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AROMATIC ARSENIC COMPOUNDS. VII. SUBSTITUTED BENZYL, PHENOXYETHYL, AND PHENACYLARSANILIC ACIDS.

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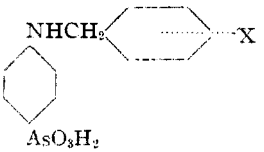
The preceding papers of this series have demonstrated that the reactivity of the amino group in arsanilic acid with chloroacetylamino compounds is such as to render possible the synthesis of a very extensive series of aromatic arsonic acids. It was thought possible that still other series, capable of similar extensive development, might be obtained by the use of other aromatic compounds containing suitable alkyl halide side chains. The present paper is a report of a few attempts in this direction which represent merely a beginning in the study of such substances, the pressure of other work having temporarily limited the development of these types of compounds.

Benzyl chloride and the substituted benzyl chlorides were found to react with sodium arsanilate under suitable conditions to form benzyl and substituted benzylarsanilic acids,



Although long boiling of the solution in 50% alcohol was required with benzyl chloride itself in order to obtain the greatest yields, owing to the stability of the halogen in this substance, the reaction proceeded far more easily and completely in the case of the negatively substituted benzyl halides such as *p*-nitrobenzyl chloride, 3-nitro-4-hydroxybenzyl chloride, *p*-carboxybenzyl chloride and *p*-carboxamidobenzyl chloride, the halogen of which is very reactive. The arsonic acids obtained from the above nitrobenzyl chlorides were reduced to the corresponding aminobenzyl arsanilic acids by means of ferrous hydroxide, a method which we have found to be especially serviceable for the selective reduction of nitroarsonic acids.[1]

Another group of substances studied was those obtained by reacting sodium arsanilate with phenoxyethyl bromide and such of its derivatives as salicylamide-bromoethyl ether and *p*-acetamino-phenoxyethyl bromide.

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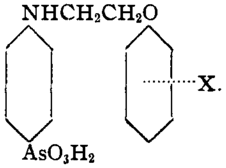
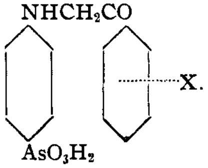
[1] Cf. THIS JOURNAL, 40, 1580 (1918).



The reaction was found to proceed very slowly and incompletely in boiling 50% alcoholic solution even in the presence of sodium iodide which strongly accelerated the condensation when chloroacetyl compounds were in question.

Finally, the reaction between sodium arsanilate and halogen-acetyl compounds such as the phenacyl halides was studied and found to proceed in the desired sense, yielding the phenacyl-arsanilic acids



These compounds are yellow in color and yield yellow solutions.

All of the above groups of substances function both as acids and feeble bases, forming salts with alkalies and strong mineral acids. With the exception of the negatively substituted benzyl derivatives they are readily displaced from their alkali salts by a slight excess of acetic acid.

Experimental.

(A) Benzyl-*p*-arsanilic Acids.

Benzyl-arsanilic Acid, *p*-$C_6H_5CH_2NHC_6H_4AsO_3H_2$.—4.4 g. of arsanilic acid were dissolved in 20 cc. of *N* sodium hydroxide solution and boiled under a reflux condenser for 4 hours with 2.7 g. of benzyl chloride, 1.5 g. of sodium iodide, and 20 cc. of alcohol. The benzylarsanilic acid separated during the heating and was washed with 50% alcohol, and finally with ether. The yield was 4.3 g. The crude substance was dissolved in dil. sodium hydroxide, treated with bone black, and precipitated while hot with acetic acid, the arsonic acid separating quickly as flat, lustrous, microscopic needles. For analysis it was best recrystallized from hot 50% alcohol, in which it is fairly readily soluble, forming arborescent masses of micro-crystals and larger prisms. The acid decomposes at about 255° with preliminary sintering, and is very sparingly soluble in hot water. Although difficultly soluble in the cold, boiling alcohol and acetic acid readily dissolve the substance. It is also soluble in methyl alcohol at room temperature and is insoluble in 10% hydrochloric acid, but stronger acid dissolves it. On adding sodium nitrite to a solution of the compound in hot acetic acid, cooling and rubbing, yellow spherules of microscopic crystals, presumably the nitroso compound, separate. On concentrating a neutral solution of the arsonic acid in aqueous sodium hydroxide to small volume and cooling, the *sodium salt* separates as glistening platelets which dissolve readily on dilution.

Subs., 0.2067; (Kjeldahl) 6.7 cc. 0.1 *N* HCl. Subs., 0.2747; $Mg_2As_2O_7$, 0.1378.
Calc. for $C_{13}H_{14}O_3NAs$: N, 4.56; As, 24.41. Found: N, 4.56; As, 24.21.

p-Nitrobenzyl-arsanilic Acid, *p*-$O_2NC_6H_4CH_2NHC_6H_4AsO_3H_2$.—8.8 g. of arsanilic acid in 40 cc. of *N* sodium hydroxide solution, 7 g. of *p*-nitrobenzyl chloride, and 40 cc. of alcohol were boiled for 3 hours, during which the molten chloride gradually disappeared. The yellow crystals which deposited on cooling were washed with 50% alcohol and then with acetone. The yield was 10 g. For purification a hot, dilute alkaline solution of the substance was precipitated with acetic acid. Recrystallized for analysis from hot 85% alcohol, in which it is sparingly soluble, it forms sheaves of flat, yellow, microscopic needles which do not melt when heated up to 280°. The acid is almost insoluble in boiling water and only sparingly so in boiling methyl alcohol or acetic acid.

Subs., 0.1598; 11.0 cc. N (22.5°, 762 mm.). Subs., 0.3023; $Mg_2As_2O_7$, 0.1320.
Calc. for $C_{13}H_{13}O_5N_2As$: N, 7.95; As, 21.28. Found: N, 7.97; As, 21.06.

p-Aminobenzyl-arsanilic Acid, *p*-$H_2NC_6H_4CH_2NHC_6H_4AsO_3H_2$.— 40 g. of ferrous sulfate dissolved in 150 cc. of water were treated with 25% sodium hydroxide solution until the mixture remained strongly alkaline to litmus after thorough shaking.[1] Ice was added and then a solution of 7 g. of *p*-nitrobenzyl-arsanilic acid in dil. sodium hydroxide. After 5 minutes' shaking the mixture was filtered, acidification of the filtrate with acetic acid yielding the crystalline amino compound contaminated with an amorphous by-product. For purification the crude substance was dissolved in cold, dil. ammonia, leaving a small amount of amorphous material which was collected in the cold with bone black. Acidification of the clear filtrate yielded the pure amino acid at once as colorless aggregates of microscopic leaflets which decompose at about 202°. The yield was 3.5 g. The acid is practically insoluble in hot water or 50% alcohol. On boiling a solution in dil. ammonia a white, amorphous alteration product is formed which is insoluble in ammonia. This does not happen with fixed alkali. The pure acid is soluble in both alkali and mineral acids, a solution in the latter being readily diazotizable, coupling with R-salt to form a deep red dye.

Subs., 0.1510; 11.9 cc. N (21.0°, 740 mm.). Subs., 0.3241; $Mg_2As_2O_7$, 0.1573.
Calc. for $C_{13}H_{15}O_3N_2As$: N, 8.70; As, 23.28. Found: N, 8.92; As, 23.41.

3-Nitro-4-hydroxybenzyl-arsanilic Acid, 3,4-$(O_2N)HOC_6H_3CH_2NH$-$C_6H_4AsO_3H_2$(*p*-).—To a hot solution of 11 g. of arsanilic acid in 50 cc. of *N* aqueous sodium hydroxide a solution of 9.5 g. of 3-nitro-4-hydroxybenzyl chloride in 50 cc. of hot alcohol was added. The condensation

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[1] *Loc. cit.*

took place rapidly but the heating was continued for 30 minutes. The alcohol was then allowed to boil off, causing the mixture to set to a thick mass of yellow crystals. These were filtered off and washed first with 50% alcohol and finally with acetone, the yield being 15 g. The crude acid was purified over the sodium salt by suspending it in a small volume of hot water and carefully treating with sodium hydroxide until solution was complete. On adding an equal volume of saturated sodium acetate solution to the reddish orange solution the *sodium salt* separated as a thick mass of long, thin, yellow, microscopic needles, which were filtered off and washed with 20% sodium acetate solution. On cautiously adding an excess of acetic acid to a hot, dilute solution of the salt the pure arsonic acid separated as aggregates of microscopic needles containing no water of crystallization. However, when recrystallized from 85% alcohol it crystallizes more slowly, forming crusts of minute, yellow crystals which contain one molecule of water of crystallization. When rapidly heated the anhydrous substance darkens and sinters above 210° and decomposes at about 245–50°. It is practically insoluble in boiling water, sparingly in the cold in alcohol, methyl alcohol, or acetic acid, and readily on boiling.

Subs., air-dry, 0.9344; loss, 0.0471, *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{13}H_{13}O_6N_2As.H_2O$: H_2O, 4.66. Found: 5.04.
Subs., anhydrous, 0.2655; (Kjeldahl) 14.5 cc. 0.1 N HCl.
Calc. for $C_{13}H_{13}O_6N_2As$: N, 7.61. Found: 7.65.

3-Amino-4-hydroxybenzyl-arsanilic Acid.—9 g. of 3-nitro-4-hydroxybenzylarsanilic acid were dissolved in dil. sodium hydroxide solution and added at once to a ferrous hydroxide suspension prepared by precipitating a solution of 50 g. of ferrous sulfate with sodium hydroxide until it remained strongly alkaline on shaking. After 5 minutes' shaking the mixture was filtered on a large Büchner funnel and the dark brown filtrate acidified with acetic acid, yielding a dark brown, crystalline precipitate of the amino acid on rubbing. For purification this was dissolved in dil. hydrochloric acid and a solution of sodium acetate added as long as the precipitate which first formed redissolved on stirring. A few dark-colored flocks were collected by the addition of bone black and the faintly colored filtrate diluted and treated further with sodium acetate solution until no longer acid to congo red, the arsonic acid separating as almost colorless, microscopic platelets which contained $^1/_2$ molecule of water of crystallization. The yield was 3 g. When heated to 285° the anhydrous substance darkens slightly, but does not melt. It is sparingly soluble in boiling water or 50% alcohol. An alkaline solution darkens rapidly on standing, while an aqueous suspension gives a deep brown color with ferric chloride solution.

Subs. air-dry, 0.6106; loss, 0.0155 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{13}H_{15}O_4N_2As.0.5H_2O$: H_2O, 2.59. Found: 2.54.

Subs., anhydrous, 0.2298; (Kjeldahl) 13.45 cc. 0.1 *N* HCl. Subs., 0.2565; $Mg_2As_2O_7$, 0.1170.

Calc. for $C_{13}H_{15}O_4N_2As$: N, 8.28; As, 22.18. Found: N, 8.20; As, 22.02.

_p_-Carboxybenzylarsanilic Acid, *p*-$HO_2CC_6H_4CH_2NHC_6H_4AsO_3H_2$.—3.5 g. of *p*-carboxybenzyl chloride in 20 cc. of *N* sodium hydroxide solution were added to a solution of 4.4 g. of arsanilic acid in 20 cc. of the same medium. The mixture was gently warmed and stirred until solution was complete and then allowed to stand at room temperature, a crop of crystals soon separating. After 24 hours the crystals were filtered off, dissolved by the addition of dil. sodium hydroxide, and the solution then heated. On adding hydrochloric acid to the hot solution a gum separated which rapidly crystallized. The collected and washed solid was boiled out with alcohol to remove impurities and converted into the *sodium salt* for final purification. After dissolving in dil. sodium hydroxide solution, neutralizing with acetic acid, and concentrating to small bulk, a large volume of alcohol was added to the hot solution, causing the separation of the salt as a colorless, microcrystalline powder. Recrystallized from a concentrated aqueous solution by adding alcohol the salt formed aggregates of flat needles containing approximately $^1/_2$ molecule of water of crystallization. The yield was 2.5 g.

Subs., air-dry, 0.2886; loss, 0.0082 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{14}H_{12}O_5NAsNa_2.0.5H_2O$: H_2O, 2.23. Found: 2.84.

Subs., anhydrous, 0.3230; (Kjeldahl) 8.3 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1260.

Calc. for $C_{14}H_{12}O_5NAsNa_2$: N, 3.55; As, 18.86. Found: N, 3.60; As, 18.83.

On adding acetic acid to a hot solution of the sodium salt the *free acid* separated as delicate, microscopic needles which did not melt below 280°. It is sparingly soluble in hot 50% alcohol or acetic acid and insoluble in other neutral solvents.

Subs., 0.2397; 8.4 cc. N (22.0°, 762 mm.). Calc. for $C_{14}H_{14}O_5NAs$: N, 3.99. Found: 4.07.

_p_-Carboxamidobenzyl-arsanilic Acid, *p*-$H_2NCOC_6H_4CH_2NHC_6H_4AsO_3H_2$.—33 g. of arsanilic acid in 150 cc. of *N* aqueous sodium hydroxide, 25.5 g. of *p*-(ω-chloromethyl)benzamide, and 150 cc. of alcohol were boiled for two hours, a thick mass of crystals separating on cooling. After filtering and washing first with water and then with alcohol, the arsonic acid was converted into the *sodium salt.* The solution of the acid in a small volume of warm, dil. sodium hydroxide was carefully neutralized with acetic acid. Separation of the salt, which commenced on cooling, was completed by adding saturated sodium acetate solution. Recrystallized from 50% alcohol the salt forms aggregates of thin plates containing 2.5 molecules of water of crystallization and is easily soluble in water. The yield was 30 g.

Subs., air-dry, 0.6617; loss, 0.0732 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{14}H_{14}O_4N_2AsNa.2.5H_2O$: H_2O, 10.79. Found: 11.08.

Subs., anhydrous, 0.3216; (Kjeldahl) 17.0 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1329.
Calc. for $C_{14}H_{14}O_4N_2AsNa$: N, 7.53; As, 20.13. Found: N, 7.41; As, 19.95.

Acetic acid added to a hot solution of the salt precipitates the *arsonic acid* as sheaves and plumes of microscopic needles. It does not melt below 280° and is almost insoluble in boiling water, 50% alcohol, or methyl alcohol.

Subs., 0.2308; (Kjeldahl) 13.1 cc. 0.1 *N* HCl.
Calc. for $C_{14}H_{15}O_4N_2As$: N, 8.00. Found: 7.95.

(B) Phenoxyethyl- and Phenacyl-*p*-arsanilic Acids.

Phenoxyethylarsanilic Acid, *p* - $C_6H_5OCH_2CH_2NHC_6H_4AsO_3H_2$. — Phenoxyethyl bromide was found to react very slowly with arsanilic acid, and although condensation was somewhat accelerated by the addition of sodium iodide, long-continued boiling of the reaction mixture was found necessary. A solution of 4.4 g. of arsanilic acid in 20 cc. of *N* aqueous sodium hydroxide, 4 g. of sodium iodide, 4 g. of phenoxyethyl bromide, and 20 cc. of alcohol were boiled for 24 hours. On cooling and diluting with water the reaction product crystallized as glistening leaflets which were filtered off and washed first with water and then with ether to remove unchanged bromide. The yield was 3 g. The acid was converted into the *sodium salt* by dissolving in a small amount of dil. sodium hydroxide solution, exactly neutralizing to litmus with acetic acid, and then treating with dry acetone until a turbidity was produced. On standing in the refrigerator the salt slowly separated as delicate needles. Recrystallized from a small volume of 85% alcohol it forms flat, microscopic needles containing 3.5 molecules of water of crystallization.

Subs., air-dry, 0.7668; loss, 0.1119 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{14}H_{15}O_4NAsNa.3.5H_2O$: H_2O, 14.89. Found: 14.59.

On treating the hot solution of the salt with acetic acid the free *arsonic acid* separated as glistening scales containing one molecule of water of crystallization. It is very sparingly soluble in boiling water or acetic acid, but is appreciably soluble in hot methyl alcohol, alcohol, or 50% alcohol. The anhydrous substance does not decompose below 280°.

Subs., air-dry, 0.4534; loss, 0.0242 *in vacuo* at 100° over H_2SO_4.
.Calc. for $C_{14}H_{16}O_4NAs.H_2O$: H_2O, 5.07. Found: 5.34.
Subs., anhydrous, 0.2263; (Kjeldahl) 7.0 cc. 0.1 *N* HCl. Subs., 0.2569; $Mg_2As_2O_7$, 0.1190.
Calc. for $C_{14}H_{16}O_4NAs$: N, 4.16; As, 22.22. Found, N, 4.33; As, 22.37.

***p*-Acetamino-phenoxyethyl-arsanilic Acid,** *p*-$CH_3CONHC_6H_4OCH_2CH_2NHC_6H_4AsO_3H_2$.—Arsanilic acid was condensed as in the previous example with *p*-acetamino-phenoxyethyl bromide. The reaction mixture was diluted with water, made alkaline with sodium hydroxide, filtered from unchanged halide, and acidified with acetic acid, yielding the crystalline arsonic acid. This was converted into the *sodium salt* by solution in a small volume of dil. sodium hydroxide, careful neutralization with acetic acid, and addition of saturated sodium acetate solution. After standing in the refrigerator the sodium salt was filtered off and washed with 20% sodium acetate solution and finally with 85% alcohol. Purified by dissolving in a small volume of water and precipitating with several volumes of alcohol, the salt forms colorless, microscopic platelets which contain about 3 molecules of water of crystallization.

Subs., air-dry, 0.5364; loss, 0.0580 *in vacuo* over H_2SO_4 at 100°.
Calc. for $C_{16}H_{18}O_5N_2AsNa.3H_2O$: H_2O, 11.49. Found: 10.81.
Subs., anhydrous, 0.3250; (Kjeldahl) 15.6 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1225.
Calc. for $C_{16}H_{18}O_5N_2AsNa$: N, 6.73; As, 18.01. Found: N, 6.72; As, 18.20.

On treating a hot solution of the salt with acetic acid the *arsonic acid* separated as delicate, glistening needles and platelets. Recrystallized from 50% alcohol it forms long, thin, narrow plates which do not melt below 275°. It is practically insoluble in boiling water and very difficultly so in hot alcohol or methyl alcohol, but dissolves in hot 50% alcohol or glacial acetic acid.

Subs., 0.2075; (Kjeldahl) 14.95 cc. 0.0714 *N* HCl.
Calc. for $C_{16}H_{19}O_5N_2As$: N, 7.11. Found: 7.21.

***o*-Carboxamido-phenoxyethyl-arsanilic Acid,** *o*-$H_2NCOC_6H_4OCH_2CH_2NHC_6H_4AsO_3H_2$.—The reaction mixture, similarly obtained from 10 g. of salicylamide-bromoethyl ether (2-bromoethoxy-benzamide)[1] was diluted with water, made alkaline with sodium hydroxide, filtered, and the filtrate acidified with acetic acid, depositing an amorphous, gelatinous precipitate followed by crystals on long standing in the refrigerator. The product was recrystallized from a small volume of hot 50% alcohol, 4 g. of the arsonic acid separating in wedge-shaped, microscopic prisms. For analysis it was again recrystallized from 50% alcohol. The substance is very difficultly soluble in boiling water, and when pure is only sparingly soluble in most hot solvents except hot acetic acid and hot 50% alcohol. When precipitated from its solution in alkali by means of acetic acid it separates slowly as rosets of broad, microscopic needles. When rapidly heated it does not melt below 280°, but if the temperature is held at this point the acid slowly melts and decomposes.

Subs., 0.2930; (Kjeldahl) 15.30 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1185.
Calc. for $C_{15}H_{17}O_5N_2As$: N, 7.37; As, 19.62. Found: N, 7.32; As, 19.52.

Phenacylarsanilic Acid, $C_6H_5COCH_2NHC_6H_4AsO_3H_2$.—4.4 g. of arsanilic acid in 20 cc. of *N* aqueous sodium hydroxide and a solution of 4 g. of ω-bromoacetophenone in 20 cc. of alcohol were boiled for one hour, the arsonic acid crystallizing during the reaction. The yield was 4 g. It was recrystallized by dissolving in dil. sodium hydroxide solution, heating and acidifying, the phenacyl compound separating as faintly yellow, arborescent aggregates of delicate, microscopic needles. It decomposes

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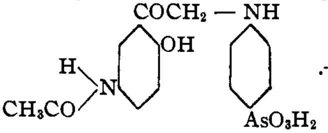
[1] *J. Biol. Chem.*, 21, 449 (1915).

at 185–7° with preliminary softening and is sparingly soluble in the usual solvents. An alkaline solution is yellow, the color deepening on standing. Conc. sulfuric acid dissolves the substance with a bright yellow color.

Subs., 0.1711; 6.4 cc. N (21.0°, 766 mm.). Subs., 0.3519; $Mg_2As_2O_7$, 0.1625.
Calc. for $C_{14}H_{14}O_4NAs$: N, 4.18; As, 22.36. Found: N, 4.38; As, 22.29.

2-Hydroxy-5-acetamino-phenacylarsanilic Acid,



.—A warm solution of 4.4 g. of arsanilic acid in 10 cc. of 2 *N* sodium hydroxide and 10 cc. of alcohol was treated with 5.5 g. of 3-acetamino-6-hydroxyphenacyl bromide.[1] The bromide dissolved rapidly and the mixture was heated on the water bath for an hour. On dilution with water an amorphous precipitate was formed, followed on standing in the refrigerator by a crystalline substance. The precipitate, washed with water and acetone, could not be recrystallized directly from neutral solvents, but purification was finally effected by taking advantage of the weakly basic properties of the arsonic acid. A suspension in 1 : 1 hydrochloric acid was treated with conc. hydrochloric acid until most of the substance had dissolved, then rapidly filtered, and the dark yellow filtrate treated with several volumes of hot water. Owing to the hydrolysis of its hydrochloride the phenacyl compound separated at once as a dark yellow powder consisting of aggregates of microscopic platelets which redden and decompose at 228°. The yield was only 1.2 g. The acid is practically insoluble in hot water or 50% alcohol and dissolves in conc. sulfuric acid with a reddish brown color.

Subs., 0.2946; (Kjeldahl) 14.5 cc. 0.1 *N* HCl; $Mg_2As_2O_7$, 0.1124.
Calc. for $C_{10}H_{17}O_6N_2As$: N, 6.86; As, 18.36. Found: N, 6.89; As, 18.43.

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[1] **3-Acetamino-6-hydroxy-phenacyl Bromide.**—From acetophenetidine, bromoacetyl chloride, and aluminum chloride with exclusion of moisture, similarly to the corresponding chloro compound [Kunckell, *Ber.*, 34, 128 (1901)]. The crude product (95% of the theory) was used for the preparation of the arsonic acid. A portion of the crude bromide was boiled with chloroform and the filtrate treated with ligroin, the bromide separating as a drab-colored precipitate melting at 133–5° with preliminary softening and slight gas evolution to a turbid, red-brown liquid which clears at 136°. The bromide dissolves readily in acetone or alcohol, less easily in boiling chloroform. The yellowish solution in alcohol changes to a deep olive green on addition of a drop of ferric chloride solution, or to orange-red on addition of aqueous sodium hydroxide.

Subs., 0.1785; 7.85 cc. N (21.0°, 758 mm.). Subs., 0.1673; (Carius) AgBr, 0.1179.
Calc. for $C_{10}H_{10}O_3NBr$: N, 5.15; Br, 29.37. Found: N, 5.09; Br, 29.99.