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The condensation of formaldehyde and methyl acridine.

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University of Louisville

The Condensation of

Formaldehyde and

Methyl Acridine.

A Thesis

Submitted to the Faculty

Of the Graduate School of the College of Arts and Sciences

In Partial Fulfillment of the

Requirements for the Degree

Of Master of Science

Department of Chemistry

By

Clifford Albin Belch

1925



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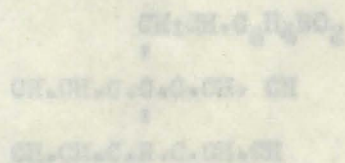
16 June '33 M.P.S.

Very little is known about the acridine ring

system. Such compounds as acriflavine, brucine and strychnine are generally believed to contain the acridine ring system. These compounds are all very important drugs. Acriflavine has been used in the treatment of diseases which are due, in whole or in part, to trypanosoma. Strychnine and brucine which have many and varied uses need not be described here but they are natural plant products. For this reason, acridine derivatives are interesting.

Other derivatives of the acridine type should be of some interest. Methylacridine lends itself to reactions readily. Its condensation with formaldehyde will be discussed in the following pages.

we give the following formula:

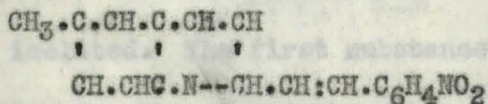


Edward Frieslander has obtained acridyle phenyl
alcohol $\text{C}_{12}\text{H}_9\text{N} \cdot \text{CH}_2\text{CH}(\text{OH}) \cdot \text{C}_6\text{H}_5$ or

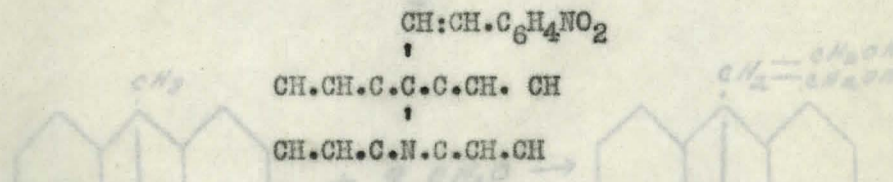


The literature concerning the products derived from the condensation of methylacridine with other substances is very incomplete.

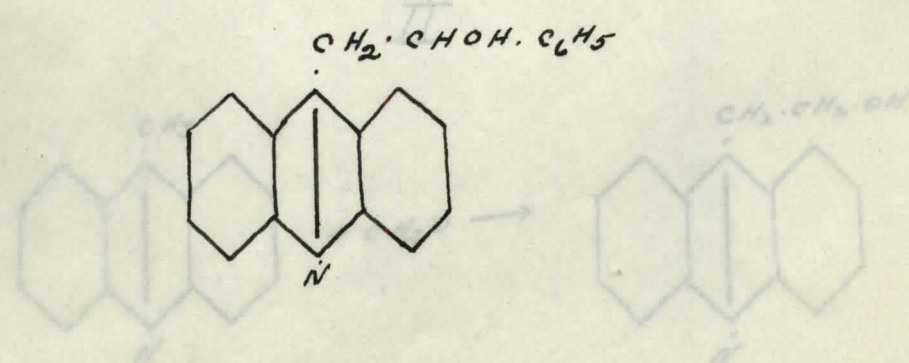
A Parai Kaschitz₁ has obtained m-nitro benzal-ms methylacridine by heating together meta nitro benzaldehyde and ms-methylacridine, with zinc chloride, hydrochloric and acetic acid. In this case water was removed and a condensation product with a double bond was obtained. To this substance he assigned the following formula:



When he melted these substances together with zinc chloride he obtained para-nitro benzal ms methylacridine. To this he gave the following formula:



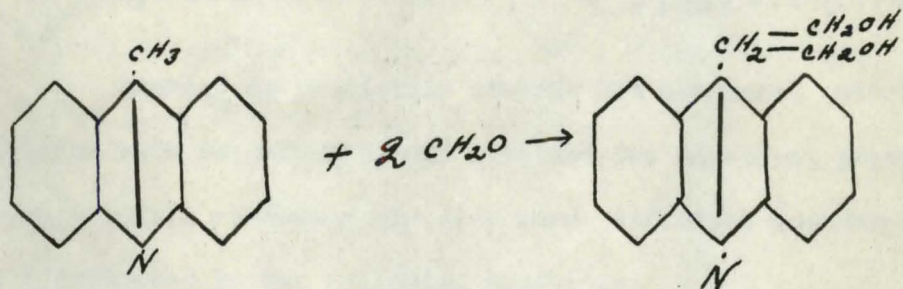
Konrad Friedlauder has obtained acridyle phenyl ethonal $\text{C}_{13}\text{H}_9\text{N} \cdot \text{CH}_2\text{CH} \cdot \text{CH}(\text{OH}) \cdot \text{C}_6\text{H}_5$ or



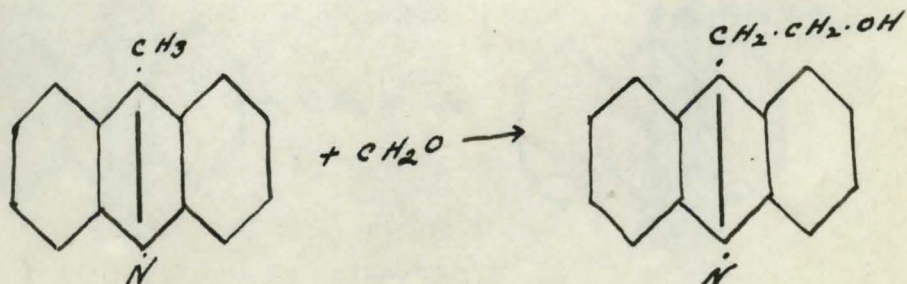
by heating benzaldehyde and methylacridine together in a sealed tube in a water bath for twenty four hours. This product was of the aldol type. He has also prepared m-nitro-cinnamenyl-acridine by heating ms-methyl acridine and m-nitro benzaldehyde in sealed tubes for twenty-four hours. This product has a double bond, water having been eliminated in the condensation process.

Keenigg has prepared condensation products of methylacridine and formaldehyde. Two different products were isolated. The first substance isolated was ^I methylacridine de ethonal and the other ^{II} methylacridine ethonal. To these compounds he assigned the following formulas as shown by these reactions:

I

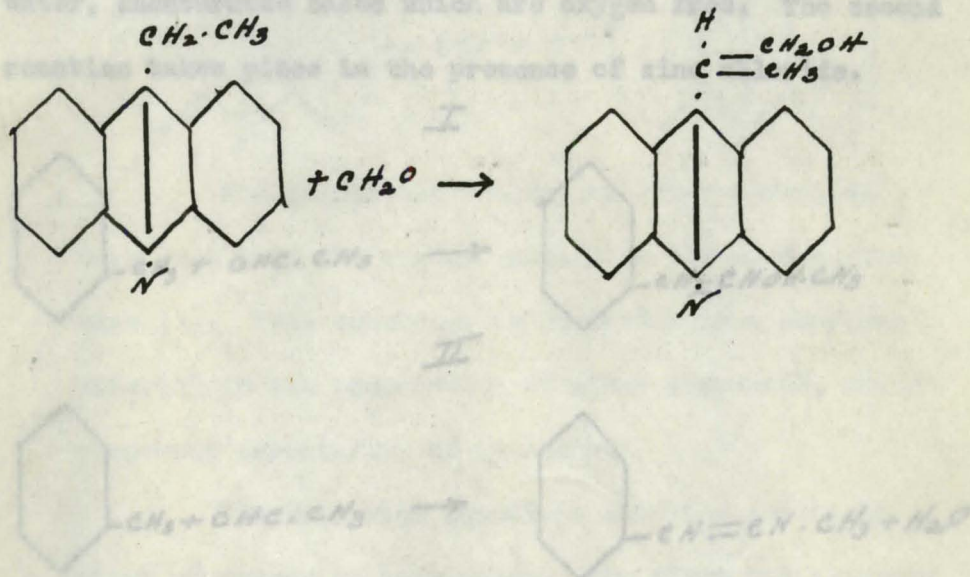


II

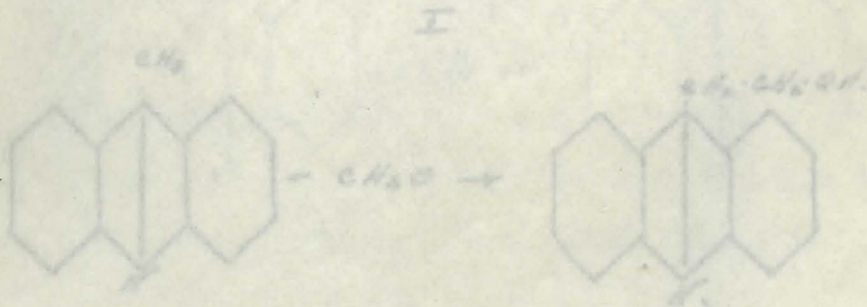


The first of these compounds was obtained in crystalline form but the latter was not so obtained.

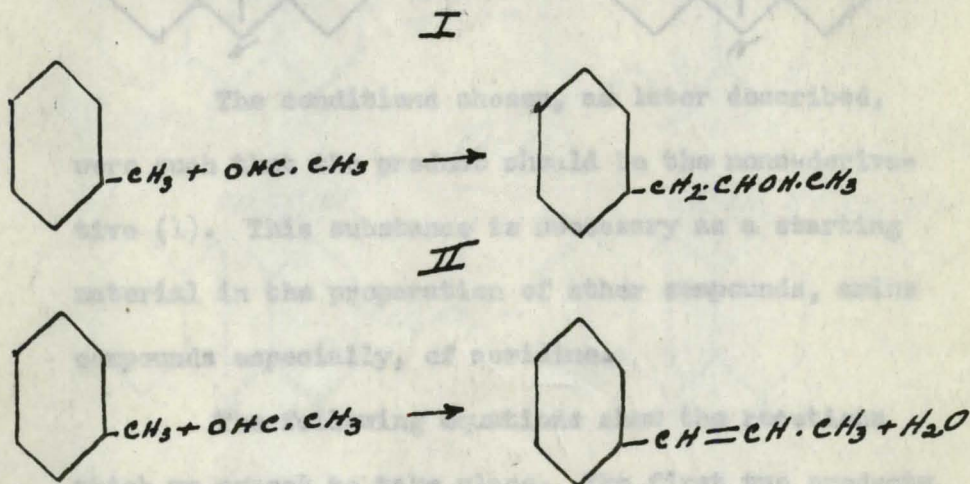
Koenig₄ also condensed ethylmethylacridine with formaldehyde by heating them together.



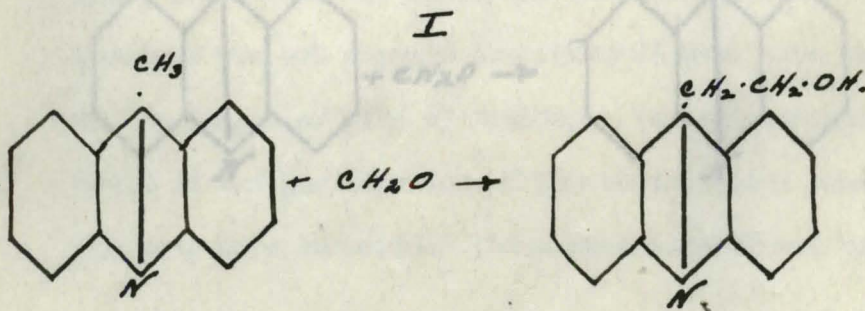
Koenig, as previously stated, has condensed methylacridine with formaldehyde and obtained two different products. Three possible reactions may give three different compounds as illustrated by the following equations:

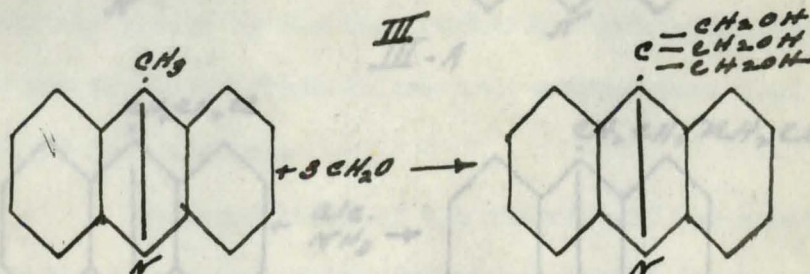
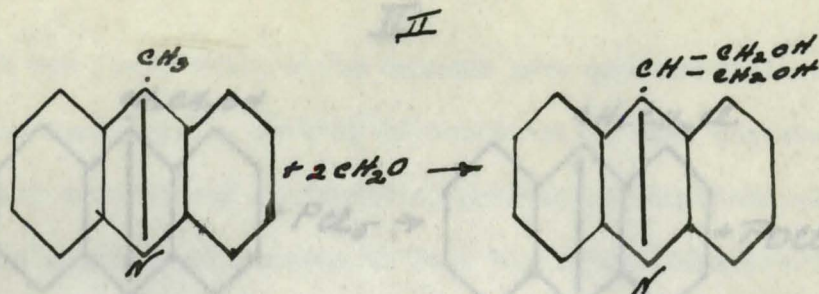


It is generally known that the methyl groups of picoline and quinoline are very reactive. The methyl group of methylacridine is likewise very reactive. The reaction may take place in two different manners. (I) The first possible reactions will give a condensation product of the aldol type. (II) The second reaction will give, by the elimination of water, unsaturated bases which are oxygen free. The second reaction takes place in the presence of zinc chloride.



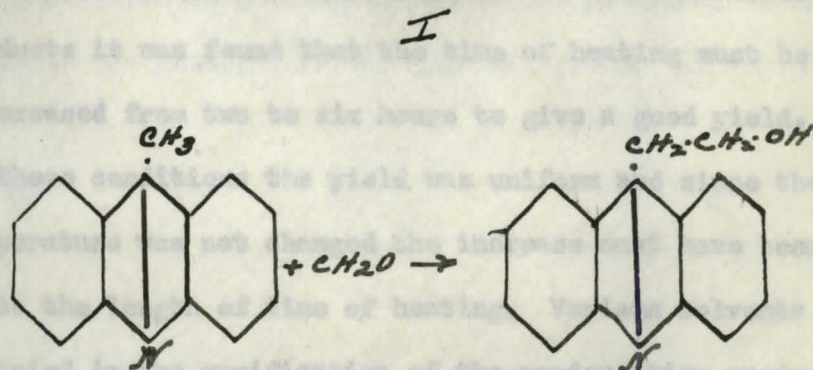
Keenig₅ as previously stated, has condensed methylacridine with formaldehyde and obtained two different products. Three possible reactions may give three different compounds as illustrated by the following equations:



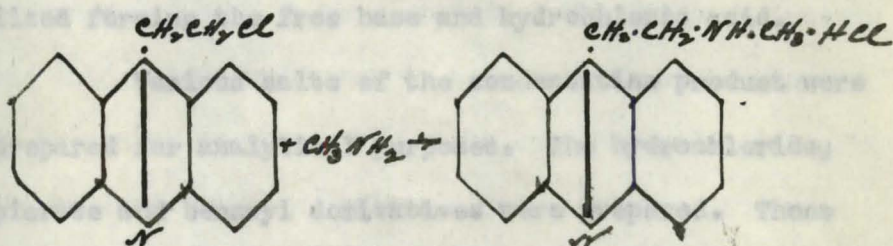
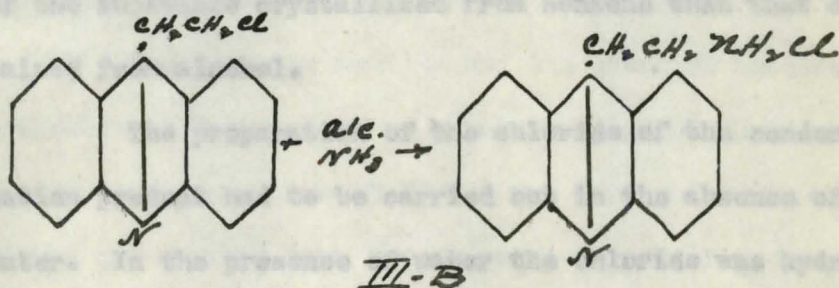
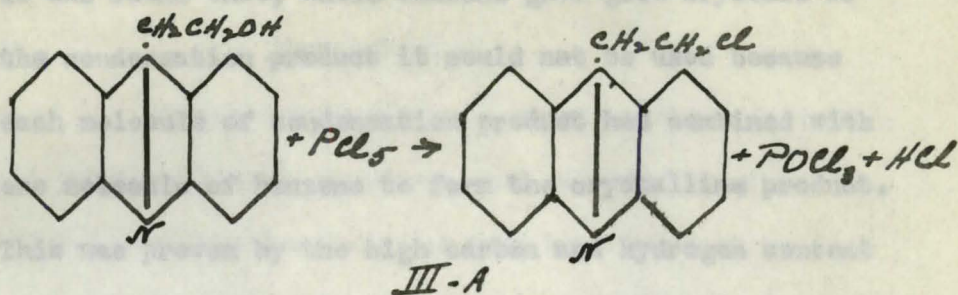


The conditions chosen, as later described, were such that the product should be the mono-derivative (1). This substance is necessary as a starting material in the preparation of other compounds, amine compounds especially, of acridine.

The following equations show the reactions which we expect to take place. The first two products have been obtained in good crystalline form.



II



Some obstacles were encountered at various stages of this work. In the preparation of the condensation products it was found that the time of heating must be increased from two to six hours to give a good yield. Under these conditions the yield was uniform and since the temperature was not changed the increase must have been due to the length of time of heating. Various solvents were tried in the purification of the condensation product but two only were selected. These were alcohol and benzene.

It was found that, while benzene gave good crystals of the condensation product it could not be used because each molecule of condensation product had combined with one molecule of benzene to form the crystalline product. This was proven by the high carbon and hydrogen content of the substance crystallized from benzene than that obtained from alcohol.

The preparation of the chloride of the condensation product had to be carried out in the absence of water. In the presence of water the chloride was hydrolyzed forming the free base and hydrochloric acid.

Various salts of the condensation product were prepared for analytical purposes. The hydrochloride, picrate and benzoyl derivatives were prepared. These were all used in combustions to determine the composition of the base. The benzoyl derivative by yielding a certain composition on combustion proved the presence, in the condensation product, of the hydroxyl group.

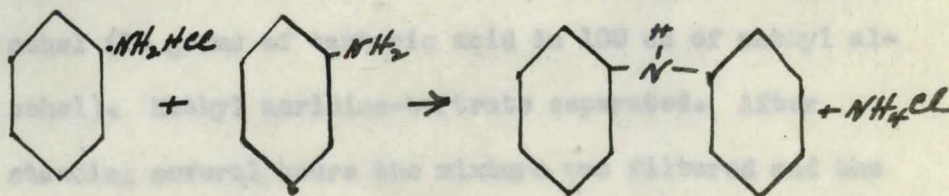


PREPARATION OF METHYLACRIDINE.

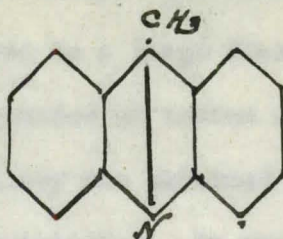
Diphenylamine.

Diphenyl amine is necessary for the preparation of methylacridine. A method₆ was selected which would give a good yield and at the same time would be practical when large amounts of starting materials were used.

100 grams of aniline and 114 grams of aniline hydrochloride were mixed in a thick walled flask and heated in an autoclave at 240° C for twenty-four hours. At the end of this time the contents of the flask were poured out into a large container. The flask was rinsed out with dilute hydrochloric acid and the washing added to the major portion. The whole was then acidified with hydrochloric acid and treated with about two liters of boiling water to hydrolyze the hydrochloride to methylacridine and hydrochloric acid. On cooling and standing, the diphenylamine separated. It was then filtered, washed and dried. It was later distilled from a retort by direct heat. At 275° the diphenylamine melts to an oily liquid and at a slightly higher temperature distilled. It was recovered in a weighed flask. The yield was 50%.



Methyl acridine.



For each 50 grams of diphenylamine 30 cc of glacial acetic acid and 85 grams of zinc chloride were added to the flask in which the diphenylamine was received. The mixture was then heated on an oil bath at 220° C for 14 hours. The melt was then dissolved in 75% sulphuric acid poured into water. This removes most of the zinc salts. After filtering the residue was repeatedly extracted with dilute (5%) hot hydrochloric acid. The filtrates were united and allowed to cool and then filtered. On neutralized with ammonium hydroxide the methylacridine precipitates as a yellow flocculent body. This was then filtered, washed with water and dried by suction. The methyl acridine was then purified by dissolving it in methyl alcohol--10 grams methylacridine to 50 cc of CH₃OH and gradually adding another solution of tartaric acid in methyl alcohol (10 grams of tartaric acid in 100 cc of methyl alcohol). Methyl acridine-tartrate separated. After standing several hours the mixture was filtered and the

residue washed with water. The well washed residue was then transferred to a large flask and covered with water. A clear solution of sodium carbonate was then added until alkalinity was obtained whereupon the methylacridine again precipitated. It was then washed with water filtered and dried. Yield 75%.

1 gram of methyl acridine and an appropriate weight of formaldehyde-20% solution were dissolved in alcohol and heated on a water bath for six hours. A brownish yellow substance separated. This was filtered and dissolved in dilute ethyl alcohol. On standing pale yellow crystalline substance precipitated. It dissolves with difficulty in dilute alcohol but is readily soluble in absolute alcohol. Melting point 154-155° C.

Analysis.

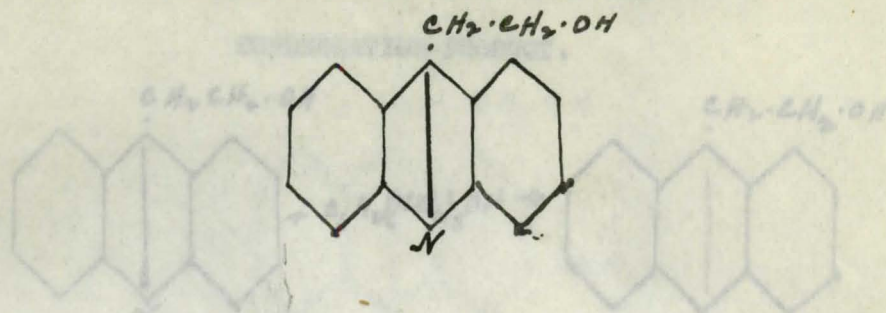
Substance used 1.000 grams. Obtained CO₂ 1.345 g. H₂O 0.2000 g.

Calculated from the theoretical formula C₁₂H₁₁NO

C = 83.7% H = 5.83%

Found C = 81.00% H = 5.15%

PREPARATION OF METHYLACRIDINE ETHANOL.



1 gram of methyl acridine and an equa-molecu-
lar weight of formaldehyde--20% solution were dissolved
in alcohol and heated on a water bath for six hours. A
brownish yellow substance separated. This was filtered
and dissolved in dilute ethyl alcohol. On standing yel-
low crystalline substance precipitated. It dissolves
with difficulty in dilute alcohol but is readily soluble
in absolute alcohol. Melting point $154-155^{\circ} C$.

Analysis.

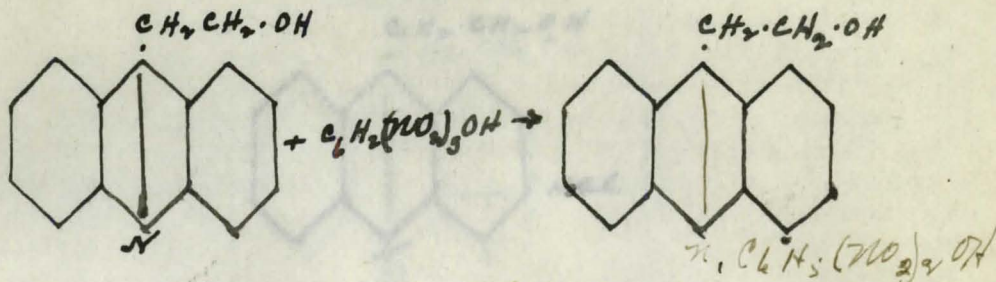
Substance used 1798 grams. Obtained CO_2 5345 g. H_2O .0986

Calculated from the imperical formula $C_{15}H_{13}NO$

$C = 80.7\%$ $H = 5.83\%$

Found $C = 81.06\%$ $H = 6.13\%$

PREPARATION OF THE PICRATE OF THE
CONDENSATION PRODUCT.



To a solution of the condensation product in alcohol a solution of picric acid in alcohol was added as long as precipitation occurred. The yellow crystalline precipitate was separated by filtering. This was recrystallized from dilute ethyl alcohol. This substance was soluble with difficulty in dilute alcohol, ether, and water. Melting Point 178° C. *begin to carbon at 240° and at 290° it blackens.*

Analysis.

Substance .1050 grams CO₂ 2163 g. H₂O 0401 g.

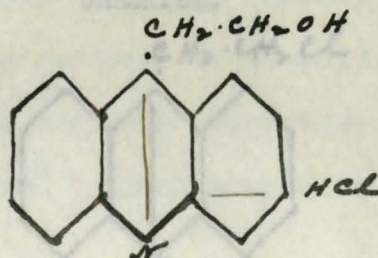
Calculated from the empirical formula C₂₁H₁₆N₄O₈

C = 55.82% H = 3.53%

Found C = 56.1% H = 4.2%

Calculated from the empirical formula
 C₂₁H₁₆N₄O₈
 Cl = 15.04%
 Found Cl = 15.04%
 Cl = 15.04%

PREPARATION OF METHYLACRIDINE ETHANOL
HYDROCHLORIDE.



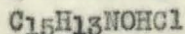
A small amount of the condensation product was dissolved in alcohol and a few drops of concentrated hydrochloric acid added. It was then boiled until solution took place. On cooling and standing the hydrochloride of methylacridine ethanol precipitated. It was filtered and dissolved in absolute alcohol. On standing long yellow needles separated. It begins to darken at 240° and at 260° C it blackens.

Analysis.

Substance .1774 g. AgCl .0999

.2128 g. AgCl .1199

Calculated from the empirical formula



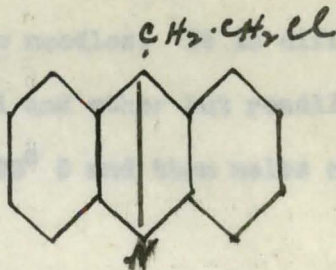
Cl = 13.66%

Found Cl = 13.93%

Cl = 13.94%

PREPARATION OF METHYLACRIDINE ETHANOL

CHLORIDE.

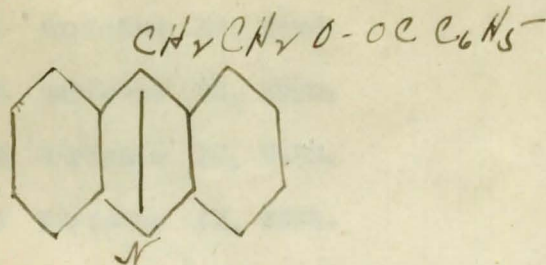


Four grams of the condensation product were treated with $4\frac{1}{2}$ grams of phosphorus pentachloride. The mixture was stirred constantly during the addition of the phosphorus pentachloride. No reaction took place. 10 cc of chloroform were then added. The reaction began at once with evolution of much heat. The mixture was heated on a water bath with water condenser. The condenser was then removed and the heating continued until the chloroform was all expelled. It was next heated under reduced pressure to remove phosphorus oxychloride and phosphorus pentachloride. It was then dissolved in petroleum-ether and a small amount of absolute alcohol. Crystals separated after long standing. This compound melts with decomposition at $114^{\circ} C$. The Bielstein test was positive.

A picrate of this compound was prepared and its melting point determined as $140^{\circ} C$. It decomposes at $160^{\circ} C$. Bielstein test positive. Difficulty soluble in alcohol but easily soluble in water.

A hydrochloride of the chloride was next prepared by treating the chloride with a small amount of hydrochloric acid. This salt crystallized from the mother liquor in yellow needles. It is difficultly soluble in absolute alcohol and ether but readily soluble in water. It darkens at 200° C and then melts at 240° C.

PREPARATION OF THE BENZOYL DERIVATIVE OF
METHYL ACRIDINE ETHANOL.



1 gram of methyl acridine ethanol was treated with benzoylchloride with constant shaking in alkaline solution. It was then heated for 1 hour on a water bath to decompose any remaining benzoyl chloride. It was then filtered and the residue dissolved in dilute ethyl alcohol from which a brownish yellow crystalline substance separated. This had a melting point of 151° C. It was soluble in alcohol but insoluble in ether and water.

Analysis.

Substance .1734 g. CO_2 5216 g. H_2O .0831 g.

Calculated from the empirical formula

C = 81.48% H = 5.3%

Found C = 82.00% H = 5.3%

BIBLIOGRAPHY

- 1 Centralblatt 1907 2nd part 1527.
- 2 Berichte 38, 2840.
- 3 Berichte 32, 3599.
- 4 Berichte 32, 3599.
- 5 Berichte 32, 3599.