

REPORT
of
COMMITTEE ON EXAMINATION

This is to certify that we the undersigned, as a Committee of the Graduate School, have given Lucile Krenz Heisig final oral examination for the degree of Master of Science..... We recommend that the degree of Master of Science be conferred upon the candidate.

Minneapolis, Minnesota

1922 191

W. H. Hunter
Chairman

Charles A. Mann

L. A. Palmer

THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report
of
Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Lucile Kranz Heisig for the degree of Master of Science.

They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science.

W. H. Brewster
Chairman
Charles A. Mann
L. J. Palmer

.....1918

June 7th, 1922.

At the suggestion of a member of the thesis committee, I desire to preface this thesis with a statement of other work done by Mrs. Heisig in organic research.

In the fall of 1919, I gave Mrs. Heisig the problem of the benzoylation of carbazole, with a view to the synthesis of a new starting point for a new series of dyestuffs, analogous to the important triphenyl methane series. She did no work on this the first quarter, but spent the winter and spring quarters on it, without achieving the required result.

The next year, 1920-1921, was all spent on this problem, as far as her research time was concerned, again without result. All the known methods of causing the reaction to occur were tried, without success. Instead, either the original material was obtained unchanged, or very insoluble substances were obtained, which could not be purified, and which, on analysis, did not correspond to any pure substance which would be expected to result from the action.

I finally decided that the problem could not be solved, at least in the time Mrs. Heisig could reasonably be expected to spend on a master's thesis, and accordingly gave her the present short problem to work out and make into a thesis.

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Meantime, in order to assure myself that Mrs. Heisig's failure to solve her first problem was not due to any fault of hers, I have had another student check over her work independently, with the same negative results.

W. H. Hunter.

The Preparation
of
Beta Quinolinic Hydroxamic Acid.

A Thesis
Submitted to the
Faculty of the Graduate School
of the
University of Minnesota

by
Lucile Kranz Heisig

In partial fulfillment of the requirements
for the degree of
Master of Science

June

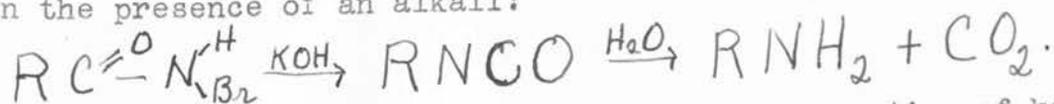
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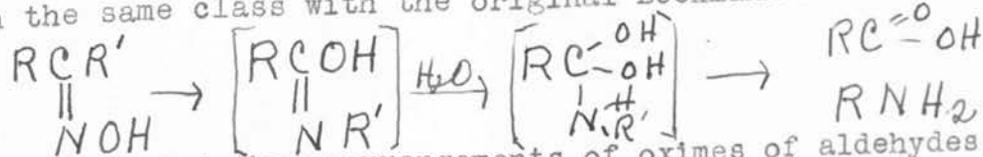
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Theoretical Part

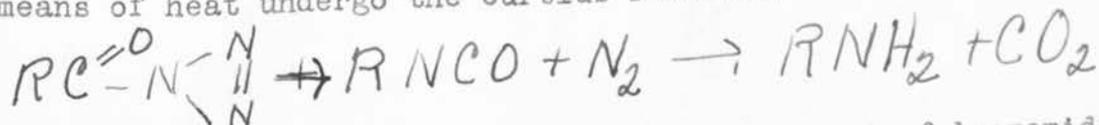
The explanation of the mechanism of the Beckmann Rearrangements has been the source of investigation and discussion ever since the discovery of such rearrangements by Beckmann and Hoffmann, and has not as yet been definitely agreed upon. Any attempt to explain these reactions must include the so called Hoffmann, Beckmann, and Curtius rearrangements. These are fundamentally the same in that they all involve the transfer of a radical from the carbon to the nitrogen atom, giving some derivative of an amine. The Hoffmann reaction is primarily the transformation of an acid halogen amide into an amine in the presence of an alkali:



In the same class with the original Beckmann reaction of ketoximes:



are included the rearrangements of oximes of aldehydes, acid salts, amides, esters, and similar substances which can be represented by the general formula: $\begin{array}{c} R \\ R' \end{array} > C=NOH$, in which R may be hydrogen, alkyl, aryl, alkoxyl, and metaloxyl. The reagents used to bring about the transformation are phosphorus tri- and pentachloride, phosphorous pentoxide, sulphuric acid, hydrochloric acid, acetic anhydride, and other dehydrating agents. The third class includes azides which by means of heat undergo the Curtius rearrangement to form amines:

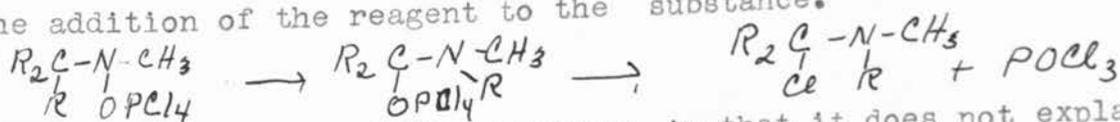


Although Hoffmann reported the rearrangement of bromamides to amines, he gave no explanation of the facts, and it was left to Hoogewerff and VanDorp to offer the first hypothesis. They said that the nitrogen tends to combine with radicals more positive than

MAR 18 28 JUN 29 26 Ad. N. J. M.

the halogens! In the bromamides the radical attached to carbon being considered more positive than the bromine, it was thought that the nitrogen would have a greater affinity for it, and would consequently exchange it for a halogen. This theory, however, was not supported by the fact that more negative radicals very often rearranged more easily than more positive ones, for example: dibromsalicylicbrom-amiderearranges below five degrees C, whereas substances with much more positive radicals do not rearrange so easily.² Furthermore this theory can not be used in conjunction with the azides, and makes no explanation as to the purpose of the reagent in all three classes of rearrangements.

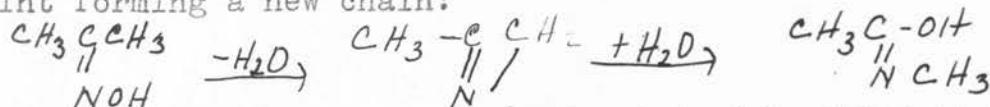
Beckmann, in reporting his reactions of ketoximes, was the first to give any theory as to the function of the reagent. He assumed that there was a direct shift of electrically charged atoms or radicals from the carbon to the nitrogen occasioned by the catalytic effect of the reagent. This view, with slight modifications by Kuhara, is still accepted by many chemists, and is the best explanation offered for some classes of compounds. Kuhara holds that in the following compound for instance, it is not the hydroxyl with which the radical changes places, but an acyl derivative of the hydroxyl resulting from the addition of the reagent to the substance.



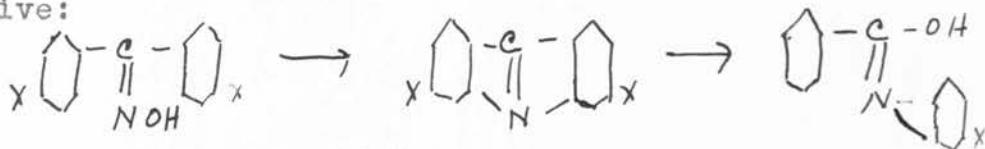
The theory fails partially, however, in that it does not explain the azides, nor does it take into account the adaptation of the reagent to the specific class of compounds, i.e. why one uses an alkali to produce rearrangement in the halogen amides and a dehydrating agent for the oximes.

1. Rec. trav. chim. 6, 373. 2. Am. Chem. J. 21, 116, (1899)

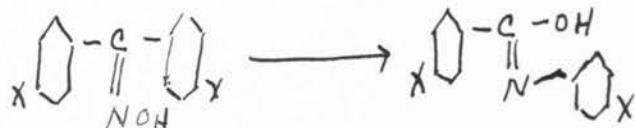
Wallach¹ and Hesse² independently advanced the hypothesis that there may be an intermediate formation of a triatomic ring by the splitting off of water and the addition of water at a different point forming a new chain:



But, as was shown by Montagne,³ the point of breaking is contrary to experimental evidence, for in the aromatics a para substituted benzophenone oxime should according to this theory give a meta-anilide, whereas in reality a para is formed. Wallach's theory would give:



but the actual result is:

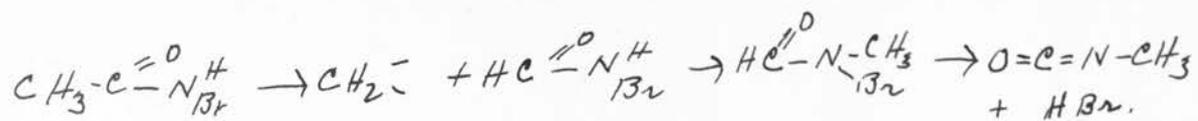


Furthermore, as Stieglitz⁴ has pointed out, a heterocyclic is much more likely to open between the carbon and the nitrogen than between the two carbons, since that is the usual method of breaking such a ring.

A new hypothesis was suggested by Ner⁵ which would connect up these rearrangements with his theory of methylene dissociation. To explain the dissociation in alcohols he holds that the substances give alkylidene divalent carbon residues: $\text{R}-\overset{\text{H}}{\underset{|}{\text{C}}}$ which recombine in different ways. He proposed to apply this hypothesis to the Beckmann rearrangements as well, so that the bromamides, for instance, would dissociate thus:

1 Ann. 346, 266 2 Am. Chem. J. 29, 49. 3 Rec. Trav. 25, 376.

4 Am. Chem. J. 29, 49. 5 Ann. 298, 308.



The bromamides and similar compounds, however, show a much greater tendency to dissociate at the nitrogen rather than at the carbon. The theory can not be adapted to the azides, nor does it make any reference to the reagent used.

In studying the relationships between the structures of the ~~xx~~ salts of pseudo acids and the free acids themselves, Hantzsch¹ incidentally applied his theory to the Beckmann rearrangement, and maintained that it was not the free acid that rearranged, but the salt formed by the potassium hydroxide used, and that the radicals shifted by virtue of the double bond between the carbon and the ~~xi~~ nitrogen. $\text{RC}=\overset{\text{O}}{\text{N}}_{\text{Br}}$ could not rearrange, but $\text{RC}=\overset{\text{O}}{\text{N}}_{\text{Br}} \rightleftharpoons \text{N}=\text{C}-\text{OBr}$ could. But Stieglitz found that the halogen imido esters do not rearrange although they have a double bond between the carbon and the nitrogen. Furthermore, and more important, the azides rearrange although they have no carbon nitrogen double bond.²

Stieglitz³ was the first to postulate the formation of univalent nitrogen as the cause of the rearrangement. The following reaction represents this hypothesis:

1 Ber. 35, 3579.

2 J. Am. Chem. Soc. 18, 751,

3 Loc. cit.

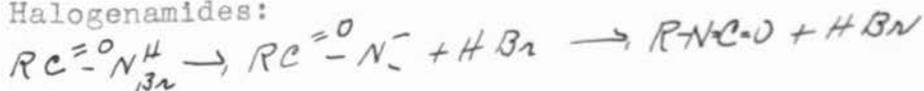
He also pointed out that the following facts must be explained by any theory of the rearrangements:

1. The nature of the Hoffmann, Beckmann, and Curtius reactions is similar.
2. The reagents used have an intimate relation to the substance rearranged.
3. If the hydrogen of the halogen amides be replaced by an alkyl group no rearrangement occurs. $R-\overset{\overset{O}{\parallel}}{C}-N^H-Cl$ does not rearrange.
4. Oximes where water can not be easily split off from the nitrogen do not rearrange. (This point, however, has been disproved by his own experiments, as will be shown later.)

This theory of the intermediate formation of univalent nitrogen, and the consequent shifting of the radical from the carbon to the nitrogen to bring about a stable system, is supported by the following facts:

1. All three sets of reactions can be explained by it.

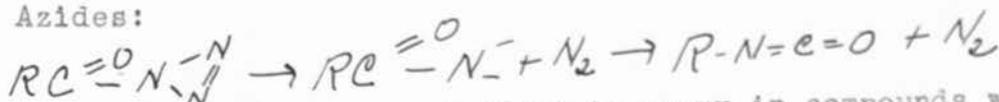
Halogenamides:



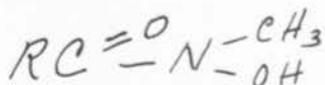
Hydroxamic acids:



Azides:



2. Rearrangements were not found to occur in compounds where the formation of univalent nitrogen was impossible.



did not rearrange.

3. The reagent used in each case is one that would be selected to make a univalent nitrogen compound. To rearrange bromamides silver carbonate and alkalis are used which readily combine with the hydrogen bromide. In the hydroxamic acids dehydrating agents are used, and

in the azides heat alone is necessary.

To explain the action of oximes, however, he was obliged to make the further assumption that the reagent added on and then water was split off:



This seemed possible until Werner found that with some stereoisomeric oximes phosphorus pentachloride could rearrange one but not the other, although there is no reason to see why both could not add hydrochloric acid. Furthermore even in cases where both rearrange, if the acid added on the double bond would be broken, and according to all conceptions of geometric isomerism, this would result in free rotation, and consequently the two oximes ought to give the same products, whereas they do not.

Jones² modernized the theories of Stieglitz by applying to them the electron theory of valence. He attributed the rearrangement to the tendency of the nitrogen to take electrons from the carbon, and showed that in all classes that underwent rearrangement the nitrogen in the intermediate stage was in the state of oxidation of $-N^{\pm}$, and that after the reaction it was in the state of oxidation of $-N^{\pm}$; whereas the carbon could be in the state of oxidation that it is in alcohol, aldehyde, or acid, but would end up in the state of aldehyde, acid, or carbon dioxide respectively. Evidently the rearrangement is an internal oxidation and reduction, the carbon being oxidized by the nitrogen. He classified the substances that undergo rearrangements into these three classes:³

1 Ber. 25, 33.

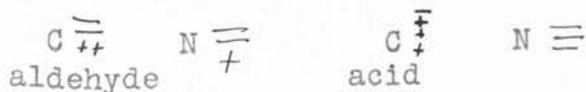
2 Jones, Am. Chem. J. 48, 1.

3 Loc. cit.

1. Azides, monohydroxylamines, monobromamines, in which the carbon is oxidised from alcohol to aldehyde stage:.



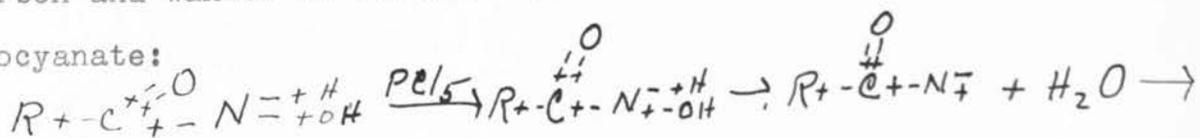
2. Aldoximes, carbon going from aldehyde to acid:



3. Hydroxamic acids, amidoximes, acid azides, halogenamides:



In his later study Jones¹ came to the conclusion that the OH of hydroxyl amine and the halogen of the amides was positive, and that therefore in an unstable condition. Before the hydroxyl or halogen could be split off as water or a hydrogen halide by the Beckmann reagent, it must gain two electrons from some place, and the nitrogen being the most convenient, it was assumed that these positive radicals acquired electrons from the nitrogen, thereby became negative and capable of forming hydrochloric acid or water. The nitrogen then being positive in respect to the carbon, acquires electrons from the carbon, thus causing the positive radical to detach itself from the carbon and wander to the now negative nitrogen giving the stable isocyanate:

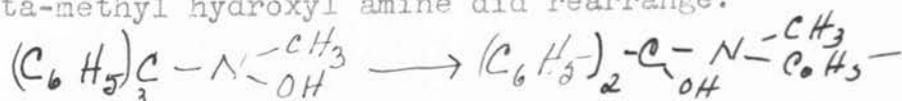


¹ Am. Chem. J. 50, 414, (1913)

The cause of the arrangement was therefore assumed to be not the formation of univalent nitrogen, but the instability of the system containing the positive hydroxyl and halogens attached to the nitrogen, and the tendency of the substance to go to a more stable form. The reagent, or heat in the case of the azides, is the push that starts the stone rolling, and upsets the unstable equilibrium of the system, forcing it in the direction of the most stability, --- that in which the carbon is as oxidized as possible in respect to the nitrogen, which is the amine or isocyanate stage.

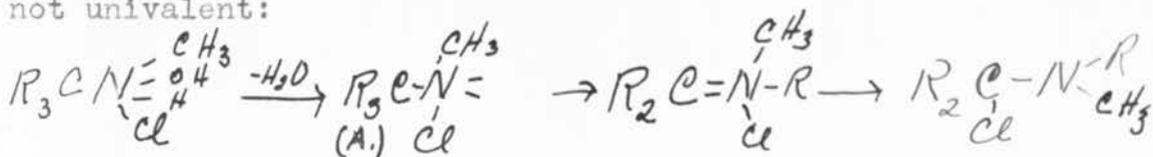
This explanation, adopted by Stieglitz, was in agreement with Stieglitz's theory, and therefore also inadequately explained the rearrangement of stereoisomeric oximes. Stieglitz

Stieglitz's theory of the formation of univalent nitrogen in all classes of Beckmann rearrangements was upset by the discovery of rearrangement in a compound which could not give univalent nitrogen by the splitting off of a simple compound. It was found by Stagner, one of Stieglitz's co-workers that beta-triphenylmethyl beta-methyl hydroxyl amine did rearrange:



In order to explain this rearrangement Stieglitz was forced to modify his theory. It was found that the hydrochloride of a substituted hydroxylamine rearranged in the presence of phosphorous pentoxide, and that acids always facilitate migrations of unstable radicals. He, therefore, postulated the addition of the acid to the substance, and the subsequent splitting off of water or some other simple molecule leaving the nitrogen unsaturated, although

not univalent:



To substantiate this theory Stieglitz prepared an electromer of A which did not rearrange:



Most electromers are interconvertible, therefore this lack of rearrangement seems to eliminate his theory. However, nitrogen electromers in which the fifth valence is involved are not interconvertible because the fifth valence is always different from the other four; therefore, if in this compound the chlorine in A is on the fifth valence, it is still possible that this electromer may rearrange and the other not.

There remain, then, two theories in the field: Beckmann's direct change of radicals, (or Kuhara's modification of it), which more easily explains the rearrangement of stereoisomeric oximes, and Stieglitz's unsaturated nitrogen theory which is supported by the following facts:

1. Azides give the same products as other classes.
2. Where univalent nitrogen is possible smooth reactions occur at low temperatures, otherwise with difficulty or not at all.
3. The reagents used are such which would be selected to give a monovalent nitrogen compound.
4. Same theory may be applied to peroxides giving univalent oxygen and then rearranging.

Jones² in a recent paper applied the Langmuir cubic atom theory

1 Loc. cit.

2 Am. Chem. Soc. 43, 2422.

to Beckmann reactions, and stated that the rearrangement was due to the tendency of the nitrogen in the intermediate compound to complete its octet, left incomplete by the splitting off of hydrogen halide or water, by sharing two electrons with the carbon, thus causing the radical to shift to the nitrogen.

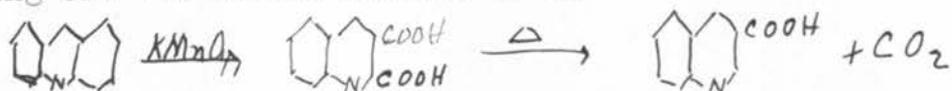
Jones¹ has now directed his research to the question: Why does one radical wander more easily than another? He postulates that the ease of rearrangement is dependent upon the ability of the radical to exist in the free state, and has been supported by experimental facts. The triphenylmethyl radical has a greater tendency to exist free than the monophenylmethyl radical, and it was found that the triphenylacetylhydroxamic acid rearranged more easily than the diphenyl and that more easily than the monophenylacetylhydroxamic acid. It is possible that if a free radical be placed in a solution with a rearranging compound it may compete with the radical of the substance for a place on the nitrogen.

The ease of rearrangement of cyclopropane, quinoline², and other radicals is being studied to have a more complete list with which to make comparisons, and it is the purpose of ~~this~~ our work to make betaquinolinichydroxamic acid so that its rearrangements may be ~~xx~~ studied and form a link in the chain of evidence on the mobility of radicals.

¹ LOC. CIT.

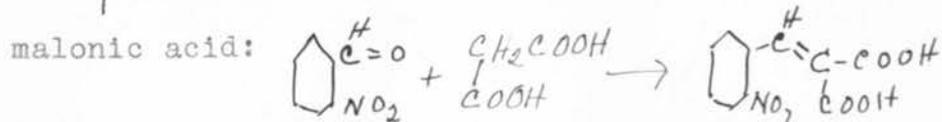
Betaquinolinic-hydroxamicacid.

There are several ways of making betaquinolinic acid, all of which are indirect methods giving low yields. In the first place it may be made by the oxidation of acridine in alkaline solution by means of potassium permanganate, giving acridinic acid which is then changed to betaquinolinic acid by heating to 120-130 degrees C, thus driving off the carbon dioxide of one of the carboxyl groups.

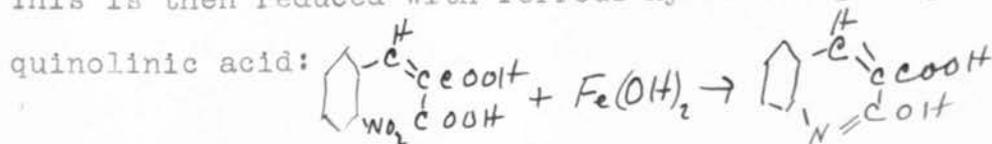


Graebe and Caro¹ used this method but obtained a very low yield.

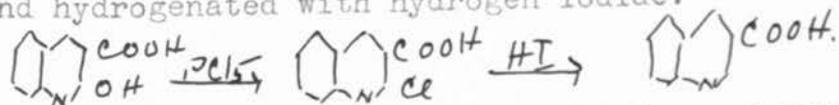
Mills and Watson² and also H. Meyer³ prepared the acid by treating ortho-nitrobenzaldehyde with malonic acid giving ortho-nitrobenzylmalonic acid:



This is then reduced with ferrous hydroxide giving alpha-oxybeta-quinolinic acid:



The oxyacid is chlorinated by means of phosphorous pentachloride and hydrogenated with hydrogen iodide:



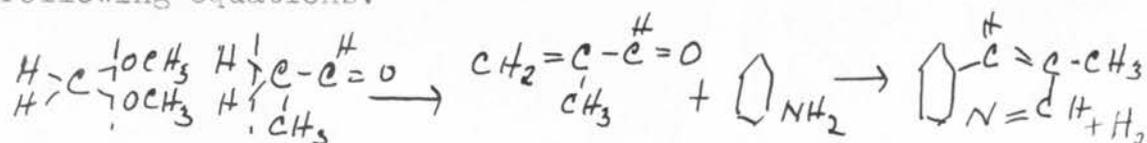
This method is reported to give fairly good results.

The acid may also be made by the oxidation of beta methyl quinoline which is made by the Doebner and Miller modification of the Skraup Synthesis. Propion-aldehyde is condensed with methylal and aniline by means of hydrochloric acid, the aniline and tertiary bases are separated with difficulty, and only a small yield results.

1 Ber. 13, 99; 2 J. Chem. Soc. 27, T 742.

3 Monatsh. 28, 47; 4 Ber. 17, 460; 5 J. Chem. Soc. 27, T 742

The reaction is complicated and may take place according to the following equations:



A number of other side products are formed and the hydrogen is not liberated but is possibly oxidized by the aldehyde. The beta methyl quinoline is oxidized with chromic acid in sulphuric acid giving ¹ less than a thirty percent yield of beta quinolinic acid, ²

None of these methods is very satisfactory. The condensation with malonic acid is supposed to give the best results, but we were unable to obtain any ortho nitrobenzaldehyde. The Skraup's Synthesis gives such small yields, and the oxidation of the methylquinoline is so uncertain, that even if the methylal were at hand it would have been a very tedious method. As we had about a hundred grams of acridine, we used that method, altho, being an oxidation reaction, the yields are also small and variable. At times we obtained no yield at all, but with experience we were able to get as good a yield as Graebe and Caro.

The beta quinolinic acid so obtained was esterified by means of methyl alcohol and sulphuric acid giving a white crystalline methyl ester, the preparation of which has not been previously recorded. Melting point 73.5°. Upon hydrolysis with concentrated hydrochloric acid the beta acid was regenerated, melting at 273°.

To make the hydroxamic acid, free hydroxylamine made from hydroxylamine hydrochloride and sodium methylate, was added to the methyl ester dissolved in methyl alcohol, and the mixture was allowed to stand several days. The hydroxamic acid is a white

crystalline solid melting at 185.5^o shortly after preparation. If allowed to stand, a slight decomposition takes place and the melting point varies. The hydroxamic acid gives ^{the} characteristic purple ferric chloride test for hydroxamic acids, and the analysis for nitrogen checks closely with the theoretical.

Experimental Part.

The acridine hydrochloride was oxidized by means of potassium permanganate and sodium hydroxide solution according to Gräbe and Caro's method. Ten grams of acridine hydrochloride dissolved in a small amount of hot water was made alkaline with sodium hydroxide and a solution of sixty grams of permanganate in one liter of water was added drop by drop, while the mixture was heated on the steam bath. According to the directions the mixture should be stirred frequently while heating for thirty six hours. We modified this method by employing an electric stirrer so that the permanganate could be added more rapidly. The success of the oxidation depends on the prevention of an excess of permanganate at any time. With a stirrer the time required was about eighteen hours. The manganese dioxide and other side products were filtered off, and the alkaline solution concentrated by evaporation on a steam bath. The solution was acidified with hydrochloric acid and upon cooling the dibasic acridinic acid precipitated out, and was filtered off. If the solution is acidified before concentration only a small yield results. The acridinic acid is heated for several hours at a temperature of from 120-130°, and the resulting quinolinic acid recrystallized from alcohol. From ten grams of acridine between one and three grams of beta quinolinic acid (melting point 274°) was usually obtained.

The oxidation was tried in a n acetic acid solution with potassium permanganate, but other oxidation products of acridine were obtained.

The methyl ester of beta quinolinic acid is made by treating the acid in methyl alcohol with concentrated sulphuric acid. To

3.6 grams of the beta acid in 50 cc of methyl alcohol, 8 cc of concentrated sulphuric acid was added, and the mixture refluxed on a water bath for four hours. The alcohol was evaporated off and the residue almost neutralized with a saturated solution of sodium carbonate, and finally brought to slight alkalinity with sodium bicarbonate. The crude ester precipitated out and was filtered off. It was recrystallized several times from alcohol by the addition of water, and also from ether by the addition of ligroin. Yield 2 grams. The methyl ester, not previously described, is a white crystalline substance soluble in ethyl alcohol, ethyl acetate, methyl alcohol, and ether, and insoluble in ligroin and water. Its melting point was found to be 73.5° . A small portion was hydrolyzed by heating with concentrated hydrochloric acid for several hours on the steam bath. On evaporation the residue was found to be practically pure beta quinolinic acid, melting at 273° .

To prepare the hydroxamic acid, free hydroxylamine was made by treating 30 grams of hydroxylamine hydrochloride dissolved in 200 cc of methyl alcohol (acetone free) with 9.9 grams of sodium in 125 cc of methyl alcohol. The sodium chloride was filtered from the carefully cooled mixture, and most of the methyl alcohol distilled off under reduced pressure. The solution was again quickly filtered and the hydroxylamine distilled under a vacuum of 32 mm. of mercury. Three grams of the methyl ester of beta quinolinic acid in 5 cc. of methyl alcohol was treated with .7 gram of free hydroxylamine, and warmed gently on a water bath. The mixture was allowed to stand several days until a precipitate was formed which gave a ferric chloride color test for hydroxamic acids. Upon repeated crystallizations from methyl acetate by the addition of

petroleum ether, and also from methyl alcohol, about one gram of pure white crystalline hydroxamic acid was obtained which gave a melting point of 185.5° if taken a half an hour after preparation. If allowed to stand slight decomposition took place, and the melting point varied. On analysis of a freshly recrystallized sample, .2234 grams of the substance gave 29.5 cc. of nitrogen measured at 20° over 23% potassium hydroxide solution, with a barometric pressure of 743 mm. at 22.5° .

% nitrogen 14.71.

Theoretical 14.89%