example, if R is phenyl, such compounds were prepared by reacting arsanilic acid with phenylchloroacetyl-amino compounds.

By the above treatment of the subject we have attempted to realize the conditions postulated at the start as essential in a logical plan for the synthesis of new arsenicals for biological study. It is our belief that a similar treatment of other leads, where chemically possible, will prove of service in chemotherapeutic investigations.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

AROMATIC ARSENIC COMPOUNDS. II. THE AMIDES AND ALKYL AMIDES OF *N*-ARYLGLYCINE ARSONIC ACIDS.

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Received July 2, 1919.

As in the case of other aromatic amino compounds, sodium *p*-aminophenylarsonate (sodium arsanilate) has been found to react with chloroacetic acid to form phenylglycine-*p*-arsonic acid.[1] In the present investigations we have found that the amide and alkyl amides of chloroacetic acid react in similar manner to form the amide and alkyl amides of phenylglycine-*p*-arsonic acid, with the following general formula

in which R and R′ may be hydrogen, alkyl, benzyl or substituted benzyl radicals. Although arsanilic acid itself may be employed in this reaction instead of the sodium salt, the reactivity of the amino group is suppressed by the negative arsonic acid radical so that the reaction proceeds very slowly, and satisfactory yields are only obtained when an extra molecule of the amino acid is employed, since the hydrochloric acid produced during the condensation renders a portion of the base inactive. On the other hand sodium arsanilate exhibits the full reactivity of the amino group and the sodium ion present neutralizes the hydrochloric acid as it is formed.

Chloroacetamide and the simpler chloroacetyl alkylamines condensed readily with sodium arsanilate in boiling aqueous solution, and although the reaction in no instance proceeded quantitatively, owing to the occurrence of side reactions, $^1/_2$ to 2 hours' boiling sufficed for obtaining optimum yields. In the case of the chloroacetylbenzyl amines, 50% alcohol was found to be the most serviceable medium owing to the spar-

[1] Ger. pat. 204,664.

ing solubility of these compounds in water. Moreover, the reactivity of the chlorine atom in these substances proved to be so much less than that of the simpler alkyl derivatives that the addition of sodium iodide was found necessary, greatly facilitating the condensation owing to the intermediate formation of the iodoacetyl derivatives.

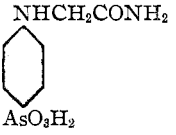
The first member of the series, *N*-phenylglycineamide-*p*-arsonic acid, was also prepared by the action of concentrated ammonia on the methyl ester of phenylglycine-*p*-arsonic acid. This method could unquestionably be employed for the preparation of the simpler homologous compounds, in which case it would necessitate the recovery of the excess of the expensive amines.

The present studies on *p*-arsanilic acid were extended to include analogous substances starting with *o*- and *m*-arsanilic acids and the homologous aminoaryl arsonic acids.

All of the glycineamide arsonic acids are colorless, crystalline substances which are as a rule but sparingly soluble in the usual neutral solvents and possess high melting or decomposition points, the latter depending greatly upon the rate of heating. As arsonic acids they dissolve in alkalies and alkaline carbonates to form neutral salts, but are completely displaced from these by so weak an acid as acetic acid. Because of the imino group they also possess basic properties and form nitroso derivatives. The basicity appears to be more feeble than that of arsanilic acid itself, since these substances dissolve or form stable hydrochlorides only in strong hydrochloric acid, the salts being easily hydrolyzed by water. On boiling with an excess of alkali or with mineral acids the amide linking is hydrolyzed with the formation of the glycine arsonic acid and the amine.

In the experimental part of this and subsequent papers a description of the sodium salts will be frequently encountered. In many cases these afforded a means for purifying such crude reaction products as could not be directly recrystallized, but the majority were prepared in order to furnish substances in a readily soluble form convenient for biological testing.

Since the results obtained with the first member of the group, *N*-phenylglycinamide-*p*-arsonic acid,



in the treatment of experimental trypanosome and spirochaete infections have been of so promising a character and because of its low toxicity, this substance has been made the subject of extensive study.[1] The biological

[1] It may be appropriate to mention here that this substance and related com-

results are being published elsewhere by our colleagues, Drs. Brown and Pearce. Because of the importance of this compound we are presenting it and the other derivatives obtained from *p*-aminophenyl arsonic acid first, the derivatives of *o*- and *m*-aminophenyl arsonic acids following these.

EXPERIMENTAL.

(A) Derivatives of *p*-Aminophenyl Arsonic Acid.

***N*-(Phenyl-4-arsonic acid)glycineamide (*N*-Phenyl-glycineamide-*p*-arsonic acid).**—Of the two methods used for the preparation of this substance that described first is perhaps to be preferred.

434 g. of arsanilic acid[1] were dissolved in 2 liters of *N* sodium hydroxide solution. After adding 375 g. of chloroacetamide[2] the mixture was boiled under a reflux condenser for 45 minutes, the clear solution setting to a solid mass of the crude product on cooling. 75 cc. of conc. hydrochloric acid were added to the cold mixture to hold any unchanged arsanilic acid in solution and the substance was then filtered off and carefully washed with cold water. For purification it was suspended in sufficient water to form a thin paste and carefully treated, with stirring, with 25% sodium hydroxide solution until the acid was completely dissolved. The filtered solution was then treated with an excess of acetic acid, whereupon the substance separated as minute, lustrous plates. After filtering, washing thoroughly, and drying, the yield was 300 g. The use of the above amount of chloroacetamide, though twice that theoretically required, was found advisable in order to obtain a good yield. The *acid* is very sparingly soluble in cold water, but dissolves readily on heating. It separates from the hot, aqueous solution in aggregates of

pounds, described in the present and following papers of the series, are covered by U. S. Patents, Nos. 1,280,119–27. Patents have also been applied for in foreign countries.

All discoveries made at the Rockefeller Institute are made freely available to the public, in accordance with the philanthropic purposes of the institution. In order to insure purity of product and protection against exploitation, it has been deemed necessary in certain instances to protect the discoveries by patents. It is the purpose of the Institute to permit any drugs which may prove of practical therapeutic value to be manufactured under license by suitable chemical firms and under conditions of production which will insure the biological qualities of the drugs and their marketing at reasonable prices. Other than through the issuance of license, the Rockefeller Institute does not participate in any way in the commercial preparation or sale of the manufactured chemicals; and it receives no royalties or other pecuniary benefits from the licenses it issues.

[1] The first portions of this and several other arylarsonic acids were kindly furnished before the war by L. Cassella and Co. and the Farbwerke Höchst. Later, when larger amounts of arsanilic acid were required it was prepared by us by heating aniline and arsenic acid, although we soon adopted a modification of this general method kindly placed at our disposal by Dr. G. W. Raiziss, of the Dermatological Research Laboratories of Philadelphia.

[2] *J. Biol. Chem.*, **21**, 145 (1915).

long, thin plates. It is insoluble in methyl alcohol, acetone or chloroform, and sparingly in hot methyl or ethyl alcohol, but dissolves in boiling acetic acid. It is sparingly soluble in dil. hydrochloric acid but dissolves readily in the strong acid, its behavior showing it to be a weaker base than arsanilic acid. On boiling its solution in sodium hydroxide ammonia is evolved. When rapidly heated in an open capillary tube it darkens and softens at 280°, but does not melt.

Subs., 0.1405 g.: 12.35 cc. N (22.0°, 761 mm.). Subs. 0.3205: $Mg_2As_2O_7$ 0.1832. Calc. for $C_8H_{11}O_4N_2As$: N, 10.22; As, 27.33. Found: N, 10.18; As, 27.59.

Salts.—The pure acid is suspended in enough water to form a thick paste and carefully treated with 25% sodium hydroxide solution until completely dissolved and the solution reacts neutral to litmus. Two volumes of alcohol are then added, the pure *sodium salt* quickly separating as thin, nacreous plates. After filtering and washing with 85% alcohol it is air dried and then contains $^1/_2$ molecule of water of crystallization. The sodium salt is extremely soluble in cold water, the solution reacting neutral to litmus.

Subs., air-dry: 0.3921. Loss, 0.0117 *in vacuo* over H_2SO_4 at 100°.
Calc. for $C_8H_{10}O_4N_2AsNa.0.5H_2O$: H_2O, 2.95. Found: 2.98.
Subs., anhydrous, 0.1503: 12.45 cc. N (25.0°, 762 mm.). Subs. 0.2300: $Mg_2As_2O_7$, 0.1195.
Calc. for $C_8H_{10}O_4N_2AsNa$: N, 9.46; As, 25.32. Found: N, 9.52; As, 25.08.

The *potassium* and *ammonium salts* were prepared in the same way as the sodium salt and form thin, glistening, hexagonal, microscopic platelets. On adding a calcium chloride solution to a solution of the sodium salt the *calcium salt* gradually separates as microscopic, wedge-shaped prisms, containing no water of crystallization. Magnesia mixture causes no precipitate in the cold, but on warming the *magnesium salt* separates as a microcrystalline powder. Heavy metal salts give immediate precipitates, the *silver salt* forming aggregates of thin, microscopic needles.

N-Phenyl-glycinamide-*p*-arsonic acid was also prepared as follows from *N*-phenyl-glycine methyl ester *p*-arsonic acid by the action of ammonia.

***N*-(Phenyl-4-arsonic acid) glycine methyl ester,** p-$H_2O_3AsC_6H_4NHCH_2COOCH_3$.—40 g. of *N*-phenyl-glycine-*p*-arsonic acid[1] were treated with 120 g. of dry methyl alcohol and 12 g. of conc. sulfuric acid. The mixture was boiled under a reflux condenser for two hours. The ester separated on cooling and scratching, the precipitation being completed by the addition of water. The filtered, washed, and dried product weighed 38 g. It can be recrystallized from hot water or hot 95% alcohol, separating from the former as microscopic needles and thin plates. It is very sparingly soluble in cold water, cold alcohol, or boiling acetone, and

[1] Ger. pat. 204,664.

is fairly easily soluble in methyl alcohol, especially on warming. When rapidly heated it softens and darkens above 200° and decomposes at about 285°.

Subs. 0.1560: 7.0 cc. N (21.0°, 747 mm.). Subs. 0.3135: $Mg_2As_2O_7$, 0.1665.
Calc. for $C_9H_{12}O_5NAs$: N, 4.84; As, 25.94. Found: N, 5.12; As, 25.63.

The ester was converted into the amide as follows: 10 g. of the ester were slowly added, with stirring, to 30 cc. of well chilled, conc. ammonia. At first a thick paste of the ammonium salt of the ester was formed, but on allowing the mixture to rise to room temperature the reaction proceeded with formation of a clear solution. After 24 hours the excess of ammonia was removed, preferably *in vacuo*. On diluting with water, filtering, and acidifying with acetic acid, phenyl-glycineamide-*p*-arsonic acid separated in characteristic form. This was purified as described above and was identical in every way with the product obtained by the direct method. The yield was 80% of the theoretical amount.

Subs. 0.1297: 11.5 cc. N (19.5°, 742 mm.).
Calc. for $C_8H_{11}O_4N_2As$: N, 10.22. Found: 10.11.

N-**(Phenyl-4-arsonic acid)glycine ethyl ester,** *p*-$H_2O_3AsC_6H_4NHCH_2CO_2C_2H_5$.—Recrystallized from 50% alcohol the ethyl ester forms flat, delicate needles which melt and decompose at about 270° with preliminary darkening and softening. It is very difficultly soluble in cold water, rather more soluble in cold alcohol, but dissolves quite readily in either solvent on boiling.

Subs., 0.1944: (Kjeldahl) 9.3 cc. 0.0714 *N* HCl. Subs., 0.3287: $Mg_2As_2O_7$, 0.1703.
Calc. for $C_{10}H_{14}O_5NAs$: N, 4.62; As, 24.72. Found: N, 4.78; As, 25.01.

N-**(Phenyl-4-arsonic acid)nitroso-glycineamide,** *p*-$H_2O_3AsC_6H_4N(NO)CH_2CONH_2$.—3 g. of the air-dry sodium salt were dissolved in 10 cc. of water and 2 cc. of 5 *N* sodium nitrite solution (1 mol.) added. On addition of 5 cc. of 1 : 1 hydrochloric acid (a little over 2 mols.) the rapid separation of characteristic crystals of unchanged phenyl-(4-arsonic acid)-glycineamide occurred, but on gentle warming the crystals suddenly changed to delicate needles and the mixture set to a solid cake. After diluting somewhat with water the cooled mixture was filtered, and the nitroso compound recrystallized from water, in which it is readily soluble at the boiling point and only sparingly in the cold. It forms rosets and sheaves of silky needles which intumesce at 182–3°, with preliminary yellowing, when rapidly heated to 180°, then slowly. The acid is difficultly soluble in cold methyl or ethyl alcohol, more easily on boiling, and dissolves only sparingly in cold acetic acid although quite readily in the boiling acid. It turns yellow under sulfuric acid, dissolving to an almost colorless solution giving a brown-red Liebermann test.

Subs., 0.1116: 13.6 cc. N (25.5°, 758 mm.). Subs., 0.2763: $Mg_2As_2O_7$, 0.1412.
Calc. for $C_8H_{10}O_5N_2As$: N, 13.87; As, 24.72. Found: N, 13.90; As, 24.65.

N-(**Phenyl-4-arsonic acid**)**glycine methyl amide,** p-$H_2O_3AsC_6H_4NHCH_2CONHCH_3$.—44 g. of arsanilic acid dissolved in 200 cc. of *N* sodium hydroxide solution,[1] and 25 g. of chloroacetyl-methylamine[2] were boiled under a reflux condenser for one hour. The acid separated from the solution on cooling and scratching and was purified by dissolving in just enough dilute sodium hydroxide solution and reprecipitating with acetic acid. The substance separated as a thick mass of thin, microscopic plates. The yield was 31 g. The acid is fairly easily soluble in hot water, from which it separates as aggregates of curved spears. It is difficultly soluble in methyl alcohol and may be recrystallized from hot 50% alcohol. It darkens and softens above 240° and decomposes after a few moments at 285°.

Subs., 0.3269: (Kjeldahl) 22.4 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1755.
Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.60; As, 25.91.

N-(**Phenyl-4-arsonic acid**)**glycine ethyl amide,** p-$H_2O_3AsC_6H_4NHCH_2CONHC_2H_5$.—44 g. of arsanilic acid and 30 g. of chloroacetyl-ethylamine,[3] were condensed as in previous examples. For purification the resulting ethylamide was dissolved in a small volume of hot water, from which it separated on cooling as a thick crust of platelets. The yield was 30 g. The acid is sparingly soluble in cold water or alcohol, but dissolves readily on warming. It is soluble in methyl alcohol, particularly on warming. The substance darkens above 250° and decomposes at 278–80°. Attempts to make a pure sodium salt were unsuccessful owing to its great solubility in water or dilute alcohol.

Subs., 0.1441: 11.6 cc. N (21.0°, 762 mm.). Subs., 0.3707: $Mg_2As_2O_7$, 0.1923.
Calc. for $C_{10}H_{15}O_4N_2As$: N, 9.27; As, 24.81. Found: N, 9.37; As, 25.04.

N-(**Phenyl-4-arsonic acid**)**glycine** *n*-**propyl amide,** p-$H_2O_3AsC_6H_4NHCH_2CONHCH_2CH_2CH_3$.—4.4 g. of arsanilic acid and 3 g. of chloroacetyl-propylamine[2] yielded after two hours an oil which crystallized when rubbed. This was purified by dissolving in hot, dil. ammonia and acidifying with acetic acid. It separated slowly on cooling as flat needles or plates and wedge-shaped prisms. The yield was 3.5 g. The substance is sparingly soluble in boiling water, but readily so in boiling 50% alcohol, from which it separates on cooling as sheaves of microscopic needles. It does not melt below 280°.

Subs., 0.1491: 11.6 cc. N (22.5°, 758 mm.). Subs., 0.3188: $Mg_2As_2O_7$, 0.1549.
Calc. for $C_{11}H_{17}O_4N_2As$: N, 8.86; As, 23.70. Found: N, 8.96; As, 23.45.

[1] Hereafter unless otherwise stated arsanilic acid was always dissolved in the equivalent amount of *N* sodium hydroxide solution and likewise equivalent quantities of the halide were employed for the reaction.

[2] THIS JOURNAL, 41, 472 (1919).

[3] *J. Biol. Chem.*, 21, 149 (1915).

N-(**Phenyl-4-arsonic acid**)**glycine dimethyl amide,** p-$H_2O_3AsC_6H_4NHCH_2CON(CH_3)_2$.—After $^1/_2$ hour's boiling the reaction product from 3 g. of chloroacetyl-dimethylamine[1] suddenly separated as a mass of thin, microscopic needles, often occurring in characteristic sheaves. After cooling the mixture was acidified with hydrochloric acid, filtered and the substance washed with water. It was recrystallized from 50% alcohol, requiring a large volume and separating in the same characteristic form. The yield was 3 g. The substance is very sparingly soluble in the neutral solvents, and when rapidly heated, decomposes at about 241–2°.

Subs., 0.1392: 11.1 cc. N (22.0°, 762 mm.). Subs., 0.3440: $Mg_2As_2O_7$, 0.1747.
Calc. for $C_{10}H_{15}O_4N_2As$: N, 9.27; As, 24.81. Found: N, 9.25; As, 24.50.

Sodium Salt.—A neutral solution of the acid in dil. sodium hydroxide, on treating with two volumes of alcohol, yielded the salt as elongated plates, which after washing with 50% alcohol and air drying contained 4 molecules of water of crystallization and dissolved easily in water.

Subs., air-dry, 0.4277: loss, 0.0782 *in vacuo* at 80° over H_2SO_4.
Calc. for $C_{10}H_{14}O_4N_2AsNa.4H_2O$: H_2O, 18.19. Found: 18.28.
Subs., anhydrous, 0.2985: (Kjeldahl) 18.35 cc. 0.1 *N* HCl.
Calc. for $C_{10}H_{14}O_4N_2AsNa$: N, 8.65. Found: 8.61.

N-(**Phenyl-4-arsonic acid**)**glycine diethyl amide,** p-$H_2O_3AsC_6H_4NHCH_2CON(C_2H_5)_2$.—After one hour 4 g. of chloroacetyl-diethylamine[2] yielded an oil on cooling which soon crystallized. This was purified by dissolving in just enough dil. sodium hydroxide solution and reprecipitating with acetic acid, forming microscopic aggregates of short needles. The yield was 4 g. When rapidly heated it sinters and darkens above 195° and melts at 199–201° with gas evolution. It is difficultly soluble in boiling water but dissolves in boiling methyl alcohol or 50% alcohol.

Subs., 0.3184: (Kjeldahl) 18.95 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1497.
Calc. for $C_{12}H_{19}O_4N_2As$: N, 8.49; As, 22.69. Found: N, 8.34; As, 22.68.

N-(**Phenyl-4-arsonic acid**)**glycine piperidide,** p-$H_2O_3AsC_6H_4NHCH_2CONC_5H_{10}$.—From 4 g. of chloroacetyl-piperidine[3] there resulted after two hours' boiling a viscous oil which readily crystallized. This was filtered off, washed with water, and finally with 50% alcohol to remove traces of an adhering oil. The residue was then recrystallized from hot 50% alcohol, separating in characteristic sheaves of thin microscopic needles which soften and darken above 200° and decompose at 218–21°. The yield was 3 g. The acid is soluble in hot methyl alcohol and hot 50% alcohol, but very sparingly soluble in hot water.

Subs., 0.1433: 9.95 cc. N (22.5°, 762 mm.). Subs., 0.3055: $Mg_2As_2O_7$, 0.1400.
Calc. for $C_{13}H_{19}O_4N_2As$: N, 8.19; As, 21.90. Found: N, 8.05; As, 22.12.

[1] *J. Biol. Chem.*, **21**, 148 (1915).
[2] *Ibid.*, **21**, 149 (1915).
[3] THIS JOURNAL, **41**, 473 (1919).

N-(**Phenyl-4-arsonic acid**)**glycine benzyl amide,** *p*-$H_2O_3AsC_6H_4NHCH_2CONHCH_2C_6H_5$.—Since chloroacetyl-benzylamine[1] and its derivatives reacted relatively slowly and incompletely with arsanilic acid, it was found that the reaction could be greatly facilitated by the addition of equivalent amounts of sodium iodide to the reaction mixture, owing to the intermediate formation of the more reactive iodoacetyl derivatives, the medium used being 50% alcohol.

4.4 g. of arsanilic acid dissolved in 20 cc. of *N* sodium hydroxide solution, 3.7 g. of chloroacetyl-benzylamine, 4 g. of sodium iodide, and 20 cc. of alcohol were heated under a reflux condenser for 4 hours. On cooling the clear solution thickened to a paste of crystals. The collected reaction product was purified by dissolving in sufficient dil. sodium hydroxide solution and acidifying with acetic acid and again recrystallized from hot 85% alcohol, from which it slowly separated as microscopic needles. The yield was 3 g. The acid is soluble in boiling 50% or 85% alcohol and in boiling methyl alcohol, but very sparingly in boiling water. It decomposes at 282–4°.

Subs., 0.2952: (Kjeldahl) 16.25 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1250.
Calc. for $C_{16}H_{17}O_4N_2As$: N, 7.70; As, 20.58. Found: N, 7.71; As, 20.43.

N-(**Phenyl-4-arsonic acid**)**glycine 3′-carboxamido benzyl amide,** *p*-$H_2O_3AsC_6H_4NHCH_2CONHCH_2C_6H_4CONH_2$(*m*-).—In a similar manner 22.5 g. of *m*-carboxamido-chloroacetyl-benzylamine,[2] gave a clear solution which on standing and scratching deposited 27.5 g. of crude product. This was purified by dissolving in the requisite amount of dil. sodium hydroxide solution or ammonia and reacidifying with acetic acid. It separated gradually as thick aggregates of microscopic needles. On continued washing with water it tends to become colloidal. The arsonic acid decomposes at 237–9° with preliminary darkening. It is sparingly soluble in hot water, and boiling acetic acid and practically insoluble in boiling alcohol.

Subs., 0.3431: (Kjeldahl) 25.42 cc. 0.1 *N* HCl; Subs. 0.3693: $Mg_2As_2O_7$, 0.1400.
Calc. for $C_{16}H_{18}O_5N_3As$: N, 10.32; As, 18,40. Found: N, 10.37; As, 18.29.

Sodium Salt.—The acid was suspended in a small volume of hot water and 25% sodium hydroxide solution added cautiously until the solution cleared and reacted neutral to litmus. On chilling the sodium salt separated in rosets and sheaves of delicate needles, which were filtered off, washed with ice water, and air-dried. The salt separates with 5 molecules of water of crystallization and is freely soluble in water and salted out from concentrated solutions by sodium acetate.

Subs., air-dry, 0.8918: loss, 0.1520 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{16}H_{17}O_5N_3AsNa.5H_2O$: H_2O, 17.35. Found: 17.05.

[1] *J. Biol. Chem.*, 20, 686 (1915).
[2] *Ibid.*, 20, 694 (1915).

Subs., anhydrous, 0.3929: (Kjeldahl) 27.35 cc. 0.1 *N* HCl.
Calc. for $C_{16}H_{17}O_5N_3AsNa$: N, 9.79. Found: 9.75.

N-(**Phenyl-4-arsonic acid**)**glycine 4′-acetamino benzyl amide,** *p*-$H_2O_3AsC_6H_4NHCH_2CONHCH_2C_6H_4NHCOCH_3$(*p*-).—After several hours' boiling the arsonic acid resulting from 4.8 g. of *p*-acetaminochloroacetyl-benzylamine,[1] separated from the hot solution, and after washing with 50% alcohol amounted to 5.5 g. It was purified by reprecipitating its solution in dil. ammonia with acetic acid, separating as flat, microscopic needles. The acid is almost insoluble in the usual solvents except hot 50% alcohol from which it separates on cooling as diamond-shaped plates. It darkens and sinters partly but does not melt below 280°.

Subs., 0.3024: (Kjeldahl) 21.4 cc. 0.1 *N* HCl. Subs., 0.3824: $Mg_2As_2O_7$, 0.1399.
Calc. for $C_{17}H_{20}O_5N_3As$: N, 9.98; As, 17.78. Found: N, 9.91; As, 17.65.

Sodium Salt.—On treatment of the clear, neutral solution of the acid in dil. sodium hydroxide with several volumes of alcohol and scratching, the salt separated as microscopic needles. These were filtered off, washed with 95% alcohol, and air-dried, then containing 4.5 molecules of water of crystallization. The salt is readily soluble in water.

Subs., air-dry, 0.6157: loss, 0.0965 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{17}H_{19}O_5N_3AsNa.4.5H_2O$: H_2O, 15.46. Found: 15.67.
Subs., anhydrous, 0.2974: (Kjeldahl) 20.2 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1050.
Calc. for $C_{17}H_{19}O_5N_3AsNa$: N, 9.48; As, 16.91. Found: N, 9.52; As, 17.03.

N-(**Phenyl-4-arsonic acid**)**glycine 3′-carboxureidobenzyl amide,** *p*-$H_2O_3AsC_6H_4NHCH_2CONHCH_2C_6H_4CONHCONH_2$(*m*-).—During the condensation with sodium arsanilate the almost insoluble *m*-(ω-chloroacetyl-aminomethyl)benzoyl-urea[2] gradually changed its appearance owing to the deposition of the reaction product. After 4 hours the mixture was diluted with water, made alkaline with ammonia, warmed, and filtered. On acidification with acetic acid the filtrate yielded a colorless, crystalline powder. This was filtered off, redissolved in hot dil. ammonia, boiled with bone black, and the hot filtrate treated with acetic acid. The arsonic acid separated as glistening, microscopic aggregates of delicate needles which decompose at 239–40° when rapidly heated and are practically insoluble in the usual neutral solvents. The yield was unusually poor.

Subs., 0.1119: 12.4 cc. N (27.0°, 754 mm.). Subs., 0.3052: $Mg_2As_2O_7$, 0.1042.
Calc. for $C_{17}H_{19}O_6N_4As$: N, 12.45; As, 16.65. Found: N, 12.52; As, 16.48.

N-(**Phenyl-4-arsonic acid**) **4′-uramino benzyl amide,** *p*-$H_2O_3AsC_6H_4NHCH_2CONHCH_2C_6H_4NHCONH_2$(*p*-).—As the reaction mixture obtained from *p*-uramino-chloroacetyl-benzylamine[3] remained clear on cool-

[1] Einhorn and Mauermayer, *Ann.*, **343**, 299 (1905).
[2] This Journal, **39**, 2432 (1917).
[3] *Ibid.*, **39**, 2442 (1917).

ing, most of the alcohol was boiled off and water added. On cooling an oil separated which gradually crystallized. The filtered product was dissolved in dil. sodium hydroxide solution and exactly neutralized with acetic acid. After standing in the refrigerator for 24 hours the solution was filtered from a slight precipitate, but as the sodium salt could not be obtained crystalline by any of the usual methods, the solution was treated with an excess of acetic acid, again causing the separation of the arsonic acid as an oil which gradually crystallized on standing. The purification process was repeated, resulting in considerable loss, the final yield being rather poor. For analysis the substance was dried *in vacuo* at 100°.

Subs., 0.3747: (Kjeldahl) 34.8 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1360.

Calc. for $C_{16}H_{19}O_6N_4As$: N, 13.27; As, 17.76. Found: N, 13.01; As, 17.52.

***N*-(Phenyl-4-arsonic acid)glycine 3′-methyl-4′-acetamino benzyl amide,** *p*-$H_2O_3AsC_6H_4NHCH_2CONHCH_2C_6H_3(CH_3)NHCOCH_3$(*m′,p′*-).—3-Methyl-4-acetamino-chloroacetyl-benzyl amine[1] yielded a reaction mixture which set to a gelatinous mass on cooling. This was broken up, filtered, and washed first with 50% alcohol, then with water. In order to obtain the acid in crystalline form it was found necessary to pass through the *sodium salt*, a process which caused a great reduction in the yield. The amorphous product was first partly purified by solution in dil. sodium hydroxide and reprecipitation with acetic acid. After filtering and washing, the precipitate was dissolved in a small volume of dil. sodium hydroxide solution, carefully neutralized with acetic acid, and treated with a large volume of absolute alcohol. On standing in the refrigerator the sodium salt separated as a voluminous, almost gelatinous mass of delicate, microscopic needles. This was filtered off, recrystallized from 85% alcohol, and air-dried.

The analysis of this salt indicated that the air-dry product contained 6 molecules of water of crystallization, of which only 4.5 molecules were removed at 100° *in vacuo* over sulfuric acid.

Subs., air-dry, 0.7383: loss, 0.1053 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{18}H_{21}O_6N_3AsNa.6H_2O$: 4.5 H_2O, 14.32. Found: 14.26.

Subs., dried, 0.1214: 9.5 cc. N (26.5°, 751 mm.). Subs., 0.3410: $Mg_2As_2O_7$, 0.1109.

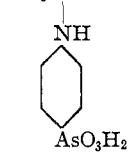
Calc. for $C_{18}H_{21}O_6N_3AsNa.1.5H_2O$: N, 8.68; As, 15.48. Found: N, 8.81; As, 15.70.

On treating the solution of the sodium salt with acetic acid the *arsonic acid* deposited slowly and was obtained as aggregates of flat, minute needles on recrystallization from 50% alcohol. When rapidly heated it decomposes at 278° and is soluble in boiling water and boiling 50% alcohol.

Subs., 0.1422: 11.7 cc. N (21.5°, 756 mm.).

Calc. for $C_{18}H_{22}O_6N_3As$: N, 9.66. Found: 9.49.

[1] *J. Biol. Chem.*, **20**, 688 (1915).

N-(**Phenyl-4-arsonic Acid**)-α-amino-propionamide,  .—

22 g. of arsanilic acid dissolved in 100 cc. of *N* sodium hydroxide solution, and 22 g. of α-bromo-propionamide were boiled for $^3/_4$ hour. The arsonic acid separated on cooling. 40 cc. of 10% hydrochloric acid were added to hold unchanged arsanilic acid in solution and the crystals filtered off and washed. After reprecipitating the solution of the acid in dil. sodium hydroxide with acetic acid 18 g. were obtained. The amide is appreciably soluble in water at room temperature and readily on boiling, crystallizing on cooling as long, thin, hexagonal plates. It is also soluble in hot 50% alcohol. When rapidly heated it darkens above 255° and decomposes at 262–3.5°.

Subs., 0.1526: 12.75 cc. N (22.5°, 765 mm.). . Subs., 0.2981: $Mg_2As_2O_7$, 0.1595.
Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.72; As, 25.81.

Sodium Salt.—A neutral solution of the acid in dil. sodium hydroxide was concentrated to dryness *in vacuo* and the residue dissolved in boiling 95% alcohol. On standing in the refrigerator the salt separated from the filtered solution as long, flat, microscopic needles, which contained approximately 2.5 molecules of water of crystallization after air drying.

Subs., air-dry, 0.5718: loss, 0.0761 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_9H_{12}O_4N_2AsNa.2.5H_2O$: H_2O 12.68. Found: 13.31.
Subs., anhydrous, 0.1443: 11.00 cc. N (20.5°, 765 mm.). Subs., 0.3333: $Mg_2As_2O_7$, 0.1643.
Calc. for $C_9H_{12}O_4N_2AsNa$: N, 9.03; As, 24.16. Found: N, 8.93; As, 23.79.

Oxanilamide-*p*-arsonic acid (***p*-oxamylamino-phenylarsonic acid**), *p*-$H_2O_3AsC_6H_4NHCOCONH_2$.—This substance, although not a glycine derivative, was suggested by its analogy to phenylglycineamide-*p*-arsonic acid, and is, therefore, described here for lack of a more appropriate place. 5 g. of anhydrous sodium arsanilate and 10 g. of ethyl oxamate were heated for 2 hours at 140–50°. The mixture was digested with water, very little going into solution, then acidified with acetic acid and filtered and washed with water. The crude mass was dissolved in dil. ammonia, and on acidifying the warm filtrate with acetic acid the substance slowly recystallized as felted masses of minute needles in a yield of 2.5 g. It does not darken or melt when heated to 280° and is very sparingly soluble in boiling water of 50% alcohol. The solution in dil. sodium hydroxide evolves ammonia on boiling.

Subs., 0.1546: 12.8 cc. N (22.5°, 761 mm.). Subs., 0.3022: $Mg_2As_2O_7$, 0.1613.
Calc. for $C_8H_9O_5N_2As$: N, 9.73; As, 26.01. Found: N, 9.58; As, 25.76.

(B) Derivatives of *o*- and *m*-Aminophenylarsonic Acids.

N-(**Phenyl-2-arsonic acid**)**glycine-amide.**—8.8 g. of *o*-aminophenyl-arsonic acid (*o*-arsanilic acid)[1] dissolved in 40 cc. of *N* sodium hydroxide solution and 7.5 g. of chloroacetamide yielded after $^3/_4$ of an hour the glycine-amide, which crystallized on cooling. The mixture was acidified to congo red with hydrochloric acid and allowed to separate more completely in the refrigerator overnight. After filtration and washing with cold water it was dissolved in a small volume of dil. ammonia and acidified to congo red with hydrochloric acid. On standing in the ice-box the arsonic acid separated as flat, microscopic needles. The yield was 5 g. In contradistinction to the *meta* and *para* isomers the *ortho* acid is not displaced completely from its salts by so weak an acid as acetic acid. The substance is soluble in hot 50% alcohol and boiling water and separates from the latter as sheaves of long, thin, narrow plates. It is sparingly soluble in hot methyl and ethyl alcohols. When rapidly heated it decomposes at 198–9°.

Subs., 0.1405: 12.2 cc. N (23.5°, 756 mm.). Subs., 0.2451: $Mg_2As_2O_7$, 0.1372.
Calc. for $C_8H_{11}O_4N_2As$: N, 10.22; As, 27.33. Found: N, 9.96; As, 27.00.

N-(**Phenyl-3-arsonic acid**)**glycineamide.**—A solution of 25 g. of *m*-arsanilic acid[1] in 115 cc. of *N* sodium hydroxide solution, and 21 g. of chloroacetamide were boiled for 45 minutes. On standing in the refrigerator the clear solution gradually deposited the reaction product as a hard crust of aggregates of needles which were contaminated with unchanged chloroacetamide. On stirring and rubbing crystallization rapidly completed itself. The substance was filtered off, washed with ice water and dried. The powdered substance was leached out with dry acetone to remove chloroacetamide and then recrystallized from a small volume of hot water. It separated slowly as aggregates of prismatic needles in a yield of 18.5 g. When rapidly heated to 170° and then slowly the substance melts at 175–7° to a liquid filled with bubbles. It is quite soluble in cold water and very easily so on warming. It is also readily soluble in hot ethyl or methyl alcohol, or glacial acetic acid, but practically insoluble in hot acetone.

Subs., 0.1334: 11.8 cc. N (24.0°, 765 mm.). Subs., 0.3140: $Mg_2As_2O_7$, 0.1783.
Calc. for $C_8H_{11}O_4N_2As$: N, 10.22; As, 27.33. Found: N, 10.23; As, 27.42.

N-(**Phenyl-3-arsonic acid**)**glycine methyl amide.**—12 g. of chloroacetyl-methylamine[2] yielded after one hour's boiling a mixture from which the methyl amide separated slowly on cooling and scratching. On recrystallizing from hot water, in which it is readily soluble, it separated as aggregates of flat, microscopic needles or platelets. The yield was 13.8 g. The substance is sparingly soluble in cold water or 50%

[1] THIS JOURNAL, 40, 1583 (1918).
[2] *Ibid.*, 41, 472 (1919).

alcohol, readily on warming. When rapidly heated it darkens and melts at 193–4.5° with gas evolution.

Subs., 0.1452: 12.45 cc. N (22.5°, 753 mm.). Subs., 0.3659: $Mg_2As_2O_7$, 0.1986.
Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.82; As, 26.21.

(C) Derivatives of Aminotolylarsonic Acids.

***N*-(2-Methylphenyl-5-arsonic acid)glycineamide.**—After one hour's boiling the product from 4.6 g. of 3-amino-4-methylphenyl arsonic acid[1] and 3.8 g. of chloroacetamide slowly crystallized on cooling and acidifying with hydrochloric acid. Reprecipitated from ammoniacal solution by acetic acid it separates slowly as delicate, interlaced needles which do not melt below 285°. It is sparingly soluble in water, alcohol or acetic acid in the cold, but readily on warming. Methyl alcohol dissolves the substance at room temperature.

Subs., 0.1702: (Kjeldahl) 11.65 cc. 0.1 *N* HCl. Subs., 0.2520: $Mg_2As_2O_7$, 0.1347.
Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.59; As, 25.79.

***N*-(2-Methylphenyl-4-arsonic acid)glycineamide.**—As in the preceding case 23 g. of 1-amino-2-methylphenyl-4-arsonic acid (from *o*-toluidine) and 19 g. of chloroacetamide yielded the glycinamide. This was purified by solution in dil. ammonia and re-precipitation with acetic acid, separating as aggregates of glistening platelets which darken above 250° and decompose at about 283°. The yield was 10 g. The substance is sparingly soluble in boiling water but more readily so in boiling 50% alcohol.

Subs., 0.1417: 12.00 cc. N (22.5°, 756 mm.). Subs., 0.2619: $Mg_2As_2O_7$, 0.1393.
Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.74; As, 25.67.

***N*-(3-Methylphenyl-4-arsonic acid)glycineamide.**—This substance was prepared in similar manner from 1-amino-3-methylphenyl-4-arsonic acid.[2] The amide is soluble in boiling water, from which it separates as lustrous, diamond-shaped platelets. It is also soluble in boiling 50% alcohol and melts at 203–5° with gas evolution.

Subs., 0.1384: 11.8 cc. N (21.0°, 757 mm.). Subs., 0.3120; $Mg_2As_2O_7$, 0.1668.
Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.87; As, 25.81.

***N*-(2,5-Dimethylphenyl-4-arsonic acid)glycineamide.**—2,5-Dimethyl-4-aminophenyl arsonic acid[3] dissolved in *N* sodium hydroxide solution was boiled for 45 minutes with 2 g. of chloroacetamide. On acidifying to congo red with hydrochloric acid and cooling, the arsonic acid crystallized. The crude product was dissolved in dil. ammonia, treated with boneblack, and the filtrate acidified with acetic acid, the arsonic acid separating slowly as aggregates of slightly brownish plates and prisms. When rapidly heated it melts and decomposes at 236–7° with preliminary dark-

[1] THIS JOURNAL, 40, 1586 (1918).
[2] *Ibid.*, 40, 1588 (1918).
[3] *Ibid.*, 40, 1590 (1918).

ening and softening. It is sparingly soluble in cold water, acetic acid, or 50% alcohol, but dissolves more easily in these solvents on boiling.

Subs., 0.1644: (Kjeldahl) 10.9 cc. 0.1 *N* HCl. Subs., 0.3224: $Mg_2As_2O_7$, 0.1644. Calc. for $C_{10}H_{15}O_4N_2As$: N, 9.27; As, 24.81. Found: N, 9.29; As, 24.61.

NEW YORK, N. Y.

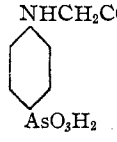
[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

AROMATIC ARSENIC COMPOUNDS. III. THE UREIDES AND β-SUBSTITUTED UREIDES OF *N*-ARYLGLYCINE ARSONIC ACIDS.

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER.

Received July 2, 1919.

On replacing the amides of chloroacetic acid by the ureide and its β-alkyl or -aryl derivatives in the reaction described in the preceding paper, the ureides and substituted ureides of the arylglycine arsonic acids were obtained,



in which R may be hydrogen, an alkyl, or an aryl radical.

When chloroacetyl-urea or its simpler β-alkyl derivatives were employed the reaction could be accomplished by boiling in aqueous solution with the sodium salt of the aminoaryl arsonic acid. In the preparation of the β-arylureides of phenylglycine arsonic acid, however, involving the use of the very sparingly soluble chloroacetyl-substituted phenyl-ureas, the reaction proceeded most satisfactorily in 50% alcohol and only after sodium iodide had been added in order to cause the intermediate formation of the more reactive iodoacetyl compounds.

The new arsonic acids of this series resemble in their general properties the amides of the arylglycine arsonic acids, forming colorless crystalline compounds which are on the whole less soluble than the corresponding substances in the amide series. Like the latter they form stable and soluble neutral salts with the alkali metals. The ureide linkage, like that of the amides, is easily ruptured, this often occurring even at room temperature in solutions containing excess fixed alkali. Therefore, it was found important to avoid undue exposure to such conditions during the manipulations employed for the preparation of the sodium salts or in the purification of the acids by solution in alkali and reprecipitation with acids. In the latter case the use of dil. ammonia avoided this danger.

Of the numerous substances of this group which were prepared and studied the methylureide of *N*-phenylglycine-*p*-arsonic acid