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A study of the replacement of the aryl amino group by hydrogen using isopropyl nitrite

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A STUDY OF THE REPLACEMENT
OF
THE ARYL AMINO GROUP BY HYDROGEN
USING
ISOPROPYL NITRITE

A thesis presented to the Department of Chemistry
of Union College in partial fulfillment of the require-
ments for the degree of Bachelor of Science in Chemistry.

By Frederick Budnik

Approved by R. W. Finkelt

Date June, 1948

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Introduction

The use of the amino group as a directing agent in the synthesis of many aryl compounds is a well known and often used process. Therefore a simple and efficient method of removing the amino group after it has served its purpose is to be desired. The purpose of this work has been to investigate the possibility of deaminating using dilute solutions and isopropyl nitrite as a diazotizing agent. The method of reacting as well as the use of different reactants was studied.

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ABSTRACT

Replacement of the aryl amino group by hydrogen was accomplished by using isopropyl nitrite for diazotizing aniline at temperatures above room temperature. Immediate reduction by a large quantity of an alcohol gave yields as high as 47.5 % with ethanol, other alcohols giving lower yields. Aniline, acetic acid, and isopropyl nitrite were allowed to mix as they dropped into the reducing solution. This method of carrying out the reaction was found to give the best results.

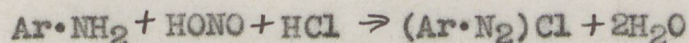
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DISCUSSION

The first aromatic diazo compound was prepared by Peter Griess in 1858. Further investigation of this class of compounds made their importance apparent. By 1863 azo dyestuffs were being manufactured and sold. The main interest in this paper, however, is the fact that diazotization provides a route for preparing many diverse compounds. The use of an aryl amino group as a blocking or directing group is a common practice and its subsequent diazotization and replacement with hydrogen by an efficient process is very important.

The preparation of diazonium compounds has been studied in some detail. At present, the most important method of preparation is by the action of nitrous acid on primary aromatic amines in the presence of a strong acid. The nitrous acid is formed by adding sodium nitrite to the strongly acidic solution.



Mieczyslaw Wojciechowski (5) reported that a twenty per cent excess of sodium nitrite was necessary for quantitative diazotization of anilines. Knoevenagel (6) used amyl nitrite in alcohol solution to prepare

diazo-amino benzene. This method had been worked out previously by Meyer and Ambuhl (7). Methyl and ethyl nitrite were also used, but chiefly for the preparation of the pure diazonium salt. It was found that pure products were obtained only in the absence of free mineral acid (8), the reason being that in the presence of excess mineral acid, additive compounds of diazo-chloride with hydrochloric acid were formed. The reaction proceeded satisfactorily in the presence of glacial acetic acid (9). However, Altschul (10) found that the tendency toward the formation of the diazoamino compounds was increased by the use of organic acids. This was overcome by using a large excess of the organic acid.

The organic nitrites can be used in non-aqueous solutions as a source of nitrous acid because they break up very easily in the presence of acids. Almost quantitative yields of solid diazonium compound are obtained by dissolving or suspending the amine salt in glacial acetic acid, cooling below 10°C., adding a slight excess of amyl nitrite, and precipitating with ether (9).

After the diazonium salt is formed, the reducing agent used will determine what the replacing group will be. In this work we are only interested in the replacement by hydrogen. The best reducing agents for reducing benzene diazonium salts are hypophosphorous acid (15), alkaline formaldehyde (16), sodium stannite

(17), and deamination by reduction to the hydrazine from which the hydrocarbon is obtained by oxidation (18). Alcohols can be used as reducing agents, but they have a tendency to form ethers. The following list indicates the relative potency of various reducing agents upon benzene diazonium salt (11):

<u>Reducing agent</u>	<u>Product and yield</u>
Ethanol	Benzene 5%, phenetole 61%
Hypophosphorous acid	Benzene 60%, biphenyl
Alkaline formaldehyde	Benzene 60%
Sodium stannite	Benzene 60%, azobenzene 10%
Deamin. via hydrazine	Benzene 45-60%

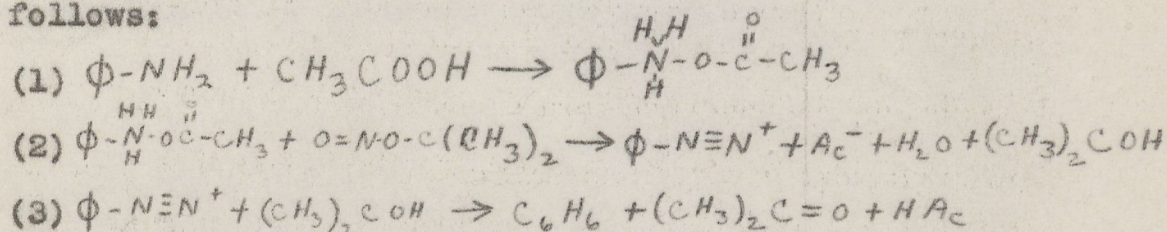
Hydroquinone is also recommended but no yields are given (4). Methanol gives poorer yields than ethanol does (1,12) but the higher alcohols give decreasing yields so ethanol is left as the best reducing alcohol. The presence of carboxyl, nitro, chloro, or bromo groups promotes diazotization and replacement by hydrogen(11), the order of diminishing effect with respect to the diazonium group being ortho > meta > para. The presence of a methyl group as in ortho or meta toluidine, decreases the yield of hydrocarbon to zero (13).

Since alcohols are cheap and easy to obtain and also give small yields in the reduction of benzene diazonium salts, they are suited for experimental work. It follows that if a fair yield is obtained by using alcohols, the stronger reducing agents might give even better yields.

SUMMARY

The purpose of this work is to investigate the use of isopropyl nitrite for removing aryl amino groups. Several different alcohols are used as reducing agents, and different methods of carrying out the reaction are devised. Time did not allow an exhaustive investigation of any one method and the investigation of some of the better experimental methods remains as an interesting problem.

The reactions involved in the process proceed as follows:



An aryl amine is reacted with an organic acid (eq. 1) and an alkyl nitrite (eq. 2). The alcohol liberated from the nitrite is used to reduce the diazonium compound (eq. 3). As the acetic acid is regenerated, only a small amount is used in the first runs. The first two runs are made in diethyl ether solution with increasing amounts of isopropyl nitrite. (See Table I for effects) Increasing the molar ratio of isopropyl nitrite to aniline gives an increased yield of benzene. The succeeding runs are made in

alcohol solution to increase the proportion of reducing agent to diazonium salt. The use of isopropyl alcohol as a solvent gives a slightly better yield but ethanol gives a considerable increase. (See Table I on page 6.)

Several different apparatus set ups are tried using ethanol both as a solvent and as a reducing agent. The yields for ethanol ranged from 8.4% in Run #6 to 47.5% in Run #7. The last Run #9 is made using n-butanol as a solvent. This gives a very low yield and further investigation into the use of the higher aliphatic alcohols seems pointless.

TABLE I

<u>Run</u>	<u>Yield</u>	<u>Ratio of nitrite to aniline</u>	<u>Reducing agent</u>	<u>Solvent</u>
1.	4.7 %	1 to 1	Isopropanol from breakdown of the isopropyl nitrite	Ether
2.	8.9 %	2 to 1	Same as #1	Ether
3.	11.0 %	2 to 1	Isopropyl alcohol	Isopropyl alcohol
4.	20.1%	2 to 1	Ethyl alcohol*	Ethyl alcohol
5.	Reaction impossible in apparatus in use.			
6.	8.4 %	2 to 1	Ethyl alcohol* Diazotization carried out at 0°C., reduction at 78°C.	Ethyl alcohol
7.	47.5%	2 to 1	Ethyl alcohol* Change in apparatus design Fig. 3.	Ethyl alcohol
8.	27.5%	2 to 1	Ethyl alcohol* Sodium hydroxide and water added to check ester formation.	Ethyl alcohol
9.	4.7%	2 to 1	n-Butyl alcohol*	n-Butyl alcohol

* Isopropyl alcohol is present as a reducing agent in all of these because it is formed from the breakdown of the isopropyl nitrite during diazotization. See eq. 2.

It seems clear from the experimental work that isopropyl nitrite can be used successfully for diazotizations of this type. Considering the reducing agent used and the other factors involved, the diazotization and subsequent replacement proceeds as well or better than the usual method of using nitrous acid in ice cold solution.

It was found that the isopropyl alcohol formed by the decomposition of the isopropyl nitrite was not sufficient to reduce the diazo compound without additional reducing agent. An excess of reducing agent was found to increase the yields considerably. Benzene diazonium acetate decomposes at the temperature where the reaction was carried out and a large excess of reducing agent probably acts to reduce the compound before it decomposes.

Of the three reducing agents tried, namely ethanol, isopropanol, and n-butanol, the ethanol gave the best results. This conforms to the reports in the literature (1, 12). The yields obtained were consistently better than those reported by other methods, and varied greatly depending upon the method of carrying out the reactions. The best yield was attained by allowing the aniline acetate and isopropyl nitrite to mix intimately as they were dropped into the reducing solution of ethanol at a temperature slightly below the boiling point of the ethanol. (See Fig. 3)

The reduction was apparently not instantaneous upon contact with the alcohol because the addition of sodium hydroxide to the boiling flask reduced the yield. The reducing action proceeded for an average of $2\frac{1}{2}$ minutes before siphoning into the basic boiling solution. The sodium hydroxide removed the acetate as sodium acetate which remained in the water solution. This reaction destroyed the conditions for stability and further reaction of the benzene diazonium acetate. The success of the process being investigated depended upon the reduction taking place rapidly because of the instability of the diazonium salt at the elevated temperatures. It therefore seemed likely that a more active reducing agent than ethanol would give higher yields. This remains to be tried.

It appears from this work that isopropyl nitrite can be used to diazotize aniline and that the replacement of the amino group by hydrogen can be accomplished in one continuous process to give better yields than are otherwise obtained with alcohol as a reducing agent.

Experimental

A supply of isopropyl nitrite was prepared (1). A mixture of 147 g. of conc. sulfuric acid (sp. gr. 1.84), 60 ml. of water, and 180 g. of 97 % isopropyl alcohol, previously cooled to 0°C., was added to a solution of 227.7 g. of 97 % sodium nitrite in 1 l. of water, cooled to -5°C. This addition was carried out over a period of two hours with the temperature maintained between -2° and 0°. The mixture was allowed to stand in an ice-salt bath until it separated into two layers. The liquid layers were decanted from the sodium sulfate into a separatory funnel. The lower aqueous layer was removed and the isopropyl nitrite layer washed twice with 50 cc. portions of a solution containing 2 g. of sodium bicarbonate and 25 g. of sodium chloride in 100 cc. of water. After drying over 15-20 g. of anhydrous sodium sulfate it was distilled from a steam bath using a 20 cm. column. Practically all distilled at 39°-40° (745 mm.) as a pale yellow oil. The yield was 193.0 g. (72.7 %) It was stored in a refrigerator because of its volatility. It has been reported to have a stimulating action on the heart therefore care was necessary in handling it.

Run # 1

Diethyl ether (solvent)	200 cc.	
Aniline	20.0 g.	} equimolar
Isopropyl nitrite	19.1 g.	
Acetic acid (glacial)	1.0 g.	

The apparatus used is illustrated in Fig. 1. The ether solution containing the aniline and acetic acid was refluxed slowly while the isopropyl nitrite was added (three hours). The ice trap was necessary to keep the fumes of isopropyl nitrite from escaping into the room. The isopropyl nitrite was introduced under the surface of the ether to give better mixing, but the benzene diazonium acetate formed on the tip of the funnel as a greyish-white crystalline solid. This repeatedly blocked the tube making the addition of the nitrite erratic. After the three hours of addition the refluxing was stopped and the bulk of the ether distilled from the solution. The residue, containing much tarry matter, was steam distilled and successive fractionation of the water insoluble portion eventually yielded 0.8 g. of impure benzene, which was a 4.8 % yield. The refractive index was 1.5150 (20°, n_D) as compared with 1.5014 for pure benzene (2). The boiling point was in the range 76°-80°, boiling point of pure benzene is 80°.

Run # 2

This run was carried out like # 1 except that two moles of isopropyl nitrite were used to one of aniline. This increased the yield to 8.9 % with a refractive index of 1.448 at 28°

Run # 3

Isopropanol	250 cc.
Aniline	20.0 g.
Isopropyl nitrite	38.2 g.
Acetic acid	1.0 g.

The isopropyl nitrite was dissolved in the isopropanol and the solution was dropped into the aniline acetic acid solution. This was done to minimize the formation of the ester, isopropyl acetate. The clogging of the tube, as experienced in the previous runs, was overcome by dropping the solution into the flask. It was hoped that the presence of a large excess of the alcohol would increase the yield. The mixing and refluxing was continued for three hours.

The resulting mixture of products was distilled over a steam bath and the portion distilling to 80° was collected. The separation of the benzene from the alcohol was a difficult problem at this point. After making test runs on different methods, it was decided to form the alcoholate with anhydrous calcium chloride. The system was then placed under reduced pressure and the distillate collected in dry ice traps. Approx-

imately 6 cc. of distillate were obtained. This was divided into 2 cc. portions and further purification attempted on each. Metallic sodium was added to one portion and the vapors formed by the heat of the reaction were condensed and collected. They distilled between 70 and 90 giving 1.1 cc. of clear liquid smelling strongly of benzene and also of the same smell as the tarry residue of the initial reaction. This distillate was then washed with a small quantity of water three times and yielded 0.7 cc. of impure benzene. This was equivalent to a yield of 11.0 %

Run # 4

Ethanol	250 cc.
Aniline	20.0 g.
Isopropyl nitrite	38.2 g.
Acetic acid	1.0 g.

In this run the aniline and acetic acid were dropped into the isopropyl nitrite, ethanol solution while refluxing in the usual manner. After three hours the mixture of products was distilled yielding 240 ml. of distillate. This was done to avoid working with the messy tars that were formed. The clear yellow liquid obtained was then analyzed by the method of Babington and Tingle (3). This method consisted of collecting the lowest boiling portion of distillation with water (benzene, water and ethyl alcohol form an azeotrope

boiling at 64.9 C. and a composition of 74.1%, 7.4%, and 18.5% respectively (19)) and then oxidizing the alcohol with acidic potassium dichromate to give water soluble acetic acid. Then adding an accurately measured quantity of benzene dissolve the benzene. The increase in volume of the ether was then taken as the volume of benzene. An error in this method was introduced by the presence of acetone which was easily carried through the distillation and not oxidized by the dichromate. A separation of the acetone by the formation of the bisulfite addition product gave no appreciable change in the results and it was therefore assumed that there was very little error due to the acetone.

The yield obtained was 3.38 g. of benzene which is a 20.1% yield.

Run # 5

Hydroquinone	47.2 g.
Ether	100 ml.
Isopropyl nitrite	38.2 g.
Acetic acid	1.0 g.
Aniline	20.0 g.

The aniline and acetic acid were to be dropped into the hydroquinone, ether, and isopropyl nitrite but the reaction was not run because the nitrite oxidized the hydroquinone to quinhydrone very rapidly.

The use of hydroquinone might be feasible in the apparatus used in later runs, it was not tried however.

Run # 6

Aniline	20.0 g.
Isopropyl nitrite	38.2 g.
Acetic acid	60 ml.
Ethanol	250 ml.

A new apparatus was set up as in Fig. 2. This apparatus permitted cold mixing of the isopropyl nitrite, aniline and acetic acid. The reactants were kept at 0° by the ice baths C. They were mixed and reacted while travelling through a third ice bath after which they were dropped into the Soxhlet extract-acetate or where the benzene diazonium_a formed was reduced by the refluxing ethyl alcohol. This method allowed the diazotization to take place separately and continuously and the large excess of reducing agent was always maintained. A larger amount of acetic acid was used in this run due to the fact that it was used up and not returned to the reactants as in the previous runs.

The reaction was carried out and the apparatus found to be faulty in operation due to the formation of tarry material in the tube entering the extractor. The reaction was carried to completion, however, and gave an apparent yield of 33.9%. This was quite high and therefore the method of analysis was checked for error. After several tests it was found that the

ethyl acetate formed during the refluxing was not entirely eliminated in the analysis. Hydrolysis of another portion of the run with sodium hydroxide destroyed the ester and subsequent analysis gave a yield of 8.4%.

Run # 7

The same quantities of reactants were used in this run as in Run # 6.

The apparatus used for Run # 6 was modified to that shown in Fig. 3. This design did not allow the diazotization to proceed at a low temperature but the low yield obtained in Run # 6 indicated that there was no great advantage in cold diazotization by this method. Allowing the reactants to drip slowly from the two dropping funnels eliminated all clogging of the apparatus. The glass plate was suspended beneath the funnel tips so that the aniline and nitrite could mix intimately before falling into the reducing agent. The reflux condenser was arranged to drop part of its condensate on the plate to keep it washed off. The periodic siphoning of the solution into the boiling flask below, kept the reacting solution dilute in the ethanol.

After hydrolyzing the ethyl acetate formed, the analysis was carried out as before and a 47.5 % yield obtained. This was extraordinarily high but several checks failed to show a lower yield.

Run #8

This run was carried out in the same manner as Run # 7 but 60 g. of sodium hydroxide was added to the boiling flask together with 200 cc. of water. This was done to prevent the formation of the ester. The result of this method was a 27.5 % yield. Additional refluxing with sodium hydroxide for 2 hours gave a final yield of 14.9 %.

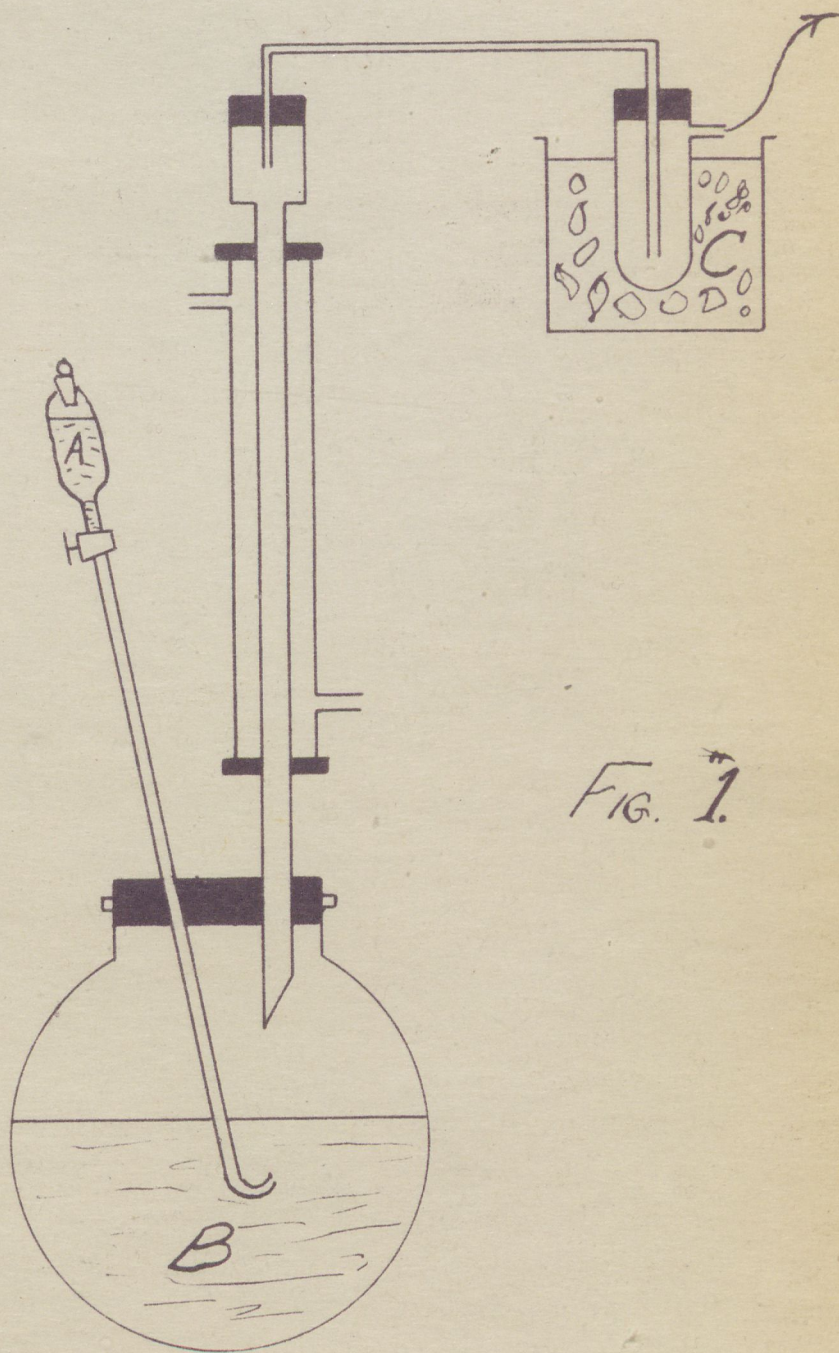
Run # 9

The same quantities and procedure were used in this run as in Run # 8 except n-butyl alcohol was used as a reducing agent instead of the ethanol. The run proceeded as before but a preliminary test showed that the method of analysis was inadequate in the separation of n-butanol. The benzene was isolated to a semi-pure form by fractional distillation. This was possible because the butanol and its azeotropes boil at substantially higher temperatures than does the benzene. The semi-pure benzene was then oxidized and treated as before to give a 4.71 % yield.

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- A. ISOPROPYL NITRITE
B. ANILINE + ACETIC
ACID IN ETHER
C. ICE TRAP



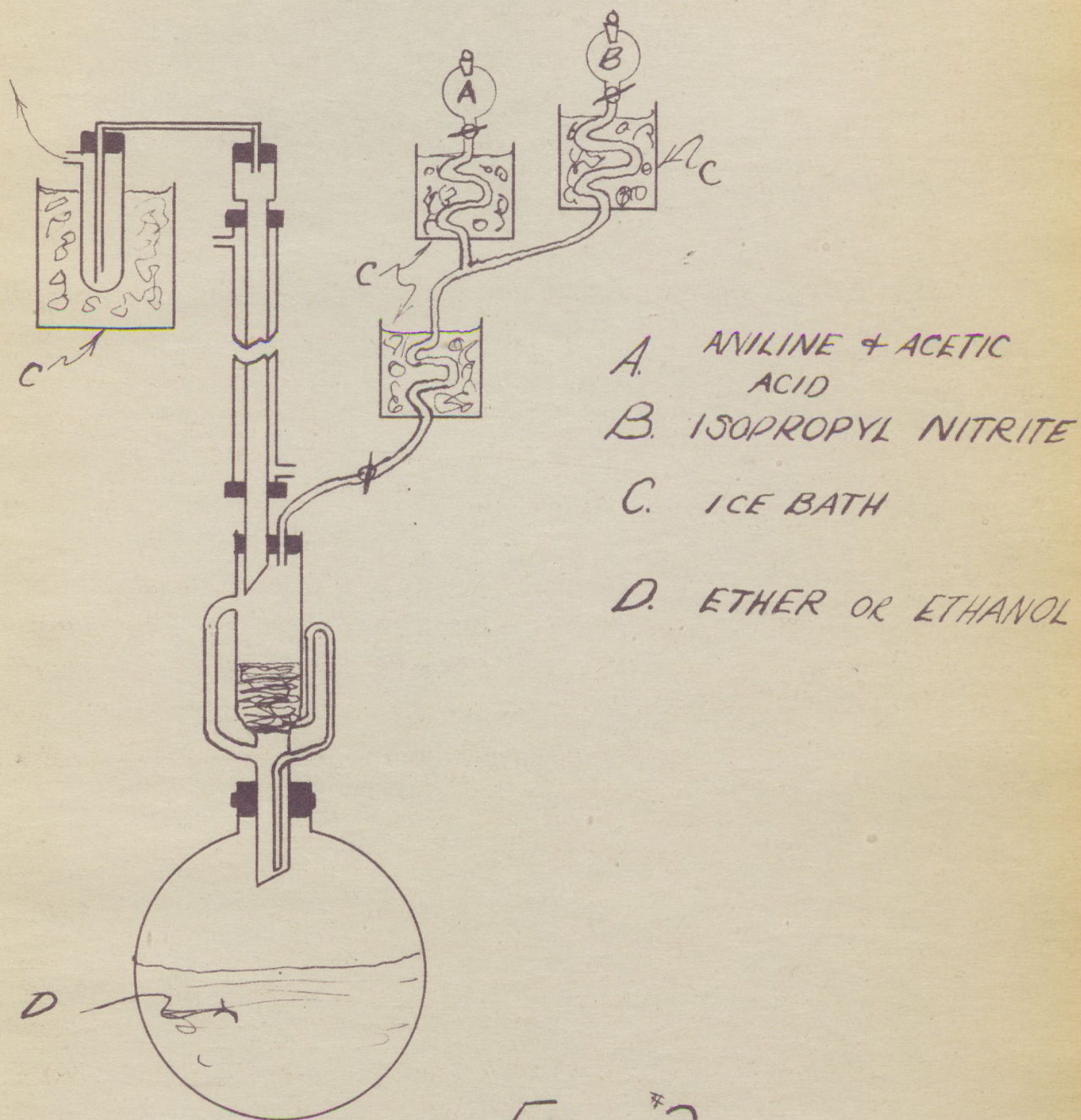
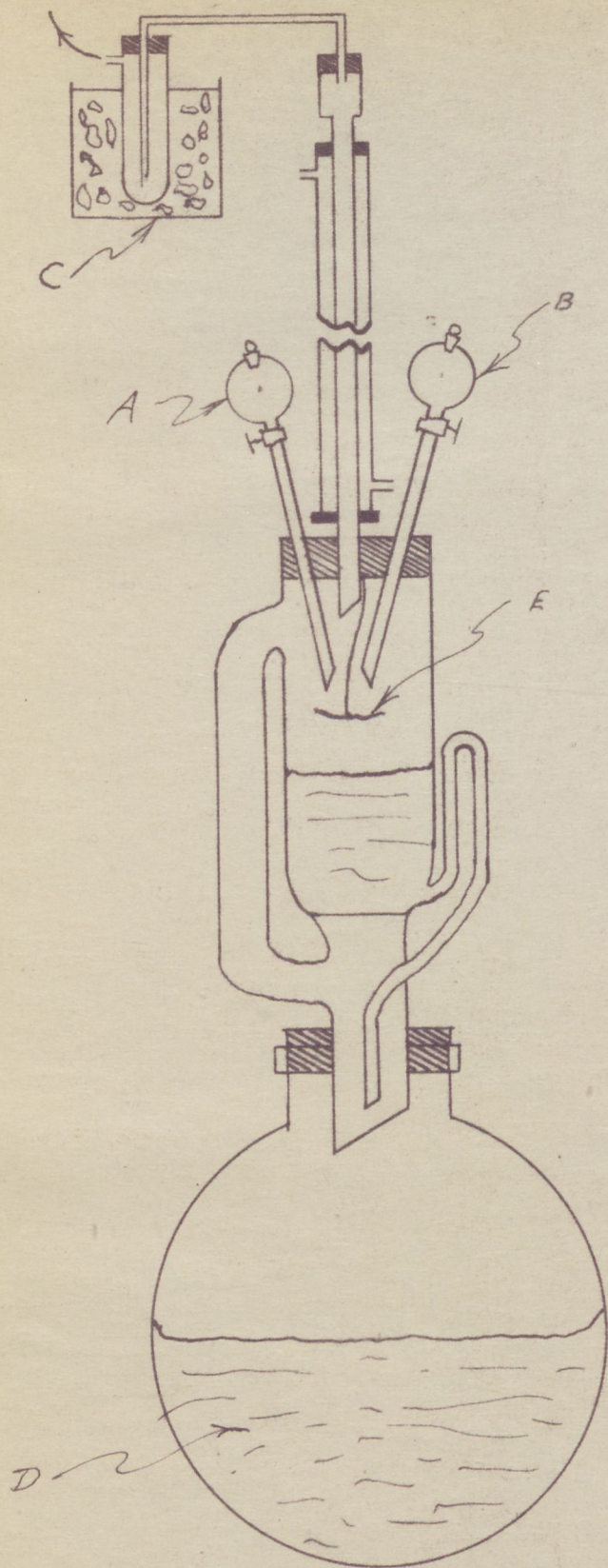


FIG. 2



- A. ANILINE & ACETIC
ACID
- B. ISOPROPYL NITRITE
- C. ICE TRAP
- D. BOILING FLASK
- E. GLASS PLATE

Fig. #3