THE IMPROVED SYNTHESIS OF *o*-PHENANTHROLINE

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INTRODUCTION

The development of the use of *o*-phenanthroline-ferrous complex as a nearly ideal, high potential, oxidation-reduction indicator by Walden, Hammett, and Chapman (6) constitutes one of the most outstanding advances of recent years in the field of analytical chemistry. Its application to many new procedures of volumetric analysis immediately followed, and former methods requiring determination by use of the potentiometric end point have been revised to include visual end point determination. The original study of the preparation of *o*-phenanthroline was made by Blau (1). The disclosure of its general and specific properties adapting it to the numerous analytical applications made its final adoption rather remarkable with regard to the time interval involved of approximately thirty-five years. As a nearly ideal example of oxidation-reduction indicator, "ferroin" (*o*-phenanthroline-ferrous ion) has its principal imperfection in the difficulty with which it is synthesized by following published descriptions of the process. The present paper has for its object the description of improvements in the preparation of *o*-phenanthroline monohydrate.

FACTORS INFLUENCING THE DEMAND FOR IMPROVED METHODS OF PREPARATION

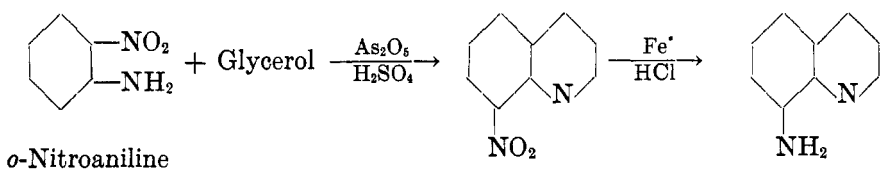
Aside from the increasing demand for the use of *o*-phenanthroline in the preparation of ferroin to be used as an indicator in volumetric determinations using such high potential oxidants as ceric sulfate, potassium permanganate, or potassium dichromate, some demand has resulted from its use as a bacteriological stain. Its use as an adsorption indicator by the process of the formation of a lake should be of possible application. It has been shown by Walden and coworkers (5) that the preparation of the nitro derivative of *o*-phenanthroline produces a product forming a ferrous complex similar to that of ferroin but having a higher oxidation potential. It would be predicted that the reduction of this nitro derivative would produce a dye base capable of the formation of a ferrous complex having a

lower oxidation potential than ferroin. Provided this amino-*o*-phenanthroline ferrous complex was not materially decreased in acid stability in the presence of oxidizing and reducing agents, its use might be desirable in titrations in the ranges of oxidation potential somewhat lower than that of ferroin. New methods for the synthesis of alkylated quinoline bases have been recently described by Darzens and Mayer (3). Following this process mono- and di-substituted *o*-phenanthroline derivatives may be synthesized. In all these cases the general principles of the improved synthesis of *o*-phenanthroline may well apply. The study of the substituted *o*-phenanthrolines of the alkylated group might be predicted to result in new types having properties more suited to their application as indicated. Unlike the nitro and amino derivatives, the oxidized forms of their ferrous complexes would be predicted to be more stable in acid solution.

OUTLINE OF THE SYNTHESIS OF *o*-PHENANTHROLINE FROM *o*-NITROANILINE

The general scheme is outlined as follows:

First Skraup synthesis:

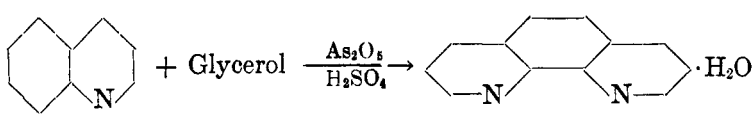


o-Nitroaniline

8-Nitroquinoline

8-Aminoquinoline

Second Skraup synthesis:



8-Aminoquinoline

o-Phenanthroline monohydrate

The first Skraup synthesis

The directions given are essentially those of Knuppel (4). A convenient amount of *o*-nitroaniline to use in this case is 2 pounds of the technical

product. A 5-liter round-bottom Pyrex flask, with one additional neck supplied, is fitted with a mercury-sealed all-metal stirring device and pulley, conveniently made by using a ball-bearing bicycle wheel hub as support. The stirrer shaft is allowed to extend for 3–4 in. through the rubber stopper closing the large opening of the flask, and a stirrer made of glass tubing is slipped over the lower portion of the drive shaft to which it is made fast, using a section of heavy-walled rubber tubing to make the attachment and protect the contents of the flask from action with metal. The design of the stirrer should be such that at 200–300 R.P.M. the contents of the flask are kept at a condition of turbulent rotary agitation. The flask is supported above an adjustable electric hot plate to provide adequate temperature control. A reflux condenser and thermometer are then attached to the second neck of the reaction flask.

Two pounds of crude *o*-nitroaniline and 2 pounds and 1 ounce of arsenic pentoxide are introduced into the flask; 4 pounds and 6.5 ounces of anhydrous glycerol are added. While stirring, 4 pounds of concentrated sulfuric acid is added gradually through the reflux condenser, in such a manner that the temperature of the reacting mixture does not exceed 110°C. After 1 hour of continuous stirring and gradual elevation of the temperature to 120°C., the stirring and elevating of the temperature is continued at the rate of 5°C. per hour until the temperature reaches 135°C. Care should be used in raising the temperature to 140°C. to prevent the reaction advancing too rapidly. Finally after 6 hours heating the reflux condenser begins to return appreciable quantities of reactants to the flask, and the amount of reflux gradually diminishes during the last 2 hours heating, as the temperature of the reaction gradually falls even while a fixed amount of heat is being applied. Finally after seven to eight hours the refluxing liquid is colorless and the reaction is complete.

The cold contents of the reaction flask are poured into a 20-gallon, acid-resisting, glazed earthenware crock to which has been added 30–40 pounds of finely chopped ice. The mixture is stirred by the use of an efficient, enameled metal, inverted, Y-shaped stirrer or substitute, saddled to the top of the earthenware container and driven by motor to provide turbulent stirring. Three and one-half pounds of caustic soda dissolved in 3 gallons of water are now added through a small-bore siphon delivery tube during a period of approximately two hours. The reaction mixture should at all times be chilled to 0°C. or lower, and additional chipped ice added as necessary. After the solution has been neutralized as tested, using litmus paper, and a slight excess of alkali has been added, the crude 8-nitroquinoline in the form of a yellowish brown precipitate is filtered, using a 14-in. Buchner funnel. The crude product precipitated from a solution of such dilution (approximately 20 gallons) requires little or no washing to be

obtained substantially free from sodium salts. The final product need not be dried before reduction to 8-aminoquinoline in the next step, and since it need not be further purified, the yield in the first two steps together is to be considered subsequently.

Reduction of 8-nitroquinoline forming 8-aminoquinoline

The directions for this reduction are followed essentially as described by Claus and Setzer (2). For working up moderately large batches of material a 12-quart, cake-mixing machine of the Hobart type is used, having a rotating and planetary motion batter-beating type of stirrer. Twelve pounds of powdered iron is mixed with just enough water to moisten the mix thoroughly, and 2.5 pounds of commercial hydrochloric acid added. To the hot mixture thus obtained the moist 8-nitroquinoline is added in small portions to maintain approximately the same temperature, adding water from time to time to replace that lost by evaporation. The iron and acid added are sufficient for the reduction of the 8-nitroquinoline from two of the first Skraup syntheses. After all the nitro compound has been added, while keeping the reaction mixture in the form of a thick paste, the reaction vessel is heated and stirred for an additional 2 hours. Finally sufficient flake caustic soda is added with stirring to neutralize the 8-aminoquinoline hydrochloride and to form sufficient iron precipitate to thicken materially the pasty reaction mixture. The aminoquinoline is then extracted, using several portions of benzene totalling 10–15 liters, and using the same mixing machine with intermediate filtration of the insoluble matter by reduced pressure in a 14-in. Buchner funnel. The benzene solution is finally concentrated by distillation at atmospheric pressure in a 5-liter, vacuum distilling, Claisen-type still until the boiling temperature reaches 100°C. Finally the 8-aminoquinoline is distilled under 25 mm. pressure, at which it boils at 175°C. A capillary air vent is used in the usual fashion to prevent bumping and to regulate pressure. The yield for the two steps thus described is approximately 50 per cent of theoretical, based upon the *o*-nitroaniline.

The second Skraup synthesis to form o-phenanthroline

Essentially the same directions and apparatus are used in the second Skraup synthesis as in the first. The reaction is much more sensitive and the heat relationships must be more closely guarded and a longer time interval should be allowed.

Two pounds of ground 8-aminoquinoline and 2 pounds of arsenic pentoxide are placed in the reaction vessel, followed by the addition of 4 pounds and 6.2 ounces of dry glycerol. Five pounds and $5\frac{1}{3}$ ounces of concentrated sulfuric acid are now added in small portions through the

reflux condenser to the well-stirred glycerol and other substances. The sulfuric acid should not be added at a rate greater than that required to keep the temperature below 100°C., approximately 30 minutes being required. The mixture after the addition of all the sulfuric acid can be gradually heated to 110°C. during 1 hour, and then in 5-degree intervals per hour until a temperature of 135°C. is reached. Finally the temperature is allowed to rise to 140°C., but no higher, and maintained at this point during 2 hours. The temperature control in the case of the second Skraup synthesis should be more carefully and uniformly regulated than in the first for best results.

The cooled Skraup mixture is neutralized as described above, using, however, 40 gallons of solution as final neutralization volume rather than 20 gallons as before. Four and one-third pounds of caustic soda dissolved in 12 gallons of water should be used as neutralizing reagent. Stronger alkali for neutralization is not advised. At a time just preceding the neutralization of the entire batch a green crystalline precipitate of side reaction product forms. As the neutralization proceeds to completion, this green precipitate coagulates to form a more or less rubber-like tar. The extent to which *o*-phenanthroline is occluded by this tar is a function of the dilution of the solution in which it is formed and of the concentration of the neutralizing alkali added.

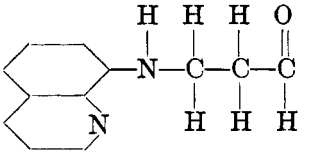
The most important controlling factors improving the yield of *o*-phenanthroline in the process described consist in the recovery of the product occluded by the tar and the preparation of water-soluble *o*-phenanthroline from the sodium salts in the neutralized Skraup mixture. Treatment of the tar as described in the literature involves drying and extraction for a long time in a Soxhlet extractor with benzene as solvent. This process, together with the formation, under unfavorable conditions, of the tar, which occludes excessive amounts of the desired product, is very tedious and inefficient. The published procedure for the separation of *o*-phenanthroline from the solution with large amounts of sodium salts involves evaporation of the solution to practically complete separation of the total solids, followed by the extraction of the desired product from the salt mass, using ethyl alcohol. This process involves the formation of considerable quantities of oily impurities and is in general unsatisfactory. Methods by which these two major difficulties can be avoided will now be described.

The separation of o-phenanthroline from the tar

The tar formed is soluble in sulfuric acid. Such a solution is prepared and diluted to 6–8 gallons with water, and the acid is then neutralized using dilute sodium hydroxide and a solution temperature of 10°C. The precipitated green crystalline product thus obtained just before the solu-

tion is neutralized now contains but little *o*-phenanthroline and by this process, repeated if necessary, a comparatively pure product can be obtained. The filtered solution of sodium sulfate and *o*-phenanthroline of approximately 10 gallons volume, if one reprecipitation is applied, is added to the main portion of 40 gallons for subsequent recovery of the indicator base.

The green precipitate was thought to be an intermediate product in the ring closure reaction of the Skraup synthesis and the following formula was postulated.



8-Aminoquinolylpropionaldehyde

The product was found to test as an aldehyde, using Schiff's reagent, and a molecular weight determination, as well as its analysis for nitrogen, carbon, and hydrogen, agree quite satisfactorily to support the assumption. The more complete identification of this compound will depend upon its purification through the formation of the picrate or perchlorate, reconversion to the parent substance, and ultimate analysis.

The product is interesting because of its reactions, which closely approach those of *o*-phenanthroline in some respects. It forms a highly insoluble perchlorate. It is a reversible oxidation-reduction indicator, giving a deep red color with oxidizing agents in mineral acid solution and a light yellow with reducing agents. Unfortunately the dye is not stable in the presence of excess of these agents, although the acid stability of the dye base is very satisfactory.

The separation of o-phenanthroline from sodium salts

Data are not at present available for the solubility of *o*-phenanthroline monohydrate in water and solutions of sodium sulfate and arsenate at different temperatures. It was originally thought possible to separate the *o*-phenanthroline from the diluted sulfuric acid solution of the second Skraup reaction products by the addition of ferrous perchlorate or ferrous sulfate, and perchloric acid in sufficient quantity to form the ferrous perchlorate complex. The product thus formed from pure *o*-phenanthroline can then be oxidized, the ferric iron thus formed removed by precipitation, and the dye base then formed by concentration of the resulting filtrate. This process was not found to be effective, for the reason that the principal impurities are precipitated as the simple perchloric acid salts at the same

time. It might well be possible to make the separation of the impurities of the nature previously described by the simple addition of perchloric acid to the dilute acid solution of the Skraup mixture, but the separation of *o*-phenanthroline from soluble sodium salts would still remain to be accomplished. It was accordingly decided to purify the tar from the neutralized reaction products as previously described, and to take advantage of the high temperature coefficient of the increase in solubility of hydrated *o*-phenanthroline in boiling aqueous solutions of the sodium salts also present, as compared with the solubility at ordinary temperatures, for the isolation of the desired product.

The 50 gallons of dilute solution of *o*-phenanthroline, sodium sulfate, and sodium arsenate is evaporated by stages in a 20-gallon, steam-jacketed, enameled, evaporating pan until the boiling solution, upon local cooling through the application of a stream of cold air, shows a cloud of minute crystals giving a milky appearance to the cooled portion of the solution. This occurs when the solution has evaporated to a volume of between 5 and 10 gallons. The reaction mixture is then allowed to cool slowly to room temperature overnight. A large portion of the crystalline *o*-phenanthroline monohydrate, together with some dark oil, is obtained. The insoluble portion containing the oily impurity is then filtered off, the concentration of the filtrate again carried out as before, and a second and third crop thus obtained. The last filtrate is finally concentrated to the point of crystallization of the inorganic salt content, which is accumulated from batch to batch until it becomes worth while to attempt to remove the last small portion of *o*-phenanthroline by extraction with hot ethyl alcohol.

The crude *o*-phenanthroline plus oily impurity is now dissolved in fifty times its weight of boiling water and clarifying carbon added, followed by filtration while still hot. The filtrate is allowed to cool and crystallize, and a second purification carried out to produce a colorless crystal mass of the finished product. The yield thus obtained is found to be 40 per cent, based upon the 8-aminoquinoline taken. The over-all yield based upon the *o*-nitroaniline used as starting material is thus found to be 20 per cent. The best over-all yield for this synthesis previously reported has been stated to be between 7 and 8 per cent.

Suggestions for further increasing production yields

The postulated composition of the side reaction product of the second Skraup synthesis suggests the possibility of so modifying conditions as to result in an increase in yield of *o*-phenanthroline at the expense of the undesired product. The failure of the 8-aminoquinolylpropionaldehyde to finish the ring closure is probably due in part to a faulty ratio of sulfuric acid to arsenic pentoxide, both of which ingredients should be altered

separately to study the effect. The last step in the ring closure is in great part a dehydration reaction. The use of a higher concentration of sulfuric acid at the end of the synthesis to increase dehydrating conditions is therefore suggested. A substitute oxidizing agent to replace arsenic pentoxide has been suggested by Darzens and Mayer (3), namely, sodium *m*-nitrobenzenesulfonate. Catalysts for the arsenic pentoxide have been suggested; for example, a small amount of vanadic acid. These questions are being investigated.

SUMMARY

1. The synthesis of *o*-phenanthroline, starting with *o*-nitroaniline, has been studied with the object in view of increasing the over-all yield from the three-stage process. The improvements described resulted in an increase in yield from that previously reported of 7 to 8 per cent to that of 20 per cent.

2. The major improvements involve steps in the process for conversion of 8-aminoquinoline into *o*-phenanthroline. The prevention of tar formation in great part has been accomplished, and an improved method for the separation of the desired product from the tar-like impurities is described. The separation of *o*-phenanthroline from the large amount of sodium salts accumulated in the Skraup reaction has been much improved.

3. Suggestions concerning the nature of side reaction products have been made, and improved conditions for the Skraup synthesis in this particular case are suggested.

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