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University of Louisville

The Preparation of Hydroxy-Acridines
and Different 5-Position
Acridine Derivatives

A Dissertation
Submitted to the Faculty
of the
Graduate School of Liberal Arts
in Partial Fulfilment
of the
Requirements
for the Degree
of
Master of Science

Department of Chemistry

By

Francis Bratton Rothwisch

1928

THE PREPARATION OF HYDROXY-ACRIDINES
AND DIFFERENT 8-POSITION
ACRIDINE DERIVATIVES

Introduction

Jensen and Friedrich¹ have outlined new methods for the preparation of acridine compounds. They have shown that the treatment of o-aminobenzaldehyde with the halogen derivatives of nitrobenzene and with the corresponding derivatives of toluene would yield the corresponding diphenylamine derivatives. These diphenylamine derivatives split off water very easily to form acridine compounds. By this method they have prepared the 1(9)-nitro and 3(7)-nitroacridine, and the 1(9)-methyl and 3(7)-methylacridine.

The general application of the reaction used in preparing these compounds has been examined, and it has been found that the reaction can be extended in two ways. Halogen derivatives of benzene compounds, other than those mentioned, can be used, or the aminobenzaldehyde can be replaced by o-amino phenylketones.

The halogen derivatives of phenols were chosen first for the following reason. K. Matsumura² has

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1 Jensen and Friedrich, J. A. C. S., 49, 1049 (1927)
2 Matsumura, J. A. C. S., 49, 816 (1927)

described the preparation of 1(9)-hydroxyacridine by reduction of the corresponding acridone compound in boiling amyl alcohol with sodium. These results seemed open to question because it was believed that the dihydroacridine should be obtained, since acridine itself will give dihydroacridine under the conditions stated. As the products obtained from the phenol are identical with those of the Japanese chemist, no hydrogenation of the acridine ring occurred during the reduction. In this work the free phenols could not be used as the hydroxy group itself reacted. For this reason the methyl and ethyl ethers were employed.

Next the o-aminobenzaldehyde was replaced by o-aminophenylketones. This reaction should lead to 6-position acridine derivatives according to the following scheme:

For R the investigations included the hydrogen, methyl, and phenyl groups, and for R₁ the methyl, nitro, and alkoxy groups, which were in either ortho or para position to the halogen. In all cases it was possible to secure the corresponding acridine compounds without great difficulty.

F. Mayer³ has shown that the chlorine in o-chloro-acetophenone is not labile enough to react with aromatic amino compounds to give the corresponding diphenylamine derivatives as is the case with o-chloro-benzophenone. It was thought that by introducing a nitro group in the para position to the halogen, that the latter could be made more reactive. It was found that the chlorine in 5-nitro 2-chloro acetophenone reacts very readily with aniline to give the corresponding diphenylamine derivative. The latter could be converted very easily into 3(7)-nitro 5-methyl acridine, which has also been prepared in a different way. Experiments indicate that the chlorine in 5-nitro 2-chloro acetophenone reacts also with o- and p- nitroaniline. These products would give dinitro methylacridines in the final step of the reactions. It would be interesting to see if the chlorine in 5-nitro 2-chloro benzaldehyde would react similarly.

Jensen and Howland⁴ have reported the synthesis of acridine-5-ethylamine. This compound has been tested for its antiseptic properties, and these preliminary experiments indicate that the compound

 3 F. Mayer and H. Freund, Ber., 55, 2054 (1922)

4 Jensen and Howland, J. A. C. S., 48, 1988 (1926)

possesses antiseptic properties which make it worth while to prepare compounds similar to this one. First it was thought worth while to prepare lower homologues of acridine ethylamine--that is, 5-amino and 5-methylamino acridine. It was intended to prepare the 5-amino acridine by converting the ester of acridine-5-carboxylic acid by the reaction of Curtius into 5-amino acridine. The preparation of the methyl and ethyl esters of the acridine-5-carboxylic acid may be reported. The acridine-5-carboxylic acid could not be esterified with alcohol and hydrochloric acid, neither by letting the mixture stand in the cold for several days, nor by heating for two days. No reaction could be obtained with sulfuric acid and alcohol. Pfitzinger⁵ observed the same phenomenon in the cases of the β -methyl- and of the β -phenyl- cinchonic acids, as did also Borsche⁶ in the case of tetrahydroacridine-5-carboxylic acid. Steric hindrance will probably account for this behavior of the acridine-5-carboxylic acid. The esters can be obtained from the acid chloride, which can be prepared by heating the acid with thionyl chloride. The esters were not carried further because the 5-aminoacridine has

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 5 Pfitzinger, J. F. pr. Ch. (2) 33, 100; 38, 582; 56, 283
 6 W. Borsche, Ann., 377, 70-123 (1910)

already been described in a patent of the Höchst Farbwerke⁷.

It was thought that the 6-methylaminoacridine could be formed thus:

Experiments indicate that HI has been split off in the condensation of the amino compound with iodobenzene, but attempts to isolate the final product were not successful. The experiments could not be repeated under other conditions because it took too much time to prepare the amino compound.

Attempts were also made to reduce the oxime prepared from the acridyl aldehyde. These too were

7 Höchst Farbwerke: Contr., 1923₂, 1249-1252

unsuccessful under the conditions used.

The melting points given in this thesis are all uncorrected. They were, however, made with the same thermometer under identical conditions.

Experimental

3(7)-Ethoxyacridine.--

2.3 g. o-aminobenzaldehyde, 5 g. p-bromophenetol, 0.4 g. copper powder, 5 g. anhydrous sodium carbonate, and 30 cc. nitrobenzene were refluxed for 3 hours at 220°. The excess of the phenetol and nitrobenzene was removed by steam distillation. The residue was extracted with ether, the ether solution dried over sodium sulfate, filtered, and then evaporated. The condensation product was dissolved in 15 cc. of glacial acetic acid and 3 cc. of conc. sulfuric acid were added³. This mixture was then heated on the water bath for 5 minutes, poured into ice water and filtered. The filtrate was made alkaline with ammonium hydroxide. The precipitate was crystallized from dilute alcohol, yielding light yellow plates having a M. P. of 99°.

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.68; H, 5.87

Found: C, 80.51; H, 6.12

Picrate of 3(7)-ethoxyacridine.--The picrate was

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 3 It was found in many cases that glacial acetic acid with a few cc. of conc. sulfuric acid was more satisfactory in closing the ring than was conc. sulfuric acid alone. If only sulfuric acid was used, sulfonation sometimes took place, and in the case of the ethoxy compound, partial hydrolysis of the ether group was effected.

made in alcoholic solution. It crystallized from acetone in fine yellow needles. It did not melt at 250° .

Anal. Calcd. for $C_{21}H_{16}O_3N_4$: C, 58.74; H, 3.57

Found: C, 58.97; H, 3.81

Hydrochloride.—To the alcoholic solution of the ethoxy compound, hydrochloric acid was added. The hydrochloride salt precipitated out. It was crystallized from alcohol in bright yellow needles. It decomposed about 200° .

Anal. Calcd. for $C_{15}H_{14}ONCl$: Cl, 13.65

Found: Cl, 13.71

3(7)-Hydroxyacridine.—The ethoxyacridine was boiled for one hour with hydriodic acid (sp. gr. 1.7) and traces of red phosphorus. This was diluted with water and made alkaline with sodium hydroxide. This was filtered again and made neutral with acetic acid. The hydroxy acridine precipitated out. It was crystallized from alcohol in yellow needles. It did not melt at 250° .

Anal. Calcd. for $C_{13}H_9ON$: C, 79.97; H, 4.65

Found: C, 79.83; H, 5.02

1(9)-Methoxyacridine.—

The condensation was made in the same way as the 3(7)-ethoxyacridine except that o-bromoanisole was used in place of the p-bromophenetol. The extrac-

tion of the condensation product and ring closure were done similarly. The methoxy compound was recrystallized from 75% alcohol. The light yellow needles melt at 130-131°.

Anal. Calcd. for $C_{14}H_{11}ON$: C, 80.35; H, 5.30

Found: C, 80.28; H, 5.44

Isolation of the condensation product of o-amino-benzaldehyde and o-bromoanisole⁹.—

The first time the preceding reaction was carried out, the condensation product was extracted with alcohol. When water was added to the alcoholic solution some crystals were formed along with an oil. These crystals were recrystallized from petroleum ether as light yellow crystals, M. P. 99°.

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 73.96; H, 5.77

Found: C, 73.91; H, 6.04

Picrate of 1(9)-methoxyacridine.—The picrate was made in alcoholic solution. It was recrystallized from alcohol as orange-red needles. It decomposed about 250°.

9 The intermediate diphenylamine derivatives in these reactions are hard to isolate because at the high temperature used some ring closure takes place. For this reason much time was not spent in trying to isolate them.

Anal. Calcd. for $C_{20}H_{14}O_8N_4$: C, 54.79; H, 3.22

Found: C, 54.63; H, 3.18

1(9)-Hydroxyacridine.—This was prepared similar to the 3(7)-hydroxyacridine. It crystallized from dilute alcohol as yellow needles, M. P. 116.5° . The properties are the same as stated by Matsumura¹⁰.

Anal. Calcd. for $C_{13}H_9ON$: C, 79.97; H, 4.65

Found: C, 80.00; H, 4.77

Picrate of 1(9)-hydroxyacridine.—The picrate was made in alcoholic solution and crystallized from alcohol as red needles, M. P. 216° ¹⁰.

Anal. Calcd. for $C_{19}H_{12}O_8N_4$: C, 53.77; H, 2.85

Found: C, 53.62; H, 3.14

5-Methylacridine.—

3.4 g. o-aminoacetophenone, 7 g. iodobenzene, 0.4 g. copper powder, 5 g. anhydrous sodium carbonate, and 30 cc. of nitrobenzene were refluxed for 4 hours at 220° . The excess of iodobenzene and nitrobenzene was removed by steam distillation. The residue was extracted with ether, this solution dried over sodium sulfate, filtered, and evaporated. The residue was dissolved in 15 cc. of glacial acetic acid, 3 cc. of conc. sulfuric acid were added and the

¹⁰ See reference 2

mixture was then heated on a water bath for 5 minutes. It was then poured into ice water and filtered. The filtrate was made alkaline with ammonium hydroxide. The precipitate was purified from alcohol, M. P. 94° . For analysis it was purified from petroleum ether, M. P. 114° . The properties agree with the properties of 5-methylacridine prepared by other methods.

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74

Found: C, 87.13; H, 5.92

Picrate of 5-methylacridine.—The picrate is made in alcoholic solution and crystallized from alcohol, M. P. $213-214^{\circ}$.

Anal. Calcd. for $C_{20}H_{14}O_7N_4$: C, 56.86; H, 3.34

Found: C, 56.14; H, 3.61

5, 3(7)-Dimethylacridine.—

2 g. o-aminoacetophenone, 4.2 g. p-bromotoluene, 0.4 g. copper powder, 4 g. anhydrous sodium carbonate, and 30 cc. of nitrobenzene were refluxed for 3 hours at 220° . The product was subjected to steam distillation and extracted with ether similar to the preceding procedure. The oil which remained after evaporation of the ether was heated with 15 cc. of conc. acetic acid and 4 cc. of conc. sulfuric acid on a water bath for 15 minutes and then poured into ice

water. This was filtered and the filtrate was made alkaline with ammonium hydroxide. Then it was shaken out with ether, the solution dried over sodium sulfate, filtered, and evaporated. The residue crystallized from petroleum ether as cream colored plates, M. P. 90° .

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.91; H, 6.32

Found: C, 86.84; H, 6.52

Picrate of 5, 3(7)-dimethylacridine.—The picrate was made in alcoholic solution and crystallized from alcohol as yellow needles. It began to darken at 215° and melted at 225° .

Anal. Calcd. for $C_{21}H_{16}O_7N_4$: C, 57.79; H, 3.70

Found: C, 57.96; H, 3.92

The melting point of 5, 3(7)-dimethylacridine is not in agreement with the melting point given by Bonna¹¹. For this reason his experiment was repeated.

15 g. of pure acetyl phenyl p- tolyl amine were heated with 20 g. of anhydrous zinc chloride for 10 hours at 220° . The method of isolation is the same as that used by Bonna. M. P. 90° . The mixed melting point showed no depression. The product of Bonna might be the 5, 2(8)-dimethyl compound¹². This has

11 Bonna, Ann., 239, 63 (1887)

12 Borsche, Ann., 377, 97 (1902)

the M. P. of 122-123° which is given by Bonna for his product.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.91; H, 6.32

Found: C, 87.12; H, 6.60

The picrate had the same melting point as the product prepared from o-aminoacetophenone.

Anal. Calcd. for $C_{21}H_{16}O_7N_4$: C, 57.79; H, 3.70

Found: C, 57.89; H, 4.07

Condensation of o-aminoacetophenone with p-nitro-bromobenzene.—

3.4 g. o-aminoacetophenone, 7 g. p-nitrobromobenzene, 0.4 g. copper powder, 5 g. anhydrous sodium carbonate, and 30 cc. nitrobenzene were refluxed for 3 hours at 220°. After steam distillation an oil was left which solidified on cooling. This solid was crystallized from alcohol. After several recrystallizations the yellow needles melted at 152°.

Anal. Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.60; H, 4.72

Found: C, 65.51; H, 5.03

3(7)-Nitro 5-methyl acridine.—

1 g. of the 2-acetyl 48-nitro diphenylamine was dissolved in 15 cc. of glacial acetic acid and then 3 cc. of conc. sulfuric acid were added. This was

heated on a water bath for 10 minutes, poured into ice water and filtered. The filtrate was made alkaline with ammonium hydroxide. The precipitate was recrystallized from alcohol as brownish yellow crystals which did not melt at 300° .

Anal. Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.57; H, 4.23

Found: C, 70.63; H, 4.42

Condensation of 5-nitro 2-chloro acetophenone with aniline.--

4 g. nitrochloroacetophenone¹³, 4 g. potassium carbonate, and 5 cc. freshly distilled aniline were heated for 3 hours at $170-180^{\circ}$. It was then extracted with hot alcohol. The crystals from this were crystallized from alcohol as light yellow needles, M. P. 125° .

Anal. Calcd. for $C_{14}H_{12}O_2N_2$: C, 65.60; H, 4.72

Found: C, 65.66; H, 5.07

The condensations of 5-nitro 2-chloro acetophenone with o- and p- nitroaniline were carried out in a similar way.

3(7)-Nitro 5-methyl acridine.--

2 g. of 2-acetyl 4-nitro diphenylamine were dissolved

13 Meisenheimer, Ann., 464, 220 (1926)

in 10 cc. glacial acetic acid, 3 cc. conc. sulfuric acid were added, and the mixture was heated for 10 minutes on a water bath. The method for purification is the same as for the other compound. It did not melt at 300°.

Anal. Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.57; H, 4.23

Found: C, 70.48; H, 4.53

1(9)-Nitro 8-phenyl acridine.—

1.5 g. o-aminobenzophenone¹⁴, 1.7 g. o-nitrobromobenzene, 0.3 g. copper powder, 1.0 g. anhydrous sodium carbonate, and 15 cc. of nitrobenzene were refluxed at 210° for 2½ hours. A steam distillation was made. After cooling over night the residue was filtered and dried. The usual procedure was followed in effecting the ring closure. After pouring the acid solution into ice water and making alkaline with ammonium hydroxide, the precipitate was purified from alcohol. The yellow needles melt at 189-190°. F. Mayer¹⁵ gives the M. P. of this product as 218°. Time was not available for repeating the experiment of Mayer.

Anal. Calcd. for $C_{19}H_{12}O_2N_2$: C, 75.98; H, 4.03

Found: C, 75.92; H, 4.21

14 Ullmann and Bleier, Ber., 35, 4273 (1902)

15 See reference 3

3(7)-Nitro 5-phenyl acridine.—

The procedure throughout was the same as that for the preceding compound, except that p-nitrobromobenzene was used instead of the o- compound. The yellow needles melt at 209-210°. The properties are the same as given by F. Ullmann¹⁶.

Anal. Calcd. for $C_{19}H_{12}O_2N_2$: C, 75.98; H, 4.03

Found: C, 76.07; H, 4.18

3(7)-Methyl 5-phenyl acridine.—

The procedure was the same as for the 1(9)-nitro derivative except that 2.0 g. of p-bromotoluene were used in place of the o-nitrobromobenzene. The brown needles melt at 135°¹⁷.

Anal. Calcd. for $C_{20}H_{15}N$: C, 89.18; H, 5.62

Found: C, 89.27; H, 5.87

The picrate which crystallized as yellow needles melted at 226°.

3(7)-Ethoxy 5-phenyl acridine.—

16 Ullmann, Ber., 39, 301 (1906)

17 See reference 11

3.2 g. o-aminobenzophenone, 4.0 g. p-bromophenetol, 0.3 g. copper powder, 1.5 g. sodium carbonate, and 15 cc. of nitrobenzene were refluxed for 2½ hours at 210°. The method of extraction, ring closure, and precipitation was similar to that of the other compounds. It crystallized from alcohol as yellow plates, M. P. 105-107°.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.25; H, 5.73

Found: C, 84.18; H, 5.96

3(7)-Hydroxy 5-phenyl acridine.—The hydrolysis of the ethoxy compound was carried out similar to that of the 3(7)-ethoxyacridine. It crystallized from dilute alcohol in yellow leaves. It became brown at 260° and sintered without melting at 275° 10.

Anal. Calcd. for $C_{19}H_{13}ON$: C, 84.10; H, 4.83

Found: C, 84.23; H, 5.03

Reduction of bromo o-nitro acetophenone-potassium phthalimide condensation product.—

One gram of the phthalimide compound, which is dissolved in 10 cc. of acetic acid is mixed with a solution of 2.5 grams of crystallized $SnCl_2$ in 3 cc. of fuming HCl . The solution gets a yellow color and

18 W. Hess and Bernthsen, Ber., 18, 695 (1885)
F. Kohnmann, Ber., 41, 4138 (1908)

when 25 cc. of hot water are added, a precipitate is formed. M. P. 201°.

Condensation of the amino compound with iodobenzene.—

4 g. of the amino compound, 4.7 g. iodobenzene, 0.3 g. copper powder, 3 g. anhydrous sodium carbonate, and 30 cc. nitrobenzene were refluxed for 4 hours at 210°. The excess of iodobenzene and nitrobenzene was removed by steam distillation, when a shiny black precipitate was formed. This was dissolved in alcohol (difficultly soluble). It was recrystallized from alcohol, boiling with charcoal, the M. P. was 192°. Some of the black precipitate was crystallized from acetic acid with charcoal, and then recrystallized from alcohol. The M. P. was 200°. The mixed melting point with the amino compound showed no depression, indicating that there was no reaction. Experiments showed though that HI had been formed in the reaction. A small amount of a product having a M. P. of 242° was isolated, but in insufficient quantities for further work. This reaction needs further study.

Oxime of acridyl aldehyde.—

2.1 g. of acridyl aldehyde, 0.7 g. hydroxylamine hydrochloride and 0.7 g. sodium ethylate in alcoholic solution were refluxed for 2½ hours. The yellow need-

les which are formed are purified from methyl alcohol, M. P. 247°.

Attempts to reduce the oxime were unsuccessful.

Ethyl ester of acridine-5-carboxylic acid.—

6.5 g. of acridine-5-carboxylic acid¹⁹ and 20 g. of thionyl chloride were refluxed for 2 hours in a flask which was connected to a reflux condenser by a ground glass joint. The excess of thionyl chloride was removed by extracting three times with absolute benzene. Then the residue was filtered and washed several times with benzene. The acid chloride was immediately refluxed with 50 cc. of absolute ethyl alcohol. After all the chloride had gone into solution, water was added and the solution was made alkaline with sodium carbonate. The precipitate was purified from ligroin. The ethyl ester precipitates out in yellow rhombohedral plates, M. P. 78°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.47; H, 5.22

Found: C, 76.53; H, 5.18

Picrate of the ethyl ester.—The picrate of the ethyl ester was made in alcoholic solution. The flaky yellow needles melt at 226°.

Anal. Calcd. for $C_{22}H_{16}O_9N_4$: C, 54.99; H, 3.36

Found: C, 55.23; H, 3.62

19 Jenson and Homberger, J. A. C. S., 48, 800 (1926)

Hydrochloride.--The ethyl ester was dissolved in the least amount possible of 95% alcohol. To this was added conc. HCl. It was necessary to add ether to this solution to cause the hydrochloride to precipitate. The yellow needles did not melt at 250° .

Anal. Calcd. for $C_{16}H_{14}O_2HCl$: Cl, 12.33

Found: Cl, 12.25

Methyl ester of acridine-5-carboxylic acid.--The procedure is the same as that for the ethyl ester except that absolute methyl alcohol is used instead of absolute ethyl alcohol. The methyl ester crystallized from methyl alcohol in slightly yellow needles, M. P. $126.5-127.5^{\circ}$.

Anal. Calcd. for $C_{15}H_{11}O_2H$: C, 75.93; H, 4.68

Found: C, 76.12; H, 4.55

Picrate of methyl ester.--The picrate of the methyl ester was made in alcoholic solution. The yellow needles melt at $229-230^{\circ}$.

Anal. Calcd. for $C_{21}H_{14}O_9H_4$: C, 54.07; H, 3.03

Found: C, 54.35; H, 3.41

Hydrochloride.--The method of preparation of the hydrochloride salt of the methyl ester was the same as that for the ethyl ester, but the use of ether was not necessary for precipitation. The yellow needles did not melt at 250°

Anal. Calcd. for $C_{15}H_{12}O_2HCl$: Cl, 12.96

Found: Cl, 12.83

Summary

The method described by Jensen and Friedrich for the preparation of acridine derivatives has been extended and the following compounds have been prepared: 1(9)-methoxyacridine, 1(9)-hydroxyacridine, 3(7)-ethoxyacridine, 3(7)-hydroxyacridine, 5-methylacridine, 5, 3(7) dimethylacridine, 5-methyl 3(7)-nitro acridine, 5-phenyl 1(9)-nitro acridine, 5-phenyl 3(7)-nitro acridine, 5-phenyl 3(7)-methyl acridine, 5-phenyl 3(7)-ethoxy acridine, and 5-phenyl 3(7)-hydroxy acridine.

It has been shown that the chlorine in 5-nitro 2-chloro acetophenone is labile enough to react with aniline and its derivatives.

Attempts to prepare the acridine-5-methylamine were unsuccessful.

The preparation of the methyl and ethyl esters of acridine-5-carboxylic acid has been described.