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Preparation of the Diethylaminoethyl Easter of Quinaldine Acid
PREPARATION
OF THE
DIETHYLAMINOETHYL ESTER
OF QUINALDIC ACID

BY

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THE PREPARATION OF DIETHYL AMINO ETHYL ESTER OF QUINALIDIC ACID

INTRODUCTION

The object of this investigation is to prepare the diethyl amino ethyl ester of quinaldic acid, and to study its physiological action. It is indeed self-evident that this compound is very closely related to the well known anaesthetic, novocaine, or amino-4-benzoic acid diethylamino ethyl ester. Aside from the real scientific value of an investigation of this nature, this compound may prove to be of therapeutic value.

Novocaine is administered as the hydrochloride, and due to the amino group it gives a neutral reaction upon hydrolysis and therefore is very valuable as a local anaesthetic. In this investigation it was desired to show that the action of nitrogen in the quinoline ring would be similar to that of the amino group in the novocaine molecule.
HISTORICAL PART

There was very little work done on the diethyl amino ethyl esters of the quinoline acids. Alfred Einhorn\textsuperscript{1,2} made the ethyl ester of p-quinoline carboxylic acid by refluxing a mixture of the hydrochloride of p-quinoline carboxylic acid and four parts of absolute alcohol. He also prepared the diethyl amino ethyl ester of p-quinoline carboxylic acid by refluxing a mixture of p-quinoline carboxylic acid, diethyl amino ethyl alcohol and concentrated sulfuric acid for twelve hours.

Due to the close relationship of this compound to novocaine it would be interesting to outline briefly the work which has been done on novocaine.

Alfred Einhorn\textsuperscript{3} prepared novocaine from p-nitro benzoyl chloride, ethylene chlorohydrine, and diethyl amine and then reducing it.

Knorr\textsuperscript{4} prepared novocaine by condensing diethyl amine with ethylene chlorohydrine and then treating the resulting compound with sodium p-amino benzoate.
THEORETICAL PART

The methods of procedure used in this investigation are somewhat similar to the methods used in preparing novocaine. Novocaine was prepared by the following methods.

Method Number One.

\[
\begin{align*}
\text{NO}_2 & \quad + \quad \text{HOCH}_2\text{CH}_2\text{Cl} \\
\text{C} & \quad \text{Cl} \\
\rightarrow & \\
\text{NO}_2 & \quad + \quad \text{1H(C}_2\text{H}_5)_2 \\
\text{C} & \quad \text{OCH}_2\text{CH}_2\text{Cl} \\
\end{align*}
\]

Method Number Two.

\[
\begin{align*}
\text{HOCH}_2\text{CH}_2\text{Cl} & \quad + \quad \text{NH(C}_2\text{H}_5)_2 \\
\rightarrow & \\
\text{ClCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2 \\
\text{C} & \quad \text{Na} \\
\end{align*}
\]

Method Number Three.

\[
\begin{align*}
\text{NH}_2 & \quad + \quad \text{OHCH}_2\text{CH}_2\text{Cl} \\
\text{C} & \quad \text{OH} \\
\rightarrow & \\
\text{NH}_2 & \quad + \quad \text{1H(C}_2\text{H}_5)_2 \text{ pressure at 100°} \\
\text{C} & \quad \text{COCCH}_2\text{CH}_2\text{Cl} \\
\end{align*}
\]
Method Number Four.

This reaction\textsuperscript{22} is carried out under pressure at 140°C for fifteen hours.

\[
\begin{align*}
\text{C}_8\text{H}_8\text{NO}_2 + \text{BrCH}_2\text{CH}_2\text{Br} & \rightarrow \text{C}_8\text{H}_8\text{Br}_2 \\
\text{C}_8\text{H}_8\text{NO}_2 + \text{NH}_2\text{H}_2\text{CH}_2\text{CH}_2\text{H}_2\text{N}(\text{C}_2\text{H}_5)_2 & \rightarrow \text{C}_8\text{H}_8\text{NH}_2 \\
\text{C}_8\text{H}_8\text{NO}_2 + \text{H}_2 & \rightarrow \text{C}_8\text{H}_8\text{NH}_2
\end{align*}
\]

The methods used in this investigation are of the following.

Method Number One.

\[
\begin{align*}
\text{C}_8\text{H}_8\text{NH}_2 & \rightarrow \text{C}_8\text{H}_8\text{COOH} + \text{SOCl}_2 \rightarrow \text{C}_8\text{H}_8\text{COCl} \\
\text{C}_8\text{H}_8\text{COCl} + \text{HOCH}_2\text{CH}_2\text{H}_2\text{N}(\text{C}_2\text{H}_5)_2 & \rightarrow \text{C}_8\text{H}_8\text{COCH}_2\text{CH}_2\text{H}_2\text{N}(\text{C}_2\text{H}_5)_2
\end{align*}
\]

Method Number Two.

\[
\begin{align*}
\text{C}_8\text{H}_8\text{NH}_2 & \rightarrow \text{C}_8\text{H}_8\text{COOH} + \text{H}_2\text{SO}_4 + \text{HOCH}_2\text{CH}_2\text{H}_2\text{N}(\text{C}_2\text{H}_5)_2 \\
\text{C}_8\text{H}_8\text{COCH}_2\text{CH}_2\text{H}_2\text{N}(\text{C}_2\text{H}_5)_2
\end{align*}
\]
Method Number Three

\[
\begin{align*}
\text{CH}_3 & \quad \text{oxidation} \quad \rightarrow \\
& \quad \text{COOH} + \text{HOCH}_2\text{CH}_2\text{Cl}
\end{align*}
\]

Einhorn found that all aromatic esters possess local anaesthetic properties with the exception of that of \(\alpha\)-cocaine by Wilstatter; also, that a \(\text{COOH}\) or and \(\text{SO}_2\text{H}\) grouping will reduce the anaesthetic property of a compound. Amino and hydroxyl groups will increase the anaesthetic properties, however they also increase the toxicity of the compound. According to that, the ester of quinaldic acid should be more toxic than novocaine.

As stated above, the acid or carboxyl group reduces the physiological action. However, if the ester or amide is formed, the physiological action is increased.

Another fact of interest and which led to this investigation is that if we introduce an aliphatic radical into novocaine, instead of the aromatic nucleus, the physiological action will be lost. However, such radicals as furane, thiophene, pyridine, and quinoline being strictly of aromatic nature should give compounds with anaesthetic properties. The diethyl amino ethyl ester of quinaldic acid undoubtedly possesses anaesthetic properties and moreover, it would be more neutral on hydrolysis of its hydrochloride, due to the nitrogen in the quinoline group. The simplest method of preparing this ester is to prepare quinaldic
acid, and then esterify. However, great difficulty was encountered in preparing the acid. It was found that the methyl group on the quinoline molecule does not oxidize very readily. Several attempts were made to oxidize quinaldine directly to quinaldic acid using CrO₃, K₂Cr₂O₇, and HNO₃, but all of the above instances the oxidation did not seem to proceed.

According to Doebner and Miller¹³, benzylidene quinaldine is much easier to oxidize. However, it was found that even this oxidation does not proceed very easily.

The method of Whilhelm Koonig was then attempted in this preparation. In this method the quinaldine is condensed with formaldehyde at atmospheric pressure, and the resulting compound is oxidized with K₂Cr₂O₇. This method was not satisfactory, as the condensation did not proceed very readily at atmospheric pressure. The above reaction¹⁶ was then carried out under pressure and at 100 °C and after some modification of the method a 60.8% yield was obtained.

Having prepared the acid an attempt was made to prepare the acid chloride, with the intention of treating the acid chloride with diethyl amino ethyl alcohol, which reaction would proceed very readily. However, it was impossible to get the acid chloride. Since the nitrogen in the quinoline group is so reactive, the hydrochloride was always formed instead of the acid chloride.

The method of Einhorn¹ was attempted, i.e. the direct esterification of the free quinaldic acid with diethyl amino ethyl alcohol, but this reaction did not work satisfactorily.
There remained only one other method of attack, and that was to prepare the chloroethyl ester of quinaldic acid, by treating quinaldic acid with ethylene chlorohydrine, and then treat the chloro ethyl ester with the diethyl amine. This reaction, although it did proceed with ease, nevertheless, gave small yields of the chloroethyl ester of quinaldic acid.
EXPERIMENTAL PART

Preparation of Quinaldic Acid by O. Doebner Method.

10 grams of Quinaldine dissolved in (1;5) H$_2$SO$_4$ and to that a solution of 28 grams of CrO$_3$ and 40 grams of concentrated H$_2$SO$_4$ in a liter of water was added. The mixture was heated until the chromic acid was completely reduced. It took five days for the reaction to go to completion. The chromium was precipitated as Cr(OH)$_3$ by adding NH$_4$OH. It was then filtered, and to the filtrate was added Ba(OH)$_2$ until all of the SO$_4$ was precipitated. The filtrate was then steam distilled to remove all of the unchanged quinaldine. Sulfuric acid was then added to the precipitate, the barium which gives the free acid. Doebner and Miller claim a 13.9% yield of quinaldic acid. The author, in this investigation was unable to obtain the acid in this method.

The same method was then attempted using HNO$_3$, K$_2$Cr$_2$O$_7$, and KMnO$_4$, as oxidizing agents, but all of the above methods proved unsuccessful.

Preparation of Quinaldic Acid by L. Kramer Method.

It was found that if quinaldine is condensed with benzaldehyde, the resulting benzylidenequinaldine undergoes oxidation much easier.

115 grams of carefully distilled quinaldine was heated for about five hours at a temperature of about 150 C. From time to time, ZnCl$_2$ was added until upon adding another dose of ZnCl$_2$ no reaction took place. The thick mass resulting was boiled with concentrated hydrochloric acid and water. It must be noted that this boiling must be continued for a long while, with a
a lot of water in order to remove the hydrochloride of benzylidene quinaldine from the tarry brown mass. After boiling, it was filtered hot from the tarry mass. Upon cooling, the hydrochloride of benzylidene quinaldine crystallized out. It is then filtered and the hydrochloride is decomposed with ammonia. The white crystals separating out upon cooling are benzylidene quinaldine. Recrystallized from alcohol, this compound melts at 160°C.

After several attempts and much difficulty, the author was able to obtain a 70% yield of benzylidene quinaldine.

**Oxidation of Benzylidene Quinaldine.**

10 grams of benzylidene quinaldine was mixed with 200 grams of 1:5 H₂SO₄. A solution of 15 grams of chromic acid, 75 grams of concentrated H₂SO₄, 70 grams of water was added slowly to the above in a flask provided with a reflux condenser. After all of the chromic acid solution has been added, the contents were cooled and diluted to 3/4 liters with water and allowed to stand for 48 hours. At this point, the benzoic acid separated out. It was filtered and the filtrate was extracted with ether to remove the last traces of benzoic acid. To the filtrate, NH₄OH was added in sufficient amount to precipitate the chromium as chromium hydroxide. It is then heated to coagulate the precipitate, and is filtered hot. The filtrate is evaporated to dryness, and the solid is extracted with hot alcohol several times. Quinaldic acid will crystallize out of the alcohol. However, the writer has been unable in several attempts to obtain the acid.

This oxidation was also carried out with K₂Cr₂O₇, and no
positive results were obtained.

Preparation of Quinaldic Acid by Wm. Koenig Method.

In this method, quinaldine is condensed with formaldehyde to form quinolylathanol. This is then oxidized to the acid. 20 grams of pure quinaldine was mixed with 18 grams of 40% formaldehyde solution, and 20 cc. of 5% alcohol. The mixture was refluxed for 14 hours on a steam bath. The contents were then acidified with dilute hydrochloric acid and extracted with ether. The water solution was then neutralized with Na$_2$CO$_3$, and again extracted with ether. The ether layer was then steam distilled to remove the unconverted quinaldine. The non-volatile substance is then extracted with ether, dried with Na$_2$SO$_4$. The ether is then distilled off, and the quinolylathanol is recrystallized from ethyl acetate.

The writer was unable to obtain the condensation product after several attempts.

Preparation of Quinaldic Acid by E. Besthorn and J. Ibele Method.

20 grams of quinaldine was added to 30 grams of 40% formaldehyde in a sealed tube, and heated for 48 hours in a water bath. The contents of the tube were then dissolved out with alcohol and steam distilled to remove the unconverted quinaldine. (The test for complete separation of the quinaldine is to add a drop of NaOH to a few drops of condensate. If no turbidity is produced, the distillation is carried far enough). The non-volatile substance is then dried on a steam bath.

The product obtained which is

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{OH}
\end{align*}
\]
is dissolved in 450 cc. of HNO₃ (sp. gr. 1.40), and is heated until the reaction starts. The reaction will then proceed very vigorously, and no heat is necessary.

After the evolution of NO₂ gases has stopped, the contents are evaporated to dryness. The residue is treated with hot water and filtered. The filtrate is then evaporated to about 100 cc. and 150 cc. of concentrated HNO₃ is added slowly, cooling and stirring very rapidly. After the salt is formed, it is filtered off, and washed thoroughly with 1:1 HNO₃ three or four times. The salt is then suspended in water and made alkaline with NH₄OH and evaporated to dryness. The residue is dissolved in water, acidified with acetic acid, heated, and a solution of 1:5 lead acetate is added to precipitate the lead salt. Upon complete precipitation of the lead salt it is filtered and washed thoroughly with water. The salt is then suspended in water, heated and saturated with H₂S. It is then filtered and the PbS is boiled five or six times with H₂O. At this time, a large amount of the acid is lost, as the PbS occludes the quinaldic acid. The PbS must be boiled several times to assure complete removal of the acid. (Test for complete removal of acid is to add a drop of neutral FeSO₄ until there is no color produced). The filtrate is concentrated and the acid will crystallize out upon cooling. The product obtained from this reaction is yellowish in color. It is insoluble in water, soluble in hot benzol, and melts at 156 C. The largest yield obtained in this reaction was 34%.

Modification of the Above Method.

In this method the condensation is carried out as above.
The quinolylathenol is then dissolved in about 350 cc. of concentrated H₂O₃, heated until reaction begins. After the evolu-
tion of NO₂ fumes stops, it is evaporated to dryness. The resi-
due is dissolved in hot water and is filtered. The filtrate is 
evaporated to about 100 cc. and 150 cc. of concentrated HNO₃ is 
added slowly with constant, vigorous stirring, and rapid cooling. 
The salt is filtered off, and thoroughly dried for about 24 hours. 
It is well pulverized and then taken up in about 75 cc. of water. 
Hydrolysis takes place very rapidly, stirring aids the hydroly-
sis. The mixture should be well stirred and cooled, the quinal-
dic acid being insoluble in water will separate out in white 
shiny asbestos like crystals, melting at 156°C. After a few 
Attempts and experiences in manipulation, the writer was able 
to obtain about 61% yields of a very pure product.

Preparation of Diethyl amino ethyl ester of 
Quinaldic Acid by the Alfred Einhorn 
Method.

In this method 33 grams of quinaldic acid is mixed with 
330 grams of concentrated H₂SO₄ and 70 grams of diethyl amino 
ethyl alcohol. The mixture is refluxed for 12 hours. The 
reaction mixture is diluted with water, neutralized with Na₂CO₃ 
and extracted with ether. This method gave no results in several 
Attempts by varying the time of refluxing. It seemed as if the 
H₂SO₄ decomposed the acid.

Preparation of Acid Chloride of Quinaldic 
Acid by Hans Meyers Method.

In this method, the acid is treated with a large excess of 
SOCl₂. The mixture is refluxed for about 3 hours. It is then
distilled under vacuum to remove the excess SOCl₂. The residue is then taken up in chloroform and crystallized out of chloroform. The writer was unable to reth the acid chloride. A yellowish compound was obtained melting at 194°C. Due to its high melting point and insolubility in chloroform, and ether it was suspected that the compound obtained in the above method was the hydrochloride instead of the acid chloride.

The hydrochloride was then prepared from the free acid, and a mixed melting point of the compound obtained in the Meyer method, and the pure hydrochloride proved that it was the hydrochloride instead of the acid chloride which was obtained. The hydrochloride melts at 195°C.

It was then suggested that the chloro ethyl ester of quinaldic acid be prepared and then treat the chloroethyl ester with diethyl amine to get the diethyl amino ethyl ester of quinaldic acid.

**Preparation of the Chloroethyl Ester of Quinaldic Acid.**

5 grams of quinaldic acid was dissolved in a large excess of ethylene chlorohydrine and treated with HCl gas. The mixture was refluxed for 12 hours, and the resulting substance was taken up in ether. Upon neutralization, the ether was distilled off. Upon cooling a yellowish compound appeared, soluble in ether and alcohol, melting at 81°C, and recrystallized from ligroin.

Analysis of the compound showed

- Chlorine by analysis 15.96%
- Chlorine by theory 16.6%

.3 gram of chloroethyl ester of quinaldic acid used for analysis Titrated with 9.34 cc. of .0335 N silver nitrate
SUMMARY

In this investigation, the method for preparing quinaldic acid was improved to get larger yields, and with less difficulty in purifying the product. The chloroethyl ester of quinaldic acid was prepared for the first time.
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