

THE SYNTHESIS AND PROPERTIES OF FLUORINATED
ORGANIC ARSENICALS

By

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the degree of Doctor of Philosophy

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TABLE OF CONTENTS

	Page
INTRODUCTION	1
THE MODIFIED BART ARSENIATION	
Literature Survey	4
Experimental	11
FLUORINATED ARSENICALS	
Literature Survey	29
Flow Sheet	33
Experimental	34
ANALYTICAL	48
SUMMARY	52
LITERATURE CITED	53

LIST OF TABLES

	Page
I Diazonium Borofluorides	27
II Arsonic Acids Obtained From Diazonium Borofluorides	28
III Fluorophenyldiazonium Borofluorides	47
IV Fluorinated Aromatic Arsonic Acids	47

INTRODUCTION

Since the memorable work of Ehrlich which led to the introduction of arsphenamine into medicine, extensive work has been carried out in the field of organic arsenicals and is being continued at the present time. The possibilities are still far from exhausted, for as yet the "ideal" trypanocide has not been discovered.

Among the many directions which these investigations have taken is a study of the halogenated arsenicals, particularly the chlorine, bromine and iodine compounds. Many have been found to have trypanocidal action but none have been used medicinally because of high toxicity or undesirable side reactions.

A survey of the available literature has revealed that no work has been published on the organic arsenicals containing the lightest of the halogens, fluorine, in the aromatic nucleus. This is possibly due to the fact that only in the last few years has it been possible satisfactorily to introduce fluorine into the organic molecule.

The apparent lack of studies on the pharmacological properties of organic fluorine compounds plus the findings of Midgely and Henne (1-3) with regard to the low toxicity of fluoroform and dichlorodifluoromethane has stimulated an interest in the therapeutic possibilities of other fluorine derivatives.

From purely theoretical considerations, based on the periodic table, it should prove interesting to investigate the effect of fluorine substitution into a physiologically active molecule. If a comparison is made of a series of analogues containing the first, second, third, and fourth elements of groups IV, V and VI of the periodic table the general impression develops that the compound containing the first element of each group is appreciably less toxic than its analogues. For example, the organic silicon compounds have no desirable physiological effect; the phosphines, arsines, and stibines are much more toxic than the corresponding amines; the thio compounds are also generally more toxic than the corresponding oxygen analogues as may be seen by comparing the alcohols with the mercaptans, and the thioether, $(\text{ClCH}_2\text{CH}_2)_2\text{S}$, of notorious "mustard gas" fame with the relatively innocuous ether, $(\text{ClCH}_2\text{CH}_2)_2\text{O}$. If such a generalization is valid also for group VII, then the fluorine compounds certainly merit investigation. At the present time it is still impossible to say whether fluorine compounds do possess any therapeutic value over the corresponding chlorine, bromine and iodine derivatives. Certainly the low toxicity of CHF_3 and CCl_2F_2 , mentioned above, does add plausibility to such a hypothesis.

Other desirable physiological properties of organic fluorine compounds are indicated by work carried out in these laboratories by Zenitz (4), who in a preliminary report on p-fluoropropadrine found a pressor activity comparable to

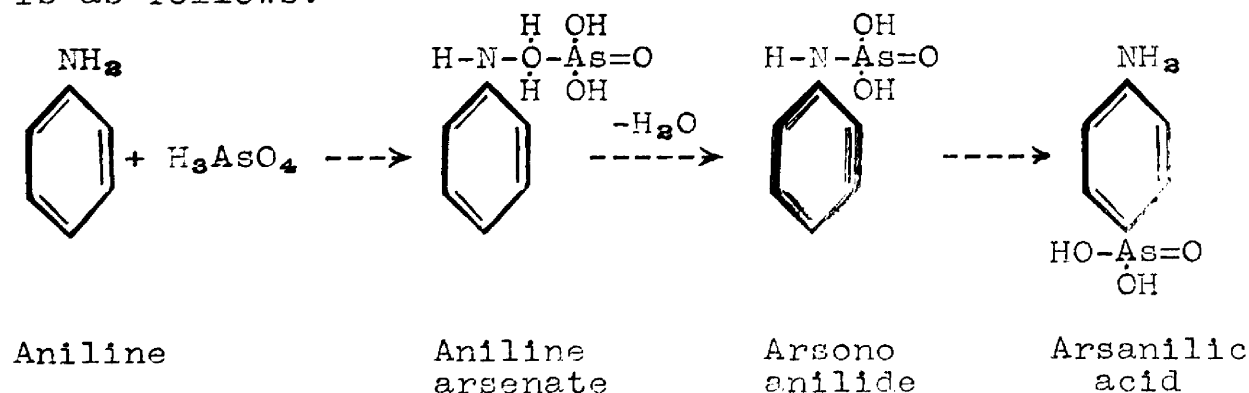
propadrine without any indication of tachyphalaxis, and by Dunker (5), who found that p-fluorophenylmercurichloride is a more effective germicide in serum than the corresponding chlorine derivative. Furthermore, Kraft (6) in his studies of fluorotyrosine made the interesting speculation that the "antithyroidal protective" postulated in the blood may be a fluorine-containing substance quite similar to fluorotyrosine.

These observations prompted an investigation into the properties of the hitherto unknown fluorinated organic arsenicals. In the preparation of such compounds the unusual stability of the diazonium borofluorides, used for the introduction of fluorine, suggested their use in the Bart reaction for introducing arsenic into the molecule. Accordingly a study was made of the use of the diazonium borofluorides in the Bart reaction preliminary to the synthesis of the fluorinated phenylarsonic acids.

THE MODIFIED BART ARSEINATION

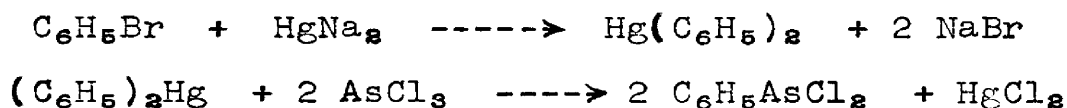
Literature Survey

The distinction of preparing the first aromatic compound of arsenic belongs to Béchamp (7) who in 1860 noted that aniline arsenate when heated with an excess of aniline did not yield colored products until a temperature of 190-200° C. had been reached. Three years later he described a colorless product which he had obtained by heating aniline arsenate under the above conditions (8). He regarded this new substance as an acidic anilide of the formula $C_{12}H_8O_6AsN$. It remained for Ehrlich and Bertheim (9) in 1907 to prove that the compound actually obtained was p-aminophenylarsonic acid (arsanilic acid). The reaction generally known as the Béchamp Reaction consists of heating arsenic acid with an excess of aniline. The conditions of the reaction as well as the methods of isolating the resulting arsanilic acid have been varied a great deal. After much speculation and study by various workers the reaction mechanism generally accepted is as follows:

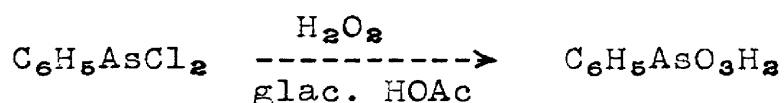


The yields of arsanilic acid by this method are upward to 30% of the theoretical. The reaction has also been applied to various substituted anilines and to phenol with varied degrees of success.

In 1875 Michaelis (10) began his investigation of aromatic arsenicals, discovering two general methods for introducing arsenic into the benzene ring. He showed that mercury diaryl derivatives, which were readily obtained by the interaction of sodium amalgam and the bromo derivatives of aromatic hydrocarbons, would react readily with arsenic trichloride to form aromatic chloroarsines.

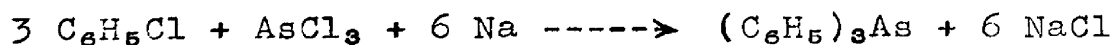


The primary dichloroarsines were readily converted into the corresponding arsonic acid by oxidation with hydrogen peroxide in glacial acetic acid.



This method, however, is limited to the preparation of dihalogenated arsines with hydrocarbon or phenol-ether residues.

In 1902 Michaelis and Reese (11) described a second general method which was found to be more convenient and more advantageous than the mercury diaryl method. Tertiary aromatic arsines were prepared by condensing halogenated hydrocarbons with arsenic trichloride in the presence of sodium.



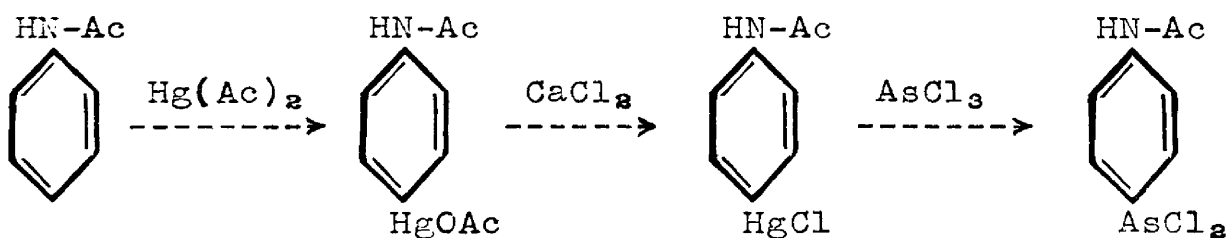
The tertiary arsines were then used in preparing primary

derivatives by heating with arsenic trichloride under pressure at 250° C. The main product was the primary dichloroarsine, while some secondary arsine was formed as a byproduct.



This method is also limited to the preparation of those arsenicals having hydrocarbon or phenol-ether residues.

In a modification of the mercury diaryl synthesis Roeder and Blasi (12) in 1914 employed the arylmercurichlorides. These aromatic mercurichlorides were readily obtained by treating benzene, its homologues and derivatives with mercuric acetate in acetic acid solution. The resulting aromatic mercuriacetates were then converted by double decomposition with calcium chloride or other suitable metallic chlorides into aryl mercurichlorides. These mercurichloride compounds were then reacted with arsenic trichloride at 100° C., and the corresponding aryldichloroarsines were formed.

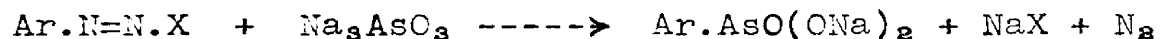


Carboxyl, hydroxyl, and amino groups, if present in the nucleus, must first be protected by alkylation or acylation to prevent interaction with arsenious chloride. The disadvantage of this method lies in the fact that in most direct mercurations there is always some dimercurated derivative formed which is difficult to remove.

Despite the fact that Rosemund (13) in 1921 succeeded

in obtaining a slight amount of phenylarsonic acid by heating bromobenzene with aqueous tripotassium arsenite and a little coppersulfate in a sealed tube at 180-200° C. for six hours, it can be safely stated that no method has yet been devised by which aromatic hydrocarbons may be directly arsenated.

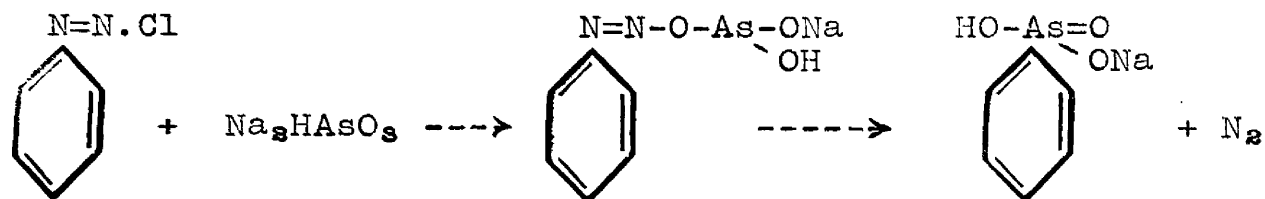
A valuable general method for synthesizing aromatic arsonic acids was developed by Bart (14), who in 1910 found that the arsenic group could be introduced into the benzene ring through use of the diazo reaction. The method consists in diazotizing aromatic amines and treating the resulting diazo or isodiazo compounds with sodium arsenite in either alkaline or neutral solution, the reaction proceeding according to the equation:



In the preparation of phenylarsonic acid by this method the yields obtained with the normal diazobenzene compound are less than with the potassium isodiazo oxide. If, however, the starting materials are nuclear substituted arylamines, the reactivity of the corresponding normal diazo compounds is increased to such an extent that conversion into the arsonic acid proceeds very readily without the necessity of first preparing the isodiazo compound.

Bart explained the mechanism of the reaction on the basis that an intermediate diazonium arsenite was formed, then the -N=N- linkage split off, and the arsonic acid group entered the ring in the position previously occupied by the

amino group:



Later that same year Bart (15) noted that the reaction with normal diazo compounds could be facilitated by the use of catalysts such as metallic copper, cuprous hydroxide or other copper salts in the absence of free alkali. In 1912 (16) he further improved his original method by employing as catalysts metallic copper, silver, nickel, cobalt or their salts in alkaline solution, thereby facilitating the removal of the diazo nitrogen at low temperatures, and at the same time obviating the formation of byproducts.

In 1919 Mouneyrat (17) modified Bart's method of synthesizing arsonic acids by causing normal diazo compounds to react with cold or warm, aqueous or dilute alcoholic solutions of arsenious acid in an acid, alkaline or neutral medium, and in the presence of special catalysts depending upon the particular medium selected. The following year H. Schmidt (18) claimed that Bart's reaction proceeded most smoothly on treating normal diazo compounds with potassium arsenite in neutral or slightly acid medium without the aid of a catalyst.

Since the time of Bart's first work his method has been used by numerous investigators in preparing arsenicals and each has made his own minor modifications of conditions for

the reaction.

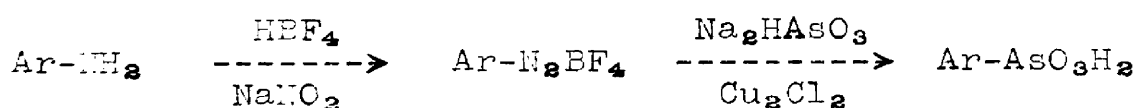
Note: While the present investigation was in progress Doak (19) published a report, "A Modified Bart Reaction", in which he developed the alcoholic Bart reaction described by Scheller (20). The aromatic amine in absolute alcohol was diazotized with sodium nitrite and then cuprous bromide added. The mixture was thoroughly stirred, warmed to 60° until no more nitrogen was evolved and then distilled with steam. This method was said to produce satisfactory yields of p-sulf-amido-, m-sulfamido-, m-nitro-, 3-nitro-4-methyl-, and m-carboxyphenylarsonic acids.

Although in many instances the yields are satisfactory when the original Bart reaction is employed, the procedure does have certain disadvantages, mostly because of the instability of the diazonium intermediate. The diazotization must be carried out at temperatures of 0° C. or lower; the diazonium chloride must be prepared just prior to its use in the arsonation; the temperature of the solution must not be allowed to rise while it is being added to the sodium arsenite solution; and it is also necessary to lower the temperature of the arsenite solution before addition of the diazonium solution. If these precautions are not observed appreciable amounts of tarry products are formed and the yields are correspondingly decreased.

Previous work in these laboratories by Dunker, Starkey, and Jenkins (21, 22) has demonstrated that the diazonium borofluoride intermediates are superior to the diazonium chlorides for the preparation of aromatic mercury compounds and for the introduction of a nitro group into an aromatic nucleus. It may now be stated that the diazonium borofluorides can also be used to advantage in the Bart reaction.

They are easily prepared and can be isolated and purified before being used in the arsonation. The diazotiazion in fluoboric acid can be carried out in an ordinary ice bath without giving particular attention to the temperature and the resulting diazonium borofluoride then filtered out in yields up to practically quantitative, washed free from impurities and dried with alcohol and ether. When thoroughly dried and placed in an evacuated desiccator they may be kept satisfactorily for long periods of time, the stability varying with the individual compound. Large quantities of these intermediates can thus be prepared and used later at one's convenience. Because of their greater stability the diazonium borofluorides in solution have less tendency to decompose before reacting with the sodium arsenite, and as a result the amount of tars formed is decreased even when the arsonation is carried out at room temperature.

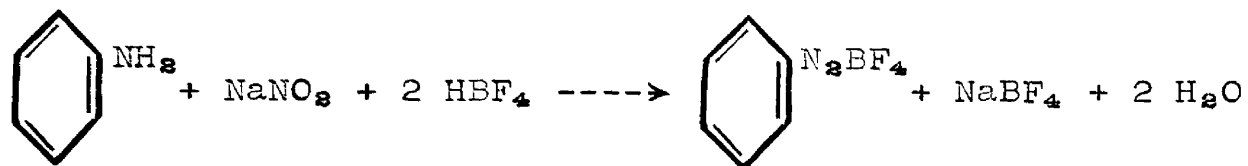
The reactions may be indicated as follows:



These reactions have been applied to aniline and to various substituted anilines to demonstrate the influence of the nature of substituents such as nitro, chloro, methyl, aceto, ethoxy, carboxy and carbethoxy as well as the effect of the position of these substituents in the original aniline molecule on the replacement of the amine by the arsonic acid group. Reference to the preparation of the individual compounds will be mentioned specifically later.

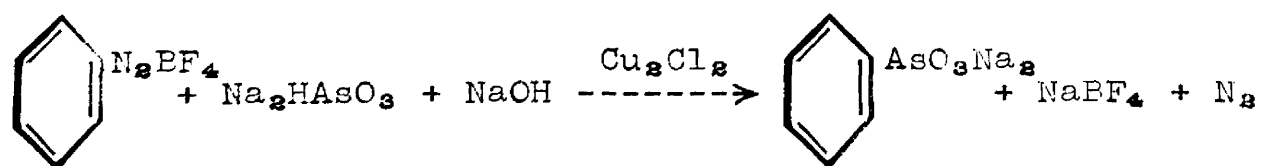
Experimental

I Preparation of Phenyl diazonium Borofluoride



The method is that given by Balz and Schiemann (23) as modified by Starkey (24). To 120 cc. (0.7 mol) of 50% fluoroboric acid in a 600 cc. beaker was added 23.3 g. (0.25 mol) of aniline while stirring. Most of the amine dissolved and crystallized upon cooling the solution in an ice bath. While stirring vigorously, a solution of 18 g. (0.25 mol) of sodium nitrite in 35 cc. of water was added slowly from a separatory funnel, keeping the temperature of the mixture below 10° C. When the addition was complete, the solid was filtered on a sintered glass funnel, washed twice with cold alcohol and then twice with ether and partially dried by drawing air through it. The resulting white crystalline solid was dried over night in an evacuated desiccator. The yield was 47.3 g. representing 98% of the theoretical.

II Preparation of Phenylarsonic Acid



The phenyldiazonium borofluoride prepared above, representing the yield from 1/4 mol of aniline, was suspended in 300 cc. of cold water and added slowly to a solution containing 52 g. (0.4 mol) of NaAsO_2 , 160 cc. of 10% sodium hydroxide solution (0.4 mol) and 10 g. of cuprous chloride in 600 cc. of water at room temperature. The diazonium borofluoride was added with vigorous stirring over the period of an hour, ether being used to control excessive foaming produced by the evolution of nitrogen. As the reaction progressed, 100 cc. of 10% sodium hydroxide solution (0.25 mol) was added to maintain the proper alkalinity. The reaction mixture was stirred for an additional half hour and allowed to stand over night. It was then heated to 65°C . for a half hour and the by-products and copper salts filtered out with suction. The filtrate was acidified to litmus paper with concentrated hydrochloric acid and any tarry material separating was filtered off. The filtrate was then concentrated with charcoal to about 200 cc, filtered and the hot filtrate acidified to congo-red paper with concentrated hydrochloric acid. The solution was chilled over night and the precipitated phenylarsonic acid filtered off. A second crop of crystals was obtained by further concentrating the mother liquor. The combined crops were then recrystallized and boneblackened from water. The weight of white crystals was 29.3 g. representing 58% of the theoretical yield. Bart (25) reported a yield of 55% by his original method.

The phenylarsonic acid melted at 156.5°C . and upon

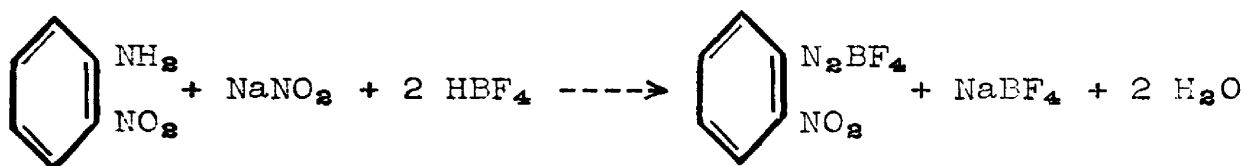
continued heating lost one molecule of water yielding the corresponding anhydride, $C_6H_5AsO_3$. The following melting points are reported in the literature: 156° , (18); 158° , (26); $158-162^\circ$, (27).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_7AsO_3$: As, 37.08%

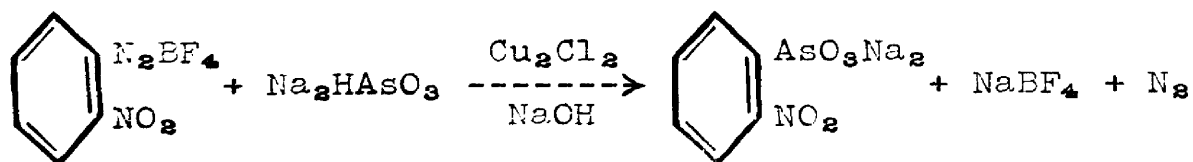
Found: As, 37.05, 37.02%

III Preparation of o-Nitrophenyldiazonium Borofluoride



The diazotization of 34.5 g. (0.25 mol) of o-nitroaniline (Eastman technical) by the method described in I, gave 58.4 g. of yellow crystals representing 98% of the theoretical yield.

IV Preparation of o-Nitrophenylarsonic Acid



The o-nitrophenylarsonic acid was prepared by the method described in II using 29.2 g. of o-nitrophenyldiazonium borofluoride (representing the yield from 1/8 mol of the amine). When recrystallized from water the nitro acid separated as pale yellow plates which contained one molecule

of water of crystallization. The yield was 20.6 g. representing 67% of the theoretical. Bart (25) reported a yield of 93% of the crude arsonic acid.

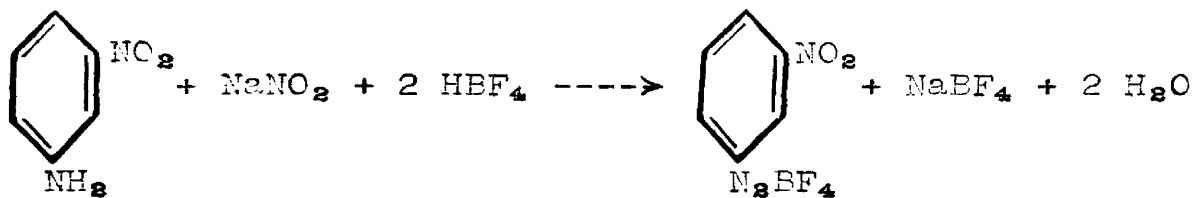
The acid melted with decomposition at 232-34° C. The following melting points are reported in the literature: 232°, (18); 233°, (25); 235-40°, (28).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_6AsNO_5 \cdot H_2O$: As, 28.26%

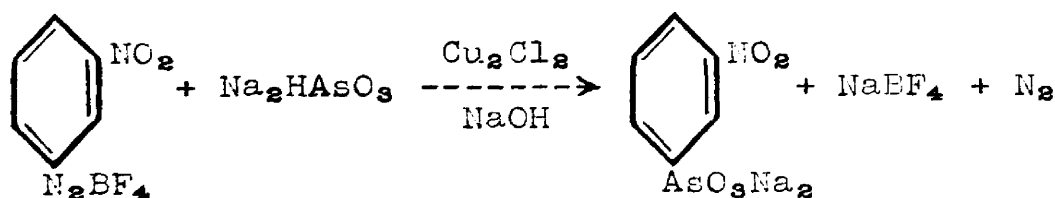
Found: As, 28.18, 28.21%

V Preparation of m-Nitrophenyldiazonium Borofluoride



When 34.5 g. (0.25 mol) of m-nitraniline was diazotized according to the method described in I a practically quantitative yield of pale tan crystals was obtained weighing 59 g.

VI Preparation of m-Nitrophenylarsonic Acid



m-Nitrophenylarsonic acid was prepared according to the method described in II using 1/4 mol of the diazonium borofluoride. The crude acid was recrystallized from water and yielded 29 g. of light yellow crystals representing 47% of

the theoretical. Bart (25) reported a yield of 28% by his method. Doak (19) obtained a 54% yield by his modification of the method of Scheller.

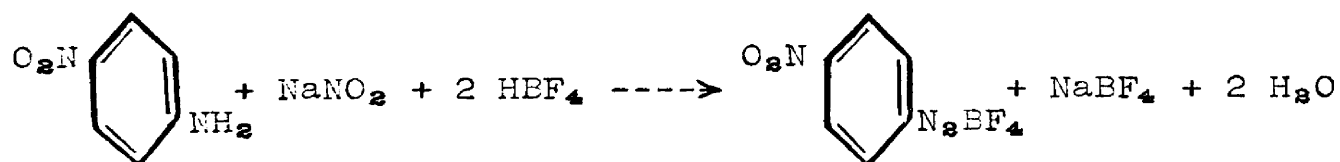
The acid melted at 182° and then gradually resolidified without further change up to 250° C. Bart reported that it loses water at 180° and carbonizes above 230° without previous melting. If, however, the tube containing the acid was introduced into sulfuric acid heated to 200°, it melted at once and quickly resolidified to the anhydride. Other melting points reported are: 196-200°, (29); 200°, (18).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_5AsNO_5$: As, 30.33%

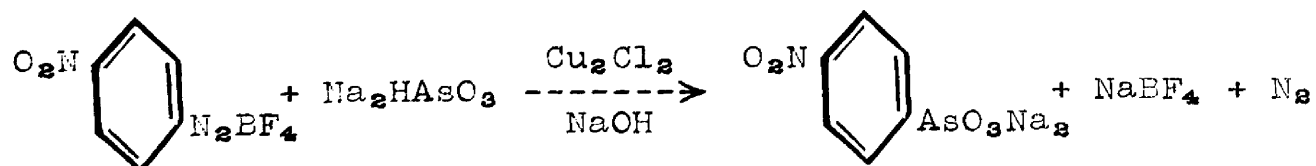
Found: As, 30.29, 30.37%

VII Preparation of p-Nitrophenyldiazonium Borofluoride



The diazotization of 34.5 g. (0.25 mol) of p-nitraniline (Eastman technical) according to the method described in I gave a practically quantitative yield of pale yellow solid.

VIII Preparation of p-Nitrophenylarsonic Acid



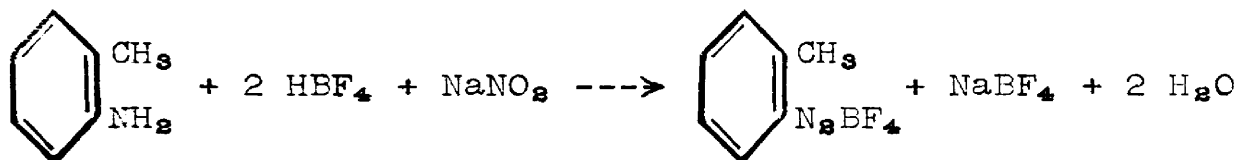
The p-nitrophenylarsonic acid was prepared by the same method as described in II using 1/8 mol of the diazonium borofluoride. When recrystallized from water 24.3 g. of pale yellow, minute leaflets were obtained representing 79% of the theoretical. Bart (25) obtained a 45% yield. The purified acid decomposed at about 300° C.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_6AsNO_5$: As, 30.33%

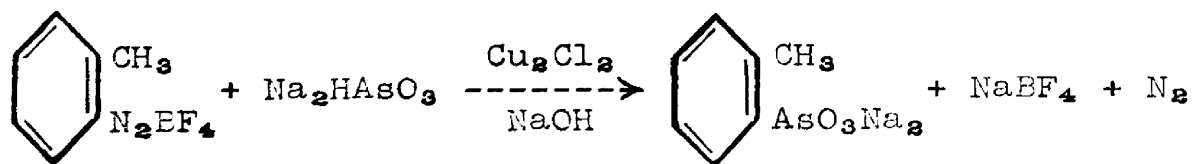
Found: As, 30.28, 30.32%

IX Preparation of o-Tolyldiazonium Borofluoride



When 26.8 g. (0.25 mol) of o-toluidine was diazotized by the method described in I a practically quantitative yield of pale pink solid was obtained.

X Preparation of o-Tolylarsonic Acid



When 25.7 g. (0.125 mol) of the above o-tolyldiazonium borofluoride was used as described in II the crude o-tolylarsonic acid was obtained as pale cream colored crystals. It was recrystallized from water and yielded 17 g. of color-

less needles representing 63% of the theoretical. Bart (25) reported a 50% yield.

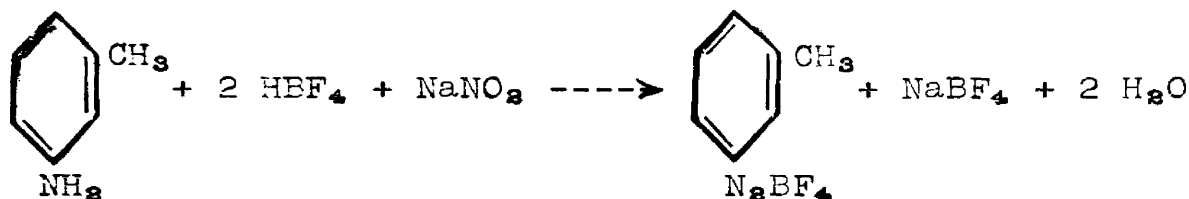
The purified acid melted at 159-60° C. without decomposition. The same melting point was reported by Falmer and Adams (30), and by La Coste and Michaelis (26).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_7H_9AsO_3$: As, 34.67%

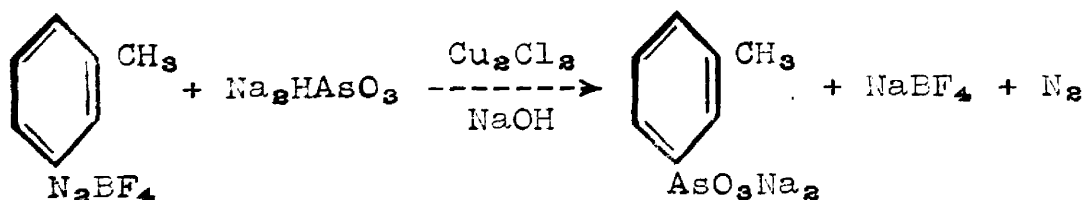
Found: As, 34.70, 34.72%

XI Preparation of m-Tolyldiazonium Borofluoride



The diazotization of 26.8 g. (0.25 mol) of m-toluidine in the manner described in I gave 50 g. of pale pink crystals representing a yield of 97%.

XII Preparation of m-Tolylarsonic Acid



The m-tolylarsonic acid was prepared according to the method described in II using 25 g. of the above diazonium borofluoride (representing the yield from 1/8 mol of the amine). When recrystallized from water the acid was obtained as small, colorless needles weighing 14.6 g. which

represents 54% of the theoretical. Bart (25) reported a 46% yield by his original method.

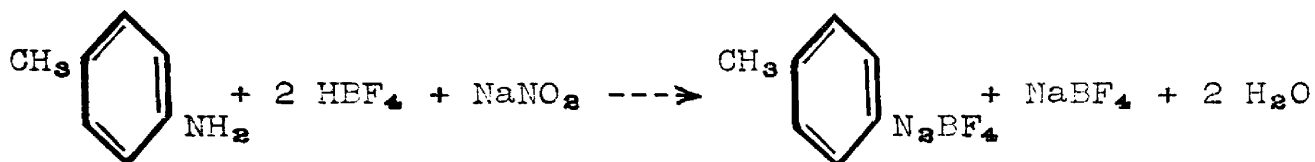
The acid melted at 150° C. without decomposition. Michaelis (31) reported a melting point of 150° and Parmalee (32) reported 149° C.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_7H_9AsO_3$: As, 34.67%

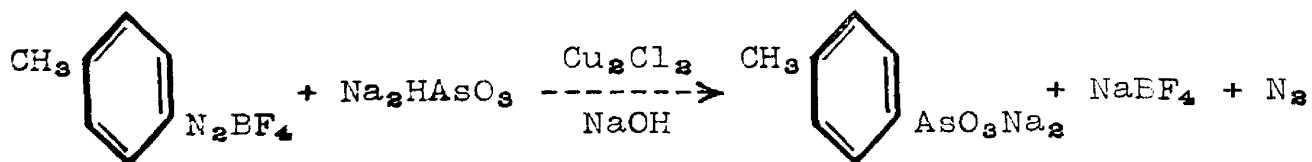
Found: As, 34.64, 34.69%

XIII Preparation of p-Tolyldiazonium Borofluoride



When 26.8 g. (0.25 mol) of p-toluidine was diazotized by the method described in I 47.4 g. of white crystals were obtained representing a yield of 92%.

XIV Preparation of p-Tolylarsonic Acid



The p-tolylarsonic acid was prepared according to the method described in II using 23.7 g. of the above diazonium borofluoride (representing the yield from 1/8 mol of the amine). When recrystallized from water 19.7 g. of small, colorless needles were obtained representing a yield of 73%.

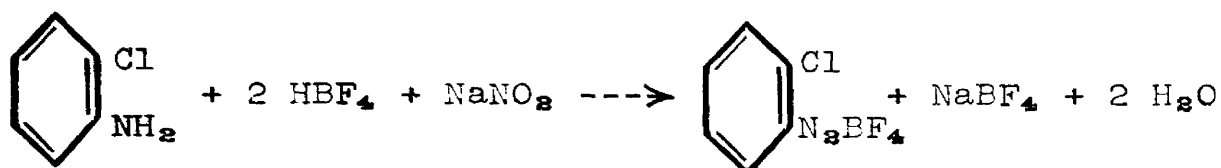
Palmer and Adams (30) reported a yield of 50-65% by the method of Bart. The acid darkened at 300° C. agreeing with the report of La Coste and Michaelis (33).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_7H_6AsO_3$: As, 34.67%

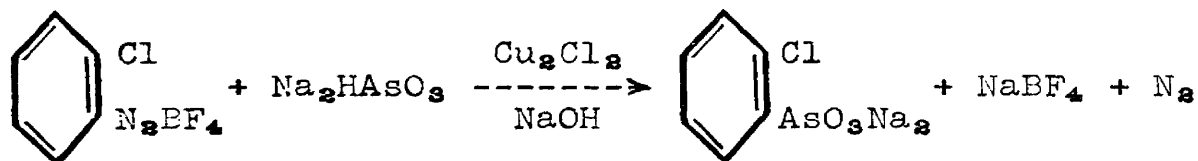
Found: As, 34.63, 34.71%

XV Preparation of o-Chlorophenyldiazonium Borofluoride



The diazotization of 31.9 g. (0.25 mol) of o-chloro-aniline by the method described in I gave 55.4 g. of a white powder representing a yield of 98%.

XVI Preparation of o-Chlorophenylarsonic Acid



When one-half of the above diazonium borofluoride (27.7 g.) was treated by the method described in II the crude o-chlorophenylarsonic acid was obtained as cream-colored needles. Decolorization with charcoal in dilute alcohol yielded 15.4 g. of white needles representing 52% of the theoretical. Palmer and Adams (30) reported a yield of 60-75%.

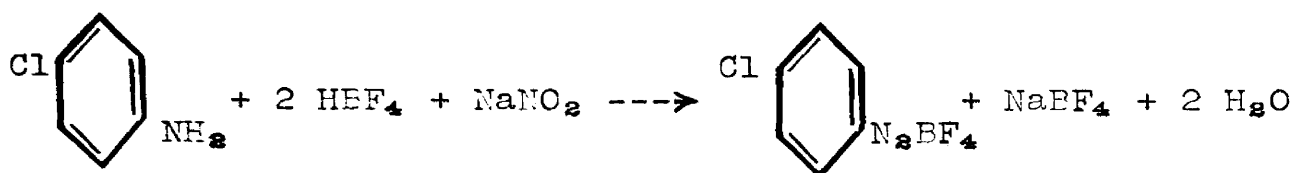
When heated rapidly the pure acid melted at 182° C. The following melting points are found in the literature: 180°, (29); 181°, (25); 182°, (34); 186-187°, (30).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for C₆H₆AsClO₃: As, 31.68%

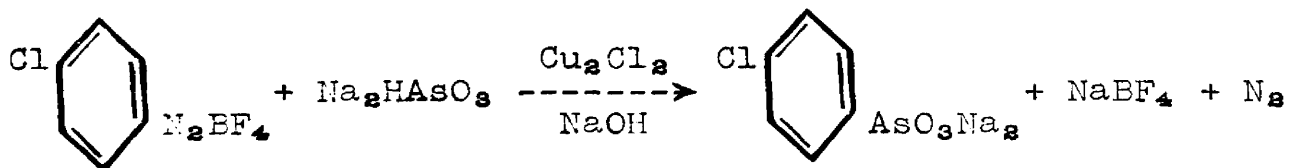
Found: As, 31.65, 31.70%

XVII Preparation of p-Chlorophenyldiazonium Borofluoride



When 31.9 g. (0.25 mol) of p-chloroaniline was diazotized by the procedure of I 54.8 g. of white crystals were obtained representing 97% of the theoretical yield.

XVIII Preparation of p-Chlorophenylarsonic Acid



One-half of the above diazonium borofluoride (the yield from 1/8 mol of amine) was treated by the procedure described in II. When recrystallized from dilute alcohol 18.6 g. of minute, colorless needles were obtained representing a yield of 63%. Palmer and Adams (30) reported a crude yield of 60-85% by the usual Bart method.

No change was observed in the acid when it was heated

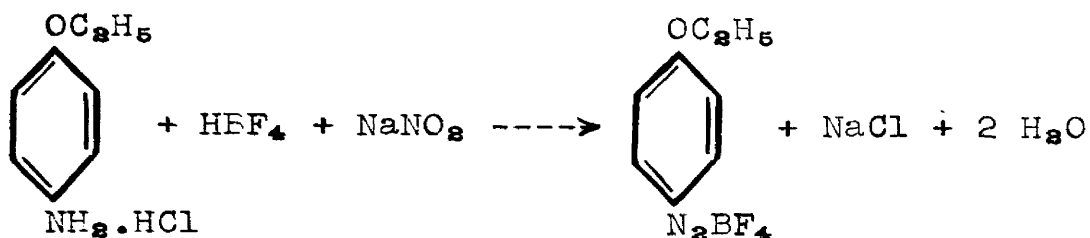
to 300° C.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_6AsClO_3$: As, 31.68%

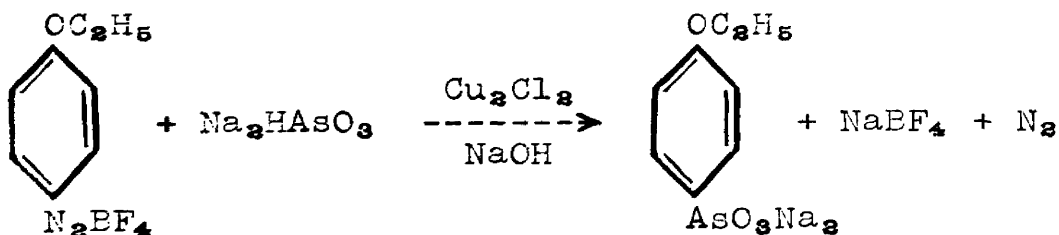
Found: As, 31.63, 31.67%

XIX Preparation of p-Ethoxyphenyldiazonium Borofluoride



One-fourth mol (43.4 g.) of p-phenetidine hydrochloride was added to a solution containing 60 cc. of fluoboric acid and 27.5 g. (0.25 mol) of sodium fluoborate in 40 cc. of water and then diazotized and purified in the manner previously described. After removing the color with difficulty 51 g. of pale purple crystals were obtained representing 87 % of the theoretical yield.

XX Preparation of p-Ethoxyphenylarsonic Acid



One-half of the above diazonium borofluoride (25.5 g.) was reacted with sodium arsenite as described in II. Recrystallization from water yielded 22.5 g. of small, white, lustrous prisms representing 73% of the theoretical. Bart (25) reported a practically quantitative yield of the acid.

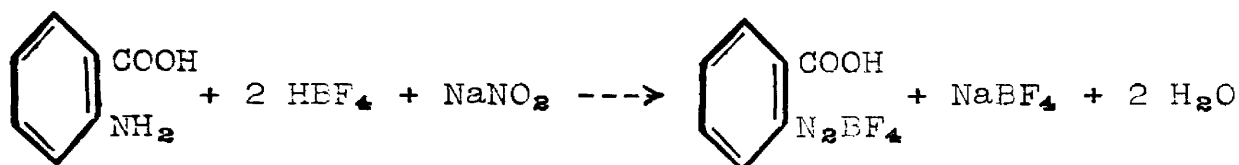
This acid melted at about 185° C. and gradually darkened as the temperature was raised further. Michaelis (35) reported a melting point of 209-10°. Bertheim (27) found that on rapid heating it melted at 185° with foaming, then resolidified and did not melt again below 245° C.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_8H_{11}AsO_4$: As, 30.44%

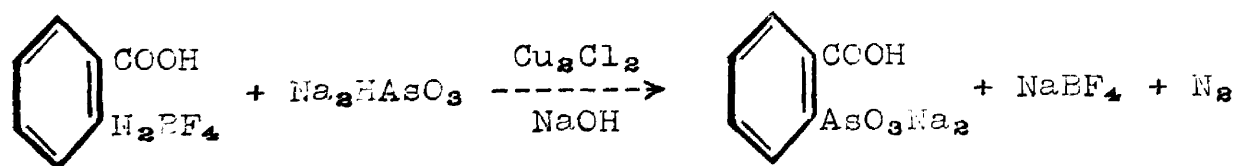
Found: As, 30.35, 30.38%

XXI Preparation of o-Carboxyphenyldiazonium Borofluoride



One-fourth mol (34.2 g.) of anthranilic acid was diazotized according to the procedure described in I. The diazonium borofluoride did not crystallize out until after all of the sodium nitrite had been added. When filtered out and dried it was obtained as white crystals. However, since it could be isolated in only a 46% yield because of its solubility the aqueous, acid suspension of the diazonium borofluoride was used for the succeeding arsonation.

XXII Preparation of o-Carboxyphenylarsonic Acid



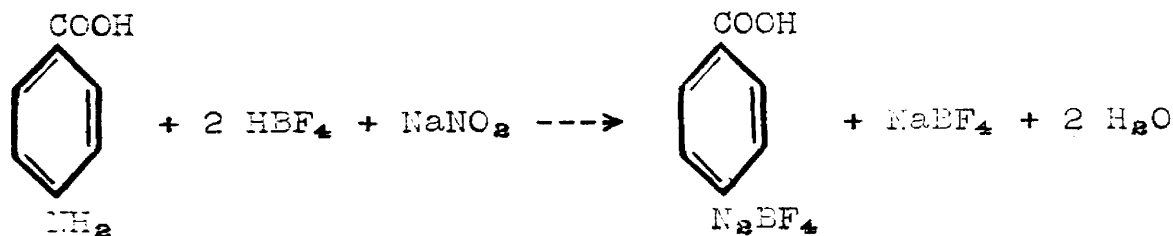
The arsonation was carried out in the usual way as described in II using the suspension of the diazonium borofluoride mentioned above. It was necessary to add more alkali in order to neutralize the excess fluoboric acid present in the suspension. When recrystallized from water 40 g. of white crystals were obtained representing 65% of the theoretical. Lewis and Cheetham (36) reported a yield of 50-60%. This acid did not melt below 300° C. which agrees with the reports of Bart (25) and of Hiratuka (29).

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_7H_7AsO_6$: As, 30.45%

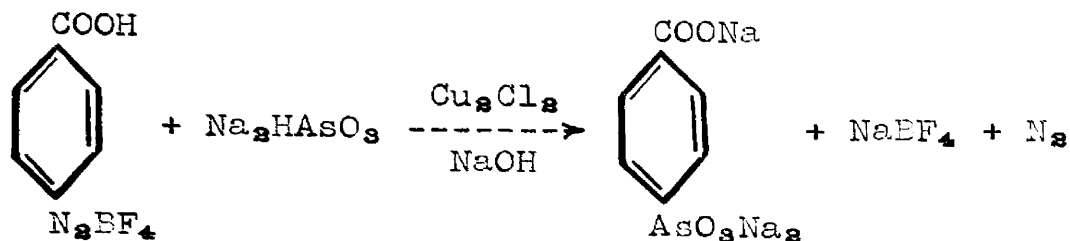
Found: As, 30.35, 30.38%

XXIII Preparation of p-Carboxyphenyldiazonium Borofluoride



When 34.3 g. (0.25 mol) of p-aminobenzoic acid was diazotized by the method described in I a yield of 49.5 g. of white crystals was obtained representing 84% of the theoretical.

XXIV Preparation of p-Carboxyphenylarsonic Acid



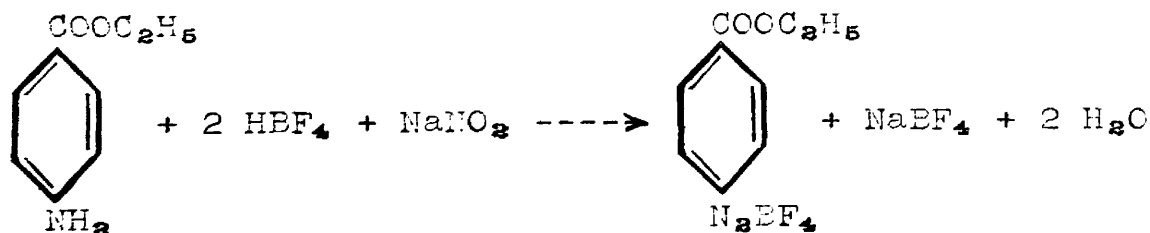
The p-carboxyphenylarsonic acid (p-benzarsonic acid) was prepared by the method described in II using all of the diazonium borofluoride obtained above. When recrystallized from water 41.2 g. of white, lustrous crystals were obtained representing a yield of 67%. Lewis and Hamilton (37) reported a 50-60% yield by the usual Bart method. This acid decomposed without melting at 232° C. which agrees with the report of Bart (25). However, Hiratuka (29) reported a melting point of 283°.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $\text{C}_7\text{H}_7\text{AsO}_5$: As, 30.45%

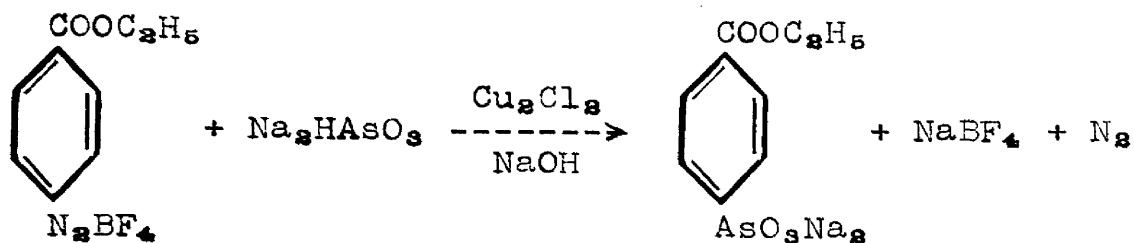
Found: As, 30.33, 30.40%

XXV Preparation of p-Carboethoxyphenyldiazonium Borofluoride



The diazotization of 41.3 g. (0.25 mol) of ethyl p-amino-benzoate by the method described in I yielded 64.8 g. of the white, crystalline diazonium borofluoride representing 98% of the theoretical.

XXVI Preparation of p-Carboethoxyphenylarsonic Acid



One-half of the above diazonium borofluoride (the yield from 1/8 mol of amine) was treated by the procedure described in II. In order to avoid possible hydrolysis of the ester the reaction mixture was concentrated at room temperature with a current of air. After recrystallization from water 20.5 g. of small, lustrous crystals were obtained representing 60% of the theoretical yield. Although this compound has been previously prepared by esterification of p-benzarsonic acid no record has been found of its preparation directly from ethyl p-aminobenzoate.

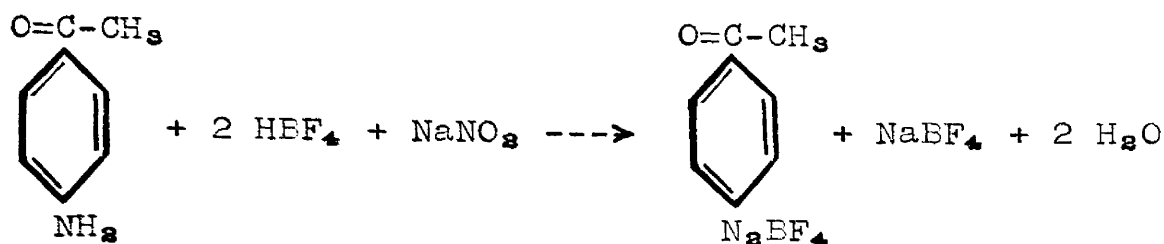
The acid melted at about 260° C. forming an infusible powder as reported by Fourneau and Cechslin (38). The analysis indicates there may have been a slight hydrolysis of the ester during the concentration process.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $\text{C}_9\text{H}_{11}\text{AsO}_5$: As, 27.33%

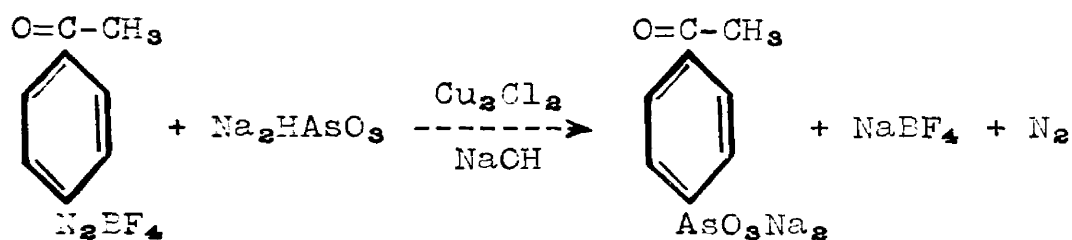
Found: As, 27.80, 27.85%

XXVII Preparation of p-Acetophenyldiazonium Borofluoride



When 33.8 g. (0.25 mol) of p-aminoacetophenone (Eastman practical) was diazotized by the method described in I a yield of 56 g. of white crystals were obtained representing 95% of the theoretical.

XXVIII Preparation of p-Acetophenylarsonic Acid



One-half of the above diazonium borofluoride was used to prepare p-acetophenylarsonic acid by the method described in II. When recrystallized and boneblackened from water 21.3 g. of cream-colored, minute needles were obtained representing 70% of the theoretical yield. Gibson and Levin (39) reported a 66% yield by the usual Bart method.

The purified acid melted at 175° C. which agrees with that found by Gibson and Levin.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $\text{C}_8\text{H}_9\text{AsO}_4$: As, 30.69%

Found: As, 30.60, 30.65%

TABLE I

DIAZONIUM BOROFLUORIDES

<u>Amine used</u>	<u>% yield</u>	<u>Amine used</u>	<u>% yield</u>
Aniline	98	o-Chloroaniline	98
o-Nitraniline	98	p-Chloroaniline	97
m-Nitraniline	99	p-Phenetidine	87
p-Nitraniline	99	o-Aminobenzoic acid	46
o-Toluidine	99	p-Aminobenzoic acid	84
m-Toluidine	97	Ethyl p-aminobenzoate	98
p-Toluidine	92	p-Aminoacetophenone	91

TABLE II

ARSONIC ACIDS OBTAINED FROM DIAZONIUM BOROFLUORIDES

<u>Arsonic acid</u>	<u>% yield obtained</u>	<u>Previously reported % yield</u>	<u>Melting point</u>	<u>Analysis As %</u>	
				<u>Calc.</u>	<u>Found</u>
Phenyl-	58	55, (25)	156.5°	37.08	37.05 37.02
o-Nitrophenyl-	67	93, (25)	232-34° dec.	28.26	28.18 28.21
m-Nitrophenyl-	47	28, (25) 54, (19)	182°	30.33	30.29 30.37
p-Nitrophenyl-	79	45, (25)	300° dec.	30.33	30.28 30.32
o-Tolyl-	63	50, (25)	159-60°	34.67	34.70 34.72
m-Tolyl-	54	46, (25)	150°	34.67	34.64 34.69
p-Tolyl-	73	50-65, (30)	300° dec.	34.67	34.63 34.71
o-Chlorophenyl-	52	60-75, (30)	182°	31.68	31.65 31.70
p-Chlorophenyl-	63	60-85, (30)	above 300°	31.68	31.63 31.67
p-Ethoxyphenyl-	73	pract. (25) quant.	185°	30.44	30.35 30.38
o-Carboxyphenyl-	65	50-60, (36)	above 300°	30.45	30.38 30.35
p-Carboxyphenyl-	67	50-60, (37)	232° dec.	30.45	30.33 30.40
p-Carbethoxy- phenyl-	60	0	260°	27.33	27.80 27.85
p-Acetophenyl-	70	66, (39)	175°	30.69	30.60 30.65

FLUORINATED ARSENICALS

Literature Survey

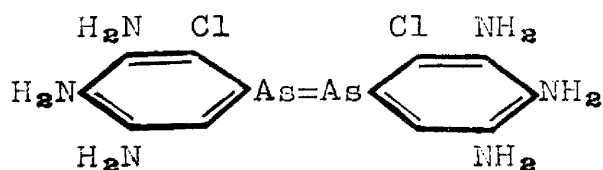
One of the earliest methods for the preparation of aromatic fluorine compounds was that proposed by Wallach (40) who heated diazopiperidides with concentrated hydrofluoric acid. The method is quite unsatisfactory because of the instability of the intermediates. In 1898 Valentiner and Schwarz (41) prepared aromatic fluorine compounds by heating a diazonium chloride solution with 70% hydrofluoric acid. Swarts (42) that same year diazotized the amine in 70% hydrofluoric acid and heated the solution of diazonium fluoride. In 1927, Balz and Schiemann (23) prepared fluorobenzene and other aromatic fluorine compounds by means of the thermal decomposition of the stable dry diazonium borofluorides. Since that time Schiemann and coworkers (43-64) have extended the reaction to the preparation of a great number of fluorine compounds.

Bockmüller (65) in a comprehensive review of the preparation of all types of organic fluorine compounds reported that direct fluorination of aromatic compounds with fluorine gas is unsatisfactory. He found that the action of fluorine on benzoic acid produced a mixture of mono- and polyfluorinated acids (66). When he treated acetanilide with lead tetrafluoride, a small amount of p-fluoroacetanilide was obtained (67). Whearty and Bancroft (68, 69) obtained a

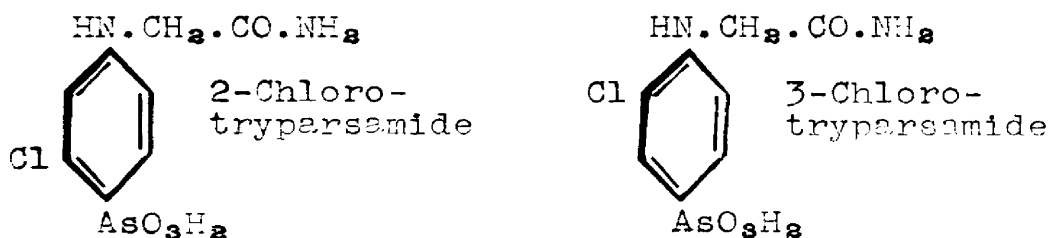
mixture of polyfluorinated chlorobenzenes by the action of fluorine gas on the chlorobenzenes. Bigelow and coworkers (70-72) have likewise found mixtures produced by direct fluorination. In 1936, Gottlieb (73) prepared 2,4-dinitrofluorobenzene from 2,4-dinitrochlorobenzene and potassium fluoride.

During the extensive work that has been done on organic arsenicals several score have been prepared containing the halogens, chlorine, bromine and iodine in their nucleus. A survey of the literature has revealed only one aromatic arsonic acid containing fluorine, however, it does not have the fluorine in the benzene ring. Steinkoph and Jaeger (73) prepared phenylarsonic acid-3-sulfonyl fluoride as one of a series of aromatic sulfonyl fluorides. No arsenicals were found in which the fluorine was substituted directly in the aromatic nucleus.

From the pharmacological results that have been reported for the halogenated arsenicals no general conclusion can be drawn as to their toxicity and therapeutic action. Ehrlich and Hata (74) reported that 3,5-dichloro-4-hydroxyphenylarsonic acid was effective against *Spirocheta recurrentis* in mice but unfortunately caused disturbances in the nervous system. A tremor of the head and neck persisting for several days was produced by a single dose. On the other hand, Giemsa (75) reported that 2,2'-dichlorohexamino-*benzene* (Dichloroarsalyt)

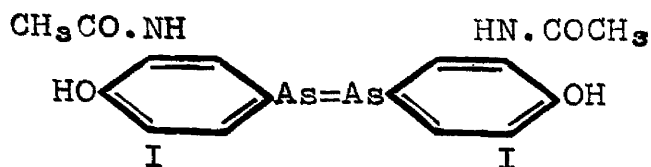


was practically as effective against rabbit syphilis as silver arsphenamine without producing any observable detrimental action on the nervous system. Karrer (76) found that the tolerated and lethal doses of 3,5-dichlorophenylarsonic acid in mice were about twice the doses for 3,5-dichloro-4-iodophenylarsonic acid and p-iodophenylarsonic acid indicating that para-substitution produces an increase in toxicity. He also found that these compounds produced icterus in the mice. Fischl and Schlossberger (77) reported that 2-chlorotryparsamide when tested against the trypanosome in mice had a higher chemotherapeutic index than "Tryparsamide" itself while the 3-chloro derivative had an index about one-half that of "Tryparsamide".



Haythornthwaite (78) produced a number of bromine derivatives of phenylarsonic acid and arsenobenzene and tested them for their toxicity and curative action against *Trypanosoma equiperdum* in mice. In no case did the compounds show an increased chemotherapeutic index over the corresponding unbrominated compounds and in most cases were much less.

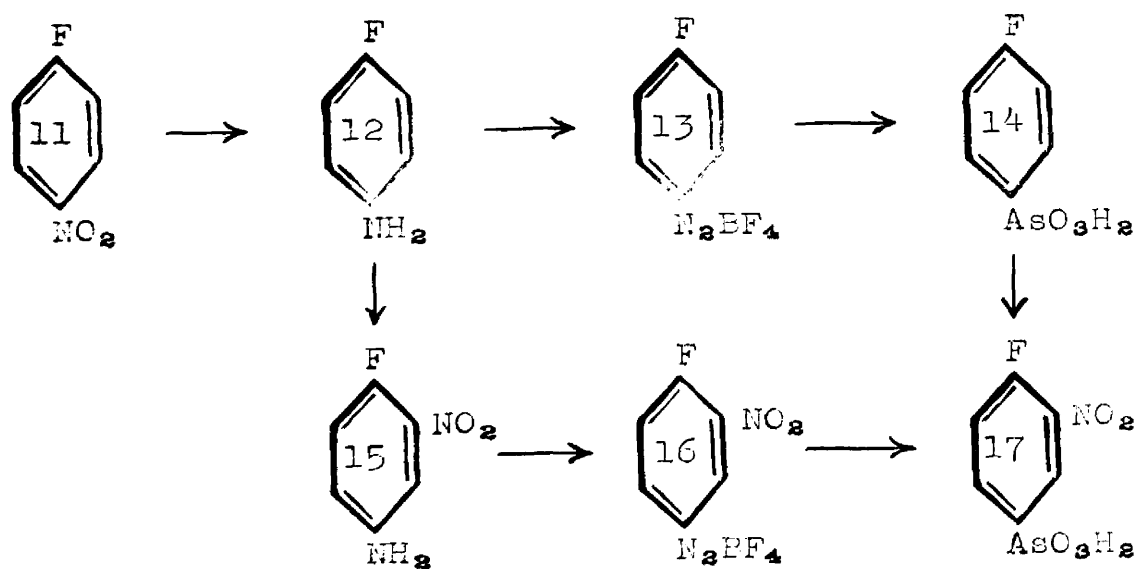
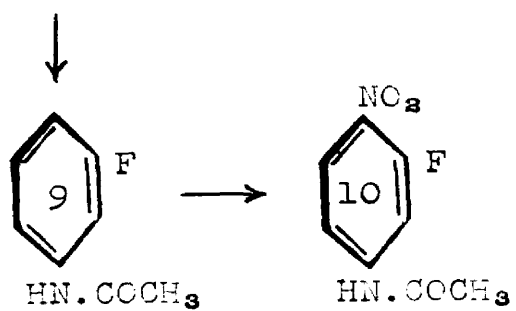
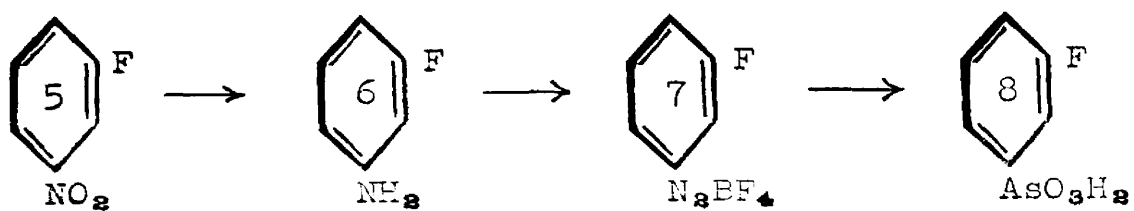
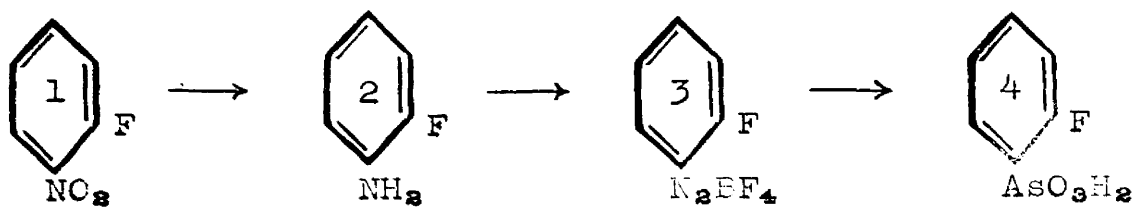
Macallum (79) prepared a number of arsenicals containing iodine and tested them against *Trypanosoma equiperdum* in mice. The most effective of these was 5,5'-diiododiacetylsalvarsan which had an index of 1:10.



In contrast to salvarsan it was remarkably stable in solution and produced no undesirable nervous effects. Karrer (80) reported that several iodophenylarsonic acids which he tested were quite toxic and produced icterus in mice.

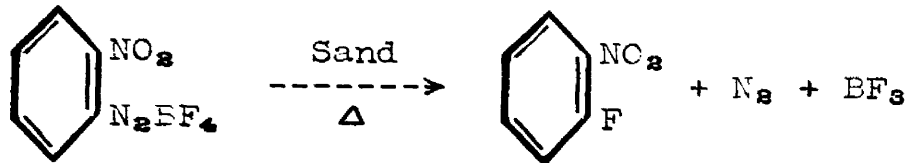
It may be readily seen that while there is no agreement on the effect of halogens in organic arsenicals, in some cases favorable results have been obtained. As has been previously mentioned (pp. 1-3) fluorine substituted hydrocarbons have been found to have low toxicities, and other fluorine substituted compounds have been suggested as possible therapeutic agents. If our reasoning from the periodic table, already mentioned, is correct that fluorinated compounds should be less toxic than the corresponding chlorine, bromine or iodine compounds then the fluorinated arsenicals conceivably may be found desirable. With this thought in mind a series of fluorinated phenylarsonic acids has been prepared. The fluorine was introduced by the method of Schiemann (23) and the arsenic was introduced by the modified Eart method described on page 12.

Flow sheet



Experimental

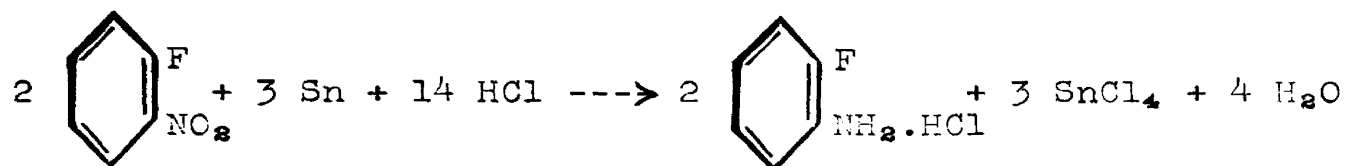
I Preparation of o-Nitrofluorobenzene



The method used was that given by Schiemann and Pillarsky (49). About 60 g. of o-nitrophenyldiazonium borofluoride (previously described pg. 13) was mixed thoroughly with about an equal quantity of sand. This mixture was placed in a 500 cc. pyrex distilling flask having the delivery tube bent so that the flask could be clamped on its side. The flask was then connected to a condenser and the compound was collected in a cooled 500 cc. filtering flask to which suction was applied by means of a water pump. A trap containing water was placed between the pump and the receiver. The flask was heated slowly, beginning near the surface of the mixture and working down as the compound was decomposed. When the decomposition was complete, the flask was heated strongly to drive over the last of the nitrofluorobenzene. After cooling, the sand was shaken out and used again in the succeeding decompositions. After each run the condenser was washed out ether and the water in the trap was extracted with ether. The combined distillates and ether extracts were treated with a saturated, aqueous solution of sodium carbonate to remove any dissolved boron trifluoride.

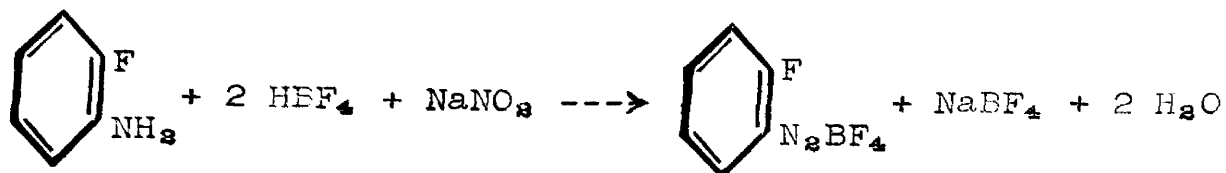
The ether was then distilled off and the remaining contents of the flask subjected to steam distillation. The distillate was saturated with sodium chloride and the o-nitrofluorobenzene removed by means of a separatory funnel. From 3 mols of diazonium borofluoride there was obtained 58 g. of a pale yellow liquid representing 13.7% of the theoretical. Schiemann and Pillarsky (49) reported a 19% yield.

II Preparation of O-Fluoroaniline



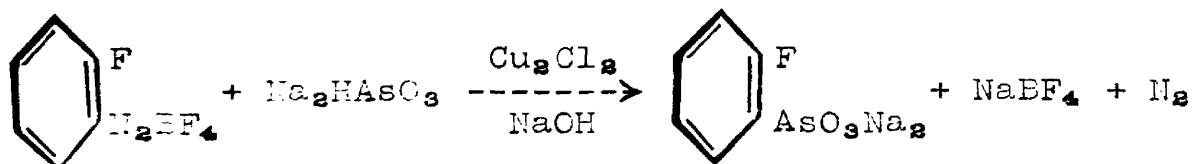
The reduction of the o-nitrofluorobenzene was carried out with tin and hydrochloric acid. To 100 g. (excess) of mossy tin and 58 g. (0.41 mol) of o-nitrofluorobenzene in a 2 l. round-bottomed flask equipped with a condenser was added with shaking and cooling when necessary, 200 cc. of concentrated hydrochloric acid. When the addition was complete the mixture was refluxed for 30 minutes and cooled. The mixture was diluted with 300 cc. of water and then made slightly alkaline with a 50% sodium hydroxide solution. The mixture was then steam distilled and the amine separated. The aqueous portion was saturated with sodium chloride, extracted with ether, the ether layer separated, dried and the ether distilled off on a water bath. The combined o-fluoroaniline weighed 29.6 g. representing 65% of the theoretical.

III Preparation of o-Fluorophenyldiazonium Borofluoride



To 27.7 g. (0.25 mol) of o-fluoroaniline in 160 cc. of fluoboric acid in an ice bath was added with stirring 18 g. (0.26 mol) of sodium nitrite dissolved in 35 cc. of water. The precipitate was filtered out with suction, washed with alcohol and ether and thoroughly dried in an evacuated desiccator over phosphorous pentoxide. A yield of 38.6 g. of pale pink crystals were obtained representing 75% of the theoretical. If allowed to stand, this compound gradually darkens in color.

IV Preparation of o-Fluorophenylarsonic Acid



o-Fluorophenylarsonic acid was prepared by the following procedure. An aqueous suspension of 19.2 g. of o-fluorophenyldiazonium borofluoride (the yield from 1/8 mol of amine) was added slowly to a solution containing 26 g. (0.2 mol) of NaAsO_2 , 80 cc. of 10% sodium hydroxide solution and 3 g. of cuprous chloride in 400 cc. of water at room temperature. The diazonium borofluoride was added with

vigorous stirring over a period of an hour. Ether was used to control excessive foaming as nitrogen was evolved. As the reaction progressed 50 cc. (0.125 mol) of 10% sodium hydroxide solution was added to maintain the proper alkalinity. The reaction mixture was stirred for an additional half hour, then heated to 65° C. for 15 minutes and filtered with suction. The filtrate was acidified to litmus paper with concentrated hydrochloric acid and any tarry material separating was filtered off. The filtrate was then concentrated on a hot plate with charcoal to about 250 cc. and filtered and the hot filtrate acidified to congo-red paper with concentrated hydrochloric acid. A small amount of dark material was filtered out and the solution further concentrated to about 100 cc. and then allowed to crystallize in the ice box over night. The crystals were filtered with suction and a second crop of crystals was obtained by concentrating the mother liquor. The combined crystals were purified by dissolving in ammonium hydroxide, filtering and reprecipitating with hydrochloric acid. There was obtained 11.5 g. of white, lustrous crystals representing 42% of the theoretical yield.

The o-fluorophenylarsonic acid melted at 152-3° C. without decomposition. It gave a positive test for fluorine by the method of Feigl and Krumholz (81) and analyzed correctly for arsenic content. It was found to be readily soluble in hot water, slightly soluble in cold water, quite soluble in hot and cold alcohol but only very slightly soluble in ether

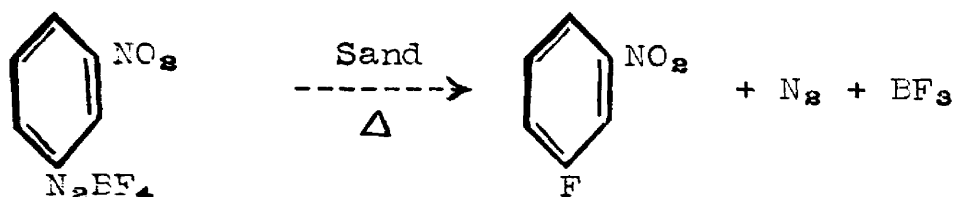
and in other organic solvents.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_5AsFO_3$: As, 34.05%

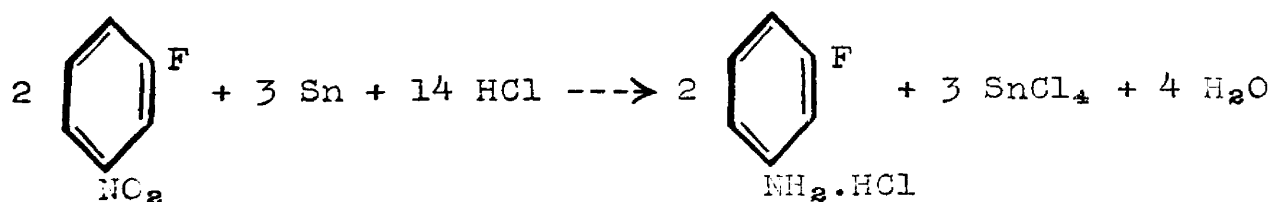
Found: As, 34.02, 33.95%

V Preparation of m-Nitrofluorobenzene



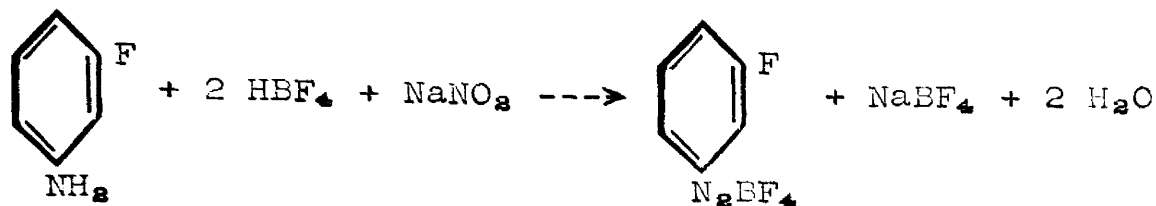
The decomposition of 2.5 moles of m-nitrophenyl-diazonium borofluoride (previously described pg. 14) by the procedure described in I yielded 183 g. of m-nitrofluorobenzene or 52% of the theoretical. Schiemann and Pillarsky (49) reported a 54% yield.

VI Preparation of m-Fluoroaniline



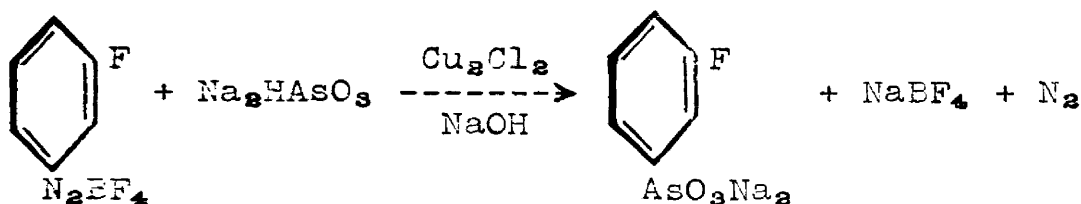
The entire amount of m-nitrofluorobenzene from above was reduced with tin and hydrochloric acid as given in II and yielded 117 g. of m-fluoroaniline representing 82% of the theoretical.

VII Preparation of m-Fluorophenyldiazonium Borofluoride



When 27.8 g. (0.25 mol) of m-fluoroaniline was diazotized by the method described in III a yield of 47.6 g. of white crystals were obtained representing 91% of the theoretical.

VIII Preparation of m-Fluorophenylarsonic Acid



When 23.8 g. of m-fluorophenyldiazonium borofluoride (the yield from 1/8 mol of amine) was used in the arsonation as described in IV there was obtained 10.3 g. of cream-colored crystals representing 37.5% of the theoretical yield.

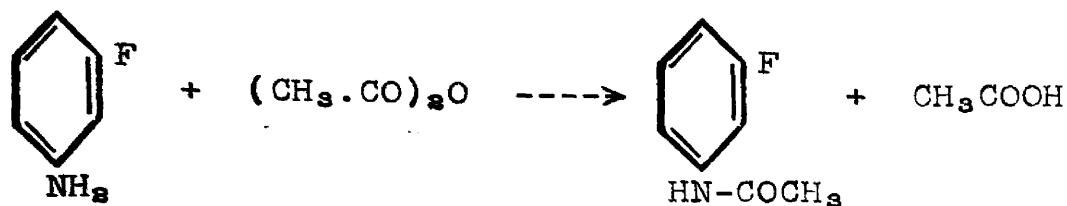
The purified acid melted and darkened at 147-48° C. It gave the qualitative test for fluorine and analyzed correctly for arsenic content. Its solubilities were found to be the same as those of its ortho isomer described in IV.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $\text{C}_6\text{H}_6\text{AsFO}_3$: As, 34.05%

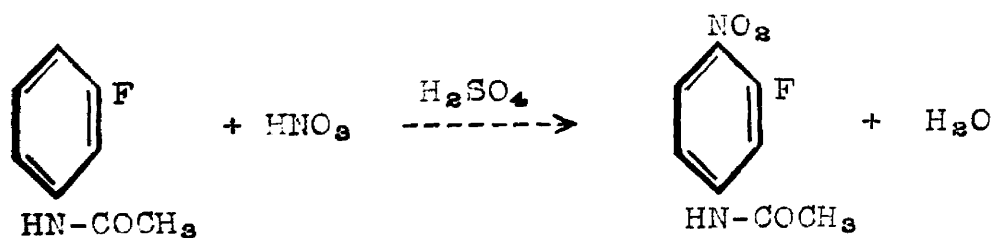
Found: As, 34.10, 34.15%

IX Preparation of m-Fluoroacetanilide



To 27.8 g. (0.25 mol) of m-fluoroaniline was added 30 g. (0.3 mol) of acetic anhydride and the mixture refluxed for one hour. The hot mixture was poured with rapid stirring into 500 cc. of cold water. The pink-colored solid was filtered out with suction and washed with water. The combined filtrates were chilled over night and yielded a small crop of white needles. The combined yield weighed 33.4 g. or 88% of the theoretical. Before recrystallization it melted at 85° C. and after recrystallization from dilute alcohol melted at 86° C. A small amount was then recrystallized from benzene and obtained as small, white needles melting at 87.5° C. Swarts (82) reported a melting point of 84.5° C., Braun and Rudolph (83) reported 88° C.

X Preparation of 4-Nitro-3-fluoroacetanilide

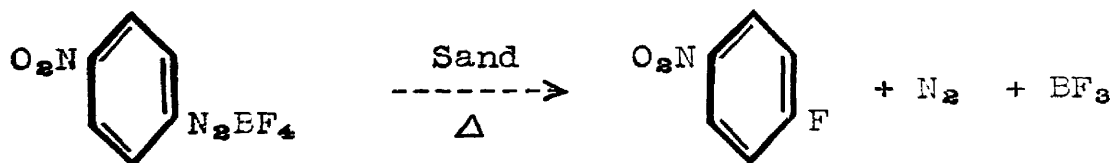


To 15.3 g. (0.1 mol) of m-fluoroacetanilide in 75 g. of concentrated sulfuric acid was slowly added 10 g. (0.11 mol) of concentrated nitric acid in 10 g. of concentrated sulfuric

acid with the temperature at 0° C. or lower. The mixture was allowed to stand in the ice box over night and then poured upon 300 g. of ice. The yellow-colored solid was filtered out with suction and thoroughly washed with cold water. The yield of compound was 18.5 g. representing 93% of the theoretical. A small amount when recrystallized from toluene yielded pale yellow crystals melting at 176.5-77° C.

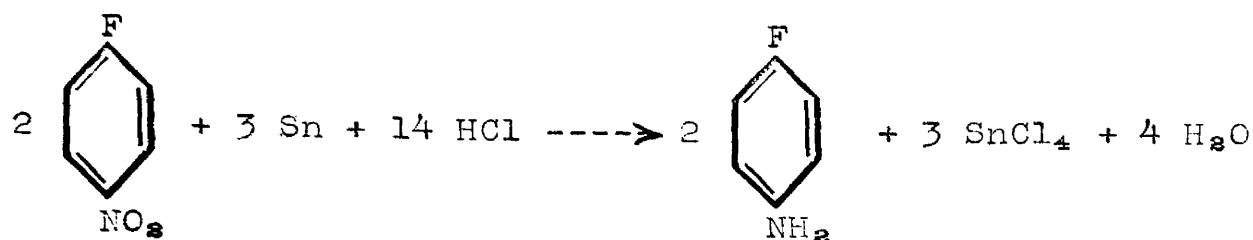
Several attempts were made to hydrolyze the compound to the free fluoronitroaniline. An aqueous hydrochloric acid solution and an alcoholic hydrochloric acid solution was used and the mixture refluxed for several hours but no satisfactory product could be isolated. Since the hydrolysis was unsuccessful the compound could not be definitely characterized and was not considered further.

XI Preparation of p-Nitrofluorobenzene



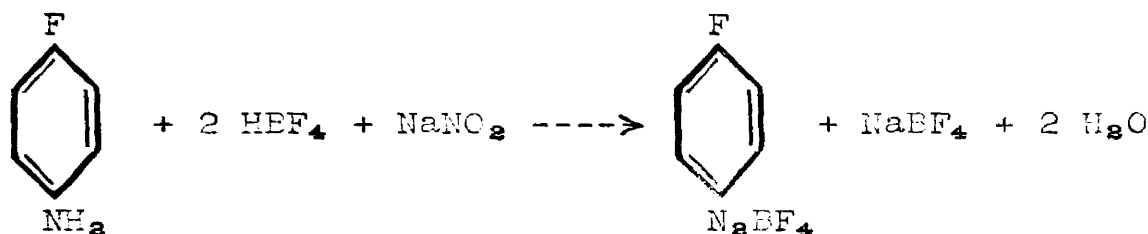
Two and one-half moles of p-nitrophenyldiazonium borofluoride (previously described on pg. 15) were decomposed by the procedure described in I and yielded 200 g. of p-nitrofluorobenzene representing 57% of the theoretical.

XII Preparation of p-Fluoroaniline



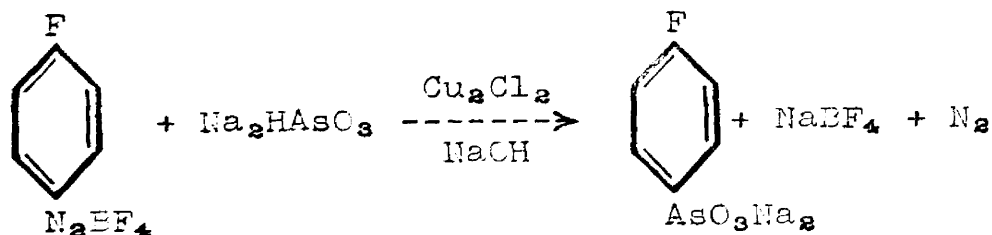
The entire amount of p-nitrofluorobenzene from above was reduced with tin and hydrochloric acid as described in II and yielded 120 g. of p-fluoroaniline representing 78% of the theoretical.

XIII Preparation of p-Fluorophenyldiazonium Borofluoride



The diazotization of 27.8 g. (0.25 mol) of p-fluoroaniline by the method described in III yielded 43.6 g. of white crystals representing 83% of the theoretical.

XIV Preparation of p-Fluorophenylarsonic Acid



The p-fluorophenylarsonic acid was prepared by the procedure described in IV using 21.8 g. (the yield from 1/8 mol of amine) of p-fluorophenyldiazonium borofluoride. There was obtained 14.3 g. of white, lustrous crystals

representing 52% of the theoretical.

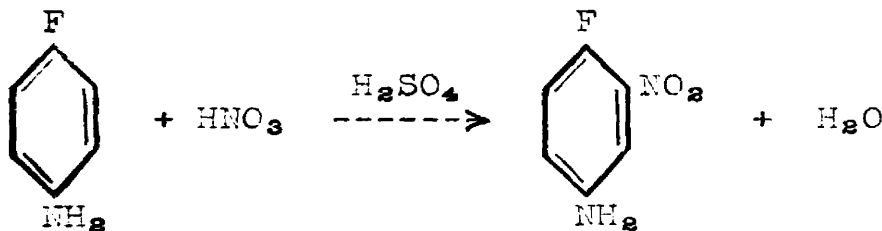
No definite melting point could be observed for this acid but as the temperature was raised it gradually changed form to an infusible powder which decomposed above 250° C. Such behavior is frequently observed in arsonic acids which lose one molecule of water to form the anhydro-acid. It gave the qualitative test for fluorine and analyzed satisfactorily for arsenic content.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_6AsFO_3$: As, 34.05%

Found: As, 34.12, 34.15%

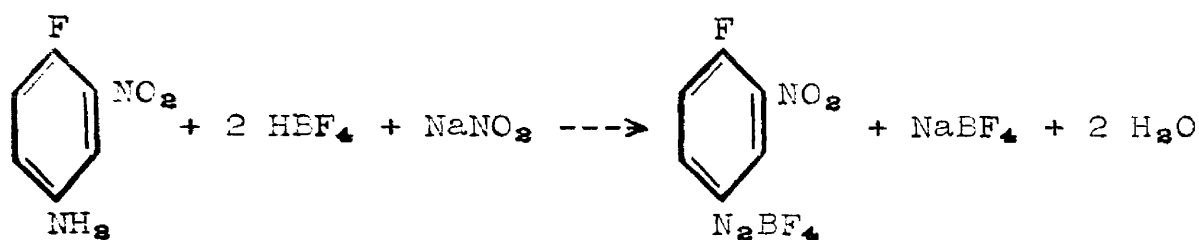
XV Preparation of 4-Fluoro-3-nitroaniline



p-Fluoroaniline was nitrated by the procedure of Holleman (84). To 27.8 g. (0.25 mol) of p-fluoroaniline in 90 cc. of concentrated sulfuric acid was added a mixture of 18 g. (0.28 mol) of fuming nitric acid (sp. gr. 1.5) and 80 g. of concentrated sulfuric acid. During the addition the temperature was not allowed to rise above 5° C. The mixture was allowed to stand at 0° C. for one hour and then poured over 800 g. of ice. While being chilled it was neutralized with 28% ammonium hydroxide and the dark precipitate then filtered off with suction. This product was

recrystallized from water using charcoal and was obtained as yellow needles weighing 16 g. which represents 41% of the theoretical. The compound melted at 96.5° C. Holleman (84) reported a melting point of 98° C. and Swarts (85) reported 96° C.

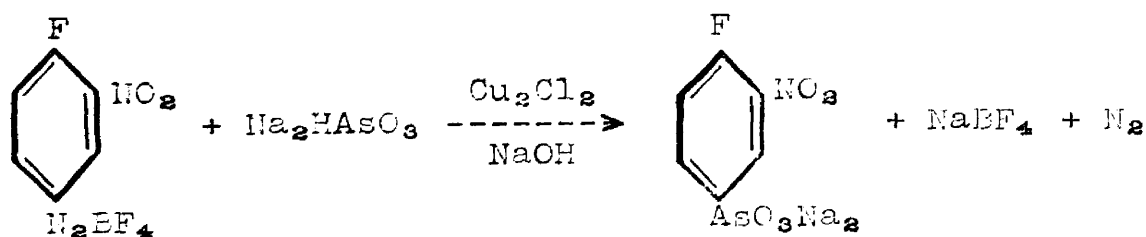
XVI Preparation of 4-Fluoro-3-nitrophenyldiazonium Borofluoride



The diazotization of 15.6 g. (0.1 mol) of 4-fluoro-3-nitroaniline by the method described in III yielded 25.3 g. of yellow-brown crystals representing 99% of the theoretical. When heated rapidly it decomposed between 171° and 178° C. This compound has not been previously reported in the available literature.

XVII Preparation of 4-Fluoro-3-nitrophenylarsonic Acid

A. From 4-Fluoro-3-nitrophenyldiazonium Borofluoride



The entire amount of the diazonium borofluoride from above was used in the arsonation as described in IV. When recrystallized and boneblacked from water there was obtained

9.3 g. of yellow compound representing 35% of the theoretical.

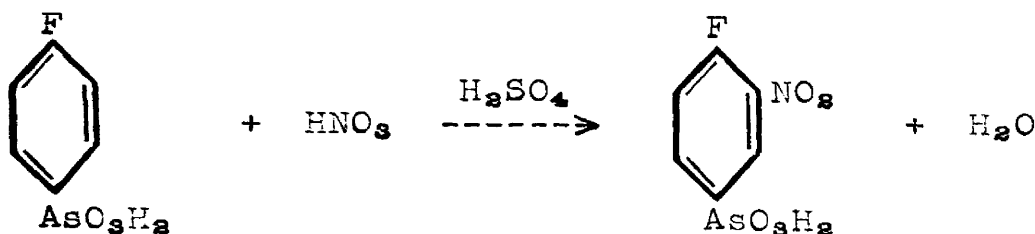
The purified acid did not melt but decomposed above 300° C. It gave a positive test for fluorine and analyzed satisfactorily for arsenic content.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_5AsFNO_5$: As, 28.27%

Found: As, 28.07, 28.15%

B. Preparation by direct nitration



p-Fluorophenylarsonic acid (described pg. 42) was nitrated by the method of Barber (26). To 22 g. (0.1 mol) of p-fluorophenylarsonic acid in 45 cc. of concentrated sulfuric acid was added 9 g. (0.14 mol) of fuming nitric acid (sp. gr. 1.5). The mixture was heated on a water bath for 2 hours and when cool was poured over 250 g. of ice. While being cooled the acid was partially neutralized with sodium carbonate. The yellow colored arsonic acid which precipitated was filtered out and washed with cold water. By concentrating the filtrate and chilling for several days a second crop of crystals was obtained. The combined pale yellow crystals weighed 18.5 g. representing 70% of the theoretical.

When heated slowly this acid did not melt but gradually changed in form to a powder which decomposed above 300° C. If, however, the compound was placed in the melting point bath already heated to 145° it melted at 148-53° C. It gave the positive test for fluorine. The arsenic analysis and the melting point behavior indicate that the arsenic acid isolated by this method contained one molecule of water of crystallization. The structure of this compound is assumed to be as indicated because of the analogy in preparing the corresponding chloro compound. However, the 2-nitro isomer is not ruled out on the basis of evidence thus far available.

Analysis: Sample weight, 0.2004, 0.2004 g.

Calculated for $C_6H_5AsFNO_5$: As, 28.27%

Calculated for $C_6H_5AsFNO_5 \cdot H_2O$: As, 26.47%

Found: As, 26.55, 26.60%

TABLE III

FLUOROPHENYLDIAZONIUM BOROFLUORIDES

<u>Amine used</u>	<u>Percent yield of diazonium borofluoride</u>
o-Fluoroaniline	75
m-Fluoroaniline	91
p-Fluoroaniline	83
4-Fluoro-3-nitroaniline	99

TABLE IV

FLUORINATED AROMATIC ARSONIC ACIDS

<u>Arsonic acid</u>	<u>Percent yield</u>	<u>Melting point</u>	<u>Analysis</u>	
			<u>Calc.</u>	<u>As % Found</u>
o-Fluorophenyl-	42	152-3°	34.05	34.02 33.95
m-Fluorophenyl-	37.5	147-8°	34.05	34.10 34.15
p-Fluorophenyl-	52	above 250°	34.05	34.12 34.15
4-Fluoro-3-nitrophenyl-	35	above 300°	28.27	28.07 28.15
4-Fluoro-3-nitrophenyl- (a)	70	148-53°	26.47	26.55 26.60

(a) From direct nitration of p-fluorophenylarsonic acid; isolated with one molecule of water of crystallization; structure not conclusively proved.

ANALYTICAL

The arsenicals which have been prepared were analyzed for their arsenic content by the method of Cislak and Hamilton (87). Because they have modified the procedure since their work was published the exact details are given here.

In the potentiometric determination of arsenic an approximately N/20 potassium bromate solution is used. The following equation illustrates the reaction involved.

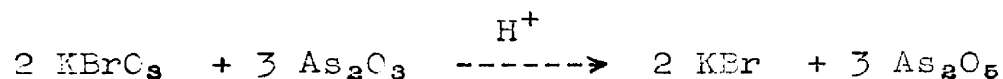
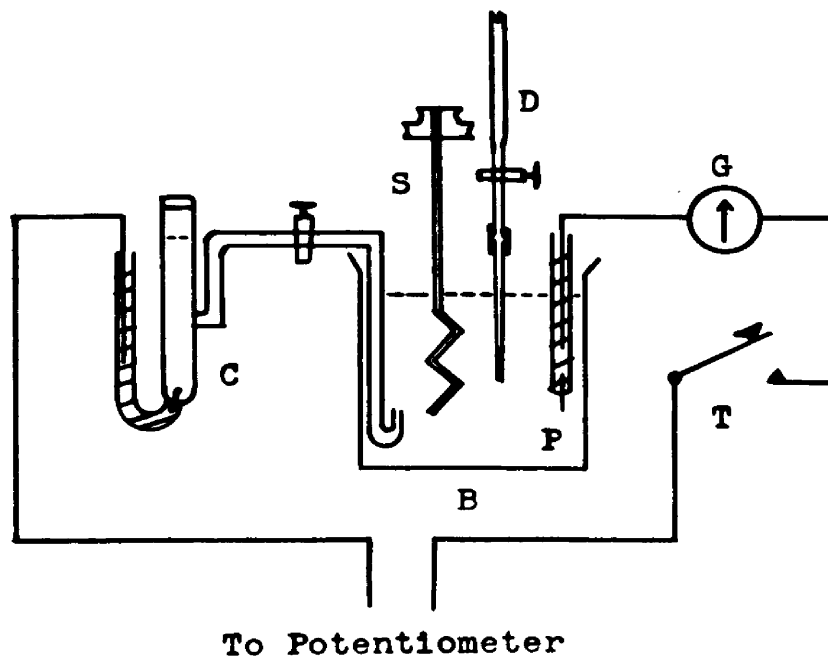


DIAGRAM OF APPARATUS



Key to symbols:

C = Calomel electrode
 P = Platinum electrode
 E = Beaker
 T = Tap key

G = Galvanometer
 D = 50 cc. burette
 S = Mechanical stirrer

As illustrated in the diagram a saturated calomel electrode was used as the cathode, a platinum electrode as the anode and these electrodes were connected directly to a Leeds-Northrup portable potentiometer. A mechanical stirrer was provided. A single dry cell furnished the opposing circuit.

Procedure:

The exact factor weight of the substance was weighed on a cigarette paper and the paper and sample introduced into a 300 cc. Kjeldahl flask. Twenty grams of anhydrous sodium sulfate and 30 cc. of Conc. sulfuric acid was then added to the sample in the flask and the mixture heated gently over a small flame for about 15 minutes. The flame was then increased and the digestion continued until the solution became clear and colorless which usually required about 30 minutes. The flask was removed and cooled to about 80° C. and diluted with about 70 cc. of distilled water. The solution was transferred quantitatively into a 600 cc. beaker and to this solution 30 cc. of conc. sulfuric acid was added and sufficient water to make the total volume of the solution about 400 cc. The solution was then ready for titration.

A few cc. of the potassium chloride solution was run through the cell and then the arm of the half cell and the platinum wire were rinsed with distilled water. The two electrodes were then immersed in the solution to be titrated and the stirrer started.

The resistance of the potentiometer was adjusted so that there was no deflection of the galvanometer when this instrument was thrown into the circuit by means of the tap key. The bromate solution was then added slowly from the burette with the tip under the surface of the solution. At this stage of the titration the solution was added at the rate of 4 cc. per minute. After the addition of each cc. of the standard solution the galvanometer was thrown into the circuit and the deflection of the galvanometer needle observed. The deflection at this point was so slight that by merely increasing the resistance a very small amount, corresponding to one or two hundredths of a volt, the null point was again reached. When the end point was only about 2 cc. away from that calculated, the rate of addition was slowed down until barely perceptible. When the end point was reached, one drop of the bromate solution caused a rather complete deflection of the galvanometer needle. This single drop threw the needle to one side so strongly that resistance of at least .2-.4 volt was necessary to balance the circuit.

The potassium bromate solution was standardized against pure arsenilic acid by the above procedure. In this way the manipulative errors were nullified. Since there is no indication when one is approaching the end point an exact factor weight was taken each time for a sample so that the end point could be anticipated. The percent of arsenic was then read directly from the burette. For example, 100 cc.

of an exactly N/20 potassium bromate solution would require 0.1873 g. of pure arsenic by the calculations,

$$\frac{74.91}{2} \times 1/20 \times 1/10 = 0.1873 \text{ g.}$$

When 0.1873 g. of arsanilic acid was titrated 32.25 cc. of the unknown bromate solution was used and since the calculated arsenic content of arsanilic acid is 34.52% a direct proportion showed that the correct factor weight for the unknown bromate solution was 0.2004 g. This calculated factor weight was verified by the titration of several samples of arsanilic acid before it was used for the analysis of the arsenicals in question. Then by taking exactly this weight of any arsenical the percent of arsenic was read directly from the burette. In order to transfer the sample without loss it was weighed on a counter-balanced cigarette paper. The paper also provided sufficient organic matter to serve as a guide in the complete digestion of the sample.

SUMMARY

Preliminary to the synthesis of a series of fluorine substituted phenylarsonic acids, an investigation was made of the use of diazonium borofluorides in the Bart synthesis of aromatic arsonic acids. These diazonium borofluoride intermediates offer definite advantages over other diazonium compounds because of their great ease of preparation and greater stability. They may be isolated, purified and stored for appreciable periods of time. The yields of arsonic acids in most instances compared favorably with yields obtained by the original and otherwise modified Bart method; in several instances the yields were increased, generally in the case of para-substituted derivatives.

Phenylarsonic acids with fluorine substituted in the nucleus have been prepared for the first time. They were synthesized using the diazonium borofluoride modification of the Bart method. Four such compounds were obtained

- viz.,
1. o-Fluorophenylarsonic acid
 2. m-Fluorophenylarsonic acid
 3. p-Fluorophenylarsonic acid
 4. 4-Fluoro-3-nitrophenylarsonic acid

The preparation of necessary fluorinated intermediates is described.

Analytical data characterizing the new compounds are given.

LITERATURE CITED

- (1) T. Midgely and A. L. Henne, *Ind. Eng. Chem.* 22, 542 (1930)
- (2) A. L. Henne, *J. Am. Chem. Soc.* 59, 1201 (1937)
- (3) A. L. Henne, *ibid.* 59, 1400 (1937)
- (4) B. L. Zenitz, *Am. Chem. Soc. Meeting*, Baltimore, 1939
- (5) Melvin F. W. Dunker and Thomas C. Grubb, *J. Eact.* 39, 243-54 (1940)
- (6) K. Kraft, *Z. physiol. Chem.* 245, 58 (1937)
- (7) Béchamp, *Compt. rend.* 50, 870 (1860); 51, 356 (1860)
- (8) Béchamp, *ibid.* 56, 1172 (1863)
- (9) P. Ehrlich and A. Bertheim, *Ber.* 40, 3929-97 (1907)
- (10) Michaelis, *Ber.* 8, 1317 (1875); 15, 2876 (1882)
- (11) Michaelis and Reese, *Ann.* 320, 271 (1902); 321, 141 (1902)
- (12) Roeder and Blasi, *Ber.* 47, 2748 (1914)
- (13) Rosemund, *Ber.* 54, 438 (1921)
- (14) H. Bart, *D. R. P.* 250,264, Jan. 8, 1910
- (15) H. Bart, *D. R. P.* 254,092, Dec. 8, 1910
- (16) H. Bart, *D. R. P.* 268,172, Sept. 20, 1912
- (17) H. Schmidt, *Ann.* 421, 159 (1920)
- (18) Mouneyrat, *Eng. P.* 142,947 (1919)
- (19) G. O. Doak, *J. Am. Chem. Soc.* 62, 167 (1940)
- (20) Scheller, *Fr. pat.* 624,028, *Chem. Zentr.* 98, II, 2229 (1927)
- (21) Melvin F. W. Dunker, Edgar B. Starkey and Glenn L. Jenkins *J. Am. Chem. Soc.* 58, 2308 (1936)
- (22) Edgar B. Starkey, *J. Am. Chem. Soc.* 59, 1479 (1937)
- (23) G. Balz and G. Schiemann, *Ber.* 60, 1186 (1927)

- (24) Edgar B. Starkey, "Organic Synthesis", Vol. XIX, pp.40 (1939), John Wiley and Sons Inc., New York.
- (25) H. Bart, Ann. 429, 55 (1922)
- (26) W. La Coste and A. Michaelis, Ann. 201, 184 (1880)
- (27) A. Berthelm, Ber. 41, 1853 (1908)
- (28) W. A. Jacobs, M. Heidelberger and I. P. Rolf, J. Am. Chem. Soc. 40, 1580 (1918)
- (29) K. Hiratuka, J. Chem. Soc. Japan 58, 1051-9 (1937) thru C. A. 33, 157 (1939)
- (30) Palmer and Adams, J. Am. Chem. Soc. 44, 1392 (1922)
- (31) A. Michaelis, Ann. 320, 328 (1902)
- (32) H. M. Parmelee, Unpublished Ph. D. thesis, Nebraska, (1931)
- (33) W. La Coste and A. Michaelis, Ann. 201, 256 (1880)
- (34) R. E. Etzelmiller, Unpublished thesis, Nebraska, (1930)
- (35) A. Michaelis, Ann. 320, 271 (1902)
- (36) Lewis and Cheetham, J. Am. Chem. Soc. 45, 510 (1923)
- (37) Lewis and Hamilton, J. Am. Chem. Soc. 45, 757 (1923)
- (38) Fourneau and Oechslin, Bull. soc. chim. (4) 11, 909 (1912)
- (39) C. S. Gibson and B. Levin, J. Chem. Soc. 1931, 2388
- (40) C. Wallach, Ann. 233, 258 (1886)
- (41) Valentiner and Schwarz, Chem. Zentr. I, 1225 (1898)
- (42) F. Swarts, Bull. soc. chim. 39 Belg. 444 (1898)
- (43) G. Schiemann and E. Lolstad, Ber. 61, 1403 (1928)
- (44) G. Schiemann, *ibid.* 62, 1794 (1929)
- (45) G. Schiemann and W. Roselius, *ibid.* 62, 1805 (1929)
- (46) G. Schiemann and R. Pillarsky, *ibid.* 62, 3035 (1929)
- (47) G. Schiemann, W. Gueffroy, W. Winkelmüller, Ann. 487, 270 (1931)
- (48) G. Schiemann, Ber. 64, 1332 (1931)

- (49) G. Schiemann and R. Pillarsky, Ber. 64, 1340 (1931)
- (50) G. Schiemann, R. Pillarsky, Kühne, W. Roselius and W. Winkel Müller, Z. physik. Chem. 156 A, 397 (1931)
- (51) G. Schiemann and W. Roselius, Ber. 65, 741 (1932)
- (52) G. Schiemann, W. Winkel Müller and W. Roselius, *ibid.* 65, 1435 (1932)
- (53) G. Schiemann, and W. Roselius, *ibid.* 65, 1439 (1932)
- (54) G. Schiemann and W. Winkel Müller, J. prakt. Chem. 135, 101 (1932)
- (55) G. Schiemann and W. Winkel Müller, Ber. 66, 727 (1933)
- (56) G. Schiemann and T. E. Miao, Angew. Chem. 46, 224 (1933)
- (57) L. Klemm, W. Klemm and G. Schiemann, Z. physik, Chem. A 165, 379 (1933)
- (58) G. Schiemann and T. E. Miao, Ber. 66, 1179 (1933)
- (59) G. Schiemann, J. prakt. Chem. 140, 97 (1934)
- (60) G. Schiemann and E. Ley, Ber. 69, 960 (1936)
- (61) G. Schiemann, W. Winkel Müller, E. Baesler and E. Ley, J. prakt. Chem. 143, 18 (1935)
- (62) G. Schiemann, and H. G. Baumgarten, Ber. 70, 1416 (1937)
- (63) G. Schiemann and M. Seyhan, Ber. 70, 2396 (1937)
- (64) G. Schiemann and W. Winkel Müller, "Organic Synthesis", Vol. 18, pp. 20-3 (1938) John Wiley and Sons Inc.
- (65) W. Bock Müller, Saml. chem. u. chem. tech. Vorträge, (1936), New series No. 28, pp.1-100
- (66) W. Bock Müller, Ann. 506, 20 (1933)
- (67) W. Bock Müller, Ber. 64, 516 (1931)
- (68) W. D. Bancroft and S. F. Whearty Jr., Proc. Nat. Acad. Sci. 17, 183 (1931)
- (69) S. F. Whearty Jr., J. Phys. Chem. 35, 3124 (1931)
- (70) L. A. Eigelow, J. H. Pearson, L. E. Cook, and W. T. Miller Jr., J. Am Chem. Soc. 55, 4614 (1933)
- (71) L. A. Eigelow and J. H. Pearson, *ibid.* 56, 2773 (1934)

- (72) L. A. Bigelow and Nobukazu Fukuhara, J. Am. Chem. Soc. 60, 427 (1938)
- (73) W. Steinkoph, and P. Jaeger, J. prakt. Chem. 128, 63 (1930)
- (74) Ehrlich and Hata, "Die experimentele Chemotherapie der Spirillosen", Springer, Berlin, pp.19 (1910)
- (75) G. Giemsa, Arch. Pharm. 257, 190 (1919)
- (76) P. Karrer, Ber. 47, 1779 (1914)
- (77) V. Fischl and H. Schlossberger, "Handbuch der Chemotherapie", pp. 414, Leipzig, (1934)
- (78) A. Haythornthwaite, J. Chem Soc. 1929, 1011
- (79) A. D. Macallum, ibid. 1926, 1645
- (80) P. Karrer, Ber. 47, 96 (1914)
- (81) F. Feigl and P. Krumholz, Ber. 62, 1139 (1929)
- (82) F. Swarts, Bull. sci. acad. roy. Belg. 1913, 241-78
- (83) J. Braun and W. Rudolph, Ber. 64, 2470 (1931)
- (84) A. F. Holleran, Rec. trav. chim. 23, 237 (1904)
- (85) F. Swarts, Rec. trav. chim. 35, 141 (1915)
- (86) H. J. Barber, J. Chem. Soc. 1929, 471
- (87) F. E. Cislak and C. S. Hamilton, J. Am. Chem. Soc. 52, 638 (1930)