

TABLE VIII (*continued*).

Alkyl.		M. p. °C.	Calc. %	Sulfur. Found. %
Ethyl	Butyl	169	15.78	15.38
	<i>iso</i> -Amyl	172	15.25	15.09
	Ethyl	228	16.34	16.26
Propyl	Butyl	128	15.25	15.45
	Propyl	210	15.25	14.80
	Butyl	200.5	14.76	14.70
Butyl	<i>iso</i> -Amyl	147.5	14.30	13.95
	Butyl	138	14.30	14.00
	<i>iso</i> -Butyl	168.5	14.30	13.95
Di- <i>iso</i> -amyl	<i>iso</i> -Amyl	154	13.87	13.94
		176	13.46	13.40

Summary.

It has been found that by heating the sodium salt of α -anthraquinone sulfonic acid with a mercaptan in presence of caustic soda, the sulfonic acid group is readily replaced yielding an anthraquinone alkyl thio-ether, $C_{14}H_7O_2SR$. When two α -sulfonic acid groups are present these are replaced in succession, yielding first alkyl thio-ether sulfonic acids, 1,5- and 1,8- $NaO_3S.C_{14}H_6O_2SR$ and then dialkyl dithio-ethers, 1,5- and 1,8- $R'S.C_{14}H_6O_2SR$. A large number of compounds have been prepared in which R is methyl, ethyl, propyl, butyl, *isobutyl* and *iso*-amyl.

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ARSENATED BENZOPHENONE AND ITS DERIVATIVES.¹

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Introduction.

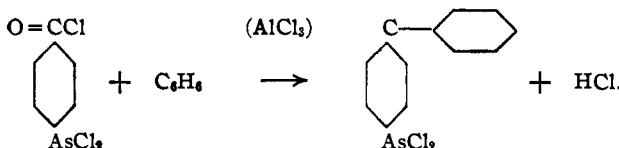
Arsenic in an aromatic nucleus does not interfere with many typical organic reactions. The Friedel and Crafts reaction, however, has found but limited² application in organic arsenical chemistry. With a view to determining whether arsenated benzoyl chloride would enter into the Friedel and Crafts reaction, thus yielding a new type of arsenic compound of possible therapeutic value,³ the work described in this paper was undertaken.

¹ This work was done under a grant from the Interdepartmental Hygiene Board, Washington, D. C., Dr. T. A. Storey, Sec'y.

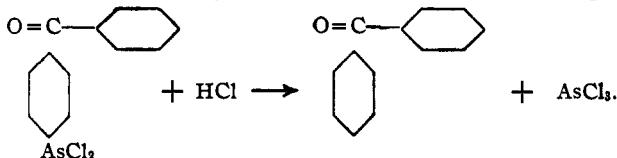
² Lewis, Lowry and Bergeim, THIS JOURNAL, 43, 892 (1921).

³ Therapeutic tests upon new compounds developed under this grant are being conducted by Dr. A. S. Loevenhart, Department of Pharmacology, University of Wisconsin.

It has been found that dichloro-*p*-arsinobenzoyl chloride condenses quite readily with aromatic hydrocarbons and phenyl ethers in the presence of anhydrous aluminum chloride using carbon disulfide as a solvent. When benzene was coupled with the arsenated acid chloride, some benzophenone itself was found among the products of the reaction, and identified by conversion into its oxime, melting at 140°. The formation of benzophenone establishes the course of the main reaction as follows.



When the reaction is too vigorous, de-arsenation of the compound results.



The amount of benzophenone never exceeded 10%, usually running 0.5–1%, while the yield of arsenated benzophenone was 50–60%. That the arsenated product is a ketone is shown by the fact that it reacts with hydroxylamine to form an oxime of the formula C₆H₅C=(NOH)C₆H₄AsO₃H₂. Furthermore, de-arsenation of the pure product by long refluxing with conc. hydrochloric acid yields benzophenone.

Experimental.

Preparation of Benzarsonic Acid.—Since a considerable quantity of benzarsonic acid (*p*-carboxy-phenylarsonic acid) was required for this work, a comparative study was made of the available methods of preparation. Of the three processes described in the literature, the first involves the oxidation of *p*-tolylarsonic acid by means of alkaline potassium permanganate.⁴ The yield is about 60% of the calculated amount, but the process is slow and tedious. A second method uses dil. nitric acid⁵ in sealed tubes in the oxidation of *p*-tolylarsonic acid. The yield is practically quantitative, but working in sealed tubes at 150° limits the amount of material, and the high pressure developed breaks a large percentage of the tubes. In the third process, arsanilic acid is diazotized,⁶ the cyanogen group introduced through the Sandmeyer reaction, and hydrolyzed to benzarsonic acid. The yield is uncertain and the method expensive.

A more economical and time-saving method was developed as follows. *p*-Nitrobenzoic acid is reduced to *p*-aminobenzoic acid, which is converted to the corresponding arsonic acid by Bart's reaction.⁷

Reduction of *p*-Nitrobenzoic Acid.—The method of Jacobs and Heidelberger⁸ was

⁴ La Coste, *Ann.*, **208**, 1 (1881).

⁵ Michaelis, *ibid.*, **320**, 303 (1902); *Ber.*, **48**, 870 (1915).

⁶ Bertheim, *Ber.*, **41**, 1857 (1908).

⁷ Bart, Ger. pat. 250,264 and 254,345.

⁸ Jacobs and Heidelberger, *THIS JOURNAL*, **39**, 1437 (1917).

applied with excellent results in this reduction. Twenty-five g. of *p*-nitro-benzoic acid (technical) is dissolved in a small amount of warm dil. ammonium hydroxide and poured with stirring into a boiling solution of 300 g. of commercial ferrous sulfate crystals in 400 cc. of water. About 100 cc. of conc. ammonium hydroxide is cautiously added, and the boiling continued for 5 minutes. The product is filtered hot after the addition of 50 cc. of ammonium hydroxide. On acidifying the filtrate with acetic acid, *p*-aminobenzoic acid crystallizes in long, light yellow needles; m. p., 186°; yield, 85-90%.

Conversion of *p*-Aminobenzoic Acid to Benzarsonic Acid.—The method of Bart is applied as follows. Fifty g. of *p*-aminobenzoic acid is dissolved in 750 cc. of water with 75 cc. of conc. hydrochloric acid and diazotized in the usual manner, using 26 g. of sodium nitrite. The arsenite solution is prepared by dissolving 46 g. of arsenic trioxide in 400 cc. of water with 54 g. of sodium hydroxide. Twenty cc. of 6 N copper sulfate solution is now added. The diazo solution is slowly poured into the arsenite-solution with vigorous stirring, the temperature being held at 20°. The alkaline solution is then warmed on the water-bath to 60° until the evolution of nitrogen ceases, when it is acidified with hydrochloric acid. A water-insoluble flocculent precipitate is filtered and discarded. The filtrate on concentrating to 500 cc., cooling, and scratching, deposits colorless crystals of benzarsonic acid. The yield is 50-60%.

Preparation of Dichloro-*p*-arsinobenzoyl Chloride,⁹ Cl₂AsC₆H₄COCl.—Twenty cc. of phosphorus trichloride in 20 cc. of chloroform is slowly added to 25 g. of benzarsonic acid suspended in 100 cc. of cold chloroform. After warming to complete the reaction, 20 g. of phosphorus pentachloride is added at once. When this second reaction has been completed by heating the solution on a water-bath for 10 to 15 minutes, the mixture is fractionated *in vacuo*. Dichloro-*p*-arsino-benzoyl chloride passes over at 190-195° under 20-25 mm. pressure. The yield is 75-80%. In later runs with larger amounts the fractionation was omitted, the material being used directly for the condensation with aluminum chloride.

Preparation of Benzophenone-*p*-arsenious Oxide, C₆H₅COC₆H₄As=O.—Twenty g. of the above acid chloride, dissolved in 100 cc. of dry carbon disulfide, is added to 25 cc. of dry benzene. Twenty-five g. of anhydrous aluminum chloride is then added in 5g. portions to reduce the intensity of the reaction. After warming at 50° on the water-bath for 2 hours under a reflux condenser, the reaction mixture is poured while warm on 300 g. of cracked ice. Ten cc. of conc. hydrochloric acid is added, and the carbon disulfide and excess benzene removed by steam distillation. The reaction flask now contains a clear aqueous solution and a gummy substance which adheres to the walls of the flask. The aqueous solution, which contains the hydrated aluminum chloride and some *p*-carboxy-phenylarsenious acid is decanted and discarded. Four hundred cc. of dil. sodium carbonate solution and 50 cc. of 6 N sodium hydroxide solution are added to the flask and warmed to decompose the gummy mass which gradually goes into solution. After filtering and cooling, benzophenone-*p*-arsenious oxide is precipitated in an amorphous condition by dil. hydrochloric acid. The yield is 60%. It is slightly soluble in boiling water, absolute alcohol, benzene, and ether, and easily soluble in warm alkalies.

Analyses. Subs., 0.2442, 0.1643: 34.5 cc., 23.3 cc. of 0.0521 N iodine solution. Calc. for C₁₃H₉O₂As: As, 27.57. Found: 27.59, 27.69.

Benzophenone-*p*-arsenious Acid, C₆H₅COC₆H₄As(OH)₂.—The above oxide, after boiling for several hours with a large amount of water, yields a small quantity of fine crystals insoluble in ether or benzene, easily soluble in cold alkalies, and somewhat soluble in absolute alcohol. It is apparently the hydrated oxide.

⁹ Poulenc, French pat. 441,215.

Analyses. Subs., 0.2681: 46.95 cc. of 0.0389 *N* iodine solution. Calc. for $C_{18}H_{11}O_3As$: As, 25.86. Found: 25.57.

Benzophenone-*p*-arsonic Acid, $C_6H_5COC_6H_4AsO_3H_2$.—The oxide is dissolved in warm dil. sodium hydroxide and a slight excess of the calculated amount of 3% hydrogen peroxide solution added. After warming for 5 minutes, the solution is acidified with hydrochloric acid, which precipitates at once the arsionic acid. From large volumes of boiling water, recrystallization yields lustrous clusters of elongated plates. The yield is quantitative. The crystals soften at 195° but do not melt below 260°. The substance is insoluble in cold water, benzene, and ether, and soluble in alkalies, ethyl alcohol, and warm glacial acetic acid.

Analyses. Subs., 0.2214, 0.1579: 27.8 cc., 19.7 cc. of 0.0521 *N* iodine solution. Calc. for $C_{18}H_{11}O_4As$: As, 24.51. Found: 24.52, 24.35.

Oxime of Benzophenone-*p*-arsonic Acid, $C_6H_5C=(NOH)C_6H_4AsO_3H_2$.—Ten g. of benzophenone-*p*-arsonic acid is heated in a slightly alkaline alcoholic solution with 5 g. of hydroxylamine sulfate on the water-bath for 2 hours. After cooling and acidifying with dil. sulfuric acid, the product is recrystallized from hot water, yielding fine colorless needles which do not melt below 260°. The yield is 80%.

Analyses. Subs., 0.4611: 12.8 cc. of 0.108 *N* sodium hydroxide (Kjeldahl). Calc. for $C_{18}H_{12}O_4NAs$: N, 4.36. Found: 4.20.

Subs., 0.1390: 17.15 cc. of 0.0497 *N* iodine solution. Calc. for $C_{18}H_{12}O_4NAs$: As, 23.36. Found: 23.01.

Mononitro-benzophenone-*p*-arsonic Acid, $(NO_2)C_6H_5COC_6H_4AsO_3H_2$.—Thirty-five g. of fuming nitric acid (sp. gr. 1.5) is added to 4 g. of benzophenone-*p*-arsonic acid and the solution heated on the water-bath for one hour. After dilution with 50 cc. of water, the mixture is slowly evaporated to a thick syrup to expel the nitrous fumes. After two recrystallizations from hot water, 2 g. of fine, light yellow needles were obtained.

Analyses. Subs., 0.5385: 12.95 cc. of 0.108 *N* sodium hydroxide (Kjeldahl). Calc. for $C_{18}H_{10}O_6NAs$: N, 3.98. Found: 3.65.

Subs., 0.3719: 40.45 cc. of 0.0521 *N* iodine solution. Calc. for $C_{18}H_{10}O_4NAs$, As, 21.36. Found: 21.24.

4-Methyl-benzophenone-4'-arsenious Oxide, $CH_3C_6H_4COC_6H_4AsO$.—This compound is made by substituting toluene for benzene in the procedure described above for benzophenone-*p*-arsenious oxide. The yield is about 50%. Due to its amorphous character, the product is difficult to purify, and arsenic analyses give results 0.5–0.7% low. Its hydrate is made by prolonged boiling with a large volume of water, giving a small quantity of fine, needle-like crystals, soluble in alkalies, insoluble in ether, or benzene, and somewhat soluble in ethyl alcohol.

Analyses. Subs., 0.2658, 0.1904: 22.5 cc., 16.05 cc. of 0.0772 *N* iodine solution. Calc. for $C_{14}H_{13}O_3As$: As, 24.67. Found: 24.50, 24.40.

4-Methyl-benzophenone-4'-arsonic Acid, $CH_3C_6H_4COC_6H_4AsO_3H_2$.—Oxidation of the above oxide in warm alkaline solution by means of 3% hydrogen peroxide gives a good yield of the corresponding arsionic acid, which crystallizes from hot water in transparent plates, easily soluble in alkalies, somewhat soluble in ethyl alcohol, insoluble in ether, benzene, etc. The crystals did not melt below 260°.

Analysis. Subs., 0.1330: 15.9 cc. of 0.0521 *N* iodine solution. Calc. for $C_{14}H_{13}O_4As$: As, 23.43. Found: 23.34.

The condensation of dichloro-*p*-arsinobenzoyl chloride with the phenyl ethers proceeds very smoothly, giving 60–75% yields. In each case the substituted arsenious oxides were found to be amorphous and difficult to purify, and they yielded no

crystalline hydrates. They were therefore oxidized to the corresponding arsonic acids, which are well crystallized and easily purified.

4-Methoxy-benzophenone-4'-arsonic Acid, $\text{CH}_3\text{OC}_6\text{H}_4\text{COC}_6\text{H}_4\text{AsO}_3\text{H}_2$.—Starting with anisole in place of benzene in the original condensation and oxidizing the intermediate arsine oxide without attempting to isolate it, the corresponding arsonic acid is obtained in 60–70% yield after recrystallization from large volumes of boiling water.

Analysis. Subs., 0.3319: 37.4 cc. of 0.0521 N iodine solution. Calc. for $\text{C}_{14}\text{H}_{13}\text{O}_5\text{As}$: As, 22.32. Found: 22.01.

4-Ethoxy-benzophenone-4'-arsonic Acid, $\text{C}_4\text{H}_9\text{OC}_6\text{H}_4\text{COC}_6\text{H}_4\text{AsO}_3\text{H}_2$.—Following the same procedure, phenetole gives a 55% yield of the ethoxy-derivative. As the molecular weight increases, the solubility of these arsonic acids in water decreases, so that it becomes difficult to use water as a solvent for recrystallization. Glacial acetic acid or 95% ethyl alcohol is found satisfactory.

Analysis. Subs., 0.2193: 24.95 cc. of 0.0497 N iodine solution. Calc. for $\text{C}_{15}\text{H}_{15}\text{O}_5\text{As}$: As, 21.42. Found: 21.21.

4-Phenoxy-benzophenone-4'-arsonic Acid, $\text{C}_6\text{H}_5\text{OC}_6\text{H}_4\text{COC}_6\text{H}_4\text{AsO}_3\text{H}_2$.—This arsonic acid is made in 50% yield by using diphenyl ether. It is practically insoluble in water, even at 100°. It is easily crystallized from hot glacial acetic acid or 95% alcohol, giving colorless platelets, which do not melt below 260°.

Analyses. Subs., 0.1745: 16.7 cc. of 0.0521 N iodine solution. Calc. for $\text{C}_{19}\text{H}_{15}\text{O}_5\text{As}$: As, 18.84. Found: 18.69.

Similar compounds have been made from the *ortho* and *meta* homologs of dichloro-*p*-arsinobenzoyl chloride, and will be reported later.

Summary.

1. It has been found possible to condense dichloro-*p*-arsinobenzoyl chloride with benzene, toluene, anisole, phenetole, and diphenyl ether in the presence of aluminum trichloride with carbon disulfide as a solvent.

2. Properties and directions for preparing the following compounds are given: benzophenone-*p*-arsenious oxide, benzophenone-*p*-arsenious acid, benzophenone-*p*-arsonic acid and its oxime and mononitro derivative, 4-methyl-benzophenone-4'-arsenic acid, 4-methoxy-benzophenone-4'-arsonic acid, 4-ethoxy-benzophenone-4'-arsonic acid, and 4-phenoxy-benzophenone-4'-arsonic acid.

3. An improved method for the preparation of benzaronic acid has been developed.

EVANSTON, ILLINOIS.