[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF LOUISVILLE]

THE SYNTHESIS OF 1(9)-NITRO- AND 3(7)-NITRO-ACRIDINE AND 1(9)-METHYL- AND 3(7)-METHYLACRIDINE[1]

BY H. JENSEN AND M. FRIEDRICH[2]

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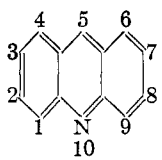
Introduction

In the nitration of acridine with concd. nitric acid, Graebe succeeded in isolating two mononitro and one dinitro derivative of acridine.[3] He called the two mono derivatives α, m. p. 214°, and β, m. p. 154°, but was unable to say anything about the position of the nitro group in the acridine ring

Looking over the acridine formula, for which we are using the following numbering one can easily see that there may exist four different mono-



substitution derivatives of acridine, not taking into consideration Position 5.

In repeating the experiment of Graebe we were also able to secure two mononitro derivatives and one dinitro derivative, but we found that the melting point of the β derivative, which we recrystallized several times from alcohol, increased to 167°. The melting point of the α derivative was found to be 216°. There is only one known nitro derivative of acridine, namely, the 1(9)-nitro-acridine; m. p., 167°.[4] Thus we believe that in the β-nitro derivative the nitro group is in the 1(9) position. There is formed only a small amount of β-nitro-acridine in the nitration of acridine; the main products are α-nitro- and the dinitro-acridine.

Now it was necessary to find a method to synthesize the α-nitro derivative in such a way that there could be no doubt about the position of the nitro group. The known methods for preparing acridine derivatives either do not apply to the nitro compounds or give very poor yields.[4,5] For this reason we thought it worth while to find a more general method for

[1] Third communication on acridine derivatives.

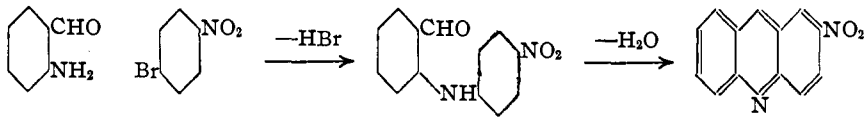
[2] This paper is an abstract of a part of a thesis presented by Martin Friedrich, in partial fulfilment of the requirements for the degree of Master of Science in Chemistry at the University of Louisville.

[3] Graebe and Caro, *Ann.*, **158**, 275 (1871).

[4] Mayer, *Ber.*, **50**, 1306 (1917).

[5] Bernthsen, *Ber.*, **18**, 689 (1885). Besthorn, *Ber.*, **24**, 2039 (1891). Graebe, *Ber.*, **25**, 1733 (1892); *Ann.*, **278**, 268 (1894). Ullmann, *Ann.*, **355**, 318 (1907); *Ber.*, **39**, 298, 356 (1906).

preparing acridine derivatives. We thought that it would be possible to condense *o*-aminobenzaldehyde with halogen derivatives of nitrobenzene to give the diphenylamine derivatives and to close the ring with concd. sulfuric acid according to the following scheme.



Mayer has already used a modification of this reaction in the preparation of some acridine derivatives.[4]

Accordingly, we condensed *o*-aminobenzaldehyde with the three different bromonitrobenzenes. In the case of the *ortho* and *para* compounds only one nitroacridine derivative, 1(9)-nitro-acridine and 3(7)-nitro-acridine, respectively, can be formed, but in the case of the *m*-bromonitrobenzene two different nitro-acridine derivatives can be formed, 4(6)- and 2(8)-nitro-acridine. We were able to secure in the two first cases the corresponding nitroacridine derivatives, and in the case of the *m*-nitrobromobenzene we were able to isolate two different nitro derivatives. In order to identify these, experiments are under way at the present time. In the same way we condensed *o*-aminobenzaldehyde with *o*-bromo- and *p*-bromotoluene and were able to isolate the corresponding methylacridine derivatives. The condensations of *o*-aminobenzaldehyde with other halogen derivatives of benzene will be studied to learn if this method is a general one.

Experimental Part

Preparation of Acridine.—The following method was found to give the best yield.

Thirty g. of acridone[6] was placed in a 2-liter flask with 1 liter of alcohol and refluxed on a water-bath. Four hundred and fifty g. of 4% sodium amalgam was added gradually and the mixture boiled for eight hours. The main part of the alcohol distilled off and the dihydro-acridine precipitated. The dihydro-acridine, which was oxidized partly by the oxygen of the air to acridine, was used without further purification.

Sixteen g. of dihydro-acridine was dissolved in a flask in 180 cc. of acetic acid. Eight g. of potassium dichromate dissolved in 30 cc. of water was run in very slowly, with stirring. After all had been added, the solution was heated for 15 minutes on the water-bath. The acridine was precipitated with hot water, the oil formed soon crystallized and was filtered by suction. More acridine precipitated from the filtrate when it was made alkaline with ammonium hydroxide.

Purification of Acridine.—Ten g. of acridine was dissolved in 50 cc. of methyl alcohol, and a solution of 10 g. of tartaric acid in 100 cc. of alcohol was added. The tartrate of acridine precipitated at once in fine, sulfur-yellow needles. The salt was filtered with suction and washed well with alcohol. The free base was formed by adding a solution of sodium carbonate in water to the salt.

The base was pure enough for the next experiment. It was purified from water and petroleum ether; m. p., 107°.

[6] Goldberg, *Ber.*, **39**, 1691 (1906).

Anal. Calcd. for C_3H_9N: C, 87.15; H, 5.03. Found: C, 87.03; H, 5.17.

Nitration of Acridine.[6]—The nitration of acridine was conducted according to the directions of Graebe. To obtain the β-nitro derivative in pure state (m. p., 167°) was rather troublesome and could be accomplished only by several fractional crystallizations from alcohol.

The α-nitro-acridine crystallized from alcohol in golden-yellow, shiny leaves; m. p., 216°.

Anal. Calcd. for $C_{13}H_8O_2N_2$: C, 69.62; H, 3.59. Found: C, 69.68; H, 3.65.

The β-nitro-acridine crystallized from alcohol in silvery, shiny leaves which caused sneezing; m. p., 167°.

Anal. Calcd. for $C_{13}H_8O_2N_2$: C, 69.62; H, 3.59. Found: C, 69.53; H, 3.73.

The dinitro-acridine crystallized from acetic acid in red-yellow plates which did not melt when heated to 250°.

Preparation of 1(9)-Nitro-acridine.—Four and eighty-four hundredths g. of *o*-aminobenzaldehyde, 8.08 g. of *o*-nitrobromobenzene and 0.5 g. of copper powder were heated with 2.12 g. of anhydrous sodium carbonate and 40 g. of freshly distilled nitrobenzene in a round-bottomed flask, with an air condenser, for three hours in an oil-bath, at 220°. The nitrobenzene was distilled with steam. The residue, after filtration with suction, was heated with 10 cc. of concd. sulfuric acid on a water-bath for an hour. This solution was poured on ice, filtered and the filtrate made alkaline with ammonium hydroxide. The precipitate was purified from alcohol, yielding silvery, shiny leaves, m. p. 167°, and having the same properties as the product obtained by nitration of acridine. The mixed melting point showed no depression.

Anal. Calcd. for $C_{13}H_8O_2N_2$: C, 69.62; H, 3.59. Found: C, 69.48; H, 3.68.

Preparation of 3(7)-Nitro-acridine.—This compound was prepared in the same way as the 1(9) derivative except that *p*-bromonitrobenzene was used instead of the *ortho* derivative. The properties were the same as those of the so-called α-product obtained by the nitration of acridine. The melting point was 216°; the mixed melting point showed no depression.

Anal. Calcd. for $C_{13}H_8O_2N_2$: C, 69.62; H, 3.59. Found: C, 69.50; H, 3.74.

Preparation of 1(9)-Methylacridine.—Four g. of *o*-aminobenzaldehyde, 9 g. of *o*-bromotoluene and 0.5 g. of copper powder were heated with 2 g. of anhydrous sodium carbonate and 40 g. of nitrobenzene for three hours, at 220°. The nitrobenzene was distilled with steam. The diphenylamine compound was extracted with ether, dried with sodium sulfate and the ether removed by distillation. The residue was heated with 15 cc. of concd. sulfuric acid on the water-bath for one hour. The solution was poured into ice water, filtered and the filtrate made alkaline with ammonium hydroxide, when the methylacridine precipitated.

It recrystallized from ligroin in needles, m. p. 88°, with properties the same as stated by Locher.[7]

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.00; H, 5.74. Found: C, 86.85; H, 5.97.

Preparation of 3(7)-Methylacridine.—This compound was prepared in the same way as the 1(9) derivative except that *p*-bromotoluene was used instead of the *ortho* derivative. Purified from ligroin, it gave slightly yellow needles; m. p., 134°, with properties the same as stated by Kahn.[8]

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.00; H, 5.74. Found: C, 87.04; H, 6.03.

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[7] Locher, *Ann.*, **279**, 279 (1894).

[8] Kahn, *Ann.*, **279**, 273 (1894).

Summary

It has been shown that the two mononitro-acridine derivatives formed in the nitration of acridine are 1(9)- and 3(7)-nitro-acridine. The two mentioned acridine derivatives have been synthesized by condensing *o*-aminobenzaldehyde with *o*-bromonitrobenzene and with *p*-bromonitrobenzene, respectively, and closing the ring with concd. sulfuric acid. In a similar way 1(9)- and 3(7)-methylacridine have been synthesized.

LOUISVILLE, KENTUCKY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE REACTION BETWEEN NITROSOBENZENE AND PHENYLMAGNESIUM BROMIDE

BY HENRY GILMAN AND ROY MCCRACKEN

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Introduction

In connection with a study of the reaction between nitrobenzene and organomagnesium halides it was necessary to determine the mode of reaction between nitrosobenzene and phenylmagnesium bromide. Pickard and Kenyon[1] reported the formation of *p*-nitrosotoluene from *p*-nitrotoluene and an organomagnesium halide. The formation of a nitroso compound has not been confirmed in studies of the reaction of nitrobenzene, *p*- and *o*-nitrotoluene and *p*-nitrodimethylaniline with organomagnesium halides. Partly because the nitroso compounds may have been lost as a result of side reactions (no experimental details are given in the Note of Pickard and Kenyon), and particularly because both nitrobenzene and nitrosobenzene give diphenylamine when brought into reaction with phenylmagnesium bromide, it was thought that a study of the reaction with nitrosobenzene would help in an interpretation of the reaction between nitrobenzene and organomagnesium halides.

Historical Part

Many and varied compounds containing a nitrosyl (—N=O) group have been made to react with Grignard reagents. The most extensive studies have been carried out by Wieland and co-workers. Wieland[2] first studied the reaction with *p*-nitrosodimethylaniline and nitrogen dioxide. Later, with Roseeu, a more extensive study was made on nitrosobenzene;[3a] sub-

[1] Pickard and Kenyon, *Proc. Chem. Soc.*, **23**, 153 (1907).

[2] Wieland, *Ber.*, **36**, 2315 (1903).

[3] (a) Wieland and Roseeu, *Ber.*, **45**, 494 (1912). (b) See also Wieland and Offenbächer, *Ber.*, **47**, 2111 (1914), for nitrosobenzene. (c) Wieland and Gambarjan, *Ber.*, **39**, 1499 (1906), for nitrosobenzene and nitrogen dioxide. (d) Wieland and Roth, *Ber.*, **53**, 210 (1920), for nitrosobenzene and *p*-nitrosotoluene. (e) Wieland and Kögl, *Ber.*, **55**, 1798 (1922), for *p*-nitrosotoluene, *p*-nitroso-anisole and *p*-nitrosodimethylaniline. (f) Wieland and Reverdy, *Ber.*, **48**, 1112 (1915), for nitroso-*p*-ditolylamine.