comparison with an authentic specimen and by mixed melting point determinations on the base, the picrate and the very characteristic cyano derivative.

## Summary

Complete syntheses of lodal (4,5-dimethoxy-2-β-methylamino-ethylbenzaldehyde) and epinine (3,4-dihydroxyphenylethylmethylamine), from vanillin, via homoveratrylamine, have been carried out. The products were identical with those prepared by Pyman's[1,2] method from papaverine or laudanosine.

TUCKAHOE, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS OF NORTHWESTERN UNIVERSITY]

# THE ARSONATION OF AROMATIC ALDEHYDES

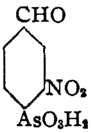
BY ALBERT B. SCOTT[1] AND CLIFF S. HAMILTON

RECEIVED AUGUST 4, 1930 PUBLISHED OCTOBER 6, 1930

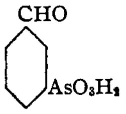
Certain organic arsenical compounds exert a specific curative action in syphilis and the trypanosomiases. Although arsonated aromatic compounds containing the amino group substituted in the nucleus have been widely investigated for many years, little attention has been devoted to arsonated aromatic molecules containing a non-cyclic carbonyl group. The present investigation deals with the preparation and properties of arsonated aromatic aldehydes, molecules which contain a nuclear arsono group ($AsO_3H_2$) and a non-cyclic carbonyl group. The only reference to this type of substance was found in certain patents. Pfleger and Albert[2] claim derivatives of *p*-arsonobenzaldehyde. Margulies claims 3-nitro-4-arsonobenzaldehyde and *p*-arsonobenzaldehyde.[3]

Kalberlah[4] claims unique effectiveness for a new aromatic arsenical compound containing a non-cyclic carbonyl group.

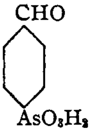
In the present investigation derivatives of three arsonated aromatic aldehydes have been prepared. The structures of the parent compounds are as follows

I


3-Nitro-4-arsono-benzaldehyde

II


*m*-Arsono-benzaldehyde

III


*p*-Arsono-benzaldehyde

---

[1] Research Fellow under a grant from Parke, Davis & Co. This article is an abstract of a thesis submitted by Albert B. Scott in partial fulfilment of the requirements for the degree of Doctor of Philosophy at Northwestern University.

[2] Pfleger and Albert, United States Patent 1,472,778 (1923).

[3] Margulies, British Patent 220,688 (1924).

[4] Kalberlah, *Klin. Wochschr.*, **48**, 2185 (1924).

3-Nitro-4-arsonobenzaldehyde (I) was prepared from 3-nitro-4-aminobenzaldehyde by Bart's reaction.[5] The diazotization proved difficult and was accomplished by the use of a large volume of acetic acid and a great excess of nitrous acid. Arsonation was carried out by adding dilute sodium hydroxide solution to the strongly acid mixture of diazonium compound and arsenious acid. This procedure permits coupling to form the arsonic acid over a wide range of hydrogen-ion concentrations and is consequently advantageous in the preparation of a new arsonic acid where the optimum conditions for coupling are unknown.

Purification of 3-nitro-4-arsonobenzaldehyde was unsatisfactory. The *p*-nitrophenylhydrazone, the β-naphthylhydrazone and the semicarbazone of this arsonated aromatic aldehyde were obtained in pure condition. The method of purification found most suitable for these derivatives was solution in dilute sodium carbonate solution followed by re-precipitation with dilute hydrochloric acid. From the semicarbazone of 3-nitro-4-arsonobenzaldehyde the semicarbazone of 3-amino-4-arsonobenzaldehyde was prepared by reduction with ferrous hydroxide in alkaline medium as suggested by Jacobs, Heidelberger and Rolf[6] and modified by Palmer and Adams.[7] While the alkaline medium was quite satisfactory for the reduction of the semicarbazone it might have been incompatible with the parent aldehyde.

*m*-Arsonobenzaldehyde was prepared from *m*-aminobenzaldehyde by Bart's reaction and isolated as the *p*-nitrophenylhydrazone. A solution of *m*-aminobenzaldehyde was prepared by reduction of *m*-nitrobenzaldehyde as the sodium bisulfite addition compound with ferrous sulfate and calcium carbonate.[8] Excess iron was precipitated from the very dilute solution and the filtrate containing *m*-aminobenzaldehyde was arsonated. *m*-Aminobenzaldehyde formed tars with remarkable readiness except in neutral or nearly neutral dilute solutions. After arsonation *m*-arsonobenzaldehyde was obtained from the solution as the *p*-nitrophenylhydrazone.

To avoid the extreme difficulty of working with certain aminoaldehydes, a new and independent method of synthesis of arsonated aromatic aldehydes was developed. *p*-Methylphenylarsonic acid was oxidized to *p*-arsonobenzaldehyde by means of solid chromic oxide ($CrO_3$) in the presence of acetic anhydride, glacial acetic acid and concentrated sulfuric acid. Formation of the aldehyde diacetate prevents further oxidation of the aldehyde group. The arsonated aromatic aldehyde, *p*-arsonobenzaldehyde, prepared by this method was isolated as the *p*-nitrophenylhydra-

---

[5] Bart, *Ann.*, **429**, 55 (1922).

[6] Jacobs, Heidelberger and Rolf, This Journal, **40**, 1581 (1918).

[7] Palmer and Adams, *ibid.*, **45**, 1312 (1923).

[8] German Patent 66,241 (1892).

zone. The yield of *p*-arsonobenzaldehyde was low but the method is being improved and will be extended to other alkyl arsonic acids in the near future. The great advantage of this method of preparing certain arsonated aromatic aldehydes lies in the ease of preparation of the alkyl arsonic acids which serve as intermediates to be oxidized to the corresponding aldehydes.

In this investigation the question of qualitatively proving the presence of the arsono group ($AsO_3H_2$) arose repeatedly and lack of a suitable qualitative test for arsonation was a marked handicap. Ordinary qualitative tests for arsenic fail completely to differentiate between arsenic in inorganic combination and arsenic in organic combination. The reduction of aromatic arsonic acids to the less soluble arseno compounds by means of hypophosphorous acid was found to be adaptable for use as a rapid qualitative. test for the arsonation of aromatic compounds. With all of the arsonic acids examined a characteristic precipitate of the corresponding arseno compound was obtained within twenty minutes under the conditions described in the experimental portion of this work. Experience with this reduction indicates that a mixture of the arsine oxide and arseno compound corresponding to the arsonic acid may form in some cases but this does not affect the validity of the test. However, much more extensive study will be necessary to prove that this qualitative test is general.

## Experimental

### I. 3-Nitro-4-Arsonobenzaldehyde

**3-Nitro-4-aminobenzaldehyde.**—Following the method of Hodgson and Beard[9] 3-nitro-4-aminobenzaldehyde was prepared in approximately 10% yield, the greatest loss occurring in the conversion of *p*-nitrotoluene to *p*-acetaminobenzaldehyde. The product after recrystallization from 80% acetic acid melted at 188–189° (Hodgson and Beard give m. p. 191° for the crude product).

**Arsonation of 3-Nitro-4-aminobenzaldehyde.**—A solution of 16 g. of recrystallized 3-nitro-4-aminobenzaldehyde was obtained by stirring for thirty minutes at 95° with 200 cc. of 80% acetic acid. The hot solution was filtered and then, by cooling to 20°, a thick paste of fine crystals was formed. Diazotization was carried out at 20° with stirring by the simultaneous dropwise addition of 20% sodium nitrite solution and concentrated hydrochloric acid. The dropwise addition was carried out at such a rate that all of the hydrochloric acid (90 cc.) had been added in sixty minutes and all of the sodium nitrite solution (220 cc.) in ninety minutes. After the addition of the sodium nitrite solution was complete, stirring was continued for thirty minutes making a total of one hundred and twenty minutes for the diazotization. The bright red acid diazonium solution was then filtered, treated cautiously with urea, and poured into a 4-liter crock containing 75 cc. of a 20% sodium meta-arsenite solution and 125 cc. of water. Then with constant stirring and below 15° 4 *N* sodium hydroxide solution was added dropwise until there was 25 cc. excess over the amount necessary to make the solution just alkaline to litmus paper. After standing overnight at room temperature, the dark

---

[9] Hodgson and Beard, *J. Chem. Soc.*, 20 (1927).

brown solution was stirred for sixty minutes at 60–70°. At the end of this time a test with alkaline R-salt solution showed that all of the diazo compound had reacted. The solution was then made just acid to litmus paper with hydrochloric acid, heated to boiling with decolorizing charcoal, filtered, made acid to Congo red paper with hydrochloric acid and concentrated to 300 cc. on the steam-bath. The golden yellow solution was then made just neutral to litmus paper with 6 *N* sodium hydroxide solution added slowly with stirring and cooling. The solution of the monosodium salt of 3-nitro-4-arsonobenzaldehyde was then filtered from undissolved material and the free arsonic acid precipitated from the filtrate as a yellow paste by adding 6 *N* hydrochloric acid drop by drop with stirring and cooling until the solution was acid to Congo red paper. The pasty yellow product was combined with a further quantity recovered from the filtrate and washings and dried in vacuum over calcium chloride to form a heavy yellow amorphous powder which softened and darkened at about 155° and decomposed slowly above this temperature; wt., 12.5 g.; yield, 47%. In one run the arsonic acid was isolated as the semicarbazone and a weight of semicarbazone corresponding to 54% yield of 3-nitro-4-arsonobenzaldehyde was obtained.

The crude arsonic acid gave an arsine odor when burned; gave a precipitate with hypophosphorous acid when warmed in either aqueous or alcoholic solution; dissolved in concentrated ammonium hydroxide, dilute sodium carbonate solution and dilute sodium hydroxide solution; formed a *p*-nitrophenylhydrazone, a β-naphthylhydrazone and a semicarbazone; and was slightly soluble in water while practically insoluble in ethyl alcohol, methyl alcohol, ethyl acetate, ether, chloroform, ligroin and benzene.

*Anal.* (1) After recrystallization from water. Subs., 0.1448: 21.60 cc. of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_7H_6O_6NAs$: As, 27.25. Found: As, 27.95. (2) After solution in dilute sodium carbonate solution and re-precipitation with dilute hydrochloric acid. Subs., 0.1602: 23.17 cc. of potassium bromate (1 cc. = 0.001874 g. As). Found: As, 27.10.

Analytical values on this substance were not consistent. It was possible, however, to prepare pure derivatives.

***p*-Nitrophenylhydrazone of 3-Nitro-4-arsonobenzaldehyde.**—A clear amber solution of 3.5 g. of crude 3-nitro-4-arsonobenzaldehyde in 400 cc. of water was obtained by boiling, cooling and filtering. To the cooled solution was added 4 g. of solid sodium acetate. The solution was then heated nearly to boiling and a solution of 2 g. of *p*-nitrophenylhydrazine in 100 cc. of water and 10 cc. of 6 *N* hydrochloric acid was then poured in with vigorous stirring. A brilliant orange-red flocculent precipitate formed at once. After digestion for ninety minutes this product was filtered, washed with water and ether, and dried in vacuum over phosphorus pentoxide to form an amorphous orange powder which began to decompose at about 260–270°.

The product was purified by dissolving in 10% sodium carbonate solution, filtering and re-precipitating by making just acid to Congo red paper with 6 *N* hydrochloric acid added dropwise with stirring and cooling.[10] After washing and drying as before, an orange amorphous powder was obtained.

*Anal.* Subs., 0.2484, 0.2759: 23.90, 26.30 cc. of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_{13}H_{11}O_7N_4As$: As, 18.29. Found: As, 18.03, 17.86.

**β-Naphthylhydrazone of 3-Nitro-4-arsonobenzaldehyde.**—A solution of β-naphthylhydrazine was obtained by dissolving 0.7 g. of β-naphthylhydrazine hydrochloride

---

[10] When the sodium carbonate solution of the hydrazone came through the filter with a marked cloudy or silky appearance, it was warmed with a small amount of decolorizing charcoal and filtered again. This treatment gave a solution which was free from suspended fine particles.

in 100 cc. of boiling water, adding 0.3 g. of solid sodium acetate, cooling to about 50 and filtering. This solution was then poured, with vigorous stirring, into a hot solution of 1 g. of crude 3-nitro-4-arsonobenzaldehyde in 200 cc. of water, and the heavy brick-red precipitate digested, washed and dried. The dry dark red powder darkened at about 210° and decomposed at about 235–245°; wt., 0.75 g. For purification 3 g. of the crude hydrazone was treated with 5 cc. of 10% sodium carbonate solution and 200 cc. of water and filtered. The insoluble residue was treated with 5 cc. of 10% sodium carbonate solution and 50 cc. of water and filtered. The combined filtrates were muddy and a clear solution was obtained by warming with decolorizing charcoal and again filtering. From the final clear red solution the hydrazone was precipitated by the addition of 6 *N* hydrochloric acid added dropwise with stirring and cooling until the solution was acid to Congo red paper.

*Anal.* Subs., 0.2322, 0.2334: 22.20, 22.40 cc. of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_{17}H_{14}O_6N_3As$: As, 18.07. Found: As, 17.92, 17.99.

**The Semicarbazone of 3-Nitro-4-arsonobenzaldehyde.**—A solution of 1 g. of semicarbazide hydrochloride in 50 cc. of water was added to a clear solution of 2 g. of crude 3-nitro-4-arsonobenzaldehyde in 400 cc. of water containing 0.73 g. of solid sodium acetate. The solution became cloudy and immediately deposited heavy yellow crystals. When dried the semicarbazone was a pale yellow powder which began to darken at about 220° and decomposed at about 250°; wt., 1.62 g.

For purification the semicarbazone was recrystallized twice from methyl alcohol and then 2 g. of the recrystallized material was treated with 10% sodium carbonate until nearly all of it dissolved. The golden yellow solution obtained by filtering was then made just acid to Congo red paper by adding 6 *N* hydrochloric acid dropwise with stirring and cooling. The light yellow product dried to form an almost white crystalline powder.

*Anal.* (1) Recrystallized twice from methyl alcohol. Subs., 0.1906, 0.2385: 22.50, 28.20 cc. of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_8H_9O_6N_4As$: As, 22.59. Found: As, 22.12, 22.16. (2) Recrystallized material after solution in dilute sodium carbonate solution and re-precipitation with dilute hydrochloric acid. Subs., 0.2374: 28.40 cc. of potassium bromate (1 cc. = 0.001874 g. As). Found: As, 22.42.

The semicarbazone of 3-nitro-4-arsonobenzaldehyde was found to be readily hydrolyzed by heating on the steam-bath with dilute hydrochloric acid.

**Semicarbazone of 3-Amino-4-arsonobenzaldehyde.**—A solution of 20 g. of the semicarbazone of 3-nitro-4-arsonobenzaldehyde in 200 cc. of water and 10 cc. of 6 *N* sodium hydroxide solution was added to a mixture of 127 cc. of 3.3 molar ferrous chloride and 170 cc. of 6 *N* sodium hydroxide solution in a bottle with a wide mouth and the bottle tightly stoppered. The mixture turned reddish-brown at once but was subjected to occasional shaking during sixty minutes and was then filtered through a large Büchner funnel. The filtrate was made just acid to Congo red paper with 3 *N* hydrochloric acid. The brown pasty precipitate dried to a light brown powder; wt., 11.0 g. The material did not fuse but a gas was evolved over a considerable range of temperature.

The material was found to be moderately soluble in dilute hydrochloric acid and to give a brilliant red product when diazotized and coupled with alkaline R-salt solution.

*Anal.* Subs., 0.1980, 0.1962: 26.55, 26.40 cc. of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_8H_{11}O_4N_4As$: As, 24.83. Found: As, 25.13, 25.22.

## II. *m*-Arsonobenzaldehyde

**Preparation and Arsonation of *m*-Aminobenzaldehyde.**—To 2000 cc. of water was added 680 g. of ferrous sulfate and 250 g. of calcium carbonate, the latter as a paste with water. This mixture was heated to 85° and during twenty minutes with stirring 500 cc. of an aqueous solution containing 60 g. of *m*-nitrobenzaldehyde and 40 g. of solid C. P. sodium bisulfite were added. The mixture turned brown and carbon dioxide was evolved. After cooling the solution was acidified to Congo red paper and boiled to expel sulfur dioxide. At this point diazotization was unsuccessful because of excess ferrous salts so the solution was diluted to 4 liters, made faintly alkaline to litmus paper with sodium hydroxide solution and filtered. The *m*-aminobenzaldehyde in the filtrate as a solution was arsonated. The filtrate was made acid to Congo red paper with hydrochloric acid and then 60 cc. excess of concentrated hydrochloric acid was added. At a temperature below 10°, 207 cc of 20% sodium nitrite solution was added dropwise with stirring. The diazonium solution was then poured into 195 cc. of 20% sodium meta-arsenite solution and 6 *N* sodium hydroxide was added until the solution was just alkaline to litmus paper. Vigorous nitrogen evolution occurred. The solution, after stirring for one hour at 50°, was made just acid to litmus paper, heated to boiling with decolorizing charcoal, filtered and concentrated to 1000 cc.

**Isolation of *m*-Arsonobenzaldehyde as the *p*-Nitrophenylhydrazone.**—To 300 cc. of the solution of *m*-arsonobenzaldehyde at 100° was added a solution containing 4 g. of *p*-nitrophenylhydrazine, 500 cc. of water, 20 cc. of 6 *N* hydrochloric acid and 8.3 g. of solid sodium acetate. The brilliant orange flocculent precipitate was washed with water and ether and dried in vacuum over phosphorus pentoxide to form an amorphous orange powder which melted with decomposition between 200 and 210°; wt., 5.4 g. The product was purified by three successive re-precipitations with sodium carbonate solution and hydrochloric acid as previously described.

*Anal.* Subs., 0.1968, 0.1599: 21.60, 17.75 cc. of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_{13}H_{12}O_5N_3As$: As, 20.55. Found: As, 20.57, 20.80.

## III. *p*-Arsonobenzaldehyde

**Chromic Acid Oxidation of *p*-Methylphenylarsonic Acid.**—The quantities used in this procedure correspond to those recommended by Thiele and Winter[11] for the oxidation of *p*-nitrotoluene to *p*-nitrobenzaldehyde. A solution of 15.8 g. of *p*-methylphenylarsonic acid in 80 g. of acetic anhydride, 80 g. of glacial acetic acid, and 30 g. of concentrated sulfuric acid was treated with 20 g. of solid chromic oxide ($CrO_3$) added during thirty minutes. The temperature was maintained at 0–10°. The mixture was stirred for thirty minutes at 10° following the addition of all of the chromic oxide and was then extracted with two 175-cc. portions of ether. The ethereal extract was taken almost to dryness under diminished pressure, diluted with about 50 cc. of water and 6 g. of a gray solid filtered off.

· **Isolation of *p*-Arsonobenzaldehyde as the *p*-Nitrophenylhydrazone.**—In order to hydrolyze *p*-arsonobenzal diacetate, 2 g. of this gray solid was heated for thirty minutes on the steam-bath with 10 cc. of 6 *N* hydrochloric acid. Then 150 cc. of water was added, the solution filtered and treated with *p*-nitrophenylhydrazine. The flocculent golden-yellow precipitate was digested for sixty minutes on the steam-bath, filtered, washed and dried to a fine yellow powder; wt., 0.44 g.

*Anal.* Subs., 0.2006, 0.2047: 22.55, 23.00 cc of potassium bromate (1 cc. = 0.001874 g. As). Calcd. for $C_{13}H_{12}O_5N_3As$: As, 20.55. Found: As, 21.07, 21.06.

## IV. Rapid Qualitative Proof of Arsonation of Aromatic Compounds

Enough of the compound was placed in a test-tube to cover the bottom, about 3 cc. of water added, the mixture heated to boiling, cooled and filtered. To the perfectly clear aqueous solution was then added 5 cc. of concentrated hypophosphorous acid.

---

[11] Thiele and Winter, *Ann.*, 311, 353 (1900).

The tube was placed in a water-bath at 100° and observations made every two or three minutes. With every arsonic acid examined a characteristic precipitate of the corresponding arseno compound (with perhaps some arsine oxide) was obtained within twenty minutes. When a solution of arsenic trioxide in dilute hydrochloric acid was treated with hypophosphorous acid under these conditions, no precipitate was obtained. Table I summarizes the results obtained in testing a series of arsonic acids. In two cases it was found more satisfactory to dissolve the arsonic acid in hypophosphorous acid and omit the water.

TABLE I

ACTION OF HYPOPHOSPHOROUS ACID

| Arsonic acid | Solvent | Minutes for reduction | Color of precipitate |
|---|---|---|---|
| 1 *p*-Hydroxyphenylarsonic acid | $H_2O$ | 4 | Red |
| 2 Phenylarsonic acid | $H_2O$ | 1 | White |
| 3 Mono-sodium salt of *p*-arsonophenoxyethanol | $H_2O$ | 1 | Pale yellow |
| 4 *p*-Arsanilic acid | (a) $H_2O$ | 19 | Red |
| | (b) $H_3PO_2$ | 13 | Solid red mass |
| 5 Tryparsamide | $H_3PO_2$ | 2 | Red |
| 6 3-Nitro-4-aminophenylarsonic acid | $H_2O$ | 2 | Golden-yellow |

## Summary

1. A rapid qualitative test of arsonation for aromatic compounds has been suggested.

2. A new type of arsonic acid, the arsonated aromatic aldehyde, has been developed.

3. The preparation of three arsonated aromatic aldehydes, 3-nitro-4-arsonobenzaldehyde, *m*-arsonobenzaldehyde and *p*-arsonobenzaldehyde has been described. *p*-Arsonobenzaldehyde was prepared by a new and independent synthetic method.

EVANSTON, ILLINOIS

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# THE REACTION BETWEEN HIGHLY PHENYLATED COMPOUNDS AND ORGANIC MAGNESIUM COMPOUNDS

BY E. P. KOHLER AND E. M. NYGAARD

RECEIVED AUGUST 7, 1930 PUBLISHED OCTOBER 6, 1930

A study of the reaction between $\alpha,\beta$-unsaturated ketones and organic magnesium compounds, made many years ago, included every member except the last of a series beginning with acrolein and ending with its most highly phenylated substitution product, tetraphenyl propenone. In view of the increasing interest in highly phenylated compounds and especially of our own results with highly phenylated unsaturated nitro compounds, it was desirable to complete the study of this series.

We have, therefore, investigated the behavior of the completely phenylated unsaturated ketone I both toward methyl magnesium iodide and