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UNIVERSITY OF LOUISVILLE

"SYNTHESIS OF NITRO ACRIDINE DERIVATIVES"

A THESIS
SUBMITTED TO THE FACULTY OF
THE GRADUATE SCHOOL OF THE COLLEGE OF
LIBERAL ARTS. IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE.

DEPARTMENT OF CHEMISTRY

BY
MARTIN FRIEDRICH

1926

SYNTHESIS OF NITRO-ACRIDINE DERIVATIVES.

At the present time there is not much known about derivatives of acridine. However, there are derivatives of acridine which are important as dyes, drugs and antiseptics. Chrysaniline, rheonine, benzoflavine, are examples of leather dyes which are used extensively. The theory of Perkins and Robinson, says that the acridine ring system is probably present in strychnine and brucine, so a further study of the derivatives of acridine may shed light on the true structure of these alkaloids. Some derivatives of acridine such as rivanol and acriflavine have a specific physiological effect, others are used as silver salts in killing of bacteria or trypanosomes, also in the curing of sleeping sickness in humans. The formulas of the above named compounds of acridine are:

Chrysaniline

Rheonine

Acriflavine

Rivanol

Benzoflavine

Acridine has the formula and nomenclature according to the following scheme:

It is found with other basic substances such as pyrene carbazole, phenanthrene, chrysene, and other hydrocarbons and phenols in crude anthracene. The acridine is isolated by extracting with sulphuric acid and adding potassium dichromate. The acridine chromate is then recrystallized from water and treated with ammonia. The free base is then recrystallized from hot water. Its crystals are in the form of colorless needles with a melting point of 111° . It distills with steam. It is soluble in alcohol, ether, and carbon di-sulphide with a blue fluorescence. If treated with nitric acid it forms two mono derivatives with m. p. 154° and 214° and a dinitro derivative. If it is oxidized with potassium permanganate it forms 2-3 quinoline dicarboxylic acid.

If treated with sodium amalgam we get a di-hydro acridine².

If treated with nickel as a catalyst in reducing with hydrogen we get 2-3 di-methyl quinoline.

The salts of acridine are all yellow and form well shaped crystals, however, they all decompose on boiling.

There are many methods which can be used in the synthesis of acridine, among which are the following:

I. Bernthsen and Bender³.

Condensation of formaldehyde with diphenyl amine

II. Fischer and Korner⁴.

Reaction of chloroform, with diphenyl amine

III. Heating phenyl-o-toluidine in a hot tube.^{5.}

IV. Mohlau

Aniline treated with salicylic aldehyde^{6.}

V. Ullmann

Diphenyl amine condensed with benzoic acid.

VI. Meyer

Amino-benzaldehyde reacted with iodo benzene^{7.}

In all of these reactions we can change to other derivatives of the compounds used and then get different final products. For example, in the Bernthsen method one could take either derivatives of diphenyl amine or different acids such as acetic, butyric, benzoic,

but the latter variation always results in derivatives of 9-acridine. This method is not very satisfactory in preparation of acridine derivatives in which the substituting substance is not in the 9-position. One can vary the derivatives of nitro-diphenyl amine and in this way get different derivatives of 9-phenyl acridine. One can possibly vary the derivatives of amino benzaldehyde, also derivatives of iodo benzene in order to get different substitution products of acridine.

Meyer has taken o-chlor benzaldehyde and condensed it with o-nitroaniline and has received a nitro acridine derivative, which is the only mono nitro acridine in which we are sure of the position of the nitro group. It has a melting point of 167° . Graebe has also nitrated acridine directly, and has received two different mono nitro derivatives, which he named α and β , which had melting points of 154° and 214° respectively, and a dinitro acridine derivative.⁸

The problem of the author was to synthesize different mono nitro derivatives of acridine. The formula and nomenclature of acridine has been given above. One can easily see that it is possible to receive four different mono derivatives of acridine, as shown with the nitro group:

4-nitro acridine

2-nitro acridine

3-nitro acridine

1-nitro acridine

EXPERIMENTAL

I. During my research work, I tried a number of methods in preparation of derivatives of nitro acridine.

The first method was similar to that of Bernthsen, which involved the preparation of certain nitro diphenyl amine derivatives, and from these the acetyl and formyl derivatives which have the following formulas:

1. To prepare these nitro formyl and nitro acetyl

7.
di phenyl amines different methods were used:

- a. By treating the corresponding nitro di-phenyl amine derivatives with formic acid or acetic anhydride forming the corresponding acetyl and formyl derivatives. In the preparation of the 4-nitro di phenyl amine I condensed 3 grams of p-nitroaniline and 12 cc. brom benzene, by heating the mixture for 12 hours over a free flame, using a reflux condenser.^{9.} A gm. of potassium carbonate and a trace of copper iodide were also present. The reaction follows:

The m-nitroaniline and p-nitroaniline were also used and condensed with brom benzene in order to prepare the 3-nitro diphenyl amine and the 2-nitro diphenyl amine. It was my intention to take these nitro diphenyl amine derivatives and make the formyl and acetyl derivatives by treatment with formic acid and acetic anhydride. The reaction is as follows:

This method did not work satisfactorily, because in the acetylation either no definite products could be isolated, or else the reaction would not proceed at all.

- b. The second method used in the preparation of these acetyl and formyl nitro diphenyl amine derivatives was to nitrate formyl or acetyl di-phenyl amine directly. To prepare formyl diphenyl amine 50 gms. of diphenyl amine were treated with 75 cc. formic acid, heating the mixture for five hours using a reflux condenser. The resulting product was decomposed with water and purified from alcohol. Similarly for the acetyl derivative. The melting points for the formyl and acetyl derivatives are 73° and 95° respectively. Equations follow:

These compounds were treated in different ways with nitric acid directly. For example, by treating with nitric acid at different temperatures, in different solvents, in different amounts. In all cases it was not possible to isolate the products formed and mixtures of the mono, di, tri, tetra, and penta nitro diphenyl amines no doubt were formed.¹⁰ When adding fuming nitric acid and heating on the water bath until no more fumes evolved, a penta nitro acetyl diphenyl amine was formed which had a melting point of 185°¹¹. It was recrystallized from acetic acid. The reaction follows:

- c. The third method used in preparing these nitro formyl diphenyl amines is the method of Irma Goldberg,⁹ with the exception that formanilide is condensed with brom benzene in the presence of copper, and potassium iodide, with nitro benzene as solvent. The heating was done for 10 hours at 180°, after which the temperature was raised to 210° for 8 hours. The quantities used were 21 gms. brom benzene, 5 gms. potassium carbonate, a trace of potassium iodide and copper, and 20 gms. of nitro benzene. The formanilide was prepared by the following reaction:

30 gms. of aniline were heated with 17 gms. formic acid on a water bath, and then water was added. A deep red oil was formed. A good reaction product was secured when this was condensed with brom benzene under the conditions noted above. The reaction is:

Then nitro formanilide and nitro acetanilide^{12.} were prepared by the following reactions:

The melting point of the nitro formanilide is 193° . It is a yellow crystalline compound which separates from the formic acid solution during the heating which continued for three hours on the water bath. When nitro formanilide was condensed with brom benzene under the conditions noted above, it seems, that the high temperature needed to make the experiment go, also splits out the formyl radical, and likewise splits out the acetyl radical, as the nitro acetanilide is used, making the formation of the nitro diphenyl amines, which would be hard to isolate from the melt. I also tried to condense 5 gms. nitro diphenyl amine with 3 cc. formaldehyde in alcohol to which 1 cc. of

hydrochloric acid had been added, but no results were obtained.

In all of these experiments the intention was to treat these formyl and acetyl nitro diphenyl amines with zinc chloride at a high temperature and thereby form the acridine derivatives. The reaction follows:

II. The second method used in preparing nitro acridine derivatives was in condensing nitro diphenyl amine with formaldehyde, and oxidizing the resulting dihydro nitro acridine with ferric chloride, to form the nitro acridine. A solution of 5 cc. 40% formaldehyde and 2.5 gms. ferric chloride in 8 cc. alcohol, was added to a warm solution of 10 gms. nitro diphenyl amine in 20 cc. alcohol. This mixture was heated for five hours on a water bath using a reflux condenser. The residue formed after heating was treating with warm ammonia and washed and extracted with alcohol. It seems that no reaction occurred, and it was hard to separate anything from the melt. The reaction follows:

III. The third method used was that similar to Meyer who condensed ¹o-chlor benzaldehyde with o-nitro aniline to get a condensation product which was further treated with concentrated sulfuric acid to form the nitro acridine. He heated, for three hours at a temperature of 220° , using an air condenser, a mixture of 2.3 gms. o-nitroaniline, 7 gms. chlor benzaldehyde, 15 gms. nitro benzene, 2.3 gms. anhydrous sodium carbonate, and a trace of reduced copper. The nitro benzene was distilled over with steam. The melt was then treated with 20 cc. concentrated sulfuric acid and the solution heated on a water bath for three hours. The solution was diluted a little with water and filtered, then more water was added to the filtrate. The final solution was boiled with charcoal for half an hour. It was then filtered, and made alkaline by adding ammonium hydroxide. The precipitate formed was purified from alcohol a number of times, and the melting point of the nitro acridine produced was 167° . It is the only nitro acridine derivative in which the position

of the nitro group is known for certain. When Meyer tried condensing the m-nitroaniline and p-nitroaniline with the chlor benzaldehyde, he found that the aldehyde group reacted with an amino group. The reaction follows;

Now, it was thought that if the aldehyde group could be protected in some way so that it could not react with the amino group, then we could use all three nitro anilines, in the formation of the various nitro acridines. We tried protecting the aldehyde group with the oxime group, and treated it the same as Meyer had treated chlor benzaldehyde according to the reactions:

13.
Chlor benzaldoxime was prepared by mixing 19 gms. chlor benzaldehyde with 5.5 gms. hydroxylamine hydrochloride, and putting this into a 20% solution of sodium carbonate. This was stirred and allowed to stand for some time. A cotton-like solid gradually separated which had a melting point of 74° . On purifying from alcohol it formed long colorless needles.

The treatment of this chlor benzaldoxime with the nitro aniline was tried under the conditions of Meyer but was not successful. It seems that the chlor benzaldoxime, under the influence of the heat needed for the reaction reacts with itself, forming various products. The experiment was tried in many different ways, such as changing catalyst, temperature, time of heating, solvent, but finally the experiment had to be discarded as a method to employ in synthesizing nitro acridine.

IV. The fourth method tried in preparing derivatives of nitro acridine was the condensation of amino benzaldehyde, with halogen derivatives of benzene. Amino benzaldehyde was made by the reduction of nitro benzaldehyde as follows: 8 gms. of nitro benzaldehyde were suspended in a solution of 140 gms. of ferrous sulphate^{1A.} and 240 gms. of water, to which had been added 3 cc. of fifth normal hydrochloric acid. This was heated to 90° during the course of the experiment. The amino benzaldehyde was then received by steam distillation. 2.5 gms. were received. 4.04 gms. of o-nitro brom benzene, 2.42 gms. amino benzaldehyde, .25 gms. reduced copper, 20 gms. nitro benzene, 1.06 gms. sodium carbonate were mixed, and heated for three hours at 220° using an air condenser. The remainder of the experiment was performed similar to that of Meyer, and the identical product, was received which Meyer had received.

The experiment was extended using the meta and para nitro brom benzenes, and using the same conditions as used when the o-nitro brom benzene was used. It seems that nitro acridine derivatives are received.

V. The fifth method tried was that whereby nitro methyl acridine derivatives were prepared. O-nitro chloracetophenone was condensed with aniline and m-nitroaniline, to get condensation products.¹⁵ Condensation products were received in these cases, but when the o-or the p- nitroanilines were used, no condensation products were received. The preparation of nitro chlor acetophenone is as follows:¹⁶ To half (160 cc.) of a solution of sodium ethylate prepared by dissolving 20.7 gm. of sodium in 320 cc. absolute alcohol, add 58.5 gm. of acetoacetic ester. Cool the solution of sodium acetoacetic ester so obtained to 5°, and then add gradually 28.25 gms. o-chlor benzoyl chloride from a burette, keeping the temperature below 12°. Stir constantly. After $\frac{1}{2}$ hour add 80 cc. of sodium ethylate solution and 14.12 gms of acid chloride. After again cooling add half of the remaining acid chloride solution and half of the remaining ethylate solution until the process is complete and all of the solutions are used up. Allow the mixture to set 24 hours. Filter the resulting salt and wash with dry ether. To 300 cc. of water add 120 gms of the sodium salt of o-chlorbenzoylacetic ester, 54 gms. ammonium chloride and 60 cc. concentrated ammonium hydroxide. Heat at 40-50° for 6 hours with frequent shaking.

Extract the oil formed with ether, dry the ether with calcium chloride, distill off the ether, and put the resulting residue in a dessicator over sulphuric acid. Boil a mixture of 54 gms. of the ester, 240 cc. water, 70 cc. concentrated sulphuric acid, using a reflux condenser until carbon dioxide ceases to evolve, e. g. twelve hours. Cool the mixture and extract it with ether. Dry the ether with calcium chloride, distill off the ether, and then distill off the o-chloracetophenone. It distills over at a temperature near 227-228°. Add 10 gms. of chlor acetophenone to 100 gms. of fuming nitric acid which has been cooled to 0°. Add slowly. After all of the chlor acetophenone is added, pour the mixture on ice. After the ice is melted, filter the resulting product, and purify it from alcohol. The melting point is 61°. The reaction follows:

1 gm. nitro chlor acetophenone was condensed with 1 cc. aniline in the presence of 1 gm. sodium carbonate¹⁸. The mixture was heated for three hours at 170-180°. The melt was extracted with alcohol and the melting point of the resulting product was 123°. When .7 gm of m-nitroaniline was condensed with 1 gm. nitro chloracetophenone in the presence of 1 gm. of sodium carbonate, and heated for three hours at 150°, a condensation product was received which had a melting point of 155°. Many reactions were tried before these condensation products were received. We may use nitro amino acetophenone in place of the nitro chlor acetophenone, and then condense this with the nitro halogen derivatives of benzene, and see what we get. The reaction should go in this way:

It was my intention to then treat these condensation products received in these reactions, with sulphuric acid the same as Meyer did, and see if the nitro methyl acridines would be received. This experiment must be worked up more.

- VI. A sixth method used in preparation of nitro acridine derivatives is the condensation of nitro chlor benzaldehyde with various amino derivatives of benzene, such as aniline, and nitro aniline. Nitro chlor benzaldehyde was obtained by the following method:^{19.} To a mixture of 10 gms. chlor benzaldehyde and 23 cc. concentrated sulphuric acid, cooled to 10° , add gradually a solution of 6.3 grams fuming nitric acid and 11.5 gms. of concentrated sulphuric acid. After all is added pour the mixture into ice water and purify the resulting product from carbon disulphide. Yellow crystals which have a melting point of 80° , were received. To 1 gm. of nitro chlor benzaldehyde, 1 gm. nitro aniline, 1 gm. sodium carbonate, add .1 gm of powdered copper, and heat for five hours at 150° . Extract the melt with alcohol. Yellow crystals with a melting point above 250° were received. The experiment must be

worked up more, but should go as follows:

VII. The seventh and last method tried in preparation of nitro acridine derivatives was the condensation of nitro amino benzaldehyde with iodo benzene. The nitro amino benzaldehyde was prepared in the following way:²⁰ Para nitroso dimethyl aniline was prepared by the action of sodium nitrite on dimethyl aniline. Then 45 gm. of para nitroso dimethyl aniline was treated with 40 gm. 2-4 dinitro toluene, in the presence of 250 cc. alcohol and 75 gm. crystallized sodium carbonate, by heating for 5 hours on the water bath. The mixture gradually solidified. It was filtered with suction and washed with hot water. 67 gms. of the raw condensation product were then treated with half a liter of dilute nitric acid

and half a liter of benzene. This mixture was shaken and stirred for a few hours. The benzene was separated from the water and the melt again extracted. The benzene solution was then boiled with charcoal, filtered, and the benzene distilled off. The aldehyde remained behind as an oil, which on cooling crystallized. It was purified from dilute alcohol. The melting point is 72° . Take 66 gms. of 14% titanium trichloride solution with the same amount of concentrated hydrochloric acid and dilute with boiled water to a liter of solution.²¹ Pass in carbon dioxide, and add a hot alcoholic solution of 1.96 gms. dinitro benzaldehyde. The deep blue solution decolorizes. Upon adding an excess of sodium acetate, the nitro amino benzaldehyde precipitates out in bright yellow crystals. Shake out with benzene. Dry benzene with calcium chloride, remove the benzene and purify the amino nitro benzaldehyde from water. M. P. 124° . This nitro aminobenzaldehyde is to be condensed with iodo benzene to get the nitro acridine derivatives.

The experiment should go in this way:

It is planned to take the condensation product from nitro amino benzaldehyde with iodo benzene and treat it the same way as is done by Meyer in his experiments. In this way it is hoped to get the same product as was received when amino benzaldehyde was condensed with m-nitroaniline. This experiment needs further work.

CONCLUSIONS.

1. The Bernthsen method, namely the one of forming nitro acridine from the nitro formyl diphenyl amine derivatives does not seem to be practical.

2. The method of condensing nitro di phenyl amine with formaldehyde and oxidizing the di hydro nitro acridine with ferric chloride does not seem to be successful.

3. The method of Meyer, to protect the aldehyde group of chlor benzaldehyde with the oxime group, and the reacting of this with nitro aniline does not seem to give the expected results.

4. The condensation of amino benzaldehyde with halogen derivatives of benzene seems to be successful, but needs further work.

5. The other methods involving derivatives of amino benzaldehyde and derivatives of chlor benzaldehyde seems to be able to be worked out, and give methods which can be used in synthesis of nitro acridine derivatives.

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