

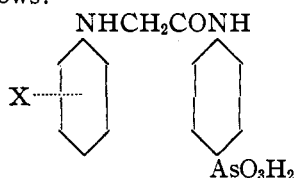
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AROMATIC ARSENIC COMPOUNDS. V. N-SUBSTITUTED GLYCYLARSANILIC ACIDS.

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The substances discussed in the present communication are closely related to the previously described substituted anilides of phenylglycine-*p*-arsonic acid,¹ but differ from these in the fact that the glycine side chain is reversed, the arsonic acid radical becoming a substituent on the anilide nucleus, as follows:



These substances were readily prepared by boiling the sodium salt of chloroacetylarsanilic acid with the aromatic amino compound, the condensation occurring in boiling aqueous solution within 15 to 30 minutes, owing to the reactivity of the chlorine in the former substance. The first member of the series, glycyllarsanilic acid, was prepared by the use of ammonia in this reaction and was accompanied by the formation of the secondary imino compound. With the aromatic amines no difficulty was experienced in any case and the reaction has proved capable of wide extension. We have confined our studies up to the present to those compounds which were prepared for biological investigation.

The fundamental compound required in this work was chloroacetylarsanilic acid. This derivative has already been mentioned in German patent 191,548, but as far as we could ascertain it has not been employed for the synthesis of other arsenic compounds. The patent contains a method for its preparation by the interaction of arsanilic acid and chloroacetyl chloride, but we have found it unsuitable for the preparation of the substance in large quantities as the reaction was difficult to control and the yields were poor and uncertain. A very serviceable and simple means was found for the large scale preparation of chloroacetylarsanilic acid, consisting in heating arsanilic acid with an excess of chloroacetic acid on the water bath, an excellent yield of the pure substance being easily obtained.

The substituted phenylglycylarsanilic acids resemble in general properties the isomeric anilides of phenylglycine-*p*-arsonic acid, functioning both as acids and feeble bases. They are but sparingly soluble in the

¹ THIS JOURNAL, 41, 1610 (1919).

usual solvents and all have high melting or decomposition points, the observed values depending upon the rate of heating. In general, the sodium salts were readily soluble in water.

Experimental.

Chloroacetyl-arsanilic Acid, $p\text{-H}_2\text{O}_3\text{AsC}_6\text{H}_4\text{NHCOCH}_2\text{Cl}$.—A method for the preparation of chloroacetyl-arsanilic acid has been given in German patent 191,548. In addition to the fact that no full description of the substance is given, we have found the following method more serviceable for its preparation in large quantity: 50 g. of arsanilic acid and 150 g. of dry chloroacetic acid are heated in an open flask on the water bath for 2 hours. The mixture gradually forms a clear melt, and towards the end the chloroacetyl-arsanilic acid occasionally begins to separate. The melt is poured into about a liter of well stirred, saturated sodium chloride solution, and the precipitated arsonic acid is filtered off and washed well with water. Yield, 50 g. A portion of the acid was dissolved in hot water, treated with bone black, and the filtered solution cooled rapidly in order to prevent decomposition. Under these conditions it separates as minute, lenticular platelets and toothed leaflets which contain no water of crystallization and which darken when rapidly heated, but melt and decompose only when the temperature of the bath is held at 285° for a few moments. The acid is readily soluble in hot alcohol, somewhat less so in boiling water or acetic acid, and sparingly soluble in the last two in the cold and in acetone. It is slowly acted upon by prolonged exposure to moist air.

Subst., 0.1867 (Kjeldahl), 6.25 cc. 0.1 *N* HCl. Subst., 0.1342 (Carius), AgCl 0.0634.

Subst., 0.2824; $\text{Mg}_2\text{As}_2\text{O}_7$, 0.1481.

Calc. for $\text{C}_8\text{H}_9\text{O}_4\text{NClAs}$: N, 4.77; Cl, 12.08; As, 25.53. Found: N, 4.69; Cl, 11.69; As, 25.31.

Practically as good an analysis was obtained on the crude product, and this was used in all of the following preparations:

Glycyl-*p*-arsanilic Acid, $p\text{-H}_2\text{NCH}_2\text{CONHC}_6\text{H}_4\text{AsO}_3\text{H}_2$.—20 g. of chloroacetyl-arsanilic acid were added to 100 cc. of conc. aqueous ammonia, warmed gently to about 30° until solution was complete, and allowed to stand overnight. The excess of ammonia was then boiled off from the clear solution, causing the crude reaction product to crystallize. After cooling this was filtered off, 12 g. being obtained. The product was purified by treating with dil. hydrochloric acid, avoiding a large excess on account of the consequent precipitation of the hydrochloride of the glycine. After filtering off the imino compound (see below) the crude glycyclaminophenyl-arsonic acid was precipitated by adding sodium acetate. For further purification it was dissolved in just enough dil. sodium hydroxide solution and then precipitated by means of a stream of carbon

dioxide. A repetition of the final purification was necessary before good analytical figures could be obtained, a considerable loss of material also taking place. The pure amino acid forms minute, toothed, glistening plates which are anhydrous, do not melt below 295° , and are very difficultly soluble in boiling water or 50% alcohol. It functions as a very weak acid, being soluble only in an excess of weak bases, such as ammonia, and is displaced from its salts by carbon dioxide.

Subs., 0.1328; 11.8 cc. N (24.5° , 751 mm.). Subs., 0.3101; $Mg_2As_2O_7$, 0.1743.

Calc. for $C_8H_{11}O_4N_2As$: N, 10.22; As, 27.34. Found: N, 10.08; As, 27.12.

Iminobisacetyl-*p*-arsanilic Acid, (*p*- $H_2O_3AsC_6H_4NHCOCH_2$) $_2$ NH.—The hydrochloric acid-insoluble fraction obtained in the preparation of the *p*-glycyarsanilic acid was dissolved in dil. sodium hydroxide solution, precipitated with an excess of hydrochloric acid, further purified by a repetition of this process, and finally recrystallized by dissolving in hot, dil. ammonium hydroxide and adding acetic acid in excess. The imino acid separated as glistening rosetts of microcrystals. Before filtering, the solution was cooled and acidified to congo red with hydrochloric acid. The substance darkens at $280-5^{\circ}$ without melting, and is practically insoluble in the usual solvents.

Subs., 0.1318; 9.2 cc. N (29.0° , 757 mm.). Subs., 0.3401; $Mg_2As_2O_7$, 0.1987.

Calc. for $C_{16}H_{19}O_8N_3As_2$: N, 7.92; As, 28.23. Found: N, 7.86; As, 28.19.

***N*-Methylglycyl-*p*-arsanilic Acid**, *p*- $CH_3NHCH_2CONHC_6H_4AsO_3H_2$.—A strong methylamine solution was prepared by treating 25 g. of methylamine hydrochloride with 60 g. of well chilled, 25% sodium hydroxide solution. Without removing the precipitated sodium chloride, 5 g. of chloroacetylarsanilic acid were added. On allowing to warm to room temperature and breaking up the lumps with a rod, the acid soon dissolved. After 24 hours' standing the excess of methylamine was removed on the water bath and on diluting the residue and acidifying strongly with acetic acid the arsonic acid slowly crystallized. Recrystallized from water it separates as long, silky, glistening needles which contain approximately two molecules of water of crystallization. The yield was 2 g. It turns brown at about 250° but does not melt below 275° . It is practically insoluble in hot alcohol and is not very freely soluble in boiling water. It dissolves in dilute mineral acids and on adding sodium nitrite to the solution in dil. hydrochloric acid the nitroso derivative deposits on rubbing as sheaves and spheres of microscopic needles.

Subs., air-dry, 0.5641; loss, 0.0670 *in vacuo* at 100° over H_2SO_4 .

Calc. for $C_9H_{13}O_4N_2As \cdot 2H_2O$: H_2O , 11.12. Found: 11.87.

Subs., anhydrous, 0.1864 (Kjeldahl); 12.85 cc. 0.1 N HCl. Subs., 0.2635; $Mg_2As_2O_7$, 0.1404.

Calc. for $C_9H_{13}O_4N_2As$: N, 9.73; As, 26.00. Found: N, 9.66; As, 25.72.

N*-Phenylglycyl-*p*-arsanilic Acid** (N*-Phenylglycineanilide-*p*'-arsonic Acid**), *p*- $C_6H_5NHCH_2CONHC_6H_4AsO_3H_2$.—This substance, isomeric

with phenylglycineanilide-*p*-arsonic acid,¹ was prepared as follows: 2 g. of aniline in 15 cc. of alcohol were added to a solution of 4.5 g. of chloroacetyl-arsanilic acid in 15 cc. of *N* sodium hydroxide solution. The solution was boiled for $\frac{1}{2}$ hour under an air-condenser, finally setting to a crystalline cake. The yield of acid was 4.4 g. Recrystallized from 50% alcohol the arsonic acid forms delicate, felted needles which are almost insoluble in boiling water. When heated it darkens slightly, but does not melt below 280°. When a suspension of the acid in hot 50% acetic acid is treated with excess sodium nitrite it dissolves at once, the nitroso compound soon crystallizing from the solution as nacreous plates.

Subs., 0.3260; (Kjeldahl) 18.70 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1435.

Calc. for $C_{14}H_{15}O_4N_2As$: N, 8.00; As, 21.39. Found: N, 8.04; As, 21.24.

***m*-Oxaminophenyl-glycyl-*p*-arsanilic Acid**, *m*-HO₂C CONHC₆H₄NH-CH₂CONHC₆H₄AsO₃H₂(*p'*).—12 g. of chloroacetyl-arsanilic acid and 7.2 g. of *m*-amino-oxanilic acid² were dissolved in 80 cc. of *N* sodium hydroxide solution and boiled for 20 minutes. The small amount of crystalline material which separated on cooling was filtered off and the filtrate made acid to congo red. A dark-colored gum separated, but the supernatant liquid, on standing overnight, deposited a crystalline crust. This was dissolved in very dilute aqueous ammonia and hydrochloric acid added to the solution until a faint turbidity persisted. This contained much coloring matter and was filtered off. It was found that if hydrochloric acid was added directly to the filtrate only a caseous precipitate could be obtained, but if acetic acid was first added in sufficient amount and then hydrochloric acid until definitely blue to congo red paper, the solution, when seeded, deposited the *hydrochloride* of the oxamino acid as aggregates of microscopic plumes, which gradually lost hydrochloric acid on standing in moist air.

Subs., 0.1546; 12.0 cc. *N* (17.5°, 750 mm.). Calc. for $C_{16}H_{16}O_7N_2As.HCl$: N, 8.88. Found: 9.00.

A portion of the hydrochloride was boiled with water, causing a change in physical appearance and the elimination of hydrochloric acid. The free *oxamino acid* was filtered off, washed well with hot water, and air-dried, one molecule of water of crystallization being retained. The substance is practically insoluble in boiling water and very sparingly so in 50% alcohol. When rapidly heated to 175°, then slowly, the anhydrous acid effervesces at 179°, with preliminary softening and darkening.

Subs., air-dry, 0.5870; loss 0.0249, at 100° *in vacuo* over H₂SO₄.

Calc. for $C_{16}H_{16}O_7N_2As.H_2O$: H₂O, 3.96. Found: H₂O, 4.24.

Subs., anhydrous, 0.1412; 11.85 cc. *N* (23.5°, 757 mm.). Subs., 0.3966; $Mg_2As_2O_7$, 0.1389.

Calc. for $C_{16}H_{16}O_7N_2As$: N, 9.61; As, 17.13. Found: N, 9.62; As, 16.90.

¹ THIS JOURNAL, 41, 1613 (1919).

² *Ibid.*, 39, 1451 (1917).

***p*-Aminophenyl-glycyl-*p*-arsanilic Acid**, $p\text{-H}_2\text{NC}_6\text{H}_4\text{NHCH}_2\text{CONH}\cdot\text{C}_6\text{H}_4\text{AsO}_3\text{H}_2$.—8 g. of *p*-acetamino-phenylglycineanilide-*p*'-arsonic acid (see below) were boiled with 8 parts of 1 : 1 hydrochloric acid for 6 minutes, cooled rapidly, shaken with bone black, filtered, and treated with saturated sodium acetate solution until the disappearance of the congo red reaction. The precipitate was filtered off, dissolved in dil. hydrochloric acid, and the solution filtered and treated again with sodium acetate. The amino acid separated as microcrystalline aggregates which tended to become colloidal on washing with water. The yield was 4.5 g. When rapidly heated the acid darkens and sinters, but does not melt below 280° . It is soluble in dilute mineral acids and alkalis and is practically insoluble in boiling water and very sparingly so in boiling 50% alcohol. It is readily diazotized, giving a red color with R-salt.

Subs., 0.1425; 14.15 cc. N (21.5° , 751 mm.). Subs., 0.3254; $\text{Mg}_2\text{As}_2\text{O}_7$, 0.1367.

Calc. for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{N}_2\text{As}$: N, 11.51; As, 20.52. Found: N, 11.38; As, 20.27.

***p*-Acetaminophenyl-glycyl-*p*-arsanilic Acid**.—Starting with 6 g. of *p*-aminoacetanilide, the reaction product began to separate after a few minutes, the heating being continued for one hour on the water bath. The yield of crude acid was 12 g. This was converted into the *sodium salt* by dissolving in warm, dil. sodium hydroxide solution, and salting out the neutral solution with saturated sodium acetate solution. Recrystallized from water containing a small amount of sodium carbonate to prevent hydrolysis to the free acid, it separated as flat, glistening needles which contain 7 molecules of water of crystallization when air-dry. It may also be precipitated from its aqueous solution by the addition of alcohol.

Subs., air-dry, 0.4734; loss 0.1057 at 100° *in vacuo* over H_2SO_4 .

Calc. for $7\text{H}_2\text{O}$: H_2O , 22.72. Found: 22.32.

Subs., anhydrous, 0.2998; (Kjeldahl) 20.50 cc. 0.1 N HCl. Subs., 0.3346; $\text{Mg}_2\text{As}_2\text{O}_7$, 0.1193.

Calc. for $\text{C}_{16}\text{H}_{17}\text{O}_6\text{N}_2\text{AsNa}$: N, 9.79; As, 17.45. Found: N, 9.58; As, 17.22.

On treating a hot dilute solution of the sodium salt with acetic acid, the free *arsonic acid* separated slowly as glistening, hexagonal platelets. It does not melt below 275° and is very sparingly soluble in boiling water or 50% alcohol.

Subs., 0.2117; (Kjeldahl) 15.4 cc. 0.1 N HCl.

Calc. for $\text{C}_{16}\text{H}_{18}\text{O}_6\text{N}_2\text{As}$: N, 10.32. Found: 10.19.

***p*-Oxaminophenyl-glycyl-*p*-arsanilic Acid**.—14 g. of chloroacetyl-arsanilic acid and 8.4 g. of *p*-amino-oxanilic acid¹ were boiled with 94 cc. of N sodium hydroxide solution for $\frac{1}{2}$ hour, the product separating after about 10 minutes. The yield was 16.5 g. Reprecipitated from very dilute, hot ammoniacal solution with acetic acid, the arsonic acid separates as slightly

¹ THIS JOURNAL, 39, 1459 (1917).

purplish aggregates of microscopic crystals containing 1.5 molecules of water of crystallization. It is almost insoluble in boiling water, very sparingly so in boiling 50% alcohol, and, when anhydrous, darkens above 200°, but does not melt below 275°. On heating with aqueous alkali in attempts to hydrolyze the oxamino group the principal products recovered were either the unchanged oxamino compound or arsanilic acid, depending on the length of heating and the strength of alkali. Heating, however, with 1 : 1 hydrochloric acid yielded the amino compound.

Subs., air-dry, 0.4539; loss, 0.0281 *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₆H₁₆O₇N₃As.1.5H₂O; H₂O, 5.82. Found: 6.19.

Subs., anhydrous, 0.1441; 12.2 cc. N (24.0°, 754 mm.). Subs., 0.4027; Mg₂As₂O₇, 0.1418.

Calc. for C₁₆H₁₆O₇N₃As: N, 9.61; As, 17.13. Found: N, 9.65; As, 16.99.

***p*-Oxamylaminophenyl-glycyl-*p*-arsanilic Acid**, *p*-H₂NCOCONHC₆H₄-NHCH₂CONHC₆H₄AsO₃H₂.—21 g. of chloroacetyl-arsanilic acid were dissolved in 70 cc. of *N* sodium hydroxide solution and added to a boiling solution of 12.6 g. of *p*-amino-oxanilamide¹ in about 300 cc. of water. On continuing the boiling the product separated as a partly gelatinous mass which gradually crystallized. After 1/2 hour the hot solution was filtered and the precipitate washed with hot water. It was then suspended in a large volume of hot water and treated with sodium carbonate solution until only a small, gelatinous residue remained. The mixture was treated with bone black and filtered through a hot-water funnel in order to prevent deposition of the sodium salt on the filter. The filtrate was warmed and treated with sodium acetate until crystallization of the salt commenced and was then let stand in the refrigerator. On treating a very dilute, hot solution of the salt with acetic acid, the free arsonic acid separated as clusters of microscopic needles in a yield of 6.5 g. It is practically insoluble in boiling water or 50% alcohol, and does not melt below 285°.

Subs., 0.1299; 14.65 cc. N (24.0°, 763 mm.). Subs., 0.2065; Mg₂As₂O₇, 0.0723.

Calc. for C₁₆H₁₇O₆N₄As: N, 12.85; As, 17.19. Found: N, 13.02; As, 16.90.

***p*-Uraminophenyl-glycyl-*p*-arsanilic Acid**, *p*-H₂NCONHC₆H₄NHCH₂-CONHC₆H₄AsO₃H₂.—12 g. of chloroacetyl-arsanilic acid, 6.1 g. of *p*-aminophenylurea,² 40 cc. of *N* sodium hydroxide solution, and 20 cc. of saturated sodium acetate solution were boiled for 1/2 hour. On cooling a small amount of precipitate was filtered off and the solution then saturated with sodium acetate and let stand in the ice-box. After 24 hours the precipitate of sodium salt was filtered off, washed with 85% alcohol, dissolved in warm water, treated with bone black, filtered, and the acid precipitated from the filtrate by means of acetic acid. The yield was 7 g. The uramino acid separates as spherular masses of microscopic leaflets

¹ THIS JOURNAL, 39, 1461 (1917).

² *Ibid.*, 39, 1456 (1917).

which dissolve in boiling 50% alcohol and very sparingly in water. When rapidly heated it changes color above 150° and darkens markedly at about 210°, but does not melt below 285°.

Subs., 0.1471; 17.7 cc. N (26.0°, 762 mm.). Subs., 0.1858; Mg₂As₂O₇, 0.0696.

Calc. for C₁₆H₁₇O₆N₄As: N, 13.72; As, 18.35. Found: N, 13.78; As, 18.08.

***m*-Hydroxyphenyl-glycyl-*p*-arsanilic Acid**, *m*-HOC₆H₄NHCH₂CONH-C₆H₄AsO₃H₂.—Since the oily reaction product from 11 g. of *m*-aminophenol was difficult to obtain in crystalline form, purification was effected by conversion into the *hydrochloride* by adding 100 cc. of 1 : 1 hydrochloric acid to the reaction mixture. The salt was filtered off and washed with 10% hydrochloric acid. A portion, recrystallized from 10% hydrochloric acid, separated as slightly purplish microcrystals which blacken above 140° but do not melt up to 280°. The hydrochloride loses most of its halogen on boiling with water.

Subs., 0.2152 (Kjeldahl); 10.6 cc. 0.1 N HCl.

Calc. for C₁₄H₁₅O₆N₂As.HCl: N, 6.96. Found: 6.90.

The main portion of this salt was suspended in water and dissolved by the addition of sodium hydroxide solution. On acidifying with hydrochloric acid until just faintly acid to congo red a considerable amount of gummy material was precipitated and was collected with bone black and quickly filtered off. The clear, almost colorless filtrate deposited the crystalline *arsonic acid* on scratching. It was purified by again dissolving in dil. sodium hydroxide solution and acidifying with an excess of acetic acid. The pure arsonic acid separated as pale pink, wedge-shaped, microscopic prisms which contained 3.5 molecules of water of crystallization after air drying. The yield was 15.5 g. On rapid heating the arsonic acid melts at about 80° in its water of crystallization, but rapidly resolidifies. On further heating it turns purple at about 180° and then gradually softens and chars as the temperature is raised. It is easily soluble in ethyl or methyl alcohol or acetone. It dissolves less readily in glacial acetic acid and then separates on scratching in a different form, presumably owing to dehydration. Dilution with water redissolves the crystals. It dissolves readily in boiling water and separates on cooling as a caseous mass.

Subs., air-dry, 0.6257; loss, 0.0893 *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₄H₁₅O₆N₂As.3.5H₂O: H₂O, 14.68. Found: 14.27.

Subs., anhydrous, 0.1682; (Kjeldahl) 9.35 cc. 0.01 N HCl. Subs., 0.2541; Mg₂As₂O₇, 0.1064.

Calc. for C₁₄H₁₅O₆N₂As: N, 7.66; As, 20.48. Found: N, 7.78; As, 20.21.

***p*-Hydroxyphenyl-glycyl-*p*-arsanilic Acid**.—(From 4.5 g. of *p*-aminophenol.) After a few minutes the reaction product separated from the clear solution and the mixture was then transferred to the water bath and heated one hour. For purification the precipitate was dissolved by

neutralization of an aqueous suspension with sodium hydroxide, and the filtered solution treated with 1 : 1 hydrochloric acid until the precipitate which first formed had redissolved. The copious precipitate of the hydrochloride of the arsonic acid which separated on scratching was filtered off. Yield, 11 g. On dissolving in a small volume of dil. sodium hydroxide solution and exactly neutralizing with acetic acid, the *sodium salt* separated on standing in the ice-box. Recrystallized from a small volume of water, it forms aggregates of microscopic needles which contain one molecule of water of crystallization and dissolve sparingly in water at 0° and readily on warming. The aqueous solution of the salt gives a slowly developing pale lilac color with ferric chloride.

Subs., air-dry, 0.3783; loss, 0.0143 at 100° *in vacuo* over H₂SO₄.

Calc. for C₁₄H₁₄O₆N₂AsNa.H₂O: H₂O, 4.43. Found: 3.78.

Subs., anhydrous, 0.2833; (Kjeldahl) 14.0 cc. 0.1 N HCl; Mg₂As₂O₇, 0.1134.

Calc. for C₁₄H₁₄O₆N₂AsNa: N, 7.32; As, 19.30. Found: N, 6.92; As, 19.32.

On acidifying a hot solution of the salt with acetic acid the free *arsonic acid* separates as aggregates of microscopic hairs which contain approximately one molecule of water of crystallization. The substance is almost insoluble in boiling water or 50% alcohol, and, when anhydrous, blackens and sinters above 200°, but does not melt entirely below 280°.

Subs., air-dry, 0.4903; loss, 0.0265 at 100° *in vacuo* over H₂SO₄.

Calc. for C₁₄H₁₄O₆N₂As.H₂O: H₂O, 4.69. Found: 5.40.

Subs., anhydrous, 0.1532; 10.2 cc. N (21.5°, 750 mm.).

Calc. for C₁₄H₁₄O₆N₂As: N, 7.65. Found: 7.62.

***m*-Carboxamidophenyl-glycyl-*p*-arsanilic Acid, *m*-H₂NCOC₆H₄NHCH₂-CONHC₆H₄AsO₃H₂(*p*).—**After one hour 5.5 g. of *m*-aminobenzamide¹ yielded an oil on cooling which readily crystallized, giving 10.5 g. of the crude arsonic acid. The neutral solution of the crude acid in dil. sodium hydroxide was salted out with several volumes of saturated sodium acetate solution, and the *sodium salt* recrystallized by treating its warm concentrated solution with alcohol until a slight permanent turbidity remained. Under these conditions the salt crystallized as radiating masses of flat needles containing one molecule of water of crystallization.

Subs., air-dry, 0.6223; loss, 0.0276 *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₅H₁₅O₆N₃AsNa.F_{1/2}O: H₂O, 4.16. Found: 4.44.

Subs., anhydrous, 0.2967; (Kjeldahl) 21.3 cc. 0.1 N HCl; Mg₂As₂O₇, 0.1098.

Calc. for C₁₅H₁₅O₆N₃AsNa: N, 10.13; As, 18.06. Found: N, 10.06; As, 17.87.

On treating a hot solution of the sodium salt with acetic acid, the *arsonic acid* gradually separated on scratching as microscopic needles. It is very difficultly soluble in boiling water or acetic acid but dissolves somewhat more easily in boiling 50% alcohol. When rapidly heated to 245°, then slowly, it darkens and then decomposes at 248°.

¹ THIS JOURNAL, 39, 1438 (1917).

Subs., 0.2137 (Kjeldahl); 23.0 cc. 0.1 N HCl.

Calc. for $C_{15}H_{16}O_6N_3As$: N, 10.68. Found: 10.76.

N-Phenylglycineanilide-*m*-carboxureide-*p*'-arsonic Acid, $p\text{-H}_2\text{O}_3\text{As-C}_6\text{H}_4\text{NHCCH}_2\text{NHC}_6\text{H}_4\text{CONHCONH}_2(m)$.—Starting with 5.4 g. of *m*-aminobenzoylurea¹ a clear solution was rapidly obtained and the arsonic acid was deposited during the heating. After cooling and filtering the acid was suspended in a little water, treated with a very slight excess of sodium hydroxide and filtered from a little insoluble material after exactly neutralizing with acetic acid. The addition of powdered, crystalline sodium acetate to the filtrate yielded the *sodium salt*. This was dissolved in a small volume of hot water and treated with an equal volume of alcohol. On standing in the cold the salt separated as flat, microscopic needles containing 3 molecules of water of crystallization. The yield was 7.3 g.

Subs., air-dry, 0.5948; loss, 0.0625 *in vacuo* at 100° over H_2SO_4 .

Calc. for $C_{15}H_{16}O_6N_4AsNa \cdot 3\text{H}_2\text{O}$: H_2O , 10.55. Found: 10.50.

Subs., anhydrous, 0.1443; 15.35 cc. N (23.0°, 756 mm.).

Subs., 0.3214; $\text{Mg}_2\text{As}_2\text{O}_7$, 0.1073.

Calc. for $C_{15}H_{16}O_6N_4AsNa$: N, 12.23; As, 16.36. Found: N, 12.21; As, 16.11.

On adding acetic acid to a dilute solution of the salt the *free acid* separated slowly as spherules of microscopic needles which darken when rapidly heated and decompose at about 280°. The acid is almost insoluble in boiling water or 50% alcohol.

Subs., 0.1441; 15.8 cc. N (20.0°, 758 mm.).

Calc. for $C_{15}H_{17}O_6N_4As$: N, 12.84. Found: 12.74.

***p*-Carboxamidophenyl-glycyl-*p*-arsanilic Acid**, $p\text{-H}_2\text{NCOC}_6\text{H}_4\text{NHCH}_2\text{-CONHC}_6\text{H}_4\text{AsO}_3\text{H}_2(p)$.—This substance, prepared from 5.5 g. of *p*-aminobenzamide,² separated from the boiling reaction mixture within a few moments, the heating being continued on the water bath for one hour longer and the arsonic acid then filtered off, washed with water and alcohol, and dried. The yield was 13 g. It was suspended in about 100 cc. of warm water, dissolved by neutralizing with sodium hydroxide, and the solution filtered and let stand in the ice-box. 13 g. of the *sodium salt* separated as glistening platelets containing 2 molecules of water of crystallization. The salt is quite sparingly soluble in ice water, more easily on warming.

Subs., air-dry, 1.0357; loss, 0.0857 *in vacuo* at 100° over H_2SO_4 .

Calc. for $C_{15}H_{15}O_6N_3AsNa \cdot 2\text{H}_2\text{O}$: H_2O , 7.99. Found: 8.27.

Subs., anhydrous, 0.2995; (Kjeldahl) 21.3 cc. 0.1 N HCl; $\text{Mg}_2\text{As}_2\text{O}_7$, 0.1135.

Calc. for $C_{15}H_{15}O_6N_3AsNa$: N, 10.13; As, 18.06. Found: N, 9.96; As, 18.29.



Addition of acetic acid to the filtrate from the sodium salt gave a small amount of the *free acid* as microscopic prisms which do not melt below 275° and are practically insoluble in boiling water or 50% alcohol.

¹ THIS JOURNAL, 39, 1439 (1917).

² *Ibid.*, 39, 1436 (1917), paragraph 2.

Subs., 0.2075; (Kjeldahl) 15.6 cc. 0.1 *N* HCl.

Calc. for $C_{18}H_{16}O_6N_3As$: N, 10.69. Found: 10.53.

***N*-Phenylglycineanilide-*p*-acetamide-*p'*-arsonic Acid**, H_2O_3As  $NHCOCH_2NH$  CH_2CONH_2 . — (From *p*-aminophenyl-acetamide.¹)

The oil which separated on cooling soon crystallized on rubbing, and after dilution of the mixture with water, the crude substance was filtered off, washed, and dissolved in dilute aqueous ammonia. On adding a slight excess of acetic acid an amorphous impurity quickly separated. This was filtered off, after which the pure acid separated slowly as aggregates of microscopic platelets which darken and soften above 180° and decompose completely at 256–8°. It dissolves with difficulty in boiling water, more easily in boiling 50% alcohol or acetic acid.

Subs., 0.1360; 12.0 cc. N (25.5°, 761 mm.). Subs., 0.3214; $Mg_2As_2O_7$, 0.1210.

Calc. for $C_{16}H_{18}O_6N_2As$: N, 10.32; As, 18.41. Found: N, 10.11; As, 18.17.



***N*-Phenylglycineanilide-*p*-acetureide-*p'*-arsonic Acid**, $H_2O_3AsC_6H_4NHCOCH_2NHC_6H_4CH_2CONHCONH_2$. — (From *p*-amino-phenylacetyl-urea.²) The clear solution which immediately formed on boiling set after a few minutes to a solid mass of crystals and it was necessary to continue the heating on the water bath. After diluting with water, the crude product was filtered off, washed, taken up in a little hot water, and treated with sodium carbonate until faintly alkaline. The insoluble, gelatinous residue was collected with bone black and the filtrate treated with sodium acetate until the sodium salt of the arsonic acid began to separate. The salt was converted into the free acid by addition of acetic acid to its hot, dilute solution. The product so obtained was further purified by reprecipitating its very dilute, hot, ammoniacal solution with acetic acid. The pure arsonic acid separated slowly as rosetts of microscopic hairs which contained 0.5 molecule of water of crystallization. The anhydrous compound darkens above 230° and decomposes at 270–3°. It is sparingly soluble in boiling water or 50% alcohol.

Subs., air-dry, 0.5047; loss, 0.0094 *in vacuo* at 100° over H_2SO_4 .

Calc. for $C_{17}H_{19}O_6N_4As \cdot 0.5H_2O$: H_2O , 1.96. Found: 1.86.

Subs., anhydrous, 0.1409; 15.3 cc. N (22.0°, 756 mm.). Subs., 0.2920; $Mg_2As_2O_7$, 0.1017.

Calc. for $C_{17}H_{19}O_6N_4As$: N, 12.45; As, 16.64. Found: N, 12.49; As, 16.81.

***N*-Phenylglycineanilide-*p*-hydroxyacetic Ether Acid-*p'*-arsonic Acid**, H_2O_3As  $NHCOCH_2HN$  OCH_2COOH . — 3 g. of chloroacetyl-arsanilic acid and 2 g. of *p*-aminophenoxyacetic acid³ were dissolved in 20 cc. of *N* sodium hydroxide solution and boiled for 1/2 hour. The crude reaction product was filtered off and recrystallized from 50%

¹ THIS JOURNAL, 39, 1444 (1917).

² *Ibid.*, 39, 2433 (1917).

³ *Ibid.*, 39, 2196 (1917).

acetic acid, separating as minute, pale brown, wedge-shaped plates containing 1.5 molecules of water of crystallization. The acid is almost insoluble in boiling water or 50% alcohol, and when anhydrous darkens above 180° and decomposes at about 275°.

Subs., air-dry, 0.6434; loss 0.0404, *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₆H₁₇O₇N₂As.1.5H₂O: H₂O, 5.99. Found: 6.28.

Subs., anhydrous, 0.3070; (Kjeldahl) 14.9 cc. 0.1 N HCl. Subs., 0.3300; Mg₂As₂O₇, 0.1205.

Calc. for C₁₆H₁₇O₇N₂As: N, 6.61; As, 17.67. Found: N, 6.80; As, 17.62.

N-Phenylglycineanilide-*p*-hydroxyacetic Ether Acid Amide-*p'*-arsonic Acid, *p*-H₂O₃AsC₆H₄NHCOCH₂NHC₆H₄OCH₂CONH₂(*p*).—(From 4 g. of *p*-amino-phenoxyacetamide.¹) The new arsonic acid separated almost at once and after heating on the water bath for an hour longer it was filtered off and washed with water. A suspension of the acid in a small volume of water was treated with a very slight excess of sodium hydroxide, quickly made exactly neutral to litmus with acetic acid, and the dark solution filtered. After adding sodium acetate to the filtrate the *sodium salt* separated on standing and was filtered off, dissolved in a little water, and reprecipitated with one to two volumes of alcohol. It crystallized in slightly grayish rosetts of flat, glistening needles which, after washing with 85% alcohol and air-drying, contained 4 molecules of water of crystallization. The yield was 3.2 g. A dilute, aqueous solution of the salt gives immediate precipitates with silver or copper ions, a slow-forming, crystalline precipitate with Ca⁺⁺, and no precipitate with Ba⁺⁺.

Subs., air-dry, 0.5303; loss, 0.0720, *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₆H₁₇O₈N₃AsNa.4H₂O: H₂O, 13.93. Found: 13.57.

Subs., anhydrous, 0.1465; 12.4 cc. N (24.0°, 750 mm.). Subs., 0.3069; Mg₂As₂O₇, 0.1055.

Calc. for C₁₆H₁₇O₈N₃AsNa; N, 9.44, As, 16.84. Found: N, 9.61; As, 16.59.

The *free acid* obtained from the salt with acetic acid separates slowly as woolly masses of delicate needles which are practically insoluble in boiling water or 50% alcohol and which darken somewhat but do not melt below 265°.

Subs., 0.1484; (Kjeldahl) 10.45 cc. 0.1 N HCl.

Calc. for C₁₆H₁₈O₈N₃As: N, 9.93. Found: 9.87.

N-Phenylglycineanilide-*p*-hydroxyacetic Ether Acid Ureide-*p'*-arsonic Acid, *p*-H₂O₃AsC₆H₄NHCOCH₂NHC₆H₄OCH₂CONHCONH₂. — Starting with 2.2 g. of *p*-amino-phenoxyacetylurea,² the new arsonic acid separated during the heating. The washed product was dissolved in hot, dil. sodium acetate solution, filtered, and saturated sodium acetate solution added to the filtrate until crystallization of the *sodium salt* started. For final purification this was dissolved in a little hot water and the solution treated

¹ THIS JOURNAL, 39, 2423 (1917).

² *Ibid.*, 39, 2435 (1917).

with alcohol until crystallization again started. After letting stand in the cold the salt was filtered off, washed with 85% alcohol, and air-dried. As so obtained it forms rosetts of minute leaflets which contain 4 molecules of water of crystallization.

Subs., air-dry, 0.4633; loss, 0.0595 *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₇H₁₈O₇N₄AsNa₄H₂O: H₂O, 12.86. Found: 12.84.



Subs., anhydrous, 0.1575; 15.4 cc. N (22.0°, 764 mm.).

Calc. for C₁₇H₁₈O₇N₄AsNa: N, 11.48. Found: 11.38.

On acidification of a hot solution of the salt with acetic acid the *free acid* was obtained as feathery aggregates of minute platelets which are almost insoluble in boiling water or 50% alcohol. When rapidly heated to 255°, then slowly, the acid decomposes at 257–8° with preliminary darkening.

Subs., 0.1680; (Kjeldahl) 14.25 cc. 0.1 N HCl. Subs., 0.3140; Mg₂As₂O₇, 0.1034.

Calc. for C₁₇H₁₈O₇N₄As: N, 12.02; As, 16.07. Found: N, 11.88; As, 15.89.

***N*-Phenylglycineanilide-*p*-glycineamide-*p*'-arsonic acid**, H₂O₃As 
 NHCOCH₂N  NHCH₂CONH₂.—Carefully purified *p*-aminophenyl-

glycineamide¹ yielded a thick oil which slowly crystallized on rubbing and letting stand, and in subsequent preparations crystallization, could be immediately induced by seeding and continued warming on the water bath. The mixture was filtered hot in order to eliminate the tar which separated from the filtrate on cooling. The arsonic acid was washed with hot water, suspended in a considerable volume of hot water, and dissolved by adding ammonia. The solution was then treated with bone black, and on adding acetic acid to the yellow filtrate the arsonic acid separated on standing overnight. It forms crusts of spherical aggregates of micro-crystals which become ochreous in color on exposure to the air. When air-dried it contains approximately 1.5 molecules of water of crystallization. The anhydrous substance darkens at about 200° but does not melt below 285°, and is rather sparingly soluble in boiling water or 50% alcohol.

Subs., air-dry, 0.7072; loss, 0.0468 *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₆H₁₉O₆N₄As.1.5H₂O: H₂O, 6.02. Found: 6.62.

Subs., anhydrous, 0.1522; (Kjeldahl) 13.90 cc. 0.1 N HCl. Subs., 0.2610; Mg₂As₂O₇, 0.0990.

Calc. for C₁₆H₁₉O₆N₄As: N, 13.27; As, 17.75. Found: N, 12.78; As, 18.31.

***N*-Phenylglycineanilide-4,4'-diarsonic acid**, H₂O₃AsC₆H₄NHCH₂CO-NHC₆H₄AsO₃H₂.—4.4 g. of arsanilic acid and 6 g. of chloroacetyl-arsanilic acid were dissolved in 40 cc. of *N* sodium hydroxide solution (2 mols.) and boiled for 30 minutes, during which the product began to separate. After cooling, the mixture was treated with an excess of hydro-

¹ THIS JOURNAL, 39, 1459 (1917).

chloric acid to complete the separation. The substance was purified by redissolving in dilute alkali and reprecipitating with hydrochloric acid. It separated at once as sheaves of microscopic needles, which contain one-half molecule of water of crystallization. The anhydrous substance does not melt up to 280°. It is insoluble in boiling water and very sparingly soluble in hot 50% alcohol.

Subs., air-dry, 0.6798; loss, 0.0103 *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₄H₁₆O₇N₂As₂·0.5H₂O: H₂O, 1.86. Found: 1.52.

Subs., anhydrous, 0.3313; (Kjeldahl) 13.4 cc. 0.1 N HCl; Mg₂As₂O₇, 0.2195.

Calc. for C₁₄H₁₆O₇N₂As₂: N, 5.91; As, 31.62. Found: N, 5.67; As, 31.98.

p-Acetophenyl-glycyl-*p*-arsanilic acid, *p*-CH₃COC₆H₄NHCH₂CONH-C₆H₄AsO₃H₂(*p*).—2.8 g of *p*-aminoacetophenone yielded the yellow arsonic acid after a few minutes and the heating was continued on the water bath for 1/2 hour. The collected solid was suspended in a moderate amount of hot water, treated with sodium hydroxide until faintly alkaline, filtered, and the acid reprecipitated from the hot solution with acetic acid. The purified product was again suspended in hot water, dissolved as above, and the solution treated with sodium acetate until the sodium salt of the arsonic acid began to separate. After cooling and washing with cold water the yield was 4.5 g. Recrystallized from water, in which it is sparingly soluble in the cold, the salt forms minute, narrow, pale yellow, glistening, platelets containing 3 molecules of water of crystallization.

Subs., air-dry, 1.0979; loss, 0.1258, *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₆H₁₆O₈N₂AsNa·3H₂O: H₂O, 11.54. Found: 11.46.

Subs., anhydrous, 0.1620; 9.85 cc. N (24.0°, 762 mm.). Subs., 0.3201; Mg₂As₂O₇, 0.1187.

Calc. for C₁₆H₁₆O₈N₂AsNa: N, 6.76; As, 18.09. Found: N, 7.00; As, 17.88.

The pure acid was obtained from a hot, dilute solution of the sodium salt with acetic acid. It forms radiating masses of faintly yellow, microscopic needles which darken and decompose partially when heated, but do not melt below 290°. The acid is practically insoluble in boiling water and only very sparingly so in boiling 50% alcohol.

Subs., 0.1323; 8.25 cc. N (24.0° 765 mm.).

Calc. for C₁₆H₁₇O₈N₂As: N, 7.15. Found: 7.22.