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Synthesis in the Glyoxaline Series

SYNTHESES IN THE GLYOXALINE SERIES

BY

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY
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BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR
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I wish to extend my sincere thanks
and appreciation to Professor Roger
Adams for the suggestion of this
problem and for the interest he has
shown during the experimental work.

John Raven Johnson.

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Syntheses in the Glyoxaline Series.

Introduction.

Glyoxaline derivatives occur commonly in nature, chiefly among compounds of plant origin. The more common naturally occurring glyoxalines are the cyclic ureas, or hydantoins; the amino acid, histidine; ergotoxin, ergothionene (the betaine of thiol-histidine), and histamine in ergot extracts; and the Jaborandi alkaloids, pilocarpine and isopilocarpine.

These glyoxalines are compounds of relatively great physiological activity, and one of the typical ones is histamine, which may be the active principle of the internal secretion of the hypophysis or pituitary gland. The application of histamine clinically is limited by its expense and difficulty of preparation.

This work was started with the purpose of synthesizing histamine by a method which would make use of cheaper and more readily accessible materials and would thus enable its clinical use to be extended. During the course of the preparation it became evident that the proposed method would not be practical and it was given up in favor of preparing other glyoxalines which might be of physiological importance. For this purpose the diethylamino ethyl esters of glyoxaline 4-carboxylic acid and benzoglyoxaline m-carboxylic acid were chosen. These esters resemble procaine in structure and would be expected to possess local anesthetic properties.

Theoretical Part.

Glyoxaline was discovered by Debus¹ in 1856 as a product of the action of ammonia on glyoxal, and was named from this method of preparation. The work of Japp² in 1882 gave the constitutional formula, $\begin{array}{c} \text{HC-N} \\ \parallel \quad \diagdown \\ \text{HC-N} \quad \text{CH} \\ \quad \quad \quad \diagup \\ \quad \quad \quad \text{H} \end{array}$ for glyoxaline which is accepted at the present time. The systematic names, imidazol and pyrro- β -monazol, have been applied to this series and in recent works the name imidazol has superceded the older historical name to some extent.

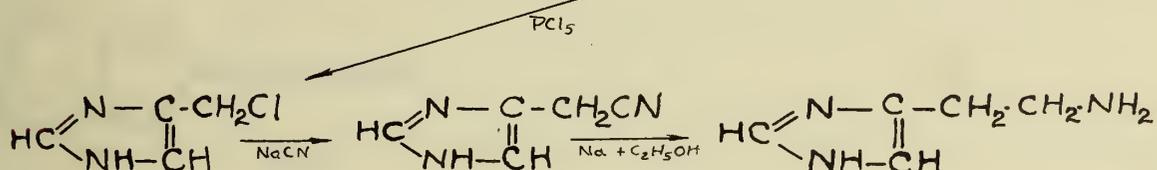
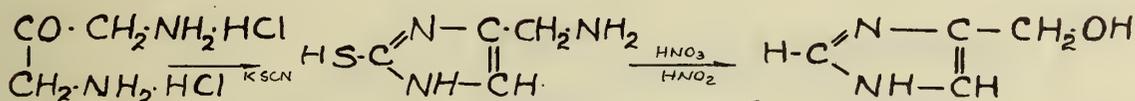
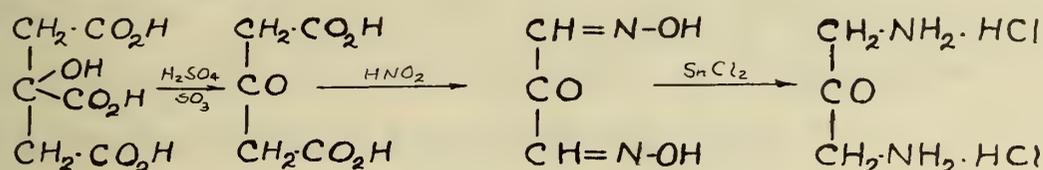
A large number of syntheses have been carried out in the glyoxaline series, especially after the discovery by Gabriel³ and Pinkus that 1,2 amino-ketones on condensation with potassium thiocyanate yield thioglyoxalines, which may be converted to glyoxalines by oxidation with nitric acid or other suitable oxidizing agents. This method of preparation has proven to be a general one and is the best method for preparing glyoxalines substituted in the 4 and 5 positions.

Histamine.

The most important syntheses carried out along these lines are the syntheses of histamine⁴ and histidine⁵ by Pyman. His original method for the preparation of histamine has been modified in some details by Koessler and Hanke⁶ to give better yields, but is at the present time the only synthesis of this interesting base. The objections to this method are that it is very long and consequently expensive.

The new method proposed for the synthesis of histamine is based upon the discovery by Gabriel⁷ and Ohle, that compounds of the type of ethylene oxide may be condensed with phthalimid yielding phthalyl derivatives of amino-alcohols. By this reaction they pre-

easily accomplished, and the subsequent steps work very smoothly. The main difficulty in this method is the production of the diamino acetone hydrochloride. The reactions involved in Pyman's synthesis are given below:

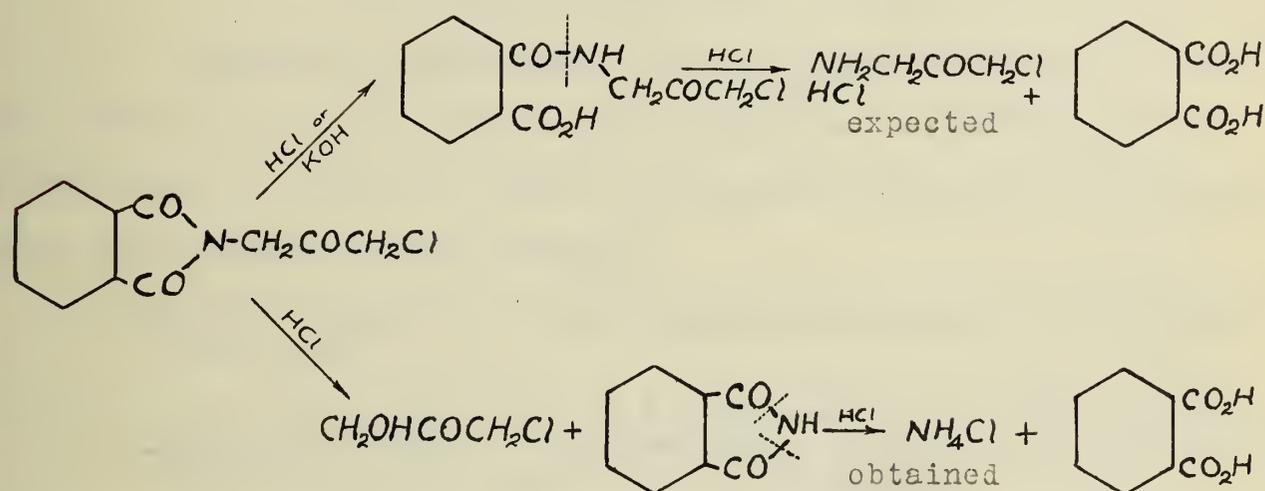


The advantages of the proposed method over that of Pyman may be shown by a comparison of the intermediate steps involved:

citric acid	epichlorohydrin
acetone dicarbonic acid	chloro-hydroxypropyl phthalimid
di-isonitrosoacetone	chloroacetyl phthalimid
diaminoacetone-chlorostannite	amino-chloroacetone
diaminoacetone-hydrochloride	thiol-4-chloromethyl glyoxaline
thiol-4-aminomethyl glyoxaline	4-chloromethyl glyoxaline
4-hydroxymethyl glyoxaline	4-cyanomethyl glyoxaline
4-chloromethyl glyoxaline	Histamine
4-cyanomethyl glyoxaline	
Histamine	

The condensation product of epichlorohydrin with phthalimid was prepared by heating these materials together, and the pro-

duct was oxidized to the corresponding ketone described by Gabriel and Ohle*. The hydrolysis of the chloroacetyl phthalimid thus obtained was attempted using hydrochloric as well as hydrobromic acid and in both cases an ammonium salt resulted instead of the desired amino-ketone. This abnormal hydrolysis of chloroacetyl phthalimid is analagous to the results obtained by Goodeckemeyer⁸ in attempting to hydrolyze acetyl phthalimid with acids.



Since the hydrolysis failed to yield the desired product, glyoxaline derivatives substituted in the 4 position could not be prepared by this method. For this reason the new method was given up, and it was decided to prepare several other glyoxalines which might be of physiological importance.

Of these derivatives the diethylamino ethyl esters of acids containing the glyoxaline nucleus seemed to be the most promising. For this purpose glyoxaline 4-carboxylic acid and benzoglyoxaline *m*-carboxylic acid were chosen. The former is a representa-

*The original article of Gabriel⁷ was not available, and the abstract in the Journal of the Chemical Society was the only source of information. The abstractor mentions that the authors hydrolyzed chlorohydroxy propyl phthalimid successfully to amino chloroiso-propyl alcohol with hydrochloric acid, but makes no mention of the hydrolysis or attempted hydrolysis of the keto compound.

ative of a true unsubstituted glyoxaline nucleus, and the latter is a representative of the condensed type of glyoxalines, in which the 4 and 5 positions are a part of another aromatic ring. The diethyl-amino ethyl esters of these acids would be similar constitutionally to procaine and would therefore be expected to have similar physiological properties.

Glyoxaline 4-Carboxylic Acid.

Glyoxaline 4-carboxylic acid was first prepared by Knoop⁹, who obtained it by the oxidation of glyoxaline 4-glyoxylic acid, prepared from histidine. Pyman has prepared glyoxaline 4-carboxylic acid synthetically by two methods;-

1. By the oxidation of 4-hydroxymethyl glyoxaline with strong nitric acid⁵.
2. By refluxing glyoxaline 4,5 dicarboxylic acid with aniline forming glyoxaline 4 carboxanilid, which on hydrolysis with hydrochloric acid gives the desired acid¹⁰.

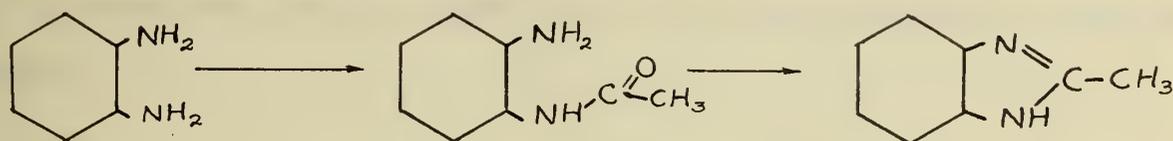
Pyman found that the acid chloride of glyoxaline 4-carboxylic acid could not be prepared by any of the usual methods, employing thionyl chloride and phosphorus pentachloride either alone or mixed with other acid chlorides. The methyl and ethyl esters were prepared by direct esterification with the alcohol and hydrochloric acid⁵. The method proposed for the preparation of the diethylamino ethyl ester is to prepare the acid by the first method of Pyman, form the chloro-ethyl ester by esterification with ethylene chlorohydrin, and treat the chloro ester with diethyl amine. A method similar to this has been applied successfully in the synthesis of procaine.

Benzoglyoxaline m-Carboxylic Acid.

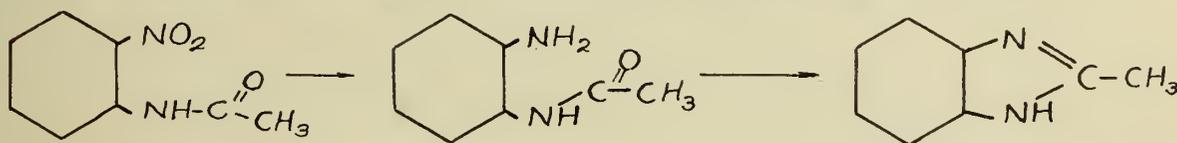
Benzoglyoxaline m-carboxylic acid was chosen as a representative of glyoxalines with a condensed nucleus. The benzoglyox-

alines are usually fairly strong bases, but weaker than the glyoxalines, and are also acidic in nature, some benzoglyoxalines being readily soluble in aqueous alkalis. Two general methods of preparation are:

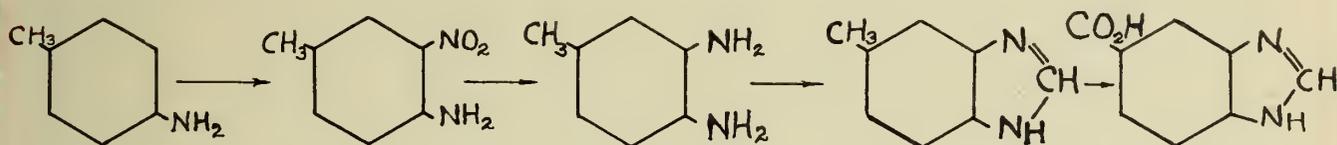
- 1: By condensation of ortho phenylene diamines with acids¹¹, their esters¹², or amides;-



2. By the reduction¹³ of ortho nitro acyl anilines;-

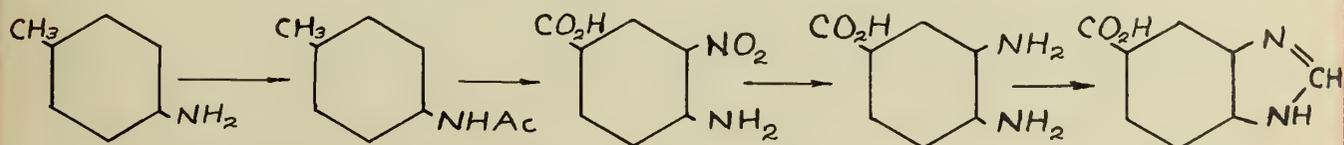


Benzoglyoxaline m-carboxylic acid has been synthesized by Bamberger¹⁴ and may easily be prepared from p-toluidin by the following series of reactions:



The acid chloride of benzoglyoxaline m-carboxylic acid may then be prepared by the action of phosphorus pentachloride in acetyl chloride solution on the acid, using the method employed by Emil Fischer in the preparation of the acid chlorides of the amino acids. The acid chloride may then be treated with diethylamino ethyl alcohol to yield the desired ester.

A second method employed for the preparation of the above acid, starting with p-toluidin is as follows:



Both methods require the same number of intermediate steps but it was found that the first one was somewhat more satisfactory, although the yields obtained on oxidation of the m-methyl benzoglyoxaline were not satisfactory. The second method would be desired for the preparation of 2 methyl benzoglyoxaline m-carboxylic acid, since this acid could be obtained directly from the nitro acetamidobenzoic acid by reduction.

Experimental Part.

1. Chloroacetyl Phthalimid.

(a) Preparation of Chlorohydroxypropyl phthalimid⁷.

15 grams of epichlorohydrin ($1\frac{1}{2}$ moles) were poured over 15 grams of pure phthalimid (1 mole) in a small flask provided with a reflux condenser, and the mixture was heated in an oil bath at 120-130°. After several hours a clear solution was obtained, and the heating continued for about thirty minutes longer. The excess of epichlorohydrin was then removed by distillation under diminished pressure.

The pale yellow viscous liquid which remained in the distillation flask was poured out into a crystallizing dish and allowed to cool. A white crystalline mass resulted, which was washed with petroleum ether to remove the last trace of epichlorohydrin, and amounted to a nearly quantitative yield of the condensation product. These crystals without further purification were used in the next step; they often melted as high as 93-94°. The melting point recorded in the literature by Gabriel and Ohle is 94-95°. In several cases, however, the melting point of the crude product was as low as 65-70° due probably to contamination with phthalimid.

In carrying out a number of the above condensations, it was noticed that the temperature at which the oil bath was maintained seemed to influence the purity of the product (as shown by the melting point). If the temperature was kept at 100-110°, the solution proceeded very slowly, and if the temperature of the bath was allowed to rise to 150-160° an impure product with low melting point was obtained. It was thought at first that the low melting point of the product in some cases might be due to an interchange

of the hydroxyl and phthalimid groups as observed by Gabriel¹⁵ in some similar phthalimid derivatives, and a contamination of the desired product with this isomer. An analysis of a sample of the low melting material indicated that the impurity was not an isomer, but probably unchanged phthalimid:

Calculated for $C_8H_5O_2N$	2.52%	N.	
			Found- 6.31% N.
Calculated for $C_{11}H_{10}O_3NCl$	5.84%	N.	

(b) Preparation of Chloroacetyl phthalimid.

10 grams of chlorohydroxypropyl phthalimid were dissolved in 75 cc. of glacial acetic acid on the water bath, and the solution placed in a water bath at 65-70°. A solution of 5 grams of chromic acid in 15 cc. of 60 per cent acetic acid was then added in small portions with stirring. The reaction mixture became dark green in color and after the addition of all of the chromic acid, was allowed to stand for an hour. On pouring the solution into a large volume of cold water, the chloroacetyl phthalimid separated out in white crystals. These were filtered off and washed free from chromium salts and acetic acid with water. The air-dried white crystals obtained in this manner had a melting point of 138-139°; that recorded by Gabriel and Ohle was 139.5°. The yield was about 6 grams or 60 per cent of the theoretical.

(c) Hydrolysis of Chloroacetyl phthalimid.

An attempt was made to hydrolyze this substance with alcoholic potash to a phthalamidic acid and then continue the hydrolysis with acids, a method employed successfully by Gabriel and others. It was found that this hydrolysis with potassium hydroxide did not proceed readily even on gentle warming, and it was inadvisable to

try long continued boiling with alkali since the halogen group might be replaced.

2.5 grams of chloroacetyl phthalimid were refluxed with a mixture of 10 cc. of glacial acetic acid, 20 cc. of water, and 30 cc. of constant boiling hydrobromic acid. The refluxing was continued for three hours, when the solution became brown colored. On cooling the solution, crystals separated out, which were filtered off and examined. They were phthalic acid, melting point 200° - 205° and the weight obtained was 1.35 grams. The solution was concentrated at 70° - 80° under diminished pressure, to a volume of 5 cc. and a second crop of phthalic acid was obtained. The filtrate was evaporated to dryness and treated with a mixture of absolute alcohol and ether. A crystalline material was obtained which proved to be chiefly ammonium salts, since a strong odor of ammonia was observed on treating an aqueous solution of the crystals with alkali.

2.5 grams of chloroacetyl phthalimid were refluxed for 4 hours with 25 cc. of 20 per cent hydrochloric acid, and the same general procedure followed as above. The white crystalline material obtained amounted to 0.6 gram and was chiefly ammonium chloride. The fact that it was not pure ammonium chloride but probably did contain a small amount of the desired amino chloroacetone was demonstrated by an analysis:

Calculated for NH_4Cl	36.36% Cl.	
Calculated for $\text{C}_3\text{H}_6\text{ONCl}$	32.97% Cl.	Found..61.34% Cl.

2. Glyoxaline 4-Carboxylic Acid.

(a) Preparation of 4-Hydroxymethyl Glyoxaline, hydrochloride.
The General procedure of Koesler and Hanke¹⁶ was employ-

ed for this synthesis, with no important modifications of the details. The yields obtained were about the same as those recorded by these authors. The preparation of diaminoacetone hydrochloride by the older method of Bugheimer¹⁶, from the condensation product of hippuric ester and sodium ethylate, was tried and found to give unsatisfactory results.

The hydrochloride of hydroxymethyl glyoxaline was used directly for the oxidation with nitric acid in the next step, and the purification and isolation of the free base was not carried out as described by Pyman⁵.

(b) Preparation of Glyoxaline 4-carboxylic acid hydrochloride.

15 grams of hydroxymethyl glyoxaline hydrochloride were treated with 70 cc. of concentrated nitric acid (sp. gr. 1.42) and warmed on a steam bath in a covered casserole until the evolution of brown fumes had ceased. The solution was then evaporated to dryness on the steam bath, and the residue of the nitrate of glyoxaline 4-carboxylic acid was converted into the hydrochloride by repeated treatments with concentrated HCl and evaporations. After the last evaporation with hydrochloric acid, a white crystalline mass of the crude hydrochloride results. This substance is very hygroscopic and must not be allowed to stand in contact with the air. This crude hydrochloride was converted directly into the ester, without use of the method of purification used by Pyman, since the latter requires conversion into the free base, and this must then be reconverted into the hydrochloride. The yield of crude hydrochloride amounted to about 60 per cent of the theoretical.

(c) Esters of Glyoxaline 4-Carboxylic Acid.

10 grams of the crude glyoxaline 4-carboxylic acid hydrochloride were refluxed with 40 cc. of ethylene chlorohydrin, which had been saturated with dry hydrogen chloride. The mixture was refluxed continually, occasionally saturating with dry hydrochloric acid, until the acid had completely gone into solution.

The dark colored esterification mixture was then cooled and poured into 250 cc. of chloroform, causing the separation of the hydrochloride of the β -chloroethyl ester as a brown crystalline solid. The picrate of the base was prepared by treating an aqueous solution of the hydrochloride with sodium carbonate solution and pouring into a boiling solution of picric acid. The picrate obtained did not melt up to 260° .

The free β -chloroethyl ester was prepared by neutralizing an aqueous solution of the hydrochloride with saturated potassium carbonate solution, and formed a crystalline substance insoluble in water, which decomposed rapidly, turning black on prolonged exposure to the air.

The hydrochloride of the diethylaminoethyl ester was obtained as a colored crystalline solid, on refluxing the hydrochloride of the β -chloroethyl ester with a large excess of diethyl amine. The excess of diethyl amine was removed by distillation, and finally by heating the solid residue under diminished pressure at $70-80^{\circ}$.

3. Benzoglyoxaline m-carboxylic Acid.

(a) Preparation of 3,4 Diaminotoluene.

40 grams of p-acetotoluid were finely pulverized and added in small portions to a mixture of 60 cc. of concentrated sulfuric acid and 150 cc. of nitric acid (sp. gr. 1.42). During the ad-

dition the temperature was kept at 30-40° and after all of the acetotoluid had been added the mixture was allowed to stand for half an hour at room temperature. The nitroacetotoluid was obtained by pouring this solution into a large volume of cold water, and filtering with suction. The pale yellow crystals were sucked dry after several washings with water, and then transferred to a small flask. 100 cc. of alcohol were poured over the nitroacetotoluid and heated nearly to boiling, when a solution of 20 grams of potassium hydroxide in 25 cc. of water was added. The heating was continued on the water bath for thirty minutes, and on cooling the 3-nitro 4-toluidin separated out in red crystals which melt at 116°. The yield obtained was 42 grams of pure material, which amounted to 80 per cent of the theoretical.

35 grams of 3-nitro 4-toluidin were covered with concentrated hydrochloric acid in a 500 cc. flask and 70 grams of metallic tin added in small portions. After the reaction had been completed the mixture was diluted with water, filtered, and made alkaline with strong sodium hydroxide solution. The 3,4 diaminotoluene was extracted from this mixture with hot benzene. Dry hydrochloric acid was passed into the benzene solution (immersed in a cold water bath) and the dihydrochloride was obtained. The yield was 35 grams of pure 3,4 diaminotoluene dihydrochloride. For one experiment the free base was needed, and this was made by treating an aqueous solution of the dihydrochloride with sodium hydroxide. The free base was obtained in small pale pink-colored crystals of melting point 87-88°.

(b) Preparation of *m*-Methyl Benzoglyoxaline.

First Method.¹¹ 10 grams of 3,4 diaminotoluene were re-

fluxed with 25 cc. of absolute formic acid for several hours. The solution was then poured into 50 cc. of water and the formic acid neutralized with ammonia. The methyl benzoglyoxaline separated first as an oil, which solidified on standing. The yield was 10 grams or 92 per cent of the theoretical.

Second Method¹². 19.5 grams of 3,4 diaminotoluene dihydrochloride and 10 grams of formamid were heated together in a large wide-mouth tube, suspended in an oil bath, until the reaction had ceased and no more vapors were evolved. The solid mass resulting was taken up in water and the free base liberated by addition of ammonia. The mixture was extracted with two 100 cc. portions of ether and the ethereal solution dried over anhydrous sodium sulfate. On evaporation of the ether the crude methyl benzoglyoxaline was obtained in pale yellow crystals, in nearly quantitative yield. The melting point of the crude product was 105-106°; that recorded in the literature for the pure substance is 114°.

(c) Preparation of Benzoglyoxaline m-Carboxylic Acid¹⁴.

In the preparation of this acid by Bamberger, the oxidation was carried out with alkaline permanganate. It was noticed that a German patent¹³ used magnesium sulfate in a similar oxidation of o-acetotoluid and the yields were improved. This was tried out with o- and with p-acetotoluid and the results obtained were very satisfactory*, and it was therefore considered advisable to try the addition of magnesium sulfate in the oxidation of methyl benzoglyoxaline.

10 grams of methyl benzoglyoxaline and 30 grams of magnes-

*In an experimental run with p-acetotoluid, by the addition of magnesium sulphate as directed in the patent, the yield of p-acetamidobenzoic acid was increased from 50 per cent of the theoretical to 85 per cent. A pure white product was obtained which melted 247-248°.

ium sulfate crystals dissolved in 1200cc. of warm water and heated to 90° in a water bath. 35 grams of potassium permanganate were dissolved in 150 cc. of boiling water and this solution added in small portions to the methyl benzoglyoxaline solution. The mixture was thoroughly mixed after each addition to prevent a local excess of oxidizing agent, since this destroys the product. After all of the permanganate solution had been added the solution was heated for a short while and then filtered from the precipitated manganese dioxide.

The filtrate was acidified with acetic acid, evaporated to a small volume and allowed to cool. The acid which separated out was contaminated with some inorganic salts and was recrystallized from hot water containing a small amount of acetic acid. The yield of pure benzoglyoxaline m-carboxylic acid amounted to 3.5 grams, which is thirty per cent of the theoretical. The material was carefully dried at 120° for several days for the next preparation.

(d) The Acid Chloride of Benzoglyoxaline m-Carboxylic Acid.

3.2 grams of dry benzoglyoxaline m-carboxylic acid were treated with 75 cc. of freshly distilled acetyl chloride and 8 grams of phosphorus pentachloride. The reaction was carried out in a tightly stoppered glass cylinder, and the general procedure employed was that used by Emil Fischer¹⁷ in the preparation of acid chlorides of amino acids. The crystalline mass of the hydrochloride of the acid chloride was washed thoroughly with carefully dried petroleum ether, and was rapidly transferred to a desiccator containing phosphoric anhydride. The yield of the hydrochloride of the acid chloride amounted to

3.4 grams, which is 80 per cent of the theoretical.

Calculated for $C_8H_9ON_2Cl_2$32.39% Cl. Found....30.57% Cl.

This low result indicated that the material was contaminated with some unchanged acid, but this might be expected since Fischer often found this to be the case with the amino acids.

(e) Esters of Benzoglyoxaline m-Carboxylic Acid.

Methyl ester. 0.5 grams of the acid chloride obtained above were treated with 5 cc. of absolute methyl alcohol and heated to boiling. A clear solution was obtained, and on pouring into dry ether the hydrochloride of the methyl ester separated as a white crystalline solid, which melted from 236-236.5° with decomposition. An analysis gave the following result:

Calculated for $C_9H_9O_2H_2Cl$16.67% Cl. Found...16.55% Cl.

The picrate of the methyl ester was prepared by dissolving the hydrochloride in water, neutralizing with sodium carbonate, and pouring into a hot solution of picric acid. Bright yellow crystals of the picrate of the methyl ester were obtained which melted from 243-244° with decomposition.

Diethylamino ethyl ester. 1.0 gram of the acid chloride was treated with an ethereal solution of 3 grams of diethylamino ethyl alcohol. The mixture warmed up, and a crystalline material resulted which was filtered off and washed with a mixture of absolute alcohol and ether, and finally with dry ether. These slightly dark colored crystals were exceedingly hygroscopic and were transferred immediately to a desiccator containing phosphoric anhydride. The melting point was observed to be around 100-120° but was found to be very indefinite, due to the fact that the substance was so very hygroscopic.

Summary.

A new synthesis of histamine was proposed, which involved the condensation of epichlorohydrin with phthalimid, and oxidation of the resulting product to σ -chloroacetyl phthalimid. It was found that the hydrolysis of σ -chloroacetyl phthalimid with acids resulted in the formation of an ammonium salt as the chief nitrogenous product, instead of the desired amino chloroacetone hydrochloride.

Glyoxaline 4-carboxylic acid was synthesized from citric acid, and the β -chloroethyl ester was made by direct esterification in the presence of dry hydrogen chloride. The preparation of the β -chloroethyl ester and of the β -diethylaminoethyl ester was described, but neither was obtained in a condition sufficiently pure for analysis.

Benzoglyoxaline *m*-carboxylic acid was prepared from *p*-toluidin through *m*-methyl benzoglyoxaline. It was found that on oxidation of *m*-methyl benzoglyoxaline, and *o*- and *p*-acetotoluid with potassium permanganate the addition of magnesium sulfate improved the yields of the corresponding acids. The hydrochloride of the acid chloride of benzoglyoxaline *m*-carboxylic acid was obtained by the action of phosphorus pentachloride and acetyl chloride on the acid. The methyl ester was formed by treating the acid chloride with methyl alcohol, and two salts of this ester were prepared and described. The β -diethylamino ethyl ester was obtained by treatment of the acid chloride with diethylamino ethyl alcohol.

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