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

AROMATIC ARSENIC COMPOUNDS. VIII. THE AMIDES OF (4-ARSONIC ACID)-PHENOXYACETIC ACID AND THE ISOMERIC PHENOXYACETYL-ARSANILIC ACIDS.

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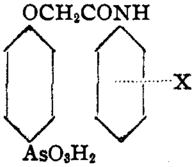
The preparation of *o*-phenylglycollic acid *p*-arsonic acid ([4-arsonic acid]-phenoxyacetic acid) by the action of sodium chloroacetate on sodium *p*-hydroxyphenyl-arsonate in boiling aqueous solution has been described in German patent 216,270. We have found that chloroacetylamino compounds also react with sodium *p*-hydroxyphenyl-arsonate to give the substituted amides of phenylglycollic acid *p*-arsonic acid with the following general formula:



In this reaction a condition for the success of the condensation was the addition of an extra molecule of sodium hydroxide in order to form the sodium phenolate, as in the preparation of phenyl ethers with alkyl halides in general. When using chloroacetyl compounds which were sufficiently stable in alkaline solution the yields of the desired products were good, but in those cases in which the halide was readily decomposed the yields suffered accordingly.

In general, the arsonic acids of this type crystallize readily when pure, possess high decomposition points, and are sparingly soluble in the usual solvents. They are stronger acids than the amides of phenylglycine-arsonic acid, since only mineral acids or a large excess of acetic acid displace them completely from their salts.

In a preceding paper it was shown that the sodium salt of chloroacetylarsanilic acid reacted smoothly with amines with the formation of substituted glycyl-arsanilic acids.[1] On replacing the amine by a phenolic compound the substituted phenoxyacetyl or phenyl ether glycollyl-arsanilic acids were obtained with the general formula

These substances are of course isomeric with the amides of (4-arsonic acid)-phenoxyacetic acid. As in the preparation of the latter substances an extra molecule of alkali was required for the conversion of the phenolic compound into the phenolate. Since the reaction of the mix-

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[1] THIS JOURNAL, 41, 1809 (1919).

ture was, therefore, strongly alkaline, the sensitive chloroacetyl-arsanilic acid suffered partial decomposition, so that the yields of the desired phenoxyacetyl compounds were poorer than in the synthesis of the glycyl-arsanilic acids.

As a rule the phenoxyacetyl-arsanilic acids crystallize readily and are sparingly soluble in the usual solvents, but yield readily soluble sodium salts. They are stronger acids than the glycyl-arsanilic acids and are completely displaced from their salts only by mineral acid or a large excess of acetic acid.

On reduction both of these groups of substances yield arsinoxides and arseno compounds, substances which will be described when our studies with this group are completed.

Experimental.

(A) Derivatives of (4-Arsonic Acid)-phenoxyacetic Acid.

(4-Arsonic Acid)-phenoxyacetic Methyl Ester, p-$H_2O_3AsC_6H_4OCH_2CO_2CH_3$.—10 g. of (4-arsonic acid)-phenoxyacetic acid[1] were refluxed for two hours with a mixture of 30 g. of dry methyl alcohol and 3 g. of conc. sulfuric acid. On dilution with water the ester separated in a yield of 9.5 g. Recrystallized from hot water it forms lustrous plates which, when rapidly heated, partially melt with gas evolution at about 192–5° and then gradually decompose at a higher temperature without melting completely. The ester is readily soluble in methyl alcohol, hot ethyl alcohol, or water, but sparingly in cold alcohol or water.

Subs., 0.2967; $Mg_2As_2O_7$, 0.1575.

Calc. for $C_9H_{11}O_6As$: As, 25.85. Found: 25.62.

(4-Arsonic Acid)-phenoxyacetamide, p-$H_2O_3AsC_6H_4OCH_2CONH_2$.—60 g. of the methyl ester were added slowly, with chilling and shaking, to 360 cc. of conc. ammonia. During the addition the mixture set to a thick mass of what appeared to be the ammonium salt of the unchanged ester and this had to be broken up occasionally during the further addition of the ester. When all had been added the mixture was vigorously shaken to disintegrate the mass as thoroughly as possible and then allowed to stand at room temperature for 24 hours. The ammonium salt changed definitely in character, presumably due to the formation of the ammonium salt of the amide. The mixture was finally diluted with water until solution was complete and the excess of ammonia removed *in vacuo,* after which the solution was made faintly acid to congo red with hydrochloric acid, causing the immediate separation of the arsonic acid. On recrystallization from hot water the amide separated as rhombic, microscopic prisms. The yield was 37.5 g. The compound does not melt below 280° and is sparingly soluble in cold water or hot alcohol, but easily soluble in boiling water.

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[1] Ger. pat. 216,270.

Subs., 0.1312; 6.1 cc. N (20.5°, 750 mm.).
Calc. for $C_8H_{10}O_5NAs$: N, 5.09. Found: 5.34.

Sodium Salt.—A solution of the acid in dil. aqueous sodium hydroxide was carefully neutralized with acetic acid and concentrated to small volume *in vacuo.* On adding alcohol the salt separated slowly as glistening platelets which contained no water of crystallization and were easily soluble in water.

Subs., 0.1371; 5.7 cc. N (22.5°, 765 mm.). Subs., 0.3120; $Mg_2As_2O_7$, 0.1617.
Calc. for $C_8H_9O_5NAsNa$: N, 4.71; As, 25.23. Found: N, 4.84; As, 25.00.

(4-Arsonic Acid)-phenoxyacetanilide, $p\text{-}H_2O_3AsC_6H_4OCH_2CONHC_6H_5$.—5 g. of sodium *p*-hydroxyphenyl-arsonate,[1] 3.4 g. of chloroacetanilide,[2] and 3 g. of sodium iodide were boiled in a mixture of 20 cc. of *N* aqueous sodium hydroxide and 20 cc. of alcohol for 3 hours. The alcohol was then allowed to boil off and the residue acidified with hydrochloric acid, resulting in a gummy precipitate which rapidly recrystallized. For purification the collected material was dissolved in dil. sodium hydroxide and the filtrate treated, preferably while hot, with an excess of hydrochloric acid. The arsonic acid separated at once as glistening platelets. When rapidly heated the anilide darkens slightly above 250° but does not melt below 280°. From hot 50% alcohol, in which it is fairly readily soluble, it separates as minute prisms and masses of thin, microscopic plates. Although but sparingly soluble in the cold it is appreciably soluble in hot water, alcohol, and acetic acid. Cold methyl alcohol also dissolves the substance.

Subs., 0.3024; (Kjeldahl) 8.6 cc. 0.1 *N* HCl. Subs., 0.3455; $Mg_2As_2O_7$, 0.1530.
Calc. for $C_{14}H_{14}O_5NAs$: N, 3.99; As, 21.34. Found: N, 3.98; As, 21.37.

(4-Arsonic Acid)-phenoxyacetyl-3-aminophenol, $p\text{-}H_2O_3AsC_6H_4OCH_2CONHC_6H_4OH(m)$.—43.6 g. of *p*-hydroxyphenyl-arsonic acid[3] dissolved in 400 cc. of *N* sodium hydroxide solution, and 38 g. of *m*-chloroacetylaminophenol[4] were boiled for 15 minutes. During the heating an amorphous substance separated and more of this material was precipitated on dilution with water. The mixture was made definitely acid with acetic acid and cleared by treating with bone black in the cold. On the addition of hydrochloric acid to the filtrate until acid to congo red a pinkish paste separated, but on standing and scratching this was followed by crystals. After 24 hours crystallization was complete. The nitrogen figures obtained with this substance were nearly 1% high and the arsenic figures too low, indicating the presence of a contaminating arsonic acid containing a higher percentage of nitrogen. It is possible that the hy-

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[1] THIS JOURNAL, 41, 1447 (1919).

[2] *Ibid.*, 39, 1441 (1917).

[3] *Ibid.*, 41, 1446 (1919).

[4] *Ibid.*, 39, 1442 (1917). An improved method will be published shortly.

droxyl group in the *m*-aminophenol may have reacted with a second molecule of *m*-chloroacetylamino-phenol giving a more complex arsonic acid. Since direct recrystallization of the crude product from a suitable solvent such as 50% alcohol or 50% acetic acid did not remove this contaminating material it was found necessary to pass through the *sodium salt,* which was fortunately found to have suitable properties.

The crude acid was suspended in a small volume of water and dissolved by the addition of sodium hydroxide solution. After neutralization with acetic acid an equal volume of saturated salt solution was added. On scratching, the pink solution gradually deposited the sodium salt, which carried the color with it. After standing in the refrigerator it was filtered off and washed with 15% salt solution. The crude salt was recrystallized from a small volume of hot water, separating as a mass of pink, lustrous, microscopic needles and long, thin platelets. On dissolving in hot water and adding hydrochloric acid a milky emulsion was formed which almost immediately crystallized. The free acid settled quicky as a heavy, sandy powder consisting of aggregates of irregular, microscopic leaflets to which the pink color still adhered. When rapidly heated it melts and decomposes at 238–40°. It is very sparingly soluble in boiling water or boiling acetic acid but dissolves more readily in hot 50% alcohol.

Subs., 0.2067; (Kjeldahl) 5.85 cc. 0.1 *N* HCl. Subs., 0.3209; $Mg_2As_2O_7$, 0.1375.

Calc. for $C_{14}H_{14}O_6NAs$: N, 3.83; As, 20.42. Found; N, 3.97; As, 20.68.

(4-Arsonic Acid)-phenoxyacetyl-4-aminophenol.—22 g. of *p*-hydroxyphenyl-arsonic acid dissolved in 100 cc. of 2 *N* sodium hydroxide solution (2 mols.), and 19 g. of *p*-chloroacetylamino-phenol[1] were boiled under a reflux condenser. A precipitate separated from the clear solution after a few seconds and was probably an alteration product of the chloroacetyl compound. After 30 minutes the mixture was considerably diluted, acidified with acetic acid, and treated with bone black in the cold. The clear filtrate yielded a crystalline arsonic acid on acidification to congo red with hydrochloric acid and scratching. After 24 hours the collected substance was repurified by reprecipitation of its solution in dil. ammonia with hydrochloric acid. As the analysis showed the product to be high in nitrogen it was finally purified over the *sodium salt.*

The acid was suspended in a small volume of hot water and carefully treated with sodium hydroxide solution until dissolved. On cooling, the colorless sodium salt crystallized and was filtered off, washed, redissolved in hot water and acidified with hydrochloric acid. The arsonic acid separated at once as curved, colorless, microscopic crystals. When rapidly heated it gradually darkens and decomposes at 238–40°. It is very difficultly soluble in boiling water, alcohol, or methyl alcohol, but dissolves more easily in hot 50% alcohol. On adding a few drops of sodium nitrite

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[1] THIS JOURNAL, 39, 1442 (1917).

solution to a suspension of the acid in hot acetic acid a clear, orange solution is obtained which deposits spherules of yellow crystals, probably a nitroso compound, in cooling.

Subs., 0.2113; (Kjeldahl) 6.15 cc. 0.1 N HCl. Subs., 0.3269; $Mg_2As_2O_7$, 0.1354.
Calc. for $C_{14}H_{14}O_6NAs$: N, 3.83; As, 20.42. Found: N, 4.07; As, 20.00.

(4-Arsonic Acid)phenoxyacetyl-4-aminophenylurea, p-$H_2O_3AsC_6H_4O$-$CH_2CONHC_6H_4NHCONH_2$(p-).—8.8 g. of p-hydroxyphenylarsonic acid in 40 cc. of 2 N sodium hydroxide solution, 8 g. of sodium iodide, 9.2 g. of p-chloroacetylamino-phenylurea,[1] and 40 cc. of alcohol were refluxed for two hours. After dilution with water an excess of acetic acid was added. On scratching a white powder separated and this was filtered off, dissolved in dil. ammonia, and treated while hot with an excess of acetic acid. On cooling the arsonic acid separated as aggregates of microscopic needles in a yield of 7 g. When rapidly heated the substance darkens and softens at about 230–40° but does not melt entirely up to 265°. It is practically insoluble in boiling water or 50% alcohol.

Subs., 0.1322; 12.0 cc. N (26.0°, 757 mm.). Subs., 0.3605; $Mg_2As_2O_7$, 0.1368.
Calc. for $C_{15}H_{16}O_6N_3As$: N, 10.26; As, 18.32. Found: N, 10.33; As, 18.32.

(B) Derivatives of Phenoxyacetyl-p-arsanilic Acid.

Phenoxyacetyl-arsanilic Acid, $C_6H_5OCH_2CONHC_6H_4AsO_3H_2$($p$-).—4.4 g. of arsanilic acid were dissolved in 50 cc. of 20% sodium acetate solution and treated, while chilling and shaking, with 4 g. of phenoxyacetyl chloride. The reaction product separated at once. After making acid to congo red with hydrochloric acid the substance was filtered off, washed with water, and finally with ether. The yield was 3.5 g. Recrystallized from hot 50% alcohol, in which it is fairly readily soluble, the pure arsonic acid separates slowly as colorless, microscopic crystals which are soluble in boiling methyl alcohol or acetic acid, and very sparingly so in boiling water. It darkens slightly above 250° but does not decompose below 280°.

Subs., 0.3120; (Kjeldahl) 8.95 cc. 0.1 N HCl; $Mg_2As_2O_7$, 0.1370.
Calc. for $C_{14}H_{14}O_6NAs$: N, 3.99; As, 21.34. Found: N, 4.02; As, 21.19.

The acid was also prepared, although in poor yield, by boiling a solution of 3 g. of chloroacetyl-arsanilic acid[1] in 20 cc. of N aqueous sodium hydroxide with 1 g. of phenol under an air condenser for 1/2 hour. The substance was rapidly precipitated on cooling and adding acetic acid and was recrystallized from 50% alcohol. It separated slowly as wedge-shaped plates and prisms which showed the same properties as when made by the first method.

Subs., 0.2347; $Mg_2As_2O_7$, 0.1052.
Calc. for $C_{14}H_{14}O_6NAs$: As, 21.34. Found: 21.63.

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[1] This Journal, **39**, 1456 (1917).

[1] *Ibid.*, **41**, 1810 (1919).

***p*-Oxamino-phenoxyacetyl-arsanilic Acid,** *p*-$HO_2CCONHC_6H_4OCH_2CONHC_6H_4AsO_3H_2$(*p*-).—In an attempt to prepare the amide of this acid by starting with *p*-hydroxy-oxanilamide, the conditions of the experiment caused the cleavage of the amide group with the formation of the carboxylic acid.

Equivalent amounts of chloroacetyl-arsanilic acid and *p*-hydroxy-oxanilamide were dissolved separately in theoretical amounts of *N* sodium hydroxide solution and mixed, an immediate precipitation of the phenolic compound occurring. The mixture was boiled for 20 minutes, after which it reacted feebly acid, and the unchanged amide was filtered off and the filtrate acidified with hydrochloric acid. The resulting precipitate was dissolved in very dilute ammonia and the hot filtrate acidified with acetic acid. The cream-colored, microscopic crystals which separated proved to be the free carbonic acid formed by saponification of the amide in the boiling alkaline solution.

The substance darkens but does not melt below 280°. It is appreciably soluble in boiling water or 50% alcohol and separates from water with one molecule of water of crystallization.

Subs., air-dry, 0.4425; loss, 0.0196 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{16}H_{15}O_6N_2As.H_2O$: H_2O, 3.95. Found: 4.43.

Subs., anhydrous, 0.1610; 9.15 cc. N (23.5°, 753 mm.). Subs., 0.3577; $Mg_2As_2O_7$, 0.1293.

Calc. for $C_{16}H_{15}O_8N_2As$: N, 6.39; As, 17.10. Found: N, 6.48; As, 17.45.

***p*-Uramino-phenoxyacetyl-arsanilic Acid,** *p* - $H_2NCONHC_6H_4OCH_2CONHC_6H_4AsO_3H_2$(*p*-).—11.8 g. of chloroacetyl-arsanilic acid, 6.5 g. of *p*-hydroxyphenylurea, and 40 cc. of 2 *N* sodium hydroxide solution were refluxed for 1/2 hour. On cooling the *sodium salt* of the reaction product crystallized and the precipitation was completed by the addition of an equal volume of saturated sodium acetate solution. This salt was filtered off, washed with 20% sodium acetate solution, and finally with alcohol. For purification the crude product was dissolved in a small volume of water, treated with bone black, and then with alcohol until crystallization began. After filtration it was washed with 85% alcohol. The yield was 3.5 g., crystallizing as radiating masses of minute needles which contain approximately 3 molecules of water of crystallization.

Subs., air-dry, 0.5095; loss, 0.0531 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{15}H_{15}O_6N_6AsNa.3H_2O$: H_2O, 11.13. Found: 10.42.

Subs., anhydrous, 0.3510; (Kjeldahl) 23.5 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1240.

Calc. for $C_{15}H_{15}O_6N_3AsNa$: N, 9.75; As, 17.38. Found: N, 9.39; As, 17.05.

The free *arsonic acid* separates from the hot solution of the salt on adding acetic acid as aggregates of microscopic spindles which are practically insoluble in boiling water or 50% alcohol. It decomposes at about 280–3° with preliminary darkening.

Subs., 0.1332; 11.75 cc. N (29.0°, 765 mm.).

Calc. for $C_{15}H_{16}O_6N_3As$: N, 10.27. Found: 10.04.

o-Carboxamido-phenoxyacetyl-arsanilic Acid, o-$H_2NCOC_6H_4OCH_2CO$-$NHC_6H_4AsO_3H_2$(p-)—The reaction mixture from 11.2 g. of salicylamide was diluted to about 250 cc. and treated with sodium carbonate solution until just alkaline to litmus. The filtrate from the unchanged salicylamide was acidified with acetic acid, and on scratching the arsonic acid separated as fine needles. The crude acid was dissolved in a small volume of dil. sodium hydroxide and carefully neutralized with acetic acid. On adding an equal volume of saturated sodium acetate to the filtered solution the *sodium salt* quickly separated, forming a thick paste of crystals. The salt was washed with 20% sodium acetate solution and finally with alcohol and recrystallized from 85% alcohol, separating as prismatic needles containing approximately 5.5 molecules of water of crystallization.

Subs., air-dry, 0.5945; loss, 0.1177, *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{15}H_{14}O_6N_2AsNa.5.5H_2O$: H_2O, 19.23. Found: 19.79.
Subs., anhydrous; 0.3026; (Kjeldahl) 14.5 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1120.
Calc. for $C_{15}H_{14}O_6N_2AsNa$: N, 6.73; As, 18.02. Found: N, 6.71; As, 17.87.

On acidifying a hot solution of the sodium salt with acetic acid the free *arsonic acid* separates as delicate needles which do not decompose below 280°. It is appreciably soluble in boiling 50% alcohol or acetic acid, but does not dissolve readily in the other hot solvents.

Subs., 0.2082; (Kjeldahl) 10.4 cc. 0.1 *N* HCl.
Calc. for $C_{15}H_{15}O_6N_2As$: N, 7.11. Found: 7.00.

p-Carboxamido-phenoxyacetyl-arsanilic Acid.—2.8 g. of p-hydroxybenzamide yielded, on cooling, a thick crystalline mass of the *sodium salt.* This was dissolved by dilution with warm water and the solution filtered from unchanged p-hydroxy-benzamide, after which the arsonic acid was precipitated as a colorless powder on acidification with acetic acid. This was reconverted into the sodium salt by dissolving in a small volume of dil. sodium hydroxide, carefully neutralizing with acetic acid, and salting out with saturated sodium acetate solution. The product so obtained was then recrystallized from a small volume of hot water, separating as rosets of long, flat, delicate needles which contained approximately 7.5 molecules of water of crystallization. The yield was 3.7 g.

Subs., air-dry, 0.4550; loss, 0.1097 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{15}H_{14}O_6N_2AsNa.7.5H_2O$: H_2O, 24.52. Found: 24.10.
Subs., anhydrous, 0.1547; 9.3 cc. N (27.0°, 758 mm.). Subs., 0.2994; $Mg_2As_2O_7$, 0.1117.
Calc. for $C_{15}H_{14}O_6N_2AsNa$: N, 6.73; As, 18.02. Found: N, 6.82; As, 18.00.

On adding acetic acid to a hot solution of the sodium salt the free *arsonic acid* separated slowly as long, glistening needles which do not melt below 280°, and are practically insoluble in the usual boiling solvents.

Subs., 0.1495; (Kjeldahl) 7.6 cc. 0.1 *N* HCl.
Calc. for $C_{15}H_{15}O_6N_2As$: N, 7.11. Found: 7.12.

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