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University of Louisville

Acridine and Its Derivatives

A Thesis

Submitted to the Faculty
Of the Graduate School of the College of Liberal Arts
In Partial Fulfillment of the
Requirement for the Degree
Of Master of Science

Department of Chemistry

by

Altemiro Ferreira Vianna

1926

ACRIDINE AND ITS DERIVATIVES

Acridine was discovered by Graebe and Caro who found that it accompanied the crude anthracene obtained from coal-tar. For its isolation, the portion of the tar distilling at 300° - 360° C. was extracted by dilute sulphuric acid and precipitated by potassium dichromate, the precipitate recrystallised from hot water and then decomposed by dilute ammonia. The free base was then dissolved in hot hydrochloric acid, from this solution acridine hydrochloride was thrown out by addition of an excess of concentrated hydrochloric acid. From this salt the free acridine was liberated by ammonia.

The isolation of pure acridine from coal-tar involves its separation from other basic compounds of a nearly related character; in the synthetic preparation from diphenylamine and formic acid a substance is obtained free from homologous bases. Bernthen has described several synthesis.

- 1) From formic acid and diphenylamine

acridine was obtained thus:

2) From chloroform and diphenylamine
acridine was obtained thus:

Other methods by which acridine was

obtained were the following:

1) By passing phenyl-o-toluidine through a red-hot tube. The equation representing the reaction is the following:

2) Acridine was obtained by reduction of o-nitrodiphenylmethane thus:

3) By distillation of o-aminodiphenylmethane over lead oxide.

4) By heating 2:2 -diaminobenzophenone with zinc dust.

5) By heating 20 grams of salhydraniline with 25 grams of phosphorus pentoxide.

6) By passing the vapour of benzylaniline through a hot tube.

Properties of Acridine and its Derivatives

Acridine crystallises in small colourless needles, or four-sided rhombic prisms, sublimes at 100°C ., melts at 111°C ., boils above 360°C without decomposition, and distils with steam. It is sparingly soluble in hot water, but readily soluble in alcohol, ether, or carbon disulphide, yielding solutions showing a blue fluorescence. When inhaled either as dust or vapour it causes violent sneezing, and in solution both it and its salts cause much irritation on the skin. On treatment with nitric acid it yields two

nitro-derivatives (m. p. 154° C. and 214° C.) and a dinitro-derivative; potassium permanganate oxidises it to 2:3 - quinolinedicarboxylic acid $C_9H_5N(CO_2H)_2$, and sodium amalgam reduces it to hydroacridine $C_{13}H_{11}N$. The salts are yellow and crystallise well, but are decomposed into their constituents on boiling. Heated with hydrogen and finely divided nickel, it forms 2:3 - dimethylquinoline. The halogen addition compounds of acridine and its derivatives are formed by the direct action of the halogen on the acridine; or by the action of a mixture of phosphorus oxychloride and pentachloride on thioacridone. When exposed to sunlight acridine forms pale-yellow crystals, M. P. 276° .

2:7 - dimethyl - 3:6 - diaminoacridine
or acridine yellow

is obtained by heating under pressure tetraminoditolylmethane with hydrochloric acid and water, the product is then oxidised with ferric chloride or potassium percarbonate $K_2C_2O_8$ or hydrogen peroxide, and the resulting metallic salt decomposed with hydrochloric acid. It forms yellow crystals melting

was determined by O. Fischer and G. Korner; probably two molecules of aniline and one of p - toluidine condense when oxidised to opp-triaminotriphenylmethane, this yielding chrysaniline when further oxidized. This view is supported by the fact that when opp-triaminotriphenylmethane is heated with arsenic acid to 150° - 180° C., chrysaniline is produced.

EXPERIMENTAL PART

Attempts were made to prepare acridine itself from:

1) By the reaction among diphenylamine, formic acid and zinc chloride (equation No. 1 above). Success, however, was not obtained in this experiment, for the yield was very poor.

Procedure:

50 grams of diphenylamine }
75 c. c. of formic acid } were heated

in a free flame for 5 hours using a reflux condenser. It was then diluted with water and let stand over night when the crystals of formyldiphenylamine separated out. The latter crystals, after being purified from

alcohol, were white and had a m. p. of 73°C .
Acridine was not obtained when the formil-
diphenylamine was heated with zinc chloride.

2) By the reaction among diphenylamine,
chloroform, aluminium chloride and zinc oxide.
(equation No. 2 above).

Procedure:

250 grams of diphenylamine	}	were
250 grams of chloroform		
250 grams of aluminium chloride		
125 grams of zinc chloride		

heated in an autoclave for 8 hours at a temperature of 210°C . The dark mass obtained was extracted several times with concentrated hydrochloric acid. This was filtered thru glass wool, the filtrate was diluted with water when the unchanged diphenylamine was precipitated out. This was filtered thru common filter paper and the filtrate was made alkaline with sodium hydroxide when the acridine was supposed to precipitate out with zinc hydroxide. This process however was not successful for all the precipitate obtained was zinc hydroxide. This was due to the autoclave not being in order, for the reaction did not take place.

3) By passing the vapours of benzyldiphenylamine

over heated lead oxide thus oxidizing it to acridine. The following equation represents the reaction.

This experiment was not successful due to the insufficient apparatus used. ?

4) By heating acridinecarboxylic acid, acridine was successfully obtained, but since acridinecarboxylic acid is an expensive product, the process becomes not practical. The following equation shows the reaction which took place:

Derivatives of Acridine.

Methylacridine was successfully prepared

from diphenylamine thus:

Procedure:

50 grams of diphenylamine }
 85 grams of zinc chloride } were
 30 c.c. of acetic acid }

mixed in an erlenmeyer flask and heated for 14 hours on an oil-bath at a temperature of 220° C. The dark cake obtained was dissolved in a 50 % solution of sulphuric acid at 100° C. (water bath), and poured into an excess of water. This was filtered thru glass wool and the filtrate discarded. The precipitate was extracted several times with 5 % solution of hydrochloric acid. The methylacridine was precipitated out with sodium hydroxide from the combined filtrates obtained from the extractions of the dark mass with 5 % solution of hydrochloric acid.

The methylacridine obtained above was purified thus:

Ten grams of it were dissolved in 50 c.c. of methyl alcohol and to this solution was added a solution of 10 grams of tartaric acid in 100 c.c. of methyl alcohol. The methylacridine precipitated out as the tartrate in fine yellow needles. This tartrate was filtered out with suction and washed several times with methyl alcohol. It was then put in a flask containing water and a solution of Na_2CO_3 added to it, when the pure methylacridine precipitated out. The latter was filtered at the pump and washed several times with water. The m.p. of methylacridine is 114°C .

PREPARATION OF ACRIDYLALDEHYDE FROM METHYLACRIDINE

In the reaction methylacridine was first condensed with p-nitrosodimethylaniline. This

condensation product was then hydrolysed in the presence of dilute hydrochloric acid thus forming the acridylaldehyde. The following equation represents the reaction which took place.

A mixture of equi-molecular weights of methylacridine and p-nitrosodimethylaniline were heated in an oil-bath at a temperature of $100^\circ - 120^\circ \text{C}$, till a green liquid formed by melting the mixture, was solidified. The solid thus obtained was extracted with methylalcohol (to remove impurities) when the condensation product (a red powder) was obtained. Its melting point was 234°C .

This product was dissolved in dilute hydrochloric acid, before heating on the water-bath, to avoid decomposition. The acridylaldehyde is purified from methylalcohol. Its melting

hydrochloric acid and from this solution the acridylaldehyde was precipitated out with a solution of sodium carbonate. The acridylaldehyde was purified from methylalcohol. The fine yellow needles of acridylaldehyde thus obtained have a m.p. of 140° C.

PREPARATION OF ACRIDYLALDOXIME FROM ACRIDYLALDEHYDE

Acridylaldoxime was prepared from acridylaldehyde thus:

Procedure: - 20 grams of acridylaldehyde are dissolved in methylalcohol and to the resulting solution are added 8 grams of hydroxylamine sulphate and 6.5 grams of sodium ethylate. This is heated on a water-bath for 2 1/2 hours. (Care should be taken not to let the mixture stand, before heating on the water-bath, to avoid decomposition). The acridylaldoxime is purified from methylalcohol. Its melting

point is 274 C.

Attempts were made to reduce the acridylaldehyde, with sodium amalgam, to the acridylmethylamine, but success in this experiment was not reached. The following equation represents the reaction which was expected to take place:

Reduction between the N and C will take place at the same time, forming a dihydroacridine derivative.

PREPARATION OF ACRIDYLMONOMETHYLOL FROM METHYLACRIDINE

The condensation product of methylacridine and formaldehyde (or acridylmonomethylol) was prepared in the following way:

Procedure:- 10 grams of 9-methylacridine were treated with 10 c.c. of 20 % formaldehyde solution during 4 hours on a water-bath. The resulting product was allowed to stand over night when the acridylmonomethylol was formed.

PREPARATION OF 9-ACRIDINECARBOXILIC ACID FROM ACRIDYLMONOMETHYLOL

Acridinecarboxilic acid was obtained from acridylmonomethylol according to the following reaction:

9-Acridinecarboxilic acid was obtained by oxidizing the acridylmonomethylol obtained above with a solution of chromic acid in sulphuric acid.

Procedure:- 2 grams of acridylmonomethylol

are dissolved in dilute sulphuric acid (1 to 5 water) then heated on a water-bath, and while this heating process is carried on, a solution of 2.5 grams of chromic acid, 4 grams of concentrated sulphuric acid and 10 c.c. of water, was gradually added to it. After having added the whole chromic acid solution to the solution of acridylmonomethylol, the whole content of the flask is further heated on the water-bath for an hour when it is diluted with water and filtered. The precipitation is extracted with diluted sodium carbonate solution and filtered (common filter paper). The filtrate is made faintly acid with acetic acid when the acridinecarboxylic acid precipitates out as a yellow powder. Its m.p. is 300° C.

PREPARATION OF THE METHYL-ESTER OF 9-ACRIDINECARBOXILIC ACID FROM 9-ACRIDINECARBOXILIC ACID

This experiment was not successful.

The ester cannot be obtained by the usual method, that is by treating the 9-acridinecarboxylic acid and the alcohol in the presence of sulphuric acid (equation above), however it can be obtained by treating the acid chloride of 9-acridine - carboxylic acid with absolute alcohol thus:

PREPARATION OF 9-BENSOYLAMINOMETHYL-ACRIDINE FROM DIPHENYLAMINE.

This experiment was very successful and the yield obtained was very good. The following equation represents the reaction which took place.

Procedure:-

10 grams of hippuric acid }
14 grams of diphenylamine } were put
20 grams of zinc chloride }

in an erlenmeyer flask and heated in an oil-bath for 8 hours at a temperature of 200 - 220 C. The reddish-brown compound formed was extracted several times with a 50 % solution of hydrochloric acid, that is, until the extracted liquid gave no more precipitate with a concentrated solution of sodium hydroxide. The precipitates thus obtained were all put together and extracted with ethyl alcohol in which the 9-benzoylaminomethylacridine is very soluble. What was left behind was zinc hydroxide.

The alcoholic solution of the 9-benzoylaminomethylacridine obtained above was divided into 3 parts.

1) The volume of the first part was slightly reduced by evaporation of its alcohol on the water-bath. It was then put in the ice-box and allowed to crystallise out. The crystals were small, needle-like and shiny. Their m.p. was 182° C.

2) Some alcoholic picric acid was added to the second part of the solution obtained above, The resulting solution was heated on the water-bath till its volume was somewhat reduced, and it was then filtered while hot. The filtrate was put into the ice-box and allowed to crystallise out. The pure crystals of the picrate formed, while in alcohol, had a beautiful appearance similar to gold dust mixed with bannana oil. The m.p. of the picrate salt was 194° C.

3) The hydrochloric salt of 9-benzoylaminomethylacridine was made by putting some dilute hydrochloric acid into the third part of the solution, evaporating some of it and letting it crystallise out.

PREPARATION OF 9-BENZOYLAMINOMETHYL- ACRIDINE FROM METHYLACRIDINE

This method has not yet been successful, because the reduction of the acridylalldoxime

to the acridylmethylaniline has not been possible. Attempts are still in progress for the reduction of the acridylaldehyde. The following equation represents the reaction which is expected to take place.

Conclusion:- Acridine itself seems to be difficult to prepare, but some of the rea-

ctions for the preparation of its derivatives take place very easily. By the method described above, methylacridine is very readily obtained. The first method described above for the preparation of 9-benzoylaminomethylacridine seems to be practical, the compound is easily obtained. The second process described for the preparation of this compound is still in the experimental stage. The reaction in this case has been carried to the preparation of the 9-acridylalldoxime, but no further due to the difficulty met in reducing the compound to the 9-acridylmethylanine.

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