern University by Ernest B. Kester in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Research Fellow under grant from the Public Health Institute of Chicago.

[3] Jacobs and Heidelberger, THIS JOURNAL, **41**, 1587 (1919); Brown and Pearce, *J. Exptl. Med.*, **30**, 417–496 (1919); Pearce, *ibid.*, **34**, supplement 1 (1921); Chesterman, *Trans. Roy. Soc. Trop. Med. Hyg.*, **16**, 394 (1923); Smillie, *J. Am. V. M. A.*, September, **1923**; Pearce, *J. Pharmacol.*, **25**, 159 (1925).

[4] Lorenz, Loevenhart, Bleckwenn and Hodges, *J. Am. Med. Assn.*, **80**, 1497 (1923); Moore, Robinson and Keidel, *ibid.*, **82**, 528 (1924); Lorenz, Loevenhart and Reitz, *Am. J. Med. Sci.*, **148**, 157 (1924); Lorenz, Loevenhart and Reese, *Z. Neur. Psych.*, **98**, 763 (1925); Loevenhart and Stratman-Thomas, *J. Pharmacol.*, **29**, 69 (1926).

extent the sodium salt (II) of *p*-arsonophenylamino-ethanol[5] has been under investigation. In the usual course of chemo-therapeutic study, when an arsonic acid, $RAsO_3H_2$, has been shown to be valuable, it is reduced to the corresponding arseno compound, RAs=AsR, in order that the effect of both pentavalent and trivalent arsenic may be determined in



combination with the same R group. The arseno compound (III) from *p*-arsonophenylamino-ethanol has been made,[6] but it is soluble only in strongly acid solutions and is therefore useless for therapeutic purposes. No arseno compound derived from tryparsamide has been described, but this substance likewise could contain no substitutions which would make possible its dissolving to form a neutral aqueous solution.

In order to obtain water-soluble arseno compounds with phenylglycineamide and phenylamino-ethanol nuclei, it was decided to prepare unsymmetrical arseno compounds (IV, V) in which one arsenic is attached to either of the above-mentioned groups and the other to a benzene ring containing solubilizing substituents, for example,—$NHCH_2OSOH$, —OH, —$NHCH_2COOH$ and —OCH_2COOH.

Four general methods for preparing unsymmetrical arseno compounds are available. *A*. The action of a primary arsine on a primary arsine oxide or halide[7]

$$RAsH_2 + R'AsCl_2 \longrightarrow 2HCl + RAs{=}AsR'$$
$$RAsH_2 + R'AsO \longrightarrow RAs{=}AsR' + H_2O$$

B. Rearrangement of two symmetrical arseno compounds when warmed in solution to give the unsymmetrical derivative[8]

$$RAs{=}AsR + R'As{=}AsR' \longrightarrow 2RAs{=}AsR'$$

[5] Hamilton, THIS JOURNAL, **45**, 2751 (1923); Rodewald and Adams, *ibid.*, **45**, 3102 (1923); Raiziss, Severac and Moetsch, *Transactions of Section on Pharmacology and Therapeutics of the American Medical Association*, 1 (1925); Loevenhart and Stratman-Thomas, *J. Pharmacol.*, **29**, 69 (1926).

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

[7] Kahn, *Chem.-Ztg.*, **36**, 1099 (1912); *Z. angew. Chem.*, **25**, 1995 (1912); German Patent, 254,187; American Patent 1,033,904; Steinkopf, Schmidt and Smie, *Ber.*, **59**, 1468 (1926).

[8] Karrer, *Ber.*, **49**, 1649 (1916); German Patent, 293,040; Hart and Payne, *J. Am. Pharm. Assoc.*, **12**, 699 (1923).

C. Simultaneous reduction of two different arsonic acids, arsine oxides or arsine halides or of an arsine oxide with an arsonic acid, etc.[9]

$$RAsO_3H_2 + R'AsO_3H_2 + 8H \longrightarrow RAs{=}AsR' + 6H_2O$$
$$RAsO + R'AsCl_2 + 4H \longrightarrow RAs{=}AsR' + H_2O + 2HCl$$

D. Substitution in only one of the two groups attached to arsenic in a symmetrical arseno compound[10]

$$RAs{=}AsR \longrightarrow RAs{=}AsR'$$

Of the above methods, *C* was selected for use since it offered a means for preparing unsymmetrical arseno compounds from the readily procurable arsonic acids.

The uniform procedure was the reduction of equimolar solutions of *p*-arsonophenylamino-ethanol or *p*-arsonophenylglycine-amide with some other arsonic acid by means of a reagent specific for the arseno group. Sodium hydrosulfite was not used since it frequently contaminates the reduced product with sulfur-containing impurities. Hypophosphorous acid or stannous chloride are free from this objection and will act at the low temperatures necessary in preparing arseno compounds of complex structure because of their instability. Those derived from *p*-arsonophenylglycine-amide and *p*-arsonophenylamino-ethanol are particularly sensitive. For example, 4-amino-4′-β-hydroxyethylamino-arsenobenzene (VI), arsenic content, 33.24%, is prepared readily at 5–10°. If, however, the reduction of arsanilic acid and *p*-arsonophenylamino-ethanol is carried out at 55–60°, the product contains 61% of arsenic, while at 100° a substance containing 78% of arsenic is formed. As a result, all of the arseno compounds described below (which were derived from *p*-arsonophenylglycine-amide or *p*-arsonophenyl-amino-ethanol) had to be made below room temperature.

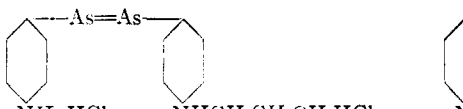
When *p*-arsonophenylglycine-amide and *p*-arsonophenylglycine were reduced simultaneously with hypophosphorous acid, it was not found possible to obtain the unsymmetrical arseno compound. Instead, a product resulted which from an arsenic analysis seemed to be tetra-arsenobenzene-4-glycine-4′-glycine-amide. Stannous chloride, on the other hand, produced the pure arseno compound, arsenobenzene-4-glycine-4′-glycine-amide (IV).

[9] Bertheim, *Chem. Ztg.*, **38**, 756 (1914); Faragher, *J. Chem. Soc.*, **117**, 866 (1920); King, *J. Chem. Soc.*, **119**, 1107 (1921); Christiansen, THIS JOURNAL, **43**, 2202 (1921); Hart and Payne, *J. Am. Pharm. Assoc.*, **12**, 688, 762 (1923); German Patents, 251,104, 253,226; American Patent, 1,017,657; Steinkopf, Schmidt and Smie, *Ber.*, **59**, 1468 (1926).

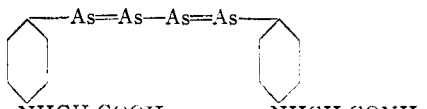
[10] German Patents, 245,756, 249,726, 250,745, 260,235, 263,460, 264,014, 271,893; American Patents, 1,024,993, 1,048,002, 1,053,300 (reissue 13,848); Binz, *Z. angew. Chem.*, **33**, 256 (1920); **36**, 551 (1923); Binz and Bauer, *Z. angew. Chem.*, **34**, 261 (1921); Voegtlin, Dyer and Thompson, *Am. J. Syphilis*, **6**, 526 (1922); Hart and Payne *J. Am. Pharm. Assoc.*, **12**, 688 (1923).

The mechanism of the formation of unsymmetrical arseno compounds is undoubtedly, first, reduction of each arsonic acid to its arseno derivative and, second, rearrangement of the two arseno compounds to the unsymmetrical according to method *B* above. Thus *p*-arsonophenylamino-ethanol can be reduced with a large excess of hypophosphorous acid in hydrochloric acid to give a solution of *p*-arsenophenylamino-ethanol (III). Within a short time after adding an equimolecular proportion of *p*-arsonophenoxyacetic acid, and an additional quantity of the reducing agent, the unsymmetrical derivative, 4-hydroxyethylamino-arsenobenzene-4′-oxyacetic acid (VIII) begins to precipitate.

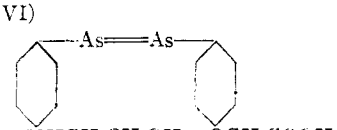
It is not to be inferred, however, that the successive or even simultaneous reduction of two arsonic acids leads invariably to the formation of the unsymmetrical arseno compound. One case, in particular, was encountered in which the two symmetricals predominated in the reaction product, regardless of experimental conditions, namely, in the reduction of phenyl arsonic acid with 3-amino-4-hydroxyphenylarsonic acid.



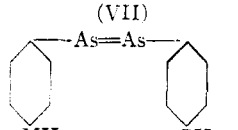
(VI)



(VII)



(VIII)



(IX)

The unsymmetrical compounds described in the experimental part show variety in the choice of conditions and reducing agents. In the earlier experiments where hypophosphorous acid was employed, no catalyst was used. Later work, however, showed that the time element could be shortened from a period of several days to a few minutes by the introduction of a small amount of potassium iodide; but with or without catalyst, in all reductions involving tryparsamide or etharsanol, the temperature needed to be kept under 15°.

The proof that each unsymmetrical arseno compound derived from *p*-arsonophenylglycine-amide or *p*-arsonophenylamino-ethanol and another arsonic acid containing a solubilizing group of an acidic nature, is not a mixture of two symmetrical products, rests on the observation that they are wholly soluble in aqueous alkalies. If any symmetrical arseno compound from *p*-arsonophenylamino-ethanol or *p*-arsonophenylglycine-amide were present it would remain as a residue insoluble in alkali. Moreover, the products behave as single definite compounds when derivatives such as hydrochlorides or methylenesulfoxylic acids are prepared. In one case,

the methylenesulfoxylic acid of the unsymmetrical was produced directly by treatment of the two arsonic acids with formaldehydesulfoxylic acid.

The pharmacological study of several of the compounds described is being carried out by Dr. A. S. Loevenhart at the University of Wisconsin, but is not yet complete.

The toxicity of arseno compounds is a function not alone of the molecular configuration but also of the method of preparation. Contact with air usually increases toxicity, probably because arsine oxides are formed. Hence, in preparing specimens for biological testing, filtrations were performed in carbon dioxide atmosphere. It was found, too, that toxicity could be reduced in the case of compounds having a phenolic function by dissolving in dilute sodium hydroxide and precipitating with carbon dioxide. By this treatment arsine oxides that may have been in the reaction product because of incomplete reduction were left in solution as the sodium salt. After filtering, the base could then be converted to the hydrochloride.

Experimental

Derivatives of *p*-Arsonophenylamino-ethanol

(1) **4-Amino-4'-β-hydroxyethylamino-arsenobenzene Dihydrochloride (VI).**—A solution of a fiftieth mole each of *p*-arsonophenylamino-ethanol and arsanilic acid in 30 cc. of water and 10 cc. of 12 *N* hydrochloric acid was prepared. This was treated with one-half mole of 50% hypophosphorous acid and kept at a temperature below 15° for three days. No precipitate appeared but the clear solution became light yellow in color. Precipitation was brought about by stirring into 100 cc. of cold, 6 *N* hydrochloric acid. The product was granular in character and could be filtered easily in the open air without discoloration due to oxidation. It was washed repeatedly with dilute hydrochloric acid and then triturated in a mortar with 30 cc. of methanol to which had been added 5 cc. of hydrochloric acid (d., 1.19). After filtering again, washing with ether left the compound almost dry; yield, 7 g. or 78%.

This compound does not dissolve in water of itself but merely turns red and gum-like. If, however, a small quantity of hydrochloric acid be added, solution proceeds quickly.

Anal. Subs., 0.1803, 0.1375: 35.35, 26.47 cc. of iodine soln. (1 cc. = 0.001703 g. of As). Calcd. for $C_{14}H_{15}ON_2Cl_2As_2$: As, 33.24. Found: As, 33.39, 32.78. Subs., 0.2231, 0.3721: AgCl, 0.1357, 0.2333. Calcd. for $C_{14}H_{15}ON_2Cl_2As_2$: Cl, 15.72. Found: 15.05, 15.51.

(2) **4-Amino-4'-β-hydroxyethylamino-arsenobenzene-N-methylenesulfoxylic Acid.**—Five grams of the preceding compound was dissolved in 50 cc. of water to which had been added 3 cc. of hydrochloric acid (d., 1.19), and a solution of 2.5 g. of sodium formaldehydesulfoxylate in 25 cc. of water added. In a few minutes a yellow precipitate began to form. Precipitation was complete in an hour at room temperature. The product was filtered in carbon dioxide and after it had been thoroughly washed with water was dried by washing with methanol and ether. The drying was completed in a vacuum desiccator over sulfuric acid for a period of eighteen hours. The yield was quantitative.

Anal. Subs., 0.1444, 0.1467: 23.80, 24.52 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{15}H_{18}O_3N_2SAs_2$: As, 32.86. Found: As, 32.29, 32.84. Subs.,

0.2649, 0.2386: $BaSO_4$, 0.1301, 0.1205. Calcd. for $C_{15}H_{15}O_2N_2SAs_2$: S, 7.03. Found: S, 6.75, 6.94.

(3) **4-Hydroxy-4'-β-hydroxyethylamino-arsenobenzene Hydrochloride.** The reduction of fiftieth moles of *p*-arsonophenol and *p*-arsonophenylamino-ethanol was carried out in a manner identical with (1). In this case the arseno compound precipitated as formed. Before filtering, 20 cc. of 12 *N* hydrochloric acid was added and the filtration then performed in a current of carbon dioxide. The product was washed repeatedly with dilute hydrochloric acid and finally with methanol acidified slightly with hydrochloric acid. It was dried in a vacuum over sulfuric acid and caustic soda and amounted to 5 g. of the hydrochloride or 60% of the theoretical. Smaller additional amounts were obtained by allowing the mother liquors to stand in the cold.

This compound is readily soluble in dilute caustic soda, somewhat soluble in methyl alcohol and acetone but only sparingly in dilute hydrochloric acid. Water turns it red and gum-like. An alkaline solution of it heated to boiling speedily clouds and on continued boiling forms a filterable precipitate. This may be the symmetrical *p*-arsenophenylamino-ethanol.

Anal. Subs., 0.1200, 0.1843: 24.75, 37.95 cc. of iodine soln. (1 cc. = 0.001758 g. of As). Calcd. for $C_{14}H_{16}O_2NClAs_2$: As, 36.07. Found: As, 36.26, 36.20.

(4) **The free base** of this compound was prepared by dissolving the hydrochloride in dilute caustic soda and precipitating with carbon dioxide. The precipitate was fairly easily filtered and could be washed rapidly with warm water. It was found to be somewhat soluble in methanol.

Anal. Subs., 0.1410, 0.1067: 28.75, 21.65 cc. iodine soln. (1 cc. = 0.001940 g. of As). Calcd. for $C_{14}H_{15}O_2NAs_2$: As, 39.54. Found: As, 39.56, 39.36. Subs. 1.2678: 7.01 cc. of 0.500 *N* HCl. Calcd. for $C_{14}H_{15}O_2NAs_2$: N, 3.70. Found: N, 3.87.

(5) **3-Amino-4-hydroxy-4'-β-hydroxyethylamino-arsenobenzene Dihydrochloride (Free Base, V).**—Following the procedure as described under (1), fiftieth moles of 3-amino-4-hydroxyphenylarsonic acid and *p*-arsonophenylamino-ethanol were reduced to the unsymmetrical arseno compound. Precipitation, however, did not come about spontaneously and it was necessary to stir the reaction mixture into 100 cc. of 12 *N* hydrochloric acid in order to bring it about. The product was purified by dissolving in 66 cc. of water and pouring into an equal volume of 12 *N* hydrochloric acid. After repeating this treatment, the product was filtered, washed with dilute hydrochloric acid, then with a mixture of 50 parts each of methanol and ether and dried in a vacuum over sulfuric acid and caustic soda; yield, 5 g. or 53%. The compound was readily soluble in water or dilute alkali.

Anal. Subs., 0.1964, 0.1188: 37.90, 22.90 cc. of iodine soln. (1 cc. = 0.001671 g. of As). Calcd. for $C_{14}H_{18}O_2N_2Cl_2As_2$: As, 32.10. Found: As, 32.25, 32.21. Subs., 0.1998, 0.2405: AgCl, 0.1214, 0.1477. Calcd. for $C_{14}H_{18}O_2N_2Cl_2As_2$: Cl, 15.18. Found: Cl, 15.03, 15.19.

(6) **3-Amino-4-hydroxy-4'-β-hydroxyethylamino-arsenobenzene-N-methylene-sulfoxylic Acid.**—The procedure for preparing this compound was identical with that of (2). The yield, also, was quantitative.

Anal. Subs., 0.1146, 0.1334: 23.65, 27.35 cc. of iodine soln. (1 cc. = 0.001526 g. of As). Calcd. for $C_{15}H_{18}O_4N_2SAs_2$: As, 31.75. Found: As, 31.49, 31.28. Subs., 0.2130, 0.2178: $BaSO_4$, 0.1057, 0.1115. Calcd. for $C_{15}H_{18}O_4N_2SAs_2$: S, 6.79. Found: S, 6.82, 7.03.

(7) **4-β-Hydroxyethylamino-arsenobenzene-4'-N-glycine Dihydrochloride.**—A solution was prepared of one-hundredth moles each of *p*-arsonophenylamino-ethanol

and *p*-arsonophenylglycine in 20 cc. of hydrochloric acid (d., 1.19) and 30 cc. of water. After cooling to 15°, one-quarter mole of 50% hypophosphorous acid was added and the solution cooled as before. While stirring rapidly, a solution of one gram of potassium iodide in 10 cc. of water was added dropwise. During this process the color of the solution changed first to deep red and back again to a very light yellow. Finally, a heavy yellow precipitate appeared that was filtered and washed with very dilute hydrochloric acid. The product did not darken on exposure to air; yield, 4 g. or 78% of the theoretical. The product was wholly soluble in sodium bicarbonate.

Anal. Subs., 0.1870, 0.1038: 28.15, 15.74 cc. of iodine soln. (1 cc. = 0.001910 g. of As). Calcd. for $C_{16}H_{20}O_3N_2Cl_2As_2$: As, 29.45. Found: As, 28.75, 28.96.

This compound was also prepared by means of stannous chloride.

(8) **The free base** of this compound was prepared by dissolving 4 g. of the dihydrochloride in 30 cc. of water to which had been added sufficient sodium hydroxide to form the sodium salt. The solution was then stirred into a solution of 10 cc. of acetic acid in 50 cc. of water. The precipitate so formed was decidedly gelatinous and difficult to filter, but the product was rendered practically free from inorganic salts by repeated triturations with warm water, and finally was dried in a vacuum over sulfuric acid.

Anal. Subs., 0.1070, 0.1242: 19.55, 22.65 cc. of iodine soln. (1 cc. = 0.001910 g. of As). Calcd. for $C_{16}H_{15}O_7N_2As_2$: As, 34.37. Found: As, 34.90, 34.83.

(9) **4-β-Hydroxyethylamino-arsenobenzene-4'-oxyacetic Acid (VIII).**—A fiftieth mole of *p*-arsonophenylamino-ethanol was dissolved in a mixture of 10 cc. of hydrochloric acid (d., 1.19) and 30 cc. of water and treated with one-quarter mole of 50% hypophosphorous acid. It was allowed to remain on ice for eighteen hours, after which time the solution had a light yellow color.

A second solution was then made of a fiftieth mole of *p*-arsonophenoxyacetic acid in 25 cc. of hydrochloric acid (d., 1.19) and 10 cc. of water, added to the above, and then a second quarter mole of hypophosphorous acid. The solution, now containing *p*-arsenophenylamino-ethanol and the unreduced *p*-arsonophenoxyacetic acid, was allowed to remain on ice for five days, during which time a yellow precipitate formed. The filtered product was washed repeatedly with warm water, methanol and ether to an almost dry yellow powder; yield, 8 g. or 92% of the theoretical. A sample was found to be completely soluble in sodium bicarbonate solution.

Anal. Subs., 0.1072, 0.2020: 18.85, 35.60 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{16}H_{17}O_4NAs_2$: As, 34.30. Found: As, 34.55, 34.63.

The independent reduction of the *p*-arsonophenylamino-ethanol to the corresponding arseno derivative before the reduction of the *p*-arsonophenoxyacetic acid shows that, as the latter was reduced, there was a rearrangement of the two arseno compounds to give a product composed entirely of the unsymmetrical. The mother liquors in the filtrate were colorless and showed no trace of any *p*-arsenophenylamino-ethanol left in solution.

Derivatives of *p*-Arsonophenylglycine-amide

(10) **4-Amino-arsenobenzene-4'-N-glycine-amide Dihydrochloride.**—A solution was prepared of one-hundredth moles each of *p*-arsonophenylglycine-amide and arsanilic acid in 30 cc. of hydrochloric acid (d., 1.19) and 10 cc. of water. Twenty grams of crystalline stannous chloride was then dissolved in it portionwise, after which a solution of one gram of potassium iodide in 5 cc. of water was added. A heavy, light yellow precipitate instantly formed. It was readily filtered and washed with dilute hydrochloric acid, after which trituration in a mortar with dilute hydrochloric acid removed

occluded tin salts. On filtering again, the cake was washed with dilute hydrochloric acid and methanol and dried in a vacuum over sulfuric acid; yield, 4 g. or 86%. This compound is not appreciably soluble in water and difficultly soluble in warm dilute hydrochloric acid. The latter seems to promote decomposition.

Anal. Subs., 0.1043, 0.1244: 17.15, 20.60 cc. of iodine soln. (1 cc. = 0.001940 g. of As). Calcd. for $C_{14}H_{17}ON_3Cl_2As_2$: As, 32.31. Found: As, 31.90, 32.12. Subs., 0.2767, 0.2549: AgCl, 0.1684, 0.1543. Calcd. for $C_{14}H_{17}ON_3Cl_2As_2$: Cl, 15.28. Found: As, 15.06, 14.97.

(11) **4-Amino-arsenobenzene-4'-glycine-amide-N-dimethylenesulfoxylic Acid.**—Owing to the difficulty encountered in obtaining a solution of the preceding compound, the methylenesulfoxylic acid derivative was produced by reduction of the two arsonic acids with sodium formaldehydesulfoxylate. The subsequent analysis showed that part at least of the product contained only one methylenesulfoxylic acid group.

To a solution of fiftieth moles each of arsanilic acid and *p*-arsonophenylglycine-amide in 30 cc. of water and 20 cc. of hydrochloric acid (d., 1.19) was added one-tenth mole of sodium formaldehydesulfoxylate in 50 cc. of water. A yellow precipitate began to form immediately and precipitation continued over a period of several days. The product was filtered and washed with cold water, methanol and ether to a dry powder. It was then placed in a vacuum desiccator over sulfuric acid; total yield, 2 g or 18% of the calculated quantity.

Anal. Subs., 0.1072, 0.1042: 17.85, 17.15 cc. of iodine soln. (1 cc. = 0.001742 g. of As). Calcd. for $C_{16}H_{15}O_5N_3S_2As_2$: As, 27.39. Found: As, 29.01, 28.67. Subs., 0.2127, 0.1905: $BaSO_4$, 0.1734, 0.1583. Calcd. for $C_{16}H_{19}O_5N_3S_2As_2$: S, 11.72. Found: S, 11.20, 11.42.

(12) **4-Hydroxyarsenobenzene-4'-N'-glycine-amide Hydrochloride.**—This compound was prepared in a manner similar to (1) from *p*-arsonophenylglycine-amide and *p*-arsonophenol except that the solvent in this case was a mixture of 30 cc. of water and 25 cc. of hydrochloric acid (d., 1.19). The unsymmetrical arseno compound precipitated during reduction and after filtering was washed well with dilute hydrochloric acid, alcohol and ether to an almost dry state. After drying over sulfuric acid in a vacuum desiccator, the product weighed 6 g., representing a yield of 67%. The analysis seemed to indicate a monohydrate. To confirm this, the free base was prepared.

Anal. Subs., 0.1050, 0.1300: 18.80, 23.15 cc. of iodine soln. (1 cc. = 0.001898 g. of As). Calcd. for $C_{14}H_{15}O_2N_2ClAs_2 \cdot H_2O$: As, 33.57. Found: As, 33.98, 33.80. Subs., 0.2409, 0.2225: AgCl, 0.0749, 0.0695. Calcd. for $C_{14}H_{15}O_2N_2ClAs_2 \cdot H_2O$: Cl, 7.94. Found: Cl, 7.69, 7.73.

(13) **The free base** was prepared in a manner similar to (4).

Anal. Subs., 0.1629, 0.1621: 33.75, 33.70 cc. of iodine soln. (1 cc. = 0.001826 g. of As). Calcd. for $C_{14}H_{14}O_2N_2As_2$: As, 38.24. Found: As, 37.83, 37.96. Subs., 0.2254, 0.1891: CO_2, 0.3498, 0.2926; H_2O, 0.0730, 0.0618. Calcd. for $C_{14}H_{14}O_2N_2As_2$: C, 42.87; H, 3.60. Found: C, 42.34, 42.21; H, 3.62, 3.66. Subs., 1.4763: 73.8 cc. of 0.100 *N* HCl. Calcd. for $C_{14}H_{14}O_2N_2As_2$: N, 7.14. Found: N, 7.00.

(14) **3-Amino-4-hydroxyarsenobenzene-4'-glycine-amide Dihydrochloride.**—The reduction was carried out as in the preparation of (7), using hundredth moles of *p*-arsonophenylglycine-amide and 3-amino-4-hydroxyphenylarsonic acid in 35 cc. of hydrochloric acid (d., 1.19), 20 cc. of water and one-quarter mole of 50% hypophosphorous acid. When the crude product was filtered, purification was brought about by dissolving in 50 cc. of water containing enough sodium hydroxide to form the sodium salt and precipitating by stirring into 100 cc. of 6 *N* hydrochloric acid. The filtered

product was washed with dilute hydrochloric acid and finally with absolute methanol containing 16% of hydrogen chloride. Drying was completed in a vacuum desiccator; yield, 3.5 g. or 73%. This compound is soluble in water and dilute caustic soda.

Anal. Subs., 0.1015, 0.1493: 16.42, 24.23 cc. of iodine soln. (1 cc. = 0.001940 g. of As). Calcd. for $C_{14}H_{17}O_2N_3Cl_2As_2$: As, 31.23. Found: As, 31.38, 31.48.

(15) **The free base** of the preceding compound was obtained after the manner of (4) and (13) except that in this case one g. of sodium sulfate was dissolved in the solution prior to passing in carbon dioxide, in order to obtain particles of larger size. The filtered product was washed repeatedly with warm water and dried in a vacuum desiccator over sulfuric acid.

Anal. Subs., 0.0959, 0.1079: 18.50, 20.80 cc. of iodine soln. (1 cc. = 0.001910 g. of As). Calcd. for $C_{14}H_{15}O_2N_3As_2$: As, 36.82. Found: As, 36.85, 36.82.

(16) **3-Amino-4-hydroxyarsenobenzene-4'-glycine-amide-N-methylenesulfoxylic Acid.**—The procedure for preparing this derivative of (14) from its parent compound was identical with that of (2) and (6).

Anal. Subs., 0.1380, 0.1878: 22.55, 30.80 cc. of iodine soln. (1 cc. = 0.001910 g. of As). Calcd. for $C_{15}H_{17}O_4N_3SAs_2$: As, 30.90. Found: As, 31.21, 31.32. Subs., 0.4790, 0.2530: $BaSO_4$, 0.2072, 0.1080. Calcd. for $C_{15}H_{17}O_4N_3As_2$: S, 6.61. Found: S, 5.94, 5.86.

(17) **Arsenobenzene-4-N-glycine-4'-N'-glycine-amide Dihydrochloride (Free Base, IV).**—To a mixture of 60 cc. of hydrochloric acid (d., 1.19) and 20 cc. of water was added fiftieth moles of *p*-arsonophenylglycine and *p*-arsonophenylglycine-amide. After warming to dissolve the solid matter and chilling again in an ice-bath, 40 g. of stannous chloride was put in portionwise. The mixture was shaken well until no stannous chloride remained undissolved, following which 2 g. of potassium iodide in a few cc. of water was added. A heavy yellow gum immediately separated. The supernatant liquor was decanted and the gum thoroughly worked with several portions of 6 *N* hydrochloric acid, and finally with oxygen-free water until it had assumed the form of a bright yellow powder. The filtered product was washed with very dilute hydrochloric acid. It was then dissolved in 200 cc. of water containing sufficient caustic soda to make the sodium salt and reprecipitated as a bright yellow, granular powder by stirring into 200 cc. of 6 *N* hydrochloric acid. The product so obtained was washed repeatedly with very dilute hydrochloric acid and dried over sulfuric acid in a vacuum; yield, 5 g. or 48%. It was entirely soluble in sodium bicarbonate solution, and also somewhat soluble in methanol.

Anal. Subs., 0.1251, 0.1806: 18.35, 26.65 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{16}H_{19}O_3N_3Cl_2As_2$: As, 28.72. Found: As, 28.82, 29.00. Subs., 0.2943, 0.2475: AgCl, 0.1628, 0.1356. Calcd. for $C_{16}H_{19}O_3N_3Cl_2As_2$: Cl, 13.58. Found: Cl, 13.68, 13.55.

(18) **Tetra-arsenobenzene-4-N-glycine-4'-N'-glycine-amide Dihydrochloride (Free Base, VII)** is formed as follows. A solution of fiftieth moles of *p*-arsonophenylglycine and *p*-arsonophenylglycine-amide was prepared in 25 cc. of hydrochloric acid (d., 1.19) and 30 cc. of water. It was treated with 53 cc. of 50% hypophosphorous acid and allowed to remain at room temperature for several days. There was a gradual color change of the solution from water white to deep red, at which stage precipitation began and yielded 4 g. of product, or 30% of the calculated. It was filtered, washed with dilute hydrochloric acid, methanol and ether and dried in a vacuum over phosphorus pentoxide.

Anal. Subs., 0.2438, 0.1462: 67.00, 40.30 cc. of iodine soln. (1 cc. = 0.001664 g. of As). Calcd. for $C_{16}H_{19}O_3N_3Cl_2As_4$: As, 44.62. Found: As, 45.73, 45.87.

(19) **Arsenobenzene-4-glycine-amide-4'-oxyacetic acid.**—Fiftieth moles of *p*-arsonophenylglycine-amide and *p*-arsonophenoxyacetic acid dissolved in 35 cc. of hydrochloric acid (d., 1.19) and 20 cc. of water were reduced with one-half mole of hypophosphorous acid without catalyst as in (12). After four or five days below 15° the reaction mixture was warmed to 40° to dissolve any crystals of unreduced *p*-arsonophenoxyacetic acid, the arseno compound immediately filtered and washed repeatedly with water, methanol and ether; yield, 6 g. or 67% of the calculated. The compound was entirely soluble in alkaline solutions.

Anal. Subs., 0.1087, 0.1058: 18.80, 18.20 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{16}H_{16}O_4N_2As_2$: As, 33.30. Found: As, 33.99, 33.87.

Other Unsymmetrical Arseno Compounds

(20) **4-Hydroxyarsenobenzene-4'-glycine Hydrochloride.**—The reduction of fiftieth moles of *p*-arsonophenylglycine and *p*-arsonophenol in 30 cc. of water and 25 cc. of hydrochloric acid (d., 1.19) was carried out as in (19). It was necessary to keep this solution on ice for five or six days before reduction was complete. The precipitated product was then filtered off, washed with dilute hydrochloric acid and a mixture of fifty parts of methanol and fifty parts of ether, and dried in a vacuum desiccator; yield, 5 g. or 56%. Analysis showed it to be a monohydrate (cf. 4-hydroxyarsenobenzene-4'-glycine-amide hydrochloride).

Anal. Subs., 0.1079, 0.1891: 18.49, 32.65 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{14}H_{13}O_3NClAs_2 \cdot H_2O$: As, 33.57. Found: As, 33.67, 33.92. Subs., 0.1995, 0.2623: AgCl, 0.0619, 0.0809. Calcd. for $C_{14}H_{13}O_3NClAs_2 \cdot H_2O$: Cl, 7.94. Found: Cl, 7.68, 7.63.

(21) **3-Amino-4-hydroxyarsenobenzene-4'-oxyacetic Acid.**—Fiftieth moles of *p*-arsonophenoxyacetic acid and 3-amino-4-hydroxyphenylarsonic acid were dissolved in an acid mixture similar to (20) and reduced with one-half mole of hypophosphorous acid at a temperature below 15°. After eighteen hours, a light yellow precipitate had developed consisting of 3.5 g. of product. Before filtering, the mixture was warmed to 50° to dissolve any unreduced *p*-arsonophenoxyacetic acid. The product was washed repeatedly with water and ethanol and dried in a vacuum. Warming the mother liquors at 100° for thirty minutes gave an additional crop of 2.5 g. that was entirely free from decomposition products; total yield, 73%.

Anal. Subs., 0.1084, 0.1457: 20.00, 26.95 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{14}H_{13}O_4NAs_2$: As, 36.65. Found: As, 36.25, 36.35.

(22) **3,4'-Diamino-4-hydroxyarsenobenzene Dihydrochloride.**[11]—This compound was prepared like several of those already described but with the use of pyridine to prevent too rapid precipitation. The reaction mixture was made up from fiftieth moles of arsanilic acid and 3-amino-4-hydroxyphenylarsonic acid, 30 cc. of water, 40 cc. of pyridine, 10 cc. of hydrochloric acid (d., 1.19) and 53 cc. of hypophosphorous acid. The mixture was warmed on a water-bath at 100° for one-half hour and acquired a light reddish tint. At this point it was poured into 100 cc. of hydrochloric acid, which caused the reaction product to precipitate. This was redissolved in 100 cc. of water, acidified with a few cc. of strong hydrochloric acid and reprecipitated by stirring into 100 cc. of 6 *N* hydrochloric acid. The compound was filtered and washed with dilute hydrochloric acid, acetone and ether; yield, 5.5 g. or 65%.

Anal. Subs., 0.2270, 0.2287: 46.00, 47.23 cc. of iodine soln. (1 cc. = 0.001742 g. of As). Calcd. for $C_{12}H_{14}ON_2Cl_2As_2$: As, 35.44. Found: As, 35.30, 35.97.

[11] German Patent, 251,104.

(23) **4-Amino-4'-hydroxyarsenobenzene Hydrochloride**[12] (**IX**).—To a solution of fiftieth moles of arsanilic acid and *p*-arsonophenol in 30 cc. of hydrochloric acid (d., 1.19) and 10 cc. of water, was added 20 g. of stannous chloride. After shaking until the latter was dissolved, 1 g. of potassium iodide in 5 cc. of water was stirred in and immediately a reddish-yellow precipitate formed. Filtration was performed with some difficulty because the solid matter was very finely divided, and it was finally washed with water, methanol and ether. Five g. of product or 67% of the calculated quantity was obtained. It was found to be completely soluble in caustic soda solution.

Anal. Subs., 0.1106, 0.1683: 22.30, 33.85 cc. of iodine soln. (1 cc. = 0.001965 g. of As). Calcd. for $C_{12}H_{12}ONClAs_2$: As. 40.35. Found: As, 39.61, 39.52.

(24) **3-Amino-4-hydroxyarsenobenzene Hydrochloride.**[13]—Repeated attempts to prepare this compound by simultaneous reduction of 3-amino-4-hydroxyarsenobenzene with phenylarsonic acid resulted in every case in mixtures of the two symmetrical arseno compounds, from which arsenobenzene and 3,3'-diamino-4,4'-dihydroxyarsenobenzene dihydrochloride (arsphenamine) were both isolated and identified.

Summary

1. A series of alkali-soluble unsymmetrical arseno compounds has been prepared by simultaneous reduction of equimolecular proportions of *p*-arsonophenylglycine-amide and an arsonic acid containing a solubilizing group, or in which solubilizing groups can be easily substituted.

2. A similar series from *p*-arsonophenylamino-ethanol has been prepared.

3. One unsymmetrical tetra-arseno compound, tetra-arsenobenzene-4-glycine-4'-glycine-amide dihydrochloride has been described.

4. Several unsymmetrical arseno compounds containing neither glycine-amide nor amino-ethanol groupings have been prepared in an effort to shed light on the mechanism by which unsymmetrical arseno compounds are formed.

EVANSTON, ILLINOIS

[12] Kahn, *Chem.-Ztg.*, **36**, 1099 (1912); Hart and Payne, *J. Am. Pharm. Assoc.*, **12**, 688 (1923); German Patents, 254,187, 251,571, 352,226; American Patent, 1,033,904.

[13] German Patents, 251,104 and 254,187.