A STUDY OF THE STRUCTURE OF SOME CYCLIC AMIDES AND RELATED TETRAZOLES

By

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A THESIS

Submitted to the School of Graduate Studies of Michigan
State College of Agriculture and Applied Science
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1952

To My Mother And Father

ACKNOWLEDGMENT

The author wishes to express his gratitude to Doctor Robert M. Herbst, who gave valuable guidance during this investigation.

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INTRODUCTION

The work described in this thesis was undertaken primarily to investigate the nature of the cyclic amides formed by Beckmann rearrangement of unsymmetrically substituted cyclohexanone oximes. The structures of the cyclic amides could be studied by degradative procedures involving ring opening, removal of the nitrogen and formation of branched chain fatty esters. The appropriate fatty esters could be synthesized by methods that would lead unequivocally to the desired esters. The esters obtained by synthesis and by degradation of the cyclic amides could be compared by physical constants and preparation of derivatives. The identification of the esters obtained by degradation of the cyclic amides would establish the structures of the cyclic amides.

The secondary objective of this investigation was to establish the structures of certain dialkyl substituted 1,5-pentamethylenetetrazoles. A number of dialkyl substituted pentamethylene tetrazoles have been described (1). The method of synthesis used in their preparation did not permit rigorous determination of the position of the substituents due to the possibility of the formation of isomeric structures. The cyclic amides, whose structures could be established by the general methods described above could be converted into dialkyl substituted 1,5-pentamethylenetetrazoles. The structures of the tetrazoles so formed would be known from the method of preparation and they would therefore serve as reference compounds for the clarification of the structure of similar tetrazoles prepared by other methods.

HISTORICAL

The preparation of oximes from ketones may lead to the formation of either the syn or the anti isomer or a mixture of both isomers. Ketones may form only one oxime due to energy differences or steric requirements of the oximes; nevertheless, failure of attempts to separate the isomers does not definitely indicate that only one isomer has been formed (2). In the Beckmann rearrangement of ketoximes one fact is clear--that the structure of the amide formed depends on the configuration of the oxime undergoing rearrangement (3, 4). The group trans to the hydroxy group migrates to the nitrogen. If the oxime is a mixture of the two isomers then the two isomeric amides will be formed. It is also possible that two isomeric amides could be obtained from a single oxime isomer if the conditions of the rearrangement were drastic enough to cause the isomerization of the oxime.

A number of oximes of cylic ketones have been separated into the isomeric syn and anti forms (5, 6, 7). The Beckmann rearrangement of a pair of stereoisomeric monocyclic ketoximes has never been investigated. In most instances no attempt to separate isomers was made prior to subjecting the cyclic ketoximes to the rearrangement. In the previous investigations of the Beckmann rearrangement of unsymmetrical cyclic ketoximes all attempts to separate isomers have been made with the lactams, which were the products of the rearrangement.

The previous investigations of the Beckmann rearrangement of substituted cyclic ketoximes can be classified as follows: (1) Rearrangements of symmetrically substituted cyclic ketoximes where only one lactam is possible. (2) Rearrangements of unsymmetrically substituted cyclic ketoximes which sterically favor only one oxime configuration and therefore favor the formation of only one lactam. Substitution in the 2-position usually favors the formation of a single ketoxime. (3) Rearrangements of unsymmetrically substituted cyclic ketoximes which form both possible lactams. In this group the ketone has an equal chance of forming both oxime configurations and thus both rearrangement products are obtained.

The first group may be disposed of quickly since the structure of the product is never in doubt. It should be noted that a few workers have investigated oximes that fall in this group in connection with other investigations (8, 9, 10). The rearrangement of 3,5-dimethylcyclohexanone oxime (10) is an example from this group and may be represented as shown in Plate 1, Figure 1.

The second group contains by far the largest number of substituted cyclic ketoximes that have been subjected to rearrangement. The formation and the Beckmann rearrangement of the oximes in these cases may be represented as taking the course shown in Plate 1, Figure 2.

Rearrangements of this type have been carried out with cyclopentanones (11-15, 16, 17) and with cyclohexanones (8, 10, 11, 18-29). The steric requirements of the substituent in the 2-position cause the hydroxyl group to assume a position anti or trans with respect to the substituent. The structure of the lactams resulting from the rearrangement of 2-substituted cyclic ketoximes is in accord with the trans configuration of these oximes. A few exceptions should be noted. Wallach (8) has succeeded in separating two isomeric lactams resulting from the Beckmann rearrangement of 2,4,4-trimethylcyclohexanone oxime; however, he did not prove the structures of the two products. Hückel and Doll (5) have separated the syn and anti forms of 2-cyclohexylcyclohexanone oxime. Wallach and Ost (18) in the rearrangement of this same oxime have nevertheless found only

PLATE 1

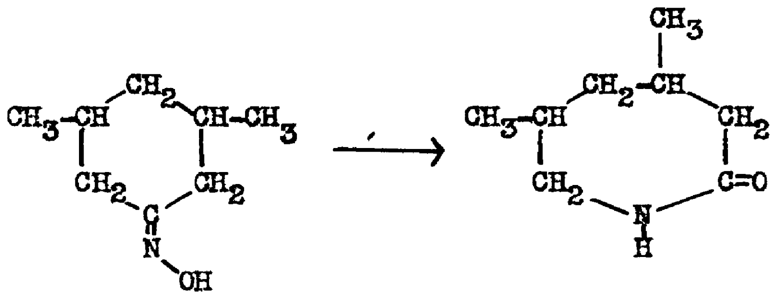


Figure 1

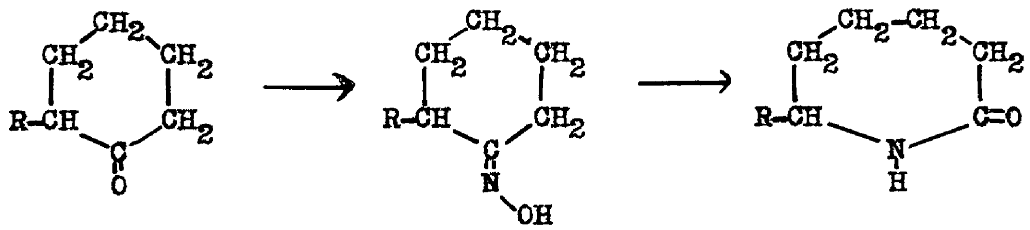


Figure 2

one lactam which they proved to be 7-cyclohexyl-2-ketohexamethylenimine by oxidation to 6-cyclohexyl-6-ketohexanoic acid. It should be noted that Shechter and Kirk (12) in a study of the very similar Schmidt reaction of 2-substituted cyclic ketones have found that the products are the same as would be expected from the Beckmann rearrangement of the oximes of these ketones. The Schmidt reaction with 2-chlorocyclohexanone, however, gave a low yield of the unexpected lactam, 3-chloro-2-ketohexamethylenimine. The favored product was not isolated but the formation of adipamide indicated that the rearrangement also occurred in the expected direction.

The compounds studied in this investigation are unsymmetrically substituted cyclohexanone oximes and properly belong in the third group. The Beckmann rearrangement of a number of oximes of this type has been studied (8, 10, 16, 17, 30-32). Wallach (8) has succeeded in isolating the two lactams resulting from the rearrangement of 3-methylcyclohexanone oxime and the two lactams resulting from the rearrangement of 3,5,5-trimethylcyclohexanone oxime. Only in the first case did he prove the structures of the products. All other investigators of the Beckmann rearrangement of unsymmetrical oximes of this type have failed to establish the structure of the lactam or mixture of lactams obtained.

It should be noted that a few simple bicyclic ketoximes have been rearranged (14, 24, 33, 34), but in no case was it unequivocally established whether a single product or mixture of products resulted.

The structures of the lactams have been proved by a variety of methods. In many cases the method of proof is specific for one compound or a group of similar compounds. If the subject were covered in detail the importance of the different methods would be lost in the mass of information. The methods of proof can be divided generally as follows: (1) synthesis of the lactam by another method or hydrolysis of the lactam to a known amino acid, (2) hydrolysis of the lactam to the amino acid and reduction of the amino acid to the saturated acid by hydriodic acid, (3) oxidation of the lactam to known compounds--the oxidation may be preceded by a preliminary treatment of the lactam such as hydrolysis to the amino acid and reaction of the latter with nitrous acid, (4) an unusual proof that cannot be classified in the foregoing. Representative examples of each method will be discussed.

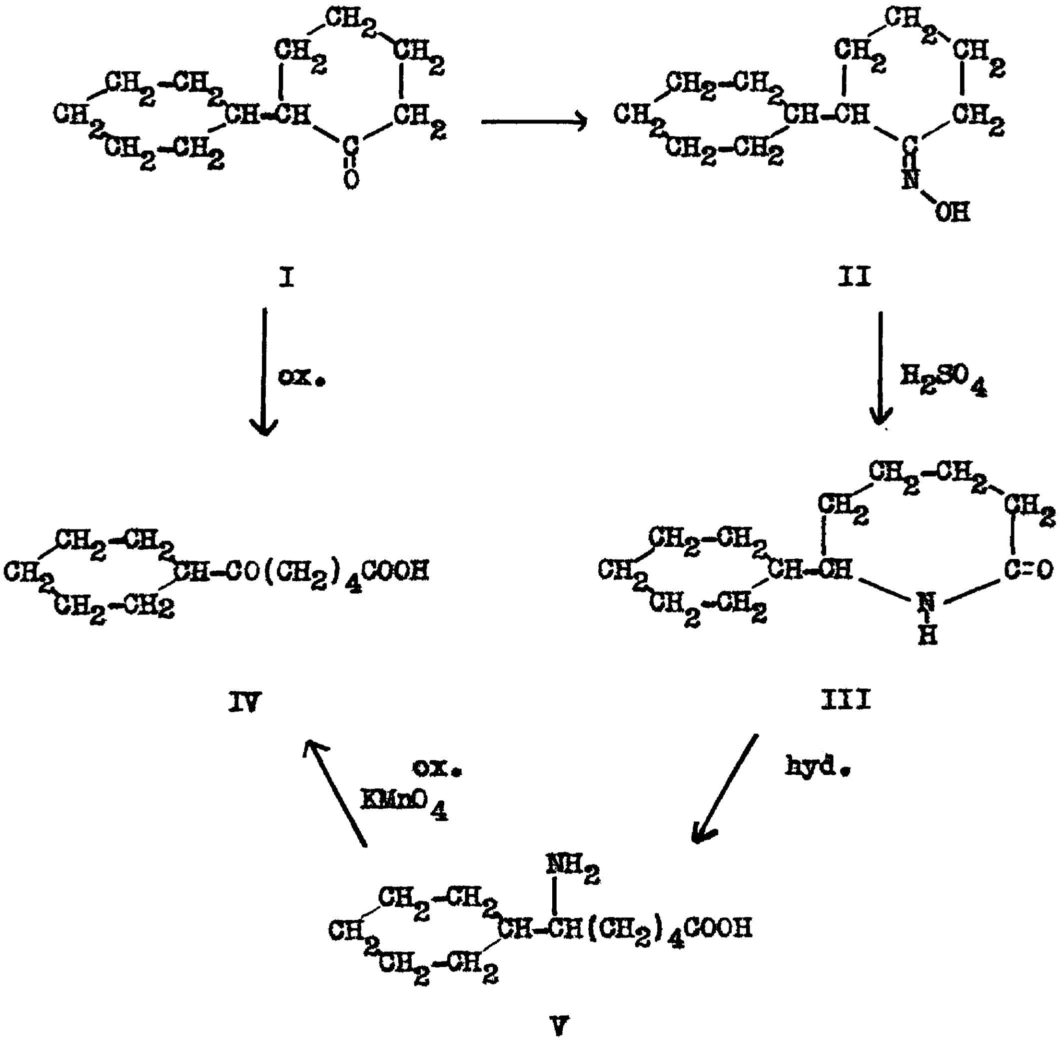
There are many instances in the literature where lactams have been synthesized by heating the appropriate amino acids. Most of these lactams have not been prepared by the Beckmann rearrangement. Hildebrand and Bogert (11) have described the only instance where the lactam was synthesized specifically to prove the structure of a product resulting from the Beckmann rearrangement. They have synthesized 6-propyl-2-ketopentamethylenimine from 2-propylpiperidine by benzoylation, oxidation with potassium permanganate to the benzoyl derivative of the amino acid, hydrolysis with concentrated hydrochloric acid to the amino acid and heating the latter to form the lactam ring. Shechter and Kirk (12), in their study of the Schmidt reaction, have proved the structure of 3-chloro-2-ketohexamethylenimine by hydrolysis followed by benzoylation to form the known 2-chloro-6-benzoylaminohexanoic acid. Other examples in this group involve simple hydrolysis to amino acids whose structures had previously been proved.

The second method used to prove the structures of lactams is based on the investigation of Kwisda (35). The amino acid prepared by hydrolysis of the lactam is heated to about 200° C. in a sealed tube for approximately twenty-four hours with concentrated hydriodic acid. It apparently is necessary to use hydriodic acid of a certain minimum concentration in order to effect satisfactory reduction (35, 36). Some useful modifications of this procedure have been made by Miescher and Billeter (37). Hildebrand and Bogert (11), as well as Shechter and Kirk (12), have used this method to prove the structures of some lactams prepared from 2-substituted cyclic ketones. None of these workers have isolated the saturated acids; but, they have made the p-phenylphenacyl derivatives from the purified residues from the reaction mixtures. These derivatives were then compared with the known compounds.

Oxidation either alone (10, 14, 16, 18) or in combination with other treatments (8, 15, 27) has been used extensively to prove the structure of lactams resulting from the Beckmann rearrangement of cyclic ketoximes. Wallach and Ost (18) studied the rearrangement of 2-cyclohexylcyclohexanone oxime. Their proof of structure can be schematically represented as shown in Plate 2.

The 7-cyclohexyl-2-ketohexamethylenimine, III, that they obtained as product from the Beckmann rearrangement was hydrolyzed to the amino acid, V, which was oxidized to the keto

PLATE 2



acid, IV. The keto acid, IV, was also obtained by oxidation of the starting ketone, 2-cyclohexylcyclohexanone, I. The structure of the keto acid, IV, was further established by rearrangement of its oxime and hydrolysis of the resulting amide to cyclohexylamine and adipic acid.

Ungnade and McLaren (10) in favorable cases have used an oxidation with hypoiodite to prove the structures of certain lactams. They studied the rearrangement of a number of mono-, di- and tri-methyl substituted cyclohexanone oximes. A majority of these methyl substituted cyclohexanone oximes contained a methyl group in the 2-position. The formation of the oximes and their rearrangement thus favored the formation of 7-methyl substituted 2-ketohexamethylenimines as has already been discussed. These lactams were then hydrolyzed to the 6-aminoheptanoic acids and the structures of the amino acids established by treatment with hypoiodite and isolation of the iodoform. The adipic acids resulting from the hypoiodite oxidation were also identified in some cases. The yield of iodoform never exceeded eleven percent of the theoretical. In one case they attempted to improve the yield of iodoform by first converting the amino acid to the keto acid by treatment with nitrous acid and oxidation of the product with chromic acid. Treatment of the resulting keto acid with hypoiodite still led to a low over-all yield of iodoform.

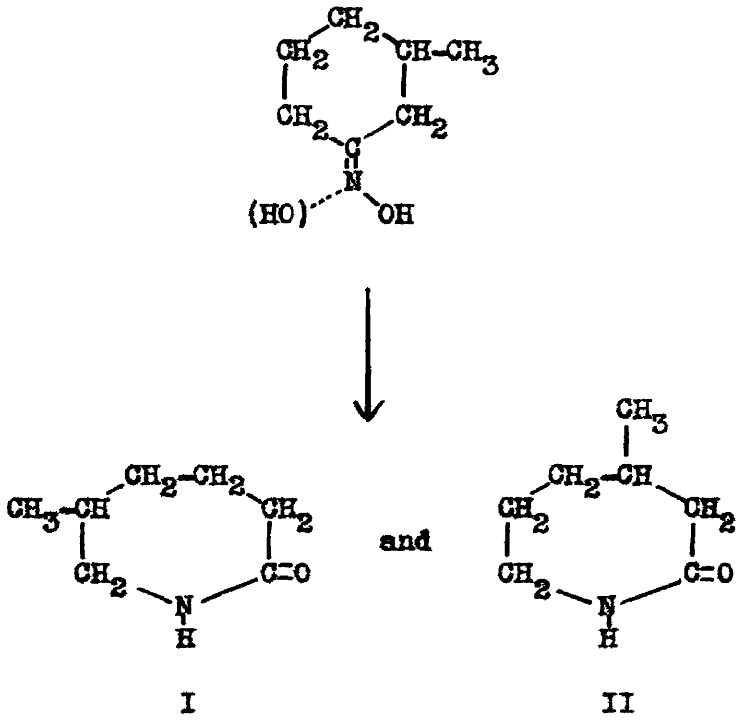
Wallach (8) has proved the structure of the two isomeric lactams resulting from the rearrangement of 3-methylcyclohexanone oxime by an oxidative degradation. His work with this oxime may be schematically represented as shown in Plate 3.

He separated the two isomeric lactams represented by Formulas I and II. The structure of 6-methyl-2-ketohexamethylenimine, I, was established by hydrolysis to the amino acid hydrochloride, III. The amino acid hydrochloride was then treated with sodium nitrite and gave an unsaturated acid that was removed by steam distillation and a residue containing a hydroxy acid, IV. The residue was oxidized with chromic acid and gave as products a dicarboxylic acid and 5-ketohexanoic acid, V, which was characterized as the semicarbazone.

The 4-methyl-2-ketohexamethylenimine, II, was hydrolyzed to its amino acid hydrochloride, VI. The amino acid hydrochloride, VI, was then oxidized with alkaline permanganate to the known 3-methyladipic acid, VII.

Wallach <u>et</u> <u>al</u>. (27) established the structure of the lactam resulting from the Beckmann rearrangement of 2,2,5-tri-

PLATE 3



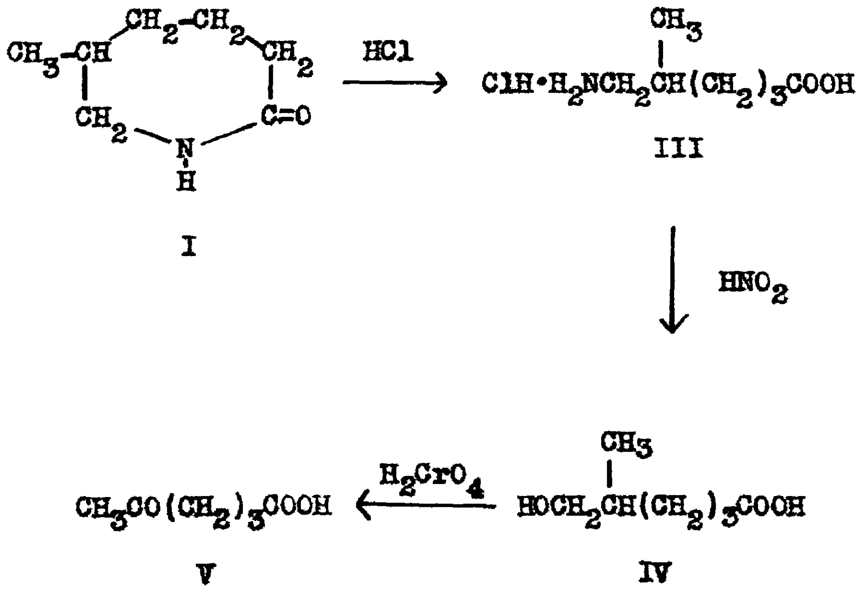


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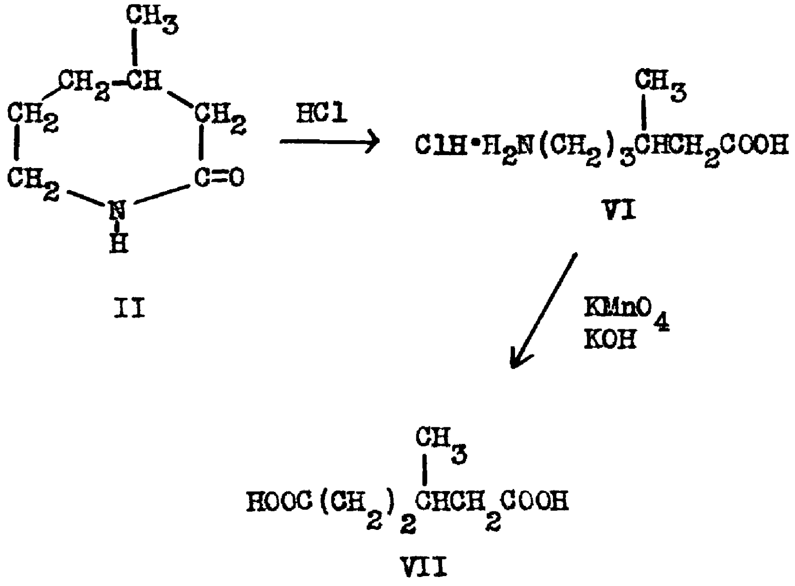
PLATE 3 (Continued)



methylcyclohexanone oxime. Their procedure may be schematically represented as shown in Plate 4.

They isolated the lactam, 4,7,7-trimethyl-2-ketohexamethylenimine, II, as product of the Beckmann rearrangement of the oxime, I. The lactam was converted to the unsaturated acid, III, by heating under pressure with concentrated sulfuric acid. The unsaturated acid, III, was then oxidized with potassium permanganate to the known products 3-methylglutaric acid, V, and acetone, IV.

Von Braun and Heymons (19) have proved the structure of the 7-methyl-2-ketohexamethylenimine resulting from the rearrangement of 2-methylcyclohexanone oxime. The structure of this lactam has since been established by more conventional methods (10, 11, 12) but the unusual method of von Braun and Heymons deserves mention here. Their method of proof may be represented as shown in Plate 5.

They had established that lactams of structure, I, with no alkyl substitution in the 3-position, would form a dichlorolactam, II, when treated with excess phosphorus pentachloride. This chlorinated lactam, II, could then be converted into the hydrochloride of the 2,2-dichloro-6-aminohexanoic acid, III. If

PLATE 4

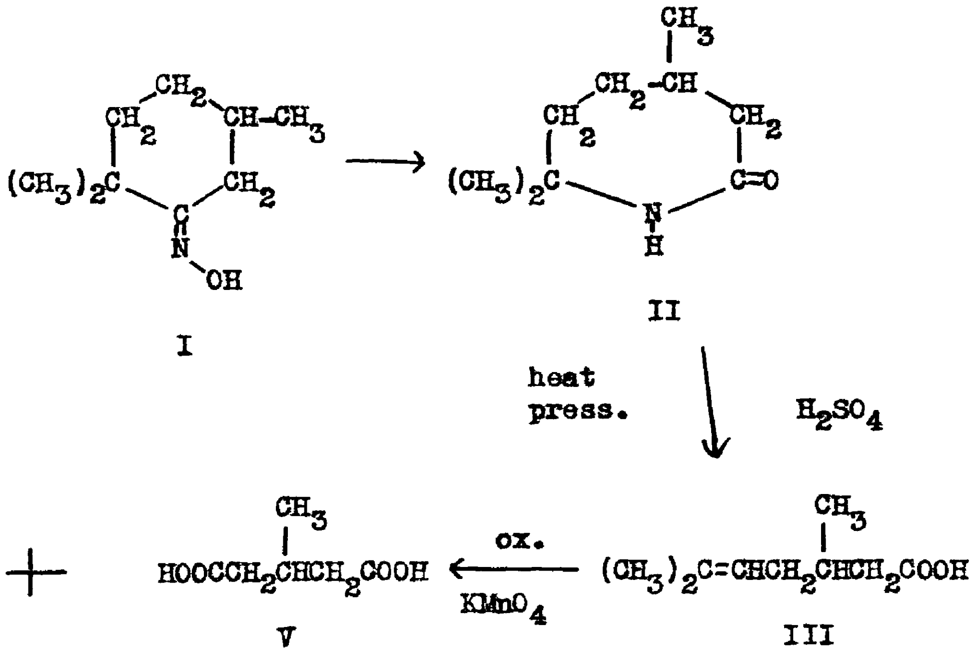

I
II
heat
press.
H2SO4
(CH3)2C=CHCH2CHCH2COOH
III
ox.
KMnO4
HOOCCH2CHCH2COOH
V
CH3COCH3
IV

PLATE 5

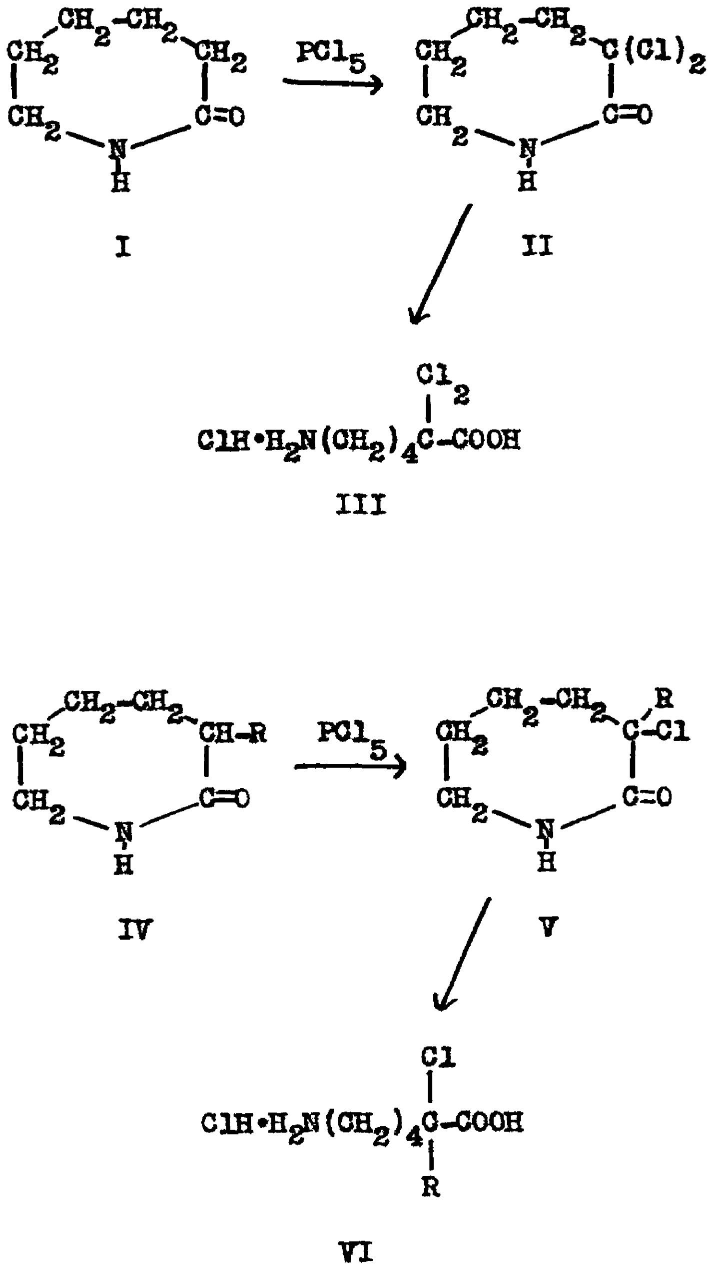


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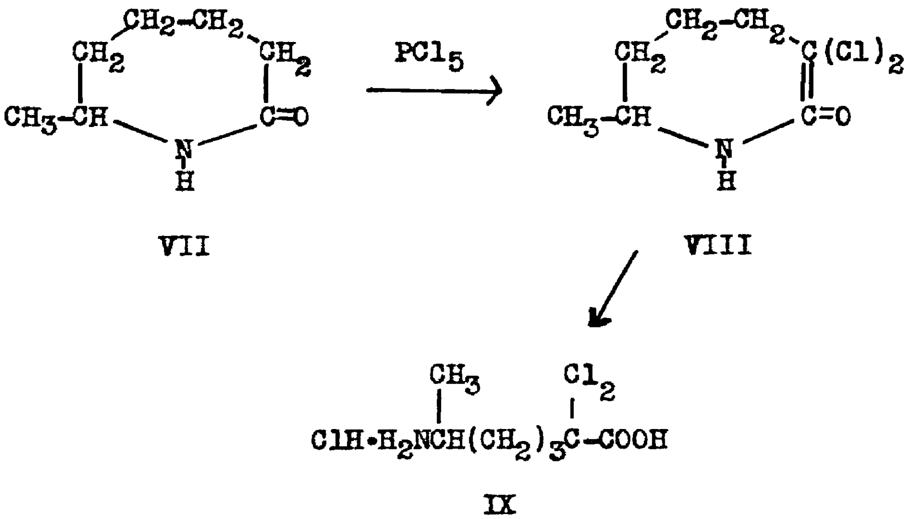
PLATE 5 (Continued)



the lactam treated in this way were substituted in the 3-position with an alkyl group, as represented by Formula IV, then the corresponding monochlorinated products V and VI would be formed. The Beckmann rearrangement of 2-methylcyclohexanone oxime can lead to the 3-methyl substituted lactam or the 7-methyl substituted lactam represented by Formula VII. Von Braun and Heymons found that the lactam formed by the rearrangement of this oxime could be transformed into a dichlorolactam and a dichloro amino acid hydrochloride. Their product was therefore 7-methyl-2-ketohexamethylenimine, VII, and it was transformed by reaction with phosphorus pentachloride into the dichlorolactam, VIII, which was further transformed into the dichloro amino acid hydrochloride, IX.

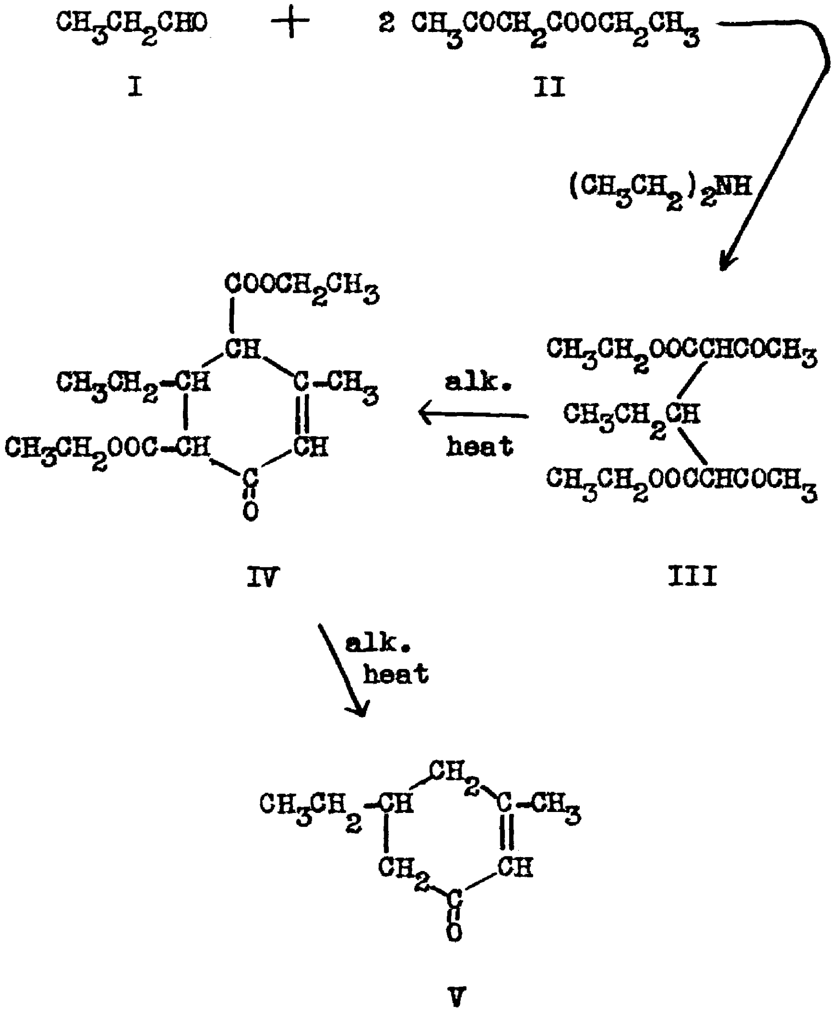
The method of proof of structure of the lactams described in this thesis is still somewhat different than the previous methods used; however, it will be evident in the following discussion that the method uses well-known reactions and can be applied to a wide variety of lactams.

DISCUSSION

A study has been made of the structures of the lactams resulting from the Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime. This oxime was not available from commercial sources and its preparation required the synthesis of the intermediate ketone. In view of the ease of preparation and the availability of the starting materials, the modified Knoevenogel technique of Horning, Denekas, and Field (38, 39, 40) was used to synthesize 3-methyl-5-ethyl-Δ^2-cyclohexenone. The preparation of the unsaturated ketone may be schematically represented as shown in Plate 6.

One mole of propionaldehyde, I, and two moles of ethyl acetoacetate, II, in the presence of diethylamine, condense to form the bis ester, III. Treatment of Compound III with alkali and heat effects the cyclization to 3-methyl-5-ethyl-4,6-dicarboethoxy-Δ^2-cyclohexenone, IV, and the further saponification and decarboxylation of IV to form 3-methyl-5-ethyl-Δ^2-cyclohexenone, V. The unsaturated ketone, V, was catalytically reduced to 3-methyl-5-ethylcyclohexanone by essentially the method of Henze, Wilson, and Townley (41).

PLATE 6



The unsaturated ketone, 3-methyl-5-ethyl-Δ^2-cyclohexenone, is asymmetric and exists as two optical isomers. The reduction of each optical isomer may lead to the cis or trans arrangement of the methyl group with respect to the ethyl group. The 3-methyl-5-ethylcyclohexanone, therefore, may exist as four isomers, one cis racemate and one trans racemate. No attempt has been made in this investigation to determine if all the possible isomers are formed, nor to separate the isomers that are formed. The related 3,5-dimethylcyclohexanone, which may exist only as cis-trans isomers, has been prepared by the method just described and has been found to have the cis configuration (42, 43). Therefore, the 3-methyl-5-ethylcyclohexanone, used in this investigation, probably is the cis racemate.

The 3-methyl-5-ethylcyclohexanone was converted into its oxime by treatment with an aqueous solution of hydroxylamine. The liquid oxime boiled over a narrow temperature range and due to the possibility of many isomers fractional distillation was not considered feasible. Each isomeric ketone may lead to a syn and an anti form of the oxime. There are four possible isomeric ketones and thus there are eight possible isomeric 3-methyl-5-ethylcyclohexanone oximes. Using the terms cis and trans to designate configurational relationships of the alkyl groups in the cyclic ketones and syn and anti to designate geometric isomerism of the oxime group, there would thus be four oxime racemates, the cis-syn oxime, the cis-anti oxime, and similarly, the trans-syn and trans-anti oxime. It has already been noted that the alkyl groups substituted on the ketone probable have the cis configuration. If this be true then only the cis-syn and the cis-anti racemates of the oxime would be formed. For the purposes of this investigation the oxime was considered to consist simply of the syn and anti forms. No attempt was made to separate the syn and anti forms of the oxime since the conditions of rearrangement probably would have been drastic enough to effect isomerization.

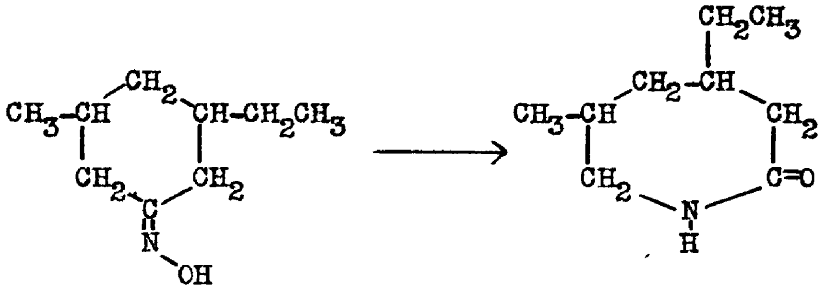
The theory of the Beckmann rearrangement has been discussed adequately elsewhere (3, 4, 44-52). Concentrated sulfuric acid was used in this investigation to effect the Beckmann rearrangements. There are indications in the literature (53-55) that a high temperature of rearrangement with this agent is not desirable and certainly the avoidance of high temperature eliminates considerable decomposition of the product by the hot concentrated acid. A preliminary investigation of the Beckmann rearrangement of cyclohexanone oxime demonstrated that the method of Marvel and Eck (56) could be modified to avoid very violent reaction with its accompanying high temperature. The sulfuric acid was heated to the temperature necessary for rearrangement and the solid cyclohexanone oxime was then added portionwise so that the temperature of the reaction did not exceed 130° C. It should be noted in passing that the temperature control was considerably easier with the 3-methyl-5-ethylcyclohexanone oxime since the rearrangement was not as exothermic in this case.

Hildebrand and Bogert (11) have demonstrated that in the case of the rearrangement of cyclohexanone oximes with sulfuric acid more concentrated acid leads to substantially better yields of lactam. A preliminary investigation of the Beckmann rearrangement of cyclohexanone oxime using larger amounts of starting materials and the modified method of rearrangement just described has substantiated the claim of these investigators. It was found in the present investigation that sulfuric acid of concentration greater than ninety percent gave substantially better yields of ϵ-caprolactam than lower concentrations. However, for sulfuric acid concentrations of 90 to 97 percent the yields were approximately the same. The commercial concentrated sulfuric acid was therefore used for later rearrangements because of the convenience.

The Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime may lead to the two structurally isomeric lactams. The course of the rearrangement may be represented as shown in Plate 7.

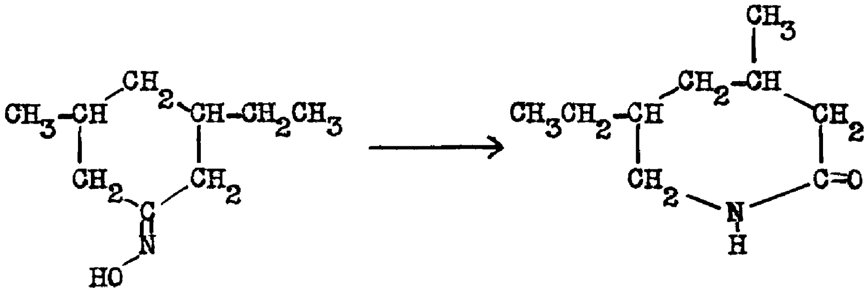
If Formula VI is designated as representing the <u>syn</u> form of the oxime, then Formula VIII would represent the <u>anti</u> form of the oxime. There are four isomeric oximes that can be represented by Formula VI, a <u>cis</u> racemate with the alkyl groups arranged in a <u>cis</u> configuration with respect to each other, and a <u>trans</u> racemate with the alkyl groups arranged in a <u>trans</u> configuration with respect to each other. All isomeric oximes represented by Formula VI, on rearrangement lead to different isomeric lactams, which may be represented by Formula VII. Similar considerations apply to the isomeric oximes and the isomeric lactams represented respectively by Formulas VIII and IX. The lactams represented by Formula VII are structurally isomeric with the lactams represented by Formula IX. There are eight possible isomeric oximes and each isomeric oxime on

PLATE 7



VI

VII



IX

VIII

rearrangement would lead to a different isomeric lactam. Therefore, there are eight possible isomeric lactams that could result from the Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime. If the alkyl groups are assumed to have the cis configuration, for the reason stated previously, then the Beckmann rearrangement of this oxime mixture could lead to the two structurally isomeric lactams represented by Formulas VII and IX, each of which is a racemate.

3-Methyl-5-ethylcyclohexanone oxime has been rearranged and the product purified by distillation. The product boiled over a narrow temperature range and fractional distillation was not considered feasible. The product solidified on cooling to room temperature and was purified further by recrystallization. Melting points of the various crops of crystals from the crystallization media indicated that at least two isomeric lactams had resulted from the rearrangement of the oxime. One pure isomer melting at 105.8 to 106.2° C. could be isolated from the mixture by a process of fractional crystallization using "hexane" as the solvent. All the remaining mixtures of varying content of isomeric lactams melted within the temperature range of 75 to 106.2° C. Another pure isomer melting at 100.3 to 101.3° C.

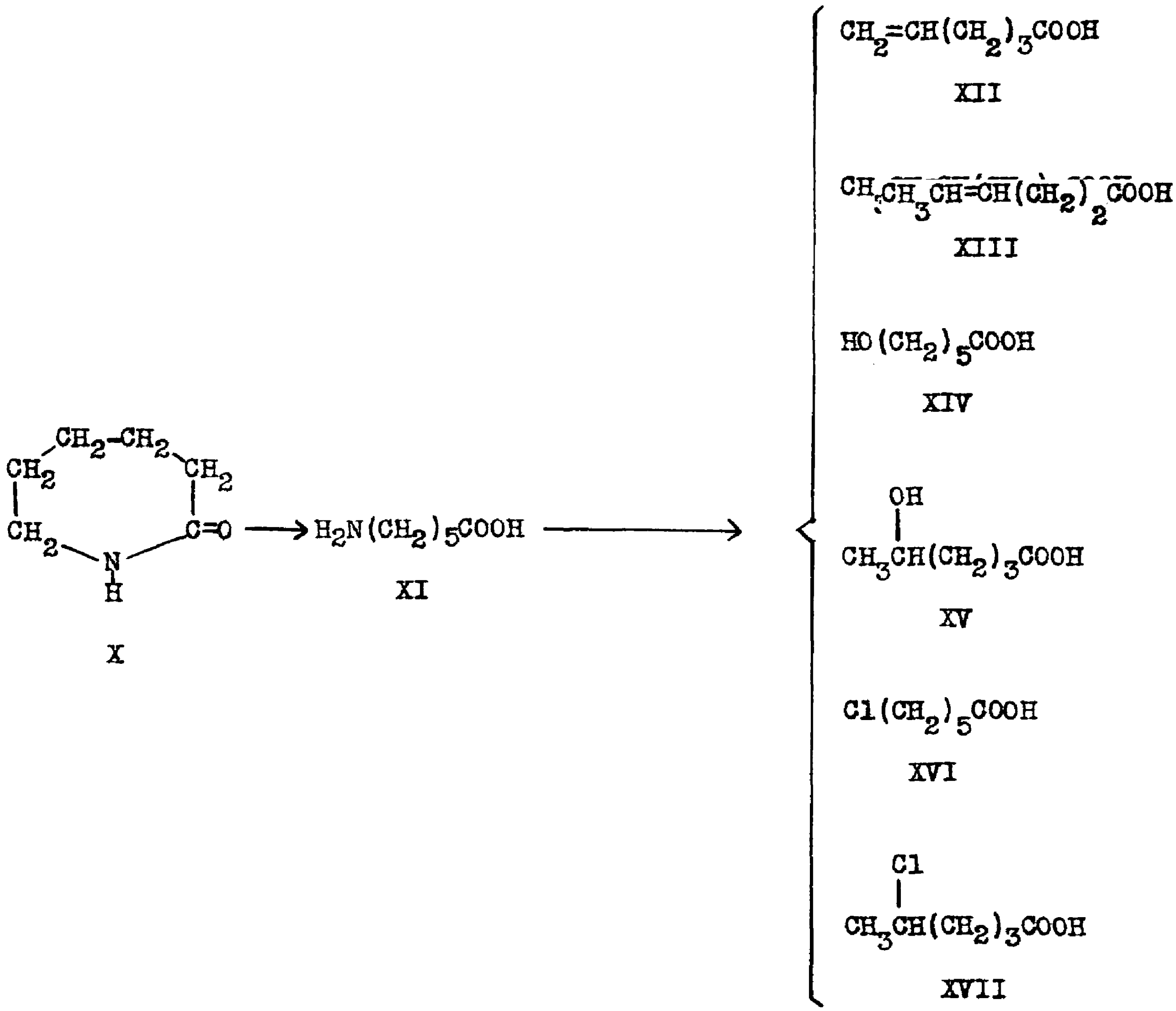
could be isolated by extraction of the low melting mixtures with cold ethyl acetate followed by extensive recrystallization from "hexane" of the residues left from the evaporation of the ethyl acetate extracts. Mixtures of the two pure isomers seemed to indicate that only these two isomers were present and that their eutectic mixture melted at approximately 75° C.

The development of a satisfactory method for proving the structures of the lactams resulting from the Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime was undertaken using the parent compound, ϵ-caprolactam. The desired result was to obtain saturated acids or esters from the lactams since the dialkyl substituted saturated acids or esters could be unequivocally synthesized with a comparatively few well-known reactions. Some preliminary attempts to reduce ϵ-caprolactam to caproic acid with concentrated hydriodic acid, following in general the procedure of Kwisda (35) showed little promise. This method suffers somewhat in that normally only small quantities of material may be reduced at one time and the aqueous solutions used develop considerable pressure at the high temperature needed for reduction (35, 36).

It is well known that nitrous acid reacts with aliphatic amines to give products devoid of nitrogen. Whitmore and Langlois (57) have investigated the reaction of nitrous acid with butylamine. The nitrous acid in their study was generated by treatment of sodium nitrite with hydrochloric acid. They found that the major products resulting from the nitrous acid treatment of butylamine were straight-chain butenes, butyl alcohols and butyl chlorides. If nitrous acid reacted analogously with ϵ-aminocaproic acid, which could be obtained by hydrolysis of ϵ-caprolactam, then the products would be unsaturated caproic acids, hydroxy caproic acids and chloro caproic acids. The reaction could be represented as shown in Plate 8.

Helferich and Malkomes (58) have investigated the reaction of sodium nitrite with ϵ-aminocaproic acid hydrochloride, resulting from the hydrolysis of ϵ-caprolactam. They obtained approximately a twenty percent yield of hexenoic acid as main product. A small quantity of a lactone was isolated by further treatment of the residue from the distillation of the hexenoic acid but no other products were identified. The possible products of their reaction have been represented previously by Formulas XII through XVII. The presence of two reaction centers in these

PLATE 8

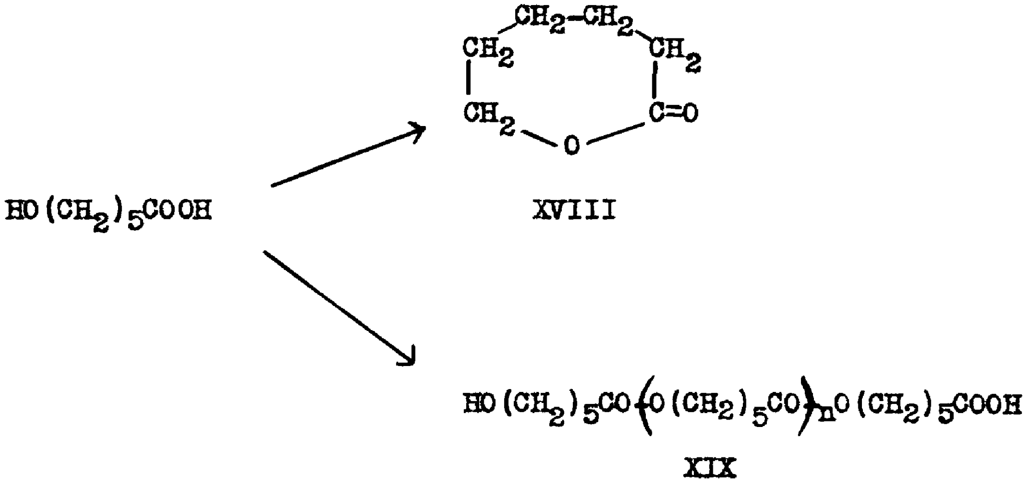

CH2-CH2
CH2
CH2
CH2
CH2
C=O
N
H
X
H2N(CH2)5COOH
XI
CH2=CH(CH2)3COOH
XII
CH3CH3CH=CH(CH2)2COOH
XIII
HO(CH2)5COOH
XIV
OH
CH3CH(CH2)3COOH
XV
Cl(CH2)5COOH
XVI
Cl
CH3CH(CH2)3COOH
XVII

compounds leads to difficulty in their isolation. For example, the ϵ-hydroxycaproic acid, represented by Formula XIV, may undergo the changes on attempted isolation shown in Plate 9.

The ϵ-hydroxycaproic acid, under the influence of heat, may cyclize to the lactone, XVIII (59, 60), or may polymerize to a long chain polyester, XIX (61, 62). The other possible hydroxy and chloro substituted caproic acids, represented by Formulas XV through XVII, could possibly undergo similar changes. The large percentage of unidentified product of Helferich and Malkomes (58) was presumably polymer resulting from the transformations just described. Wallach (15, 16) has investigated the reaction of nitrous acid with ϵ-amino caproic acids. His work demonstrated that unsaturated caproic acids and hydroxy caproic acids were among the products of the reaction. The reaction of nitrous acid with ϵ-caprolactam or the amino acid and its derivatives was chosen for further development since it promised to yield a fair amount of unsaturated acid which could be transformed easily to caproic acid.

A semiquantitative investigation of the reaction of nitrous acid with ϵ-aminocaproic acid and various of its derivatives was undertaken. The purpose of the investigation was to determine

PLATE 9



$HO(CH_2)_5COOH$

$HO(CH_2)_5CO\left(O(CH_2)_5CO\right)_nO(CH_2)_5COOH$

which procedure removed the most organically bound nitrogen. It was felt that analysis of the various solutions for nitrogen by the Kjeldahl procedure would roughly indicate the amount of organically bound nitrogen that remained in the solutions after the nitrous acid treatment. Kornblum and Iffland (63) have demonstrated that aliphatic amines do not react with nitrous acid at a pH lower than 3. The various experiments in this preliminary investigation were therefore carried out in acetic acid solutions or in mineral acid solutions buffered with potassium acetate. One exception to this will be noted later. In brief the procedures used were as follows. All were carried out below 5° C. Method A consisted of the treatment of ϵ-caprolactam dissolved in fifty percent acetic acid with sodium nitrite. The reaction mixture was extracted with an organic solvent. The residue left on evaporation of the solvent was treated further with concentrated potassium hydroxide to decompose the nitroso compound if formed, as will be explained later. The aqueous alkaline solution was made acid to Congo red and extracted again with ether. Method B consisted of the treatment with sodium nitrite of ϵ-caprolactam dissolved in twenty percent sulfuric acid. This method was the one exception noted previously where the mineral acid solution was not buffered. The residue left from the evaporation of the solvent extracts was treated as in Method A to decompose the nitroso compound if formed and then acidified to Congo red and extracted with ether. Method C consisted of the treatment with sodium nitrite of ϵ-aminocaproic acid hydrochloride dissolved in water and buffered with potassium acetate. Method D consisted of the treatment with sodium nitrite of ϵ-aminocaproic acid dissolved in fifty percent acetic acid. Method E consisted of the treatment with sodium nitrite of ethyl ϵ-aminocaproate hydrochloride dissolved in water and buffered with potassium acetate. Method F consisted of the treatment with sodium nitrite of ethyl ϵ-aminocaproate dissolved in fifty percent acetic acid. The reaction mixtures obtained in methods C to F were made acid to Congo red and extracted with ether. Aliquots of all solutions were analyzed for nitrogen by the Kjeldahl method. The composite results are summarized in Table I. Complete results are given in Table III.

Method B, which was the treatment with sodium nitrite of ϵ-caprolactam dissolved in twenty percent sulfuric acid, and Method D, which was the treatment with sodium nitrite of ϵ-aminocaproic acid dissolved in fifty percent acetic acid, apparently

TABLE I

COMPOSITE RESULTS FROM TABLE III

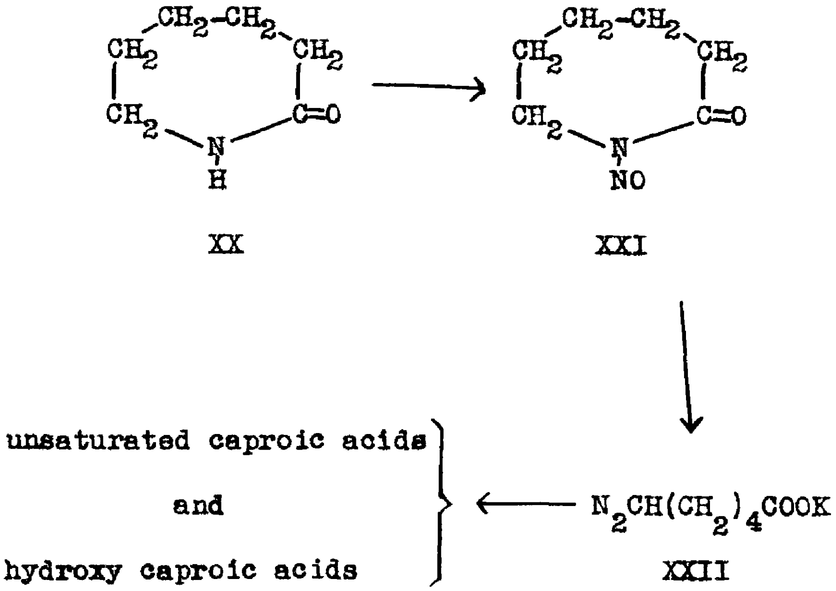
Method	Percent of Original Organically Bound Nitrogen Remaining in All Solutions
A	58.8
B	18.5
C	30.7
D	18.5
E	37.0
F	23.1

are most effective for the removal of organically bound nitrogen.

We must digress briefly here to explain the basis for the treatment of ϵ-caprolactam with sodium nitrite. The anticipated course of the reaction may be represented as shown in Plate 10.

The ϵ-caprolactam, XX, is converted into the nitroso derivative, XXI, which under the influence of potassium hydroxide may decompose to the diazo compound, XXII, or may decompose

PLATE 10



XX → XXI

$N_2CH(CH_2)_4COOK$

XXII

unsaturated caproic acids and hydroxy caproic acids to unsaturated caproic acids and hydroxy caproic acids presumably through the diazo compound. The nitroso derivatives of some lactams have been prepared and found to be unstable (64, 65). Decomposition of these nitroso derivatives leads to the unstable diazo compound (65) or directly to products that might be expected from the nitrous acid treatment of the free amino acids (64, 66). It was found in this investigation that the nitroso derivative of ϵ-caprolactam presumably decomposed as it was formed, since the further treatment of the residue from the evaporation of the ether extracts of the original nitrous acid reaction did not significantly improve the removal of organically bound nitrogen.

The final ether extracts resulting from the nitrous acid treatments of Methods B and D were analyzed further for unsaturated acids, total acids and the weights of the residues left on evaporation of the solvent. The Hanus method was used for the determination of the unsaturated acids and the results were interpreted as indicating how well the reaction had proceeded in the desired direction. The total acid content and the weights of the residues were interpreted as indicating the over-all yield of all products. Analysis indicated that both methods gave approximately ten percent of the unsaturated acid theoretically possible. The amount of unsaturated acid was the important fact since the unsaturated acid could be easily reduced to the saturated acid. Method D gave the largest over-all yield of material based on both the total acid analysis and the weight of the residue resulting from evaporation of the solvent. Though Method D gives the largest over-all yield of material, it must be remembered that the starting material was ϵ-aminocaproic acid which required an extra step in preparation plus the added disadvantage of the tedious procedure for isolation of amino acids. Further work was initiated using essentially the nitrous acid treatment of ϵ-caprolactam as described in Method B.

It can be said with reasonable certainty (15, 16, 57, 58, 64, 66-70) that the products resulting from the nitrous acid treatment of ϵ-aminocaproic acid and its various derivatives are unsaturated acids, lactones, hydroxy acids and chloro acids (57, 67), if hydrochloric acid were used to generate the nitrous acid. An attempt was made to convert all these products to caproic acid without isolation of the intermediate products. ϵ-Caprolactam was treated with nitrous acid by Method B as described previously. The mixture of products was treated with hydrogen and platinum oxide catalyst to hydrogenate the unsaturated acids present. At this point the product probably consisted of caproic acid and the hydroxy acid, XXIII, lactone, XXIV, and chloro acid, XXV, represented by the formulas shown in Plate 11, Figure 1.

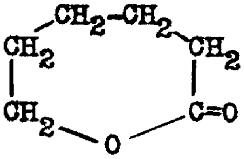
It is also possible that the hydroxy acid, XXVI, the lactone, XXVII, and the chloro acid, XXVIII, as represented by the formulas shown in Plate 11, Figure 2, would also be present.

A number of investigators (71, 72, 73) have shown that ethyl ϵ-hydroxycaproate can be converted into ethyl ϵ-bromocaproate by treatment with phosphorus tribromide (72, 73), or by treatment with concentrated hydrobromic acid (71). Further, Papa and Schwenk and co-workers (74, 75) have developed a procedure for reducing halogen containing compounds with Raney nickel alloy. Using the method of Brown and Partridge (71), the mixture of acids resulting from the hydrogenation was treated with a solution of concentrated hydrobromic and sulfuric acids to convert the hydroxy acid and lactone to the ϵ-bromocaproic acid. The acids resulting from the hydrobromic acid treatment were then treated with Raney nickel alloy and alkali to convert the ϵ-bromocaproic acid to caproic acid. The results of this procedure were very unsatisfactory. The quantity of caproic

PLATE 11

$HO(CH_2)_5COOH$

XXIII

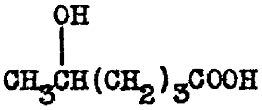


XXIV

$Cl(CH_2)_5COOH$

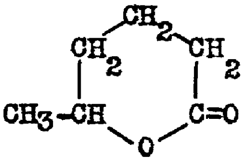
XXV

Figure 1

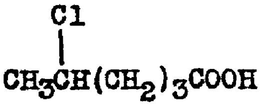


$$CH_3\overset{\overset{OH}{|}}{C}H(CH_2)_3COOH$$

XXVI



XXVII



$$CH_3\overset{\overset{Cl}{|}}{C}H(CH_2)_3COOH$$

XXVIII

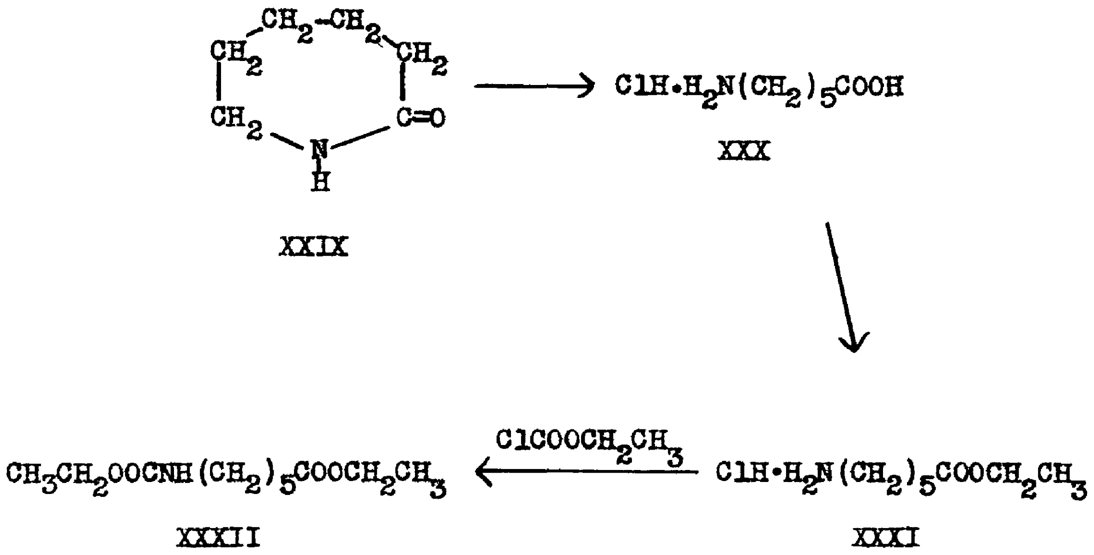
Figure 2

acid isolated was not more than could be expected from hydrogenation of the unsaturated acids originally present. No other products were isolated and attempts to find other products were unsuccessful. Further work was designed to eliminate an excessive number of reactions before isolation of the products so that the effectiveness of the individual steps could be determined.

It was felt that loss of product due to polymerization could be avoided if the carboxyl group were esterified. Consideration of other straight-chain compounds that could be prepared from ϵ-caprolactam and that might undergo reactions similar to those described previously for the nitrous acid treatment of ϵ-caprolactam led to an investigation of the reactions of ethyl ϵ-carboethoxyaminocaproate. The preparation of ethyl ϵ-carboethoxyaminocaproate (76, 77) from ϵ-caprolactam may be schematically represented as shown in Plate 12.

ϵ-Caprolactam, XXIX, was hydrolyzed to the amino acid hydrochloride, XXX, which was esterified to give ethyl ϵ-aminocaproate hydrochloride, XXXI. The crude ester hydrochloride, XXXI, on reaction with ethyl chloroformate gave ethyl ϵ-carboethoxyaminocaproate, XXXII. The nitrosation and decomposition

PLATE 12



CH2-CH2
CH2
CH2
CH2
C=O
N
H
XXIX
ClH·H2N(CH2)5COOH
XXX
ClCOOCH2CH3
CH3CH2OOCNH(CH2)5COOCH2CH3
XXXII
ClH·H2N(CH2)5COOCH2CH3
XXXI

of ethyl ϵ-carboethoxyaminocaproate may be represented as shown in Plate 13.

The urethane, XXXII, was treated with nitrous acid to give the nitroso compound (68, 77, 78), XXXIII. Decomposition of the nitroso compound (68-70, 79), XXXIII, with potassium carbonate in methyl alcohol led to a mixture of products. The boiling points of the various fractions indicated that the products probably were predominately the unsaturated ester, XXXIV, ethyl ϵ-methoxycaproate, XXXV, and ethyl ϵ-hydroxycaproate, XXXVI. The yield of unsaturated ester was approximately ten percent which was not any better than could be expected from the direct treatment of ϵ-caprolactam with nitrous acid. This line of approach was therefore discontinued since it required several extra reactions and offered no improvement in yield of unsaturated ester. It was noted that comparatively little residue was left from the distillation of the products. This indicated that esterification at some stage would eliminate considerable polymerization on distillation.

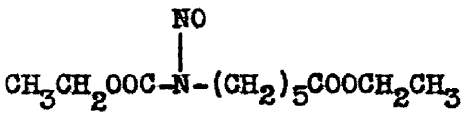
None of the preliminary investigations of the reaction of nitrous acid with ϵ-aminocaproic acid or one of its derivatives improved on the yield of hexenoic acid from ϵ-caprolactam as

PLATE 13

$CH_3CH_2OOCNH(CH_2)_5COOCH_2CH_3$

XXXII

$\downarrow$



$CH_3CH_2OOC\text{-}\overset{NO}{\overset{|}{N}}\text{-}(CH_2)_5COOCH_2CH_3$

XXXIII

$\downarrow$

$CH_2{=}CH(CH_2)_3COOCH_2CH_3$

XXXIV

+

$CH_3O(CH_2)_5COOCH_2CH_3$

XXXV

+

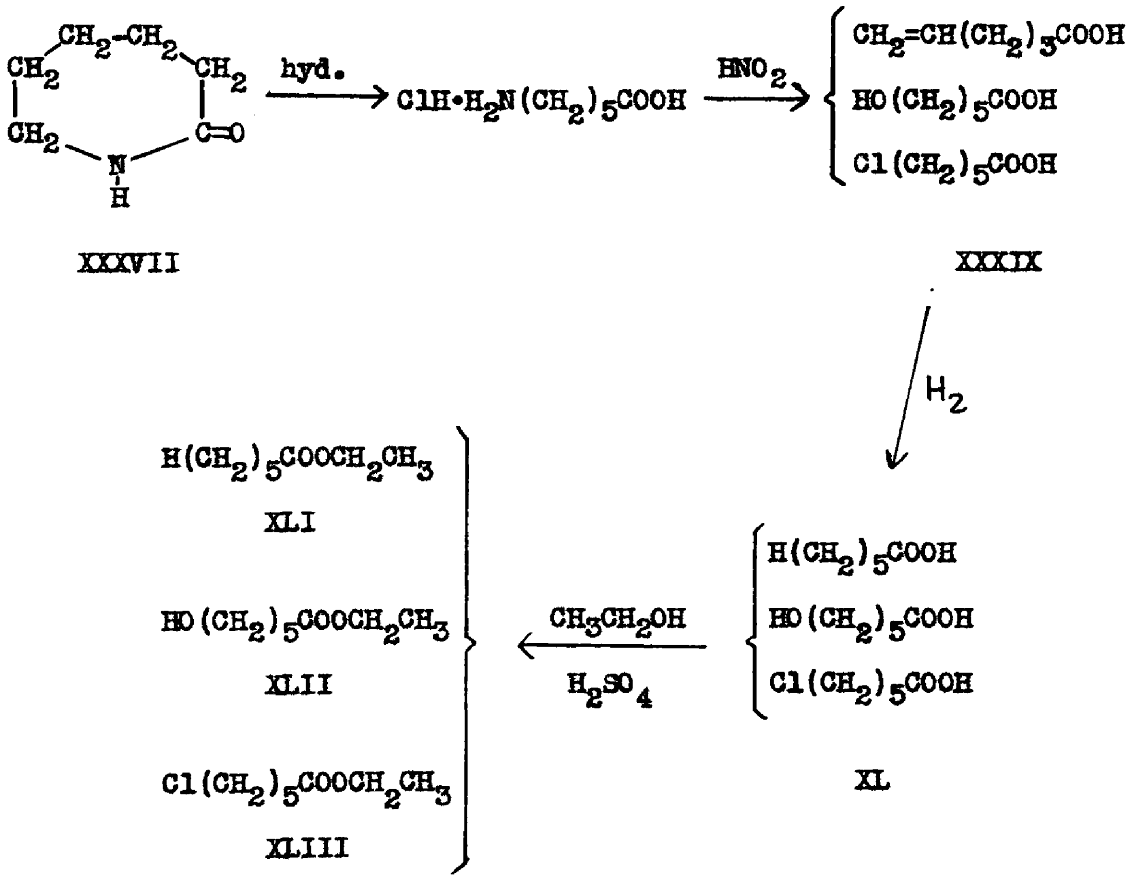
$HO(CH_2)_5COOCH_2CH_3$

XXXVI

reported by Helferich and Malkomes (58). It was felt that their procedure coupled with a hydrogenation and esterification would lead to a maximum yield of ethyl caproate and eliminate loss of material by polymerization. The suggested procedure was found to be satisfactory and was adopted for the proof of structure of the lactams. The procedure and results using ε-caprolactam may be represented as shown in Plate 14.

ε-Caprolactam, XXXVII, was hydrolyzed with the calculated amount of hydrochloric acid to give ε-aminocaproic acid hydrochloride, XXXVIII. Treatment of the amino acid hydrochloride with a concentrated solution of sodium nitrite gave a mixture, XXXIX, of the unsaturated acid, the hydroxy acid and the chloro acid. Catalytic hydrogenation of the mixture, XXXIX, using platinum oxide catalyst gave a mixture, XL, of caproic acid, ε-hydroxycaproic acid and ε-chlorocaproic acid. Esterification of the acids using ethyl alcohol and sulfuric acid gave ethyl caproate, XLI, identified by refractive index; ethyl ε-hydroxycaproate, XLII, identified by conversion to the known hydrazide; and ethyl ε-chlorocaproate, XLIII, identified by refractive index. Further evidence for the structure of the hydroxy ester was obtained by conversion to ε-iodocaproic acid, which had

PLATE 14


hyd.
ClH•H2N(CH2)5COOH
HNO2
CH2=CH(CH2)3COOH
HO(CH2)5COOH
Cl(CH2)5COOH
XXXVII
XXXIX
H2
H(CH2)5COOH
HO(CH2)5COOH
Cl(CH2)5COOH
XL
CH3CH2OH
H2SO4
H(CH2)5COOCH2CH3
XLI
HO(CH2)5COOCH2CH3
XLII
Cl(CH2)5COOCH2CH3
XLIII

previously been prepared from an authenic sample of ethyl ϵ-hydroxycaproate.

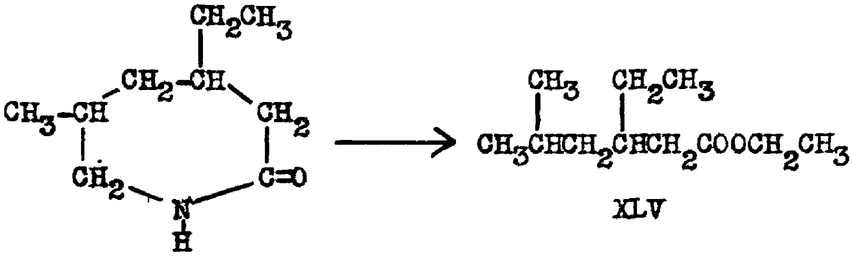
Ethyl ϵ-hydroxycaproate prepared by the method of Robinson and Smith (80) was converted into the new ϵ-iodocaproic acid by treatment with phosphorus and iodine (81-83), followed by hydrolysis. The ϵ-iodocaproic acid has been reduced with zinc and hydrochloric acid (82, 84, 85) and esterified to give ethyl caproate, identified by refractive index. It is well known that chloro or bromo substituted aliphatic compounds can be converted into iodo substituted compounds with comparative ease; and, this has already been accomplished with a bromo acid (86). If it were necessary to convert the hydroxy ester and the chloro ester to caproic acid, the conversion to the iodo acid, followed by reduction, seems to offer the best route. A number of iodo acids and esters comparable to ϵ-iodocaproic acid have been prepared previously (80, 86-88). Nevertheless, the ethyl ester of ϵ-iodocaproic acid could not be isolated in a pure state (80).

The same method used to convert ϵ-caprolactam to ethyl caproate was applied to the pure lactams resulting from the Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime. A preliminary experiment using a mixture of these lactams demonstrated that the over-all yield of products was comparable to that obtained with ϵ-caprolactam. The refractive index of the lower boiling fraction, which should have contained the saturated esters, indicated that reduction of the unsaturated esters was not complete or had not taken place. In the conversions of the pure lactams to their respective saturated esters it was necessary to isolate the unsaturated esters and catalytically hydrogenate them using platinum oxide catalyst and acetic acid solvent. The pure lactam isomer melting at 105.8 to 106.2° C., which will be designated as Lactam A, was converted into the saturated ester. The saturated ester was identified as ethyl 3-ethyl-5-methylhexanoate by its refractive index and melting points of the p-toluidide and S-benzylthiuronium salt. The derivatives showed no depression of melting point on mixture with the same derivatives obtained from ethyl 3-ethyl-5-methylhexanoate that had been prepared by an unequivocal synthesis. Melting point depressions were observed on mixture of the derivatives with the corresponding derivatives prepared from the isomeric ester, ethyl 3,5-dimethylheptanoate. Lactam A was thus identified as 4-ethyl-6-methyl-2-ketohexamethylenimine and the transformation to the saturated ester may be represented briefly as shown in Plate 15, Figure 1.

Two of the higher boiling fractions resulting from the conversion of Lactam A to the saturated ester were identified as a chloro ester and a hydroxy ester by analysis of their respective S-benzylthiuronium salts. By analogy to the results obtained with the ϵ-caprolactam the position of the substituents was probably epsilon; however, no attempt has been made to definitely establish this conclusion.

The pure isomeric lactam melting at 100.3 to 101.3° C., which will be designated as Lactam B, was converted into the saturated ester in a similar manner. The saturated ester was identified as ethyl 3,5-dimethylheptanoate by its refractive index and melting points of the p-toluidide and S-benzylthiuronium salt. The derivatives showed no depression of melting point on mixture with the same derivatives prepared from ethyl 3,5-dimethylheptanoate that had been prepared by an unequivocal synthesis. Melting point depressions or increases were observed on mixture of the derivatives with the corresponding derivatives prepared from the isomeric ester, ethyl 3-ethyl-5-methylhexanoate. Lactam B was thus identified as 4-methyl-6-ethyl-2-ketohexa-

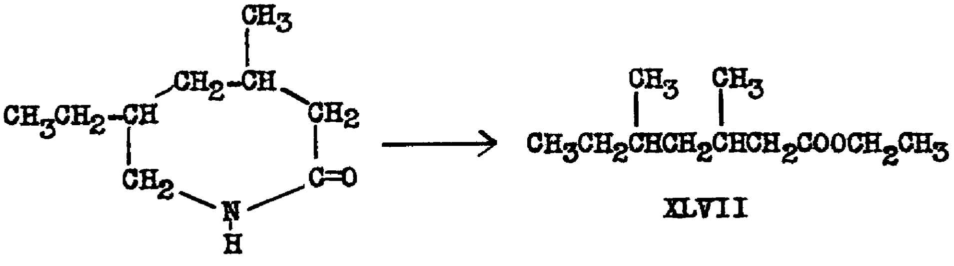
PLATE 15



XLIV

XLV

Figure 1



XLVI

XLVII

Figure 2

methylenimine and the transformation to the saturated ester may be briefly represented as shown in Plate 15, Figure 2.

The two new isomeric esters, ethyl 3-ethyl-5-methylhexanoate and ethyl 3,5-dimethylhexanoate, have been synthesized and characterized for comparison with the saturated esters that have been prepared from the isomeric Lactams A and B. The synthesis of ethyl 3-ethyl-5-methylhexanoate required the preparation of ethyl isobutyl ketone as an intermediate. This ketone has been synthesized by two methods. The first method consisted of passing a mixture of propionic acid and isovaleric acid over thorium oxide catalyst at 450° C. (89). The reaction may be represented as shown in Plate 16.

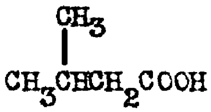
The propionic acid, XLVIII, condenses with isovaleric acid, XLIX, to form the desired ketone, ethyl isobutyl ketone, L. The side product, diethyl ketone, LI, is formed by the condensation of two molecules of propionic acid, XLVIII. The side product, diisobutyl ketone, LII, is formed by condensation of two molecules of isovaleric acid, XLIX. A forty-one percent yield of the ethyl isobutyl ketone, L, was obtained using a four-to-one mole ratio of propionic acid to isovaleric acid. When the ratio of propionic acid to isovaleric acid was decreased to two to

PLATE 16

CH_3CH_2COOH

XLVIII

+



$CH_3CH(CH_3)CH_2COOH$

XLIX

$$\Big\downarrow \mathrm{ThO_2}$$

$CH_3CH_2COCH_2CH(CH_3)_2$

L

+

$CH_3CH_2COCH_2CH_3$

LI

+

$(CH_3)_2CHCH_2COCH_2CH(CH_3)_2$

LII

one the yield of ethyl isobutyl ketone decreased to eighteen percent.

The second method used to synthesize ethyl isobutyl ketone was patterned after the general method of Cason (90-95). The reactions involved in this procedure may be represented as shown in Plate 17.

Ethyl bromide, LIII, was converted into ethyl magnesium bromide, LIV, by the usual Grignard procedure. The ethyl magnesium bromide, LIV, was converted into diethyl cadmium, LV, by treatment with anhydrous cadmium chloride. The diethyl cadmium, LV, was prepared under an atmosphere of nitrogen. Isovaleryl chloride, LVII, prepared from isovaleric acid, LVI, by treatment with thionyl chloride, was condensed with the diethyl cadmium, LV, under an atmosphere of nitrogen to form ethyl isobutyl ketone, LVIII. The yield of ketone by this method was forty-six percent. A comparison of the two procedures used for the preparation of ethyl isobutyl ketone demonstrated that the diethyl cadmium method gave the better yield. However, the simplicity of the catalytic method far outweighs the small disadvantage in yield and the catalytic method was considered to be the better of the two procedures.

PLATE 17

$$CH_3CH_2Br \xrightarrow{Mg} CH_3CH_2MgBr \xrightarrow{CdCl_2} (CH_3CH_2)_2Cd$$

LIII LIV LV

$$(CH_3)_2CHCH_2COOH \xrightarrow{SOCl_2} (CH_3)_2CHCH_2COCl$$

LVI LVII

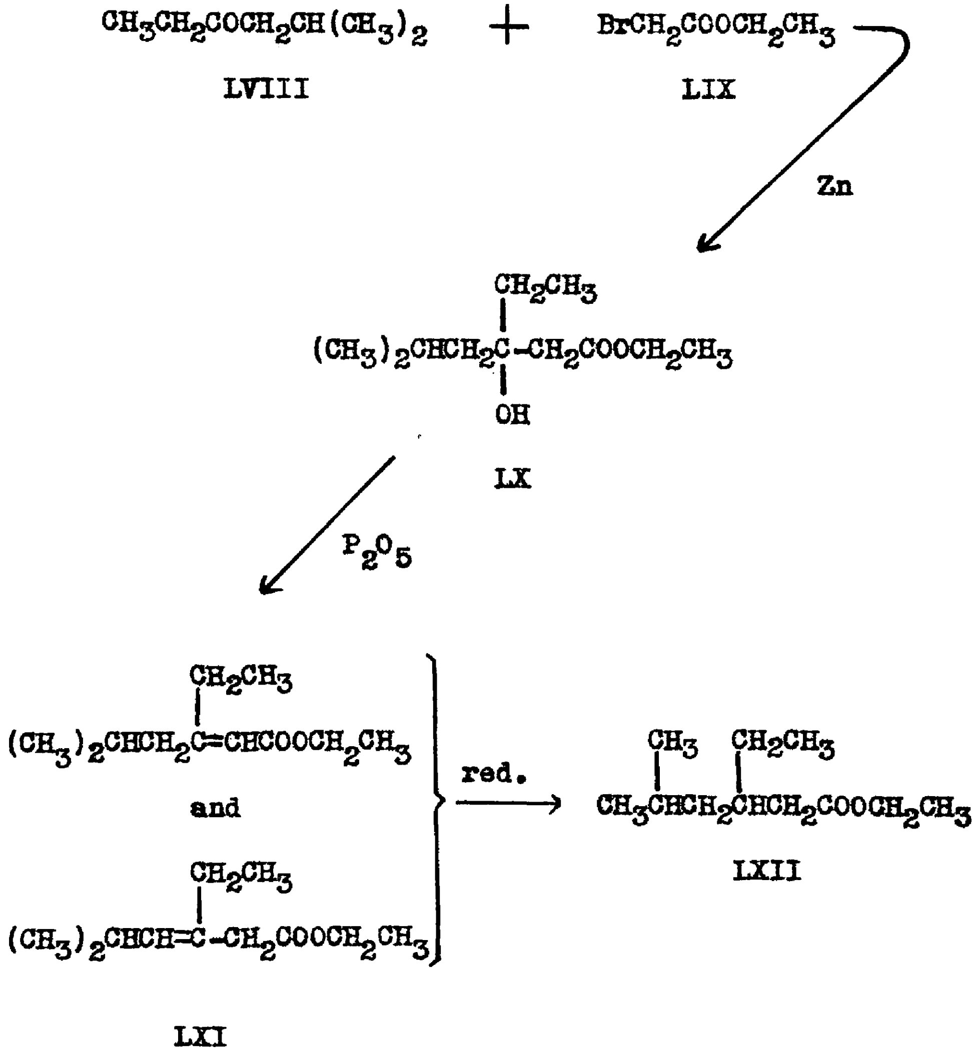
$$(CH_3CH_2)_2Cd + (CH_3)_2CHCH_2COCl \longrightarrow CH_3CH_2COCH_2CH(CH_3)_2$$

LV LVII LVIII

The ethyl isobutyl ketone, prepared by the two methods described previously, was transformed into ethyl 3-ethyl-5-methylhexanoate by a Reformatsky reaction followed by dehydration and hydrogenation. The reactions may be represented as shown in Plate 18.

The Reformatsky reaction as modified by Natelson and Gottfried (96) was used to prepare the mixture, LXI, of unsaturated acids. Ethyl isobutyl ketone, LVIII, and ethyl bromoacetate, LIX, dissolved in an approximately fifty percent mixture of benzene and toluene, were condensed by reaction with zinc to form the hydroxy ester LX. The hydroxy ester, LX, was not isolated but was dehydrated in solution by reaction with phosphorus pentoxide (97) to form the mixture, LXI, of unsaturated esters. An attempted dehydration of the hydroxy ester with acetic anhydride was not successful and probably led to the acetyl derivative of the hydroxy ester. The mixture, LXI, of unsaturated esters was catalytically hydrogenated at low pressure of hydrogen using platinum oxide catalyst and acetic acid solvent to form ethyl 3-ethyl-5-methylhexanoate, LXII. Low pressure hydrogenation of the mixture of unsaturated esters using platinum oxide catalyst and ethyl alcohol solvent was not successful (98).

PLATE 18


CH3CH2COCH2CH(CH3)2
LVIII
+
BrCH2COOCH2CH3
LIX
Zn
CH2CH3
(CH3)2CHCH2C-CH2COOCH2CH3
OH
LX
P2O5
CH2CH3
(CH3)2CHCH2C=CHCOOCH2CH3
and
CH2CH3
(CH3)2CHCH=C-CH2COOCH2CH3
LXI
red.
CH3
CH2CH3
CH3CHCH2CHCH2COOCH2CH3
LXII

Partial reduction of the mixture of unsaturated esters could be effected using high pressure hydrogenation at 60° C. with Raney nickel catalyst and ethyl alcohol solvent (98, 99).

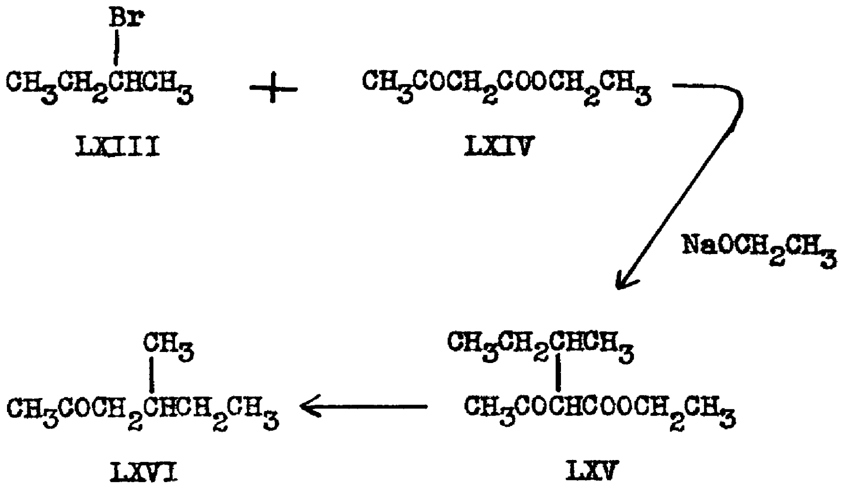
The synthesis of the isomeric ethyl 3,5-dimethylheptanoate made necessary the preparation of 4-methyl-2-hexanone as an intermediate. The reactions used for the preparation of the ketone may be represented as shown in Plate 19.

Ethyl acetoacetate, LXIV, was alkylated with secondary butyl bromide (100), LXIII, using sodium ethylate as the condensing agent. The crude keto ester, LXV, formed by the alkylation was saponified with sodium hydroxide and the free acid decarboxylated to give 4-methyl-2-hexanone, LXVI.

Ethyl 3,5-dimethylheptanoate was prepared from the 4-methyl-2-hexanone by essentially the same procedure used for the preparation of ethyl 3-ethyl-5-methylhexanoate.

The two new esters, ethyl 3-ethyl-5-methylhexanoate and ethyl 3,5-dimethylheptanoate were characterized by analysis, physical constants, and analysis of their respective p-toluidides and S-benzylthiuronium salts. Each ester was converted into the respective parent acid by saponification and acidification and the acids were characterized by analysis and physical constants.

PLATE 19



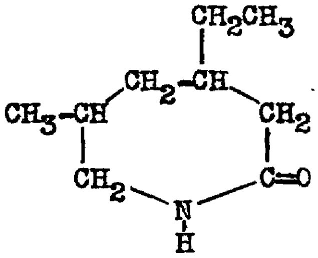
$$\underset{\text{LXIII}}{CH_3CH_2\overset{\overset{\displaystyle Br}{|}}{C}HCH_3} + \underset{\text{LXIV}}{CH_3COCH_2COOCH_2CH_3} \xrightarrow{NaOCH_2CH_3} \underset{\text{LXV}}{CH_3CO\overset{\overset{\displaystyle CH_3CH_2CHCH_3}{|}}{C}HCOOCH_2CH_3} \longrightarrow \underset{\text{LXVI}}{CH_3COCH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_3}$$

It has further been demonstrated in this investigation that the two new isomeric Lactams A and B, prepared by the Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime, can be transformed into the respective substituted 1,5-pentamethylenetetrazole by treatment with phosphorus pentachloride followed by reaction with a solution of hydrazoic acid dissolved in benzene (101). The formation of the tetrazoles may be represented as shown in Plate 20.

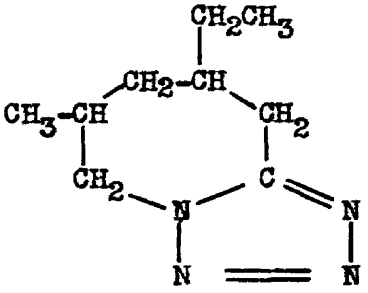
The two tetrazoles, LXVII and LXVIII, have been characterized by analysis.

Harvill, Roberts, and Herbst (1) have described a methyl ethyl pentamethylenetetrazole which had been obtained by the interaction of 3-methyl-5-ethylcyclohexanone oxime with sodium azide and chlorosulfonic acid. The method of formation which involved an expansion of the cyclohexanone ring similar to that encountered in the Beckmann rearrangement could have led to two isomeric tetrazole structures. These authors arbitrarily assigned a tentative structure, LXVIII, to their compound. The tetrazole of Harvill, Roberts, and Herbst (1) has been compared with these tetrazoles of known structure by melting points and mixed melting points. It has thus been shown that the tetrazole

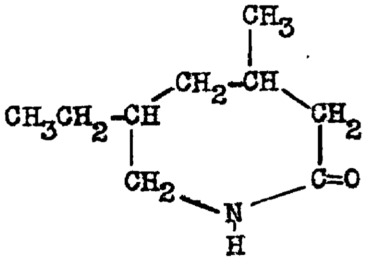
PLATE 20



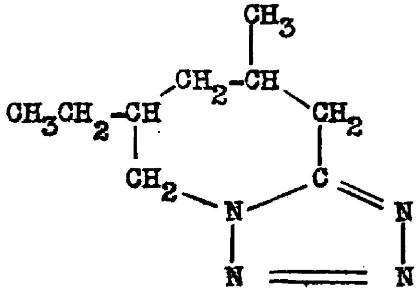
LACTAM A



LXVII



LACTAM B



LXVIII

prepared by Harvill, Roberts, and Herbst (1) is 7-ethyl-9-methyl-1,5-pentamethylenetetrazole, LXVII, and does not have the structure, LXVIII, which had been arbitrarily assigned to it previously.

EXPERIMENTAL[1, 2]

Preparation of Compounds for Preliminary Experiments

ε-Caprolactam

ε-Caprolactam was prepared essentially as described by Marvel and Eck (56) in Organic Syntheses. However, the method of rearrangement of the cyclohexanone oxime was changed. Using the same proportions of sulfuric acid to oxime, the total amount of sulfuric acid was placed in a beaker of appropriate size and was heated to the temperature necessary for rearrangement, 105° C. The solid oxime was added portionwise by means of a spatula so that the temperature was maintained between 105 and 130° C. After all the oxime had been added the mixture was cooled to 10° C. and double its weight of ice was added all at

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[1] All melting points in this thesis are corrected.

[2] All Kjeldahl analyses for nitrogen were completed in this laboratory. All other analyses were completed by Micro-Tech Laboratories, Skokie, Illinois.

once. The product was isolated as already described (56) and recrystallized from hexane.

Hildebrand and Bogart (11) have found that in the rearrangement of 2-alkylcyclohexanone oximes better yields were obtained with sulfuric acid more concentrated than 85 percent. Their results have been substantiated here by an investigation of the rearrangement of 25 g. of cyclohexanone oxime effected with sulfuric acid of various concentrations. The results of this investigation are summarized in Table II. The product was not isolated by distillation as previously described (56) but was isolated by recrystallization of the solid residue remaining after evaporation of the extracts.

The results indicate that the more concentrated sulfuric acid gives the better yield. There was little difference between the yields given by the 90, 95, and 97.1 percent acid. The commercial concentrated sulfuric acid was therefore used for the rearrangement of cyclohexanone oxime and the 3,5-alkylated cyclohexanone oximes.

TABLE II

THE BECKMANN REARRANGEMENT OF CYCLOHEXANONE OXIME USING SULFURIC ACID OF VARIOUS CONCENTRATIONS

Percent H_2SO_4	Wt. of First Crop	Wt. of Second Crop	Total Wt. of Product	Percent Yield
97.1	16.3 g.	2.6 g.	18.9 g.	75.6
95	16.5 g.	2.9 g.	19.4 g.	77.6
90	16.1 g.	3.4 g.	19.5 g.	77.9
85	15.0 g.	1.3 g.	16.3 g.	65.2
80	13.9 g.	2.8 g.	16.7 g.	66.8

ϵ-Aminocaproic Acid Hydrochloride

ϵ-Aminocaproic acid hydrochloride was prepared by the method of Eck (102) in Organic Syntheses.

ϵ-Aminocaproic Acid

ϵ-Aminocaproic acid was prepared from ϵ-caprolactam by hydrolysis with sulfuric acid and neutralization with an equivalent amount of barium hydroxide. The product melted at 200 to 202° C. (uncorrected). (Reported melting point [102], 201 to 203° C.)

Ethyl ϵ-Aminocaproate Hydrochloride

Ethyl ϵ-aminocaproate hydrochloride was prepared by the method of Marvel et al. (103). Crystallization from ethyl alcohol-diethyl ether solution gave hydroscopic crystals melting at 58.3 to 61.8° C. (reported melting point, 54 to 58° C. [103]).

Ethyl ϵ-Aminocaproate

Ethyl ϵ-aminocaproate was prepared by the method of Marvel et al. (103). The product boiled at 123-125° C./23 mm. (The reported boiling points are 122° C./28 mm. [103]; 90-92° C./4 mm. [103]; 105° C./18 mm. [77].)

Preliminary Experiments for Conversion of Lactam to Saturated Ester

Method A

Five grams, 0.044 mole, of ε-caprolactam was dissolved in 20 ml. of 50 percent acetic acid and was cooled below 5° C. Three grams, 0.044 mole, of sodium nitrite was added to the mixture in three portions in fifteen minutes. The reaction mixture was placed overnight in a refrigerator at 5 to 10° C.

The mixture was made acid to Congo red with 1:1 hydrochloric acid and extracted with five 20 ml. portions of ether. The remaining aqueous solution will be designated as Solution I. The ether was evaporated and the mixture neutralized with 40 percent potassium hydroxide in an ice-bath. Ten milliliters of 40 percent potassium hydroxide was added and the reaction allowed to stand for thirty minutes. The mixture was cooled, made acid to Congo red with 1:1 hydrochloric acid and was extracted with five 20 ml. portions of ether. The remaining aqueous solution will be designated as Solution II. The ether extracts will be designated as Solution III.

Aliquots of Solutions I, II, and III were analyzed for nitrogen by the Kjeldahl method.

Method B

Five grams of ϵ-caprolactam was dissolved in 20 ml. of 20 percent sulfuric acid and was treated with 3 g., 0.044 mole, of sodium nitrite as described in Method A. The reaction mixture, in this case, was already acid to Congo red and therefore no hydrochloric acid was added. Solutions I, II, and III were obtained in a manner identical to Method A and were analyzed.

Method C

Six and six-tenths grams, 0.044 mole, of ϵ-aminocaproic acid hydrochloride was dissolved in 20 ml. of water and was buffered with 4.3 g., 0.044 mole, of potassium acetate. The solution was cooled below 5° C. and 3 g., 0.044 mole, of sodium nitrite was added in three portions in fifteen minutes. The reaction mixture was placed overnight in a refrigerator at 5 to 10° C.

The mixture was made acid to Congo red with 1:1 hydrochloric acid and extracted with five 20 ml. portions of ether. The remaining aqueous solution will be designated as Solution I. The ether extracts will be designated as Solution III.

Aliquots of Solutions I and III were analyzed for nitrogen by the Kjeldahl method.

Method D

Five and eight-tenths grams, 0.044 mole, of ϵ-aminocaproic acid was dissolved in 20 ml. of 50 percent acetic acid and was treated with 3 g., 0.044 mole, of sodium nitrite as described in Method C. Solutions I and III were obtained in a manner identical to Method C and were similarly analyzed.

Method E

Seven and eight-tenths grams, 0.044 mole, of ethyl ϵ-aminocaproate hydrochloride was dissolved in 20 ml. of water and the solution was buffered with 4.3 g., 0.044 mole, of potassium acetate. This solution was treated with 3 g., 0.044 mole, of sodium nitrite as described in Method C. Solutions I and III were obtained in a manner identical to Method C and were similarly analyzed.

Method F

One and one-half grams, 0.011 mole, of ethyl ϵ-aminocaproate was dissolved in 4.8 ml. of 50 percent acetic acid and was cooled below 5° C. Seventy-three hundredths grams, 0.011 mole, of sodium nitrite was added to the mixture in three portions in five minutes. One-to-one hydrochloric acid was added until the solution tested positive to starch-iodide paper. The reaction mixture was set overnight in a refrigerator at 5 to 10° C.

The mixture was treated further as described in Method C and gave similar Solutions I and III which were analyzed as before.

The results of nitrogen analyses on Solutions I, II, and III obtained in the experiments just described are summarized in Table III.

The results indicate that Methods B and D are most effective for removing nitrogen from the respective amino acid derivatives.

Aliquots of Solutions III from Methods B and D were further tested for unsaturated acid by the Hanus method; total acid by titration of an alcoholic solution with standard sodium hydroxide using a phenolphthalein indicator and, for the amount of residue left after evaporation of solvent. The total acid for Solution III of Method D was determined by the difference between a direct titration of an aliquot and titration of the acetic acid separated from an aliquot by azeotropic distillation with benzene. The results are summarized in Table IV.

TABLE III

NITROGEN ANALYSIS USED TO INDICATE EFFECTIVENESS OF VARIOUS METHODS OF DEGRADATION OF ϵ-AMINOCAPROIC ACID DERIVATIVES

Method	Percent of Organically Bound Nitrogen Remaining in Solution			
	Solution I	Solution II	Solution III	Total
A	36.2	13.8	8.8	58.8
B	8.3	4.2	6.0	18.5
C	28.1	-	2.6	30.7
D	14.4	-	4.1	18.5
E	30.5	-	6.5	37.0
F	16.5	-	6.6	23.1

Methods B and D both gave approximately ten percent of the unsaturated acid theoretically possible. The amount of unsaturated acid is the important consideration since the unsaturated acid may be reduced easily to the saturated acid. Method D gives the largest yield of material based on the values for total acid and residue weight, but it must be remembered that the starting material was -aminocaproic acid which required

TABLE IV

FURTHER ANALYSIS OF SOLUTIONS RESULTING FROM THE DEGRADATION OF ε-AMINOCAPROIC ACID DERIVATIVES

	Comparative Values for One-fifth Aliquots				
Method	Unsaturated Acid	Total Acids	Acetic Acid	Total Caproic Acids	Weight of Residue
B	0.805 m.e.	3.66 m.e.	-	3.66 m.e.	0.598 g.
D	0.835 m.e.	32.54 m.e.	25.56 m.e.	6.98 m.e.	0.862 g.*

* Residue remaining after azeotropic distillation of the acetic acid with benzene and evaporation of the benzene by heating on a steam bath.

an extra step in preparation plus the added disadvantage of the tedious procedure for isolation of amino acids.

Reaction of Nitrous Acid with ϵ-Caprolactam and Attempted Conversion of All Products to Caproic Acid

Fifty grams, 0.442 mole, of ϵ-caprolactam was dissolved in 300 ml. of 20 percent sulfuric acid and the solution was cooled to 5° C. Forty-six grams, 0.663 mole, of sodium nitrite dissolved in 100 ml. of water was added to the stirred sulfuric acid mixture. The temperature was kept below 7° C. After complete addition of the sodium nitrite solution the reaction mixture was stirred for eight hours with the temperature maintained below 7° C. with an ice-bath. The mixture was kept in a refrigerator overnight.

The following day the mixture was stirred four hours longer with the temperature below 7° C. and then was neutralized with 40 percent sodium hydroxide with the temperature kept below 15° C. The precipitate of sodium sulfate was filtered and washed with chloroform. The aqueous layer was extracted with seven 70 ml. portions of chloroform. The aqueous solution remaining after chloroform extraction will be designated as Solution I. The combined organic layers were dried over anhydrous sodium sulfate. The sodium sulfate was filtered and the filtrate diluted to 500 ml. with chloroform. This chloroform solution will be designated as Solution II.

Titration of a 10 ml. aliquot of Solution II with standard alkali indicated 151 m.e. of total acid in the chloroform extract. (The theoretical total acid was 442 m.e.)

The chloroform was removed by distillation and 100 ml. of 40 percent sodium hydroxide was added to the residue with stirring and cooling. The mixture was stirred for four hours at room temperature, cooled and made strongly acid to Congo red with 60 percent sulfuric acid. The temperature was kept below 25° C. during the neutralization by cooling in an ice-bath. The mixture was extracted with six 70 ml. portions of chloroform. The aqueous solution left after chloroform extraction will be designated as Solution III. The combined organic layers were dried over anhydrous sodium sulfate. The sodium sulfate was filtered and the filtrate diluted to 500 ml. with chloroform. This chloroform solution will be designated as Solution IV.

Aliquots of solutions I, II, III, and IV were analyzed for nitrogen by the Kjeldahl method (Table V).

TABLE V

NITROGEN ANALYSIS OF VARIOUS SOLUTIONS OBTAINED FROM THE DEGRADATION OF ϵ-CAPROLACTAM WITH NITROUS ACID

Solution	Percent of Original Organically Bound Nitrogen Remaining in Solution
I	5.5
II	9.5
III	1.1*
IV	6.8*

* The percent of nitrogen obtained by analysis of solutions III and IV should add up to the percent of nitrogen obtained by analysis of solution II if no organically bound nitrogen is removed by the sodium hydroxide treatment. The results indicate that the treatment with sodium hydroxide is of doubtful value.

Reduction of the Unsaturated Acids

The solvent was removed from the second chloroform extract by distillation through a Vigreux column. The residue was dissolved in 100 ml. of ethyl alcohol and hydrogenated on the low pressure Parr hydrogenator at an initial hydrogen pressure of 50 lbs./sq. in. in the presence of platinum oxide catalyst. The observed hydrogen pressure drop of 6.9 lbs. was equivalent to the formation of 9.5 g. of caproic acid from hexenoic acids.

The platinum was filtered, the solution was made alkaline to litmus and the ethyl alcohol was removed by steam distillation. The aqueous residue was made strongly acid to Congo red and extracted with six 80 ml. portions of chloroform. Total acid content was determined by titration of an aliquot and was equivalent to 110 m.e.

The remaining chloroform solution was dried over anhydrous sodium sulfate. After filtration and removal of the solvent by distillation through the Vigreux column on a steam bath a residue of 41 g. remained.

Formation of Bromo Acids (63-65)

The residue from the last step was added to a mixture of 170 ml. of 48 percent hydrobromic acid and 41 ml. of 97.1 percent sulfuric acid. The mixture was allowed to stand for two hours at room temperature and then was heated for three hours on a steam bath. The cooled reaction mixture was poured into 350 ml. of water, and was saturated with sodium sulfate and extracted with six 80 ml. portions of ether. Total acid, determined by titration of an aliquot, was 110 m.e.

After drying the ethereal solution and removing the solvent by distillation as previously described, 37 g. of residual material remained.

Attempted Reduction of Bromo Substituted Caproic Acids with Raney Nickel (66, 67)

The residue from the previous step was dissolved in 100 ml. of a solution of 113 g. of sodium hydroxide in 450 ml. of water. Ninety grams of Raney nickel alloy was added portionwise to the stirred solution. The remaining sodium hydroxide solution was added over a one hour period. The mixture was heated one and one-half hours at 90 to 100° C. After cooling and filtering to remove the nickel, the solution was made strongly acid to Congo red with 60 percent sulfuric acid.

The acidic mixture was steam distilled until 600 ml. of distillate was collected. The distillate was saturated with sodium sulfate, extracted with six 80 ml. portions of ether and the combined ethereal extracts were dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the solvent was removed by distillation from a steam bath. Fractionation of the residue gave 6.9 g. of product boiling at 109 to 110° C./20 mm., n_d^{30} 1.4134; and 2.9 g. of material boiling at 109 to 112° C./19 mm., $n_d^{31.5}$ 1.4140 (reported refractive index for caproic acid, n_d^{15} 1.41877, n_d^{25} 1.41489 [108]; reported boiling point for caproic acid, 107.3° C./16 mm. [115]).

If both fractions were considered to be caproic acid then their combined weight would represent a 19.1 percent yield of the theoretical amount. This percentage yield was not significantly greater than could be expected by isolation of the caproic acid obtained by hydrogenation of the hexenoic acid. The reactions following the hydrogenation step were apparently not very effective.

Preparation of Ethyl ϵ-Carboethoxyaminocaproate

$$CH_3\text{-}CH_2OOC\text{-}NH\text{-}(CH_2)_5\text{-}COO\text{-}CH_2\text{-}CH_3$$

Fifty grams, 0.442 mole of ϵ-caprolactam was hydrolyzed by refluxing for one hour with a mixture of 36.8 ml. of concentrated hydrochloric acid (37.3 percent) and 70 ml. of water. The water was removed by distillation on a steam bath under reduced pressure. The white crystalline residue was dissolved in 70 ml. of water. One hundred and sixty milliliters of ethyl alcohol and 120 ml. of benzene were added and the mixture refluxed forty-three hours through a Barrett modification of the Dean-Stark trap, at which time no more water collected in the trap. The solvent was removed by distillation and left a gray solid residue.

The crude ester hydrochloride was dissolved in 150 ml. of water and 100 ml. of ether was added. A solution of 17.7 g., 0.442 mole, of sodium hydroxide dissolved in 50 ml. of water, was added slowly with the temperature maintained below 5° C. until the mixture had turned basic to litmus. Forty-eight grams, 42.3 ml., 0.442 mole, of ethyl chloroformate was added slowly with the temperature kept below 12° C. When approximately three quarters of the ethyl chloroformate had been added the mixture became acidic. A solution of 30.5 g., 0.442 mole, of potassium carbonate dissolved in 50 ml. of water was now added together with the ethyl chloroformate solution so that they both were completely added at the same time. The mixture was stirred thirty minutes. The ether layer was separated and the aqueous layer extracted with two 50 ml. portions of ether. The ether solutions were dried by shaking with two separate portions of anhydrous potassium carbonate. The solvent was removed by distillation on a steam bath under reduced pressure. Fractionation of the residue gave 75.5 g. of product (73.7 percent of the theoretical amount) boiling at 183 to 189° C./17 mm. (reported boiling point [77] is 185° C./20 mm.).

Conversion of Ethyl ϵ-Carboethoxyaminocaproate to Ethyl Caproate and Other Products

Nitrosation (68, 78)

A 500 ml., three-necked flask was equipped with a thermometer and a dropping funnel with an attachment to allow addition of reagents to the bottom of the flask. Twenty-three grams, 0.1 mole, of ethyl ϵ-carboethoxyaminocaproate dissolved in 40 ml. of diethyl ether and 32.5 g., 0.45 mole, of sodium nitrite dissolved in 60 ml. of water were placed in the flask. The mixture was cooled to 10° C. and maintained below this temperature throughout the reaction. A solution of cold 35 percent nitric acid (60 g., 0.33 mole) was added slowly in seventy-five minutes. The mixture was allowed to stand three hours in an ice-bath. The ether layer had now turned blue-green. The ether layer was separated and washed with ten 10 ml. portions of ice-cold water. The last wash solution still tested acid to Congo red paper. The ether solution was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure on a water bath heated no higher than 40° C. The light orange liquid residue weighed 21.3 g.

Decomposition (68-70, 79)

The residue from the last step was added slowly to a mixture of 12 ml. of methyl alcohol (previously dried over anhydrous potassium carbonate) and 0.05 g. of finely powdered anhydrous potassium carbonate. The reaction mixture became hot and was cooled in an ice-bath during the addition and until the completion of the reaction. Vigorous bubbling took place for three hours. The mixture was allowed to stand overnight at room temperature. The next day the solution had turned yellow and bubbling had ceased. The mixture was refluxed one hour on a steam bath, cooled, filtered, and diluted with 100 ml. of ethyl alcohol. This solution was hydrogenated at 50 lbs. hydrogen pressure with 0.1 g. of platinum oxide catalyst. A 2.6 lb. pressure drop was observed in fifty minutes. The platinum was filtered off and the solvent was removed by distillation on a hot water bath. The residual liquid was distilled under reduced pressure and the following fractions were collected:

I	1.4 g.	66-99° C./16 mm.
II	3.7 g.	99.5-110° C./16 mm.
III	7.1 g.	110-165° C./16 mm.
IV	1.9 g.	190-198° C./16 mm.

Two grams of black residue was left in the distillation flask.

Consideration of the possible products that might be formed by the decomposition of the nitroso compound leads to the tentative identification of the fractions as follows: Fraction I is probably predominately ethyl caproate; Fraction II is probably a mixture of ethyl ϵ-methoxycaproate and ethyl ϵ-hydroxycaproate (reported boiling point of ethyl ϵ-methoxycaproate, 94-95° C./15 mm. [72]; reported boiling point of ethyl ϵ-hydroxycaproate, 135° C./15 mm. [80]); Fraction III is probably predominately ethyl ϵ-hydroxycaproate; Fraction IV might be 5-carbethoxyamyl-6-hydroxyhexanoate (reported boiling point of 5-carbethoxyamyl-6-hydroxyhexanoate, 191° C./1.5 mm. [80]).

If Fraction I were all ethyl caproate then this fraction would represent a ten percent conversion to the desired product. This percentage yield is approximately the same as obtained with other procedures.

No further investigation of this reaction was made since the yield of saturated ester was no better than obtained with other simpler methods.

Nitrous Acid Treatment of ϵ-Caprolactam

Twenty-five grams, 0.22 mole, of ϵ-caprolactam was hydrolyzed with the calculated amount of hydrochloric acid as previously described (58). The solvent was removed by distillation under reduced pressure on a steam bath. Twenty-three grams, 0.33 mole, of sodium nitrite in 40 ml. of water was added slowly to the white solid residue during one hour. A vigorous exothermic reaction took place. The temperature was kept below 90° C. by intermittent cooling in an ice-bath. The solution was allowed to stand three hours at room temperature, made strongly acid to Congo red with 20 percent sulfuric acid and heated on a steam bath for one hour. The mixture was cooled and extracted with five 50 ml. portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered, and the solvent was distilled through a Vigreux column leaving 33 g. of residue. The residue was esterified by refluxing overnight with 100 ml. of absolute alcohol and 10 ml. of concentrated sulfuric acid. The mixture was cooled and neutralized with a concentrated solution of sodium carbonate; it was filtered and extracted first with one 100 ml. portion of benzene followed by three 50 ml. portions of benzene.

The combined benzene extracts were washed twice with 25 ml. of cold saturated sodium chloride solution. The solvent was removed by distillation through a Vigreux Column. Fractionation through a Claisen flask with a one foot Vigreux side arm gave the following fractions:

I	1.8 g.	59-60° C./13 mm.
II	7.0 g.	58-67° C./1 mm.
III	1.4 g.	67-89° C./1 mm.
IV	5.6 g.	89-92° C./1 mm.
V	0.2 g.	92° C./1 mm. and above

and four grams of residue remained in the distillation flask.

<u>Fraction I</u>, $n_d^{20.5}$ 1.4230, was probably the unsaturated ester. In a similar experiment a low pressure reduction was effected before the esterification step. In this instance the first fraction from the distillation boiled at 57-58° C./13 mm., n_d^{20} 1.4072, and was identified as ethyl caproate, n_d^{20} 1.4076 (108).

<u>Fractions II, III, IV, and V</u> were recombined and refractionated through a one foot tall, eight millimeter diameter Vigreux column with distillation head and cow type vacuum take-off using a 10:1 reflux ratio to give the following fractions:

A	2.8 g.	66-72° C./1 mm.
B	1.1 g.	72-91° C./1 mm.
C	4.6 g.	91-95° C./1 mm.

<u>Fraction A</u>, $n_{d}^{20.5}$ 1.4379, gave a positive Beilstein test for halogen and was identified as ethyl ϵ-chlorocaproate; reported boiling point 106° C./14 mm. and n_{d}^{18} 1.4398 (73).

<u>Fraction B</u>, $n_{d}^{20.2}$ 1.4377, was apparently a mixture of the compounds obtained in fractions A and C and thus was not further investigated.

<u>Fraction C</u>, n_{d}^{20} 1.4360, was identified as ethyl ϵ-hydroxycaproate; reported boiling points 134° C./15 mm. (80), 104-6° C./4 mm. (62), 135-140° C./16 mm. (104); n_{d}^{25} 1.4381 (62). Part of this fraction was converted to ϵ-iodocaproic acid by the method described in the experimental section. The ϵ-iodocaproic acid, so formed, melted at 42.5-44° C. and showed no depression of melting point on mixing with an authentic sample. In a similar experiment the hydrazide (105) was prepared from the fraction boiling at 93-99° C./3 mm. The hydrazide melted at 114.8-116.3° C. and the high boiling fraction was thus identified as ethyl ϵ-hydroxycaproate; reported melting point of hydrazide, 114-115° C. (61, 62).

Preparation of ε-Iodocaproic Acid (81, 82, 83)

$$I - (CH_2)_5 - COOH$$

One and one-quarter grams, 0.04 mole, of red phosphorus, 15.4 g., 0.096 mole, of ethyl ε-hydroxycaproate (prepared by the method of Robinson and Smith [80] in 33 percent yield, boiling point 149-154° C./19 mm.), and 15.3 g., 0.06 mole, of iodine were mixed and refluxed on a steam bath for five hours. The mixture was cooled, 100 ml. of ether was added and the phosphorus was filtered off. The ether solution was washed with four 20 ml. portions of 10 percent sodium bisulfite, once with water and dried over calcium chloride. The calcium chloride was filtered and the ether was evaporated by passing a stream of dry air over the surface of the solution.

The residue was stirred at room temperature for four hours with 100 ml. of 10 percent sodium hydroxide. The unsaponified layer was separated and the aqueous layer made strongly acid to Congo red with dilute sulfuric acid. Solid precipitated on the addition of the acid. The mixture was set in a refrigerator overnight and filtered. The crystals were suspended in 100 ml. of water and stirred to dissolve the sodium sulfate. Filtration gave 10 g. of crude material (43 percent of the theoretical amount).

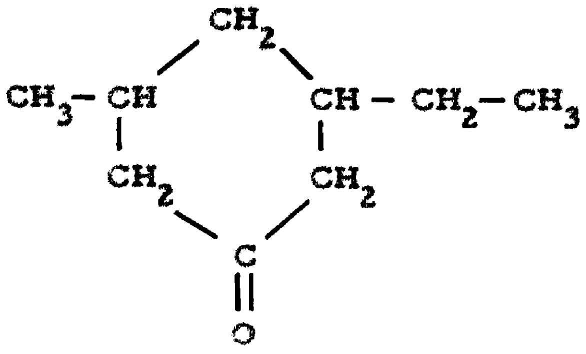
A small amount of the crude material was recrystallized from ethyl alcohol - water and melted at 42.5-44° C.

Anal: Calc'd for $C_6H_{11}O_2I$: I, 52.4. Found: I, 52.4, 52.7

Reduction of ϵ-Iodocaproic Acid to Ethyl Caproate (82, 84, 85)

Two and four-tenths grams, 0.01 mole, of ϵ-iodocaproic acid was placed in an eight inch test tube equipped with a condenser. The acid was partially dissolved in 15 ml. of ethyl alcohol. To this mixture was added 2.6 g., 0.04 mole, of 30 mesh zinc which had been previously cleaned by washing successively with dilute acid, water, and alcohol. Five ml. of concentrated hydrochloric acid was added from a dropper to this mixture over a fifteen minute period. The mixture was refluxed for twenty minutes and allowed to stand four hours. Five ml. more of concentrated hydrochloric acid was added and the mixture refluxed for thirty minutes at which time the zinc had all reacted. The reaction mixture was steam distilled and the distillate extracted with three 10 ml. portions of ether. The ether was evaporated on a steam bath and 20 ml. of benzene was added to the mixture to aid in the evaporation of the alcohol and water. Distillation of the residue gave 0.55 ml. of product, n_d^{20} 1.4080 (reported [106] refractive index of ethyl caproate is n_d^{20} 1.4076). This represents a 43 percent yield of the theoretical amount.

Preparation of 3-Methyl-5-Ethylcyclohexanone (38-41)



One hundred and seventy-four grams, 3 moles, of freshly distilled propionaldehyde (b. 47.2 - 49.5° C./731 mm.) and 780 g., 6 moles, of freshly distilled ethyl acetoacetate (b. 170 - 173° C./731 mm.) were placed in a 3 liter, three-necked, round-bottom flask equipped with mechanical stirrer, thermometer, and dropping funnel. The mixture was cooled to -5° C. by means of an ice-salt bath. Fifteen milliliters of diethyl amine was then added in small portions over a two hour period so that the temperature never rose above +5° C. The mixture was stirred for twenty-four hours in an ice-bath and stirred another twenty-four hours at room temperature.

Two preparations using the quantities above were combined for the next phases of the reaction. Saponification and decarboxylation were accomplished by boiling thirty minutes with 900 g. of sodium hydroxide dissolved in 6 liters of water. The mixture was steam distilled until 14 liters of distillate was collected. The organic layer was separated and the aqueous layer again distilled until the distillate became clear. This operation was repeated twice more. The final water solution was extracted with three 100 ml. portions of ether. The combined organic layers were dried over calcium chloride, filtered, and distilled to remove solvent.

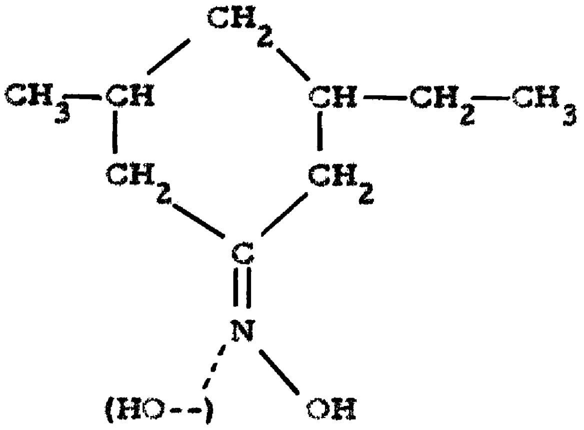
Fractionation of the residue gave 298 g. of 3-methyl-5-ethyl- Δ^2-cyclohexenone (36 percent of the theoretical amount) boiling at 102 - 112° C./11 mm.

Sixty grams of 3-methyl-5-ethyl- Δ^2-cyclohexenone, 0.1 g. of platinum oxide, and 60 ml. of ethyl alcohol were placed in a heavy-walled glass bottle and hydrogenated on the low pressure Parr hydrogenator. The initial pressure was 50 lbs. The mixture absorbed the calculated amount of hydrogen (36 lb. drop in pressure) during thirty minutes to three hours in different experiments.

The products of five runs were then combined, the platinum filtered, and the solvent was removed by distillation. Fractionation of the residue gave 232 g. of product boiling at 89.5-94° C./17 mm. (reported boiling point 200-201.5° C. [1];

204-205° C./747 mm. [41]). Redistillation of the forerun and residue gave an additional 26 g. of product. The total yield was 258 g. and represented an 85.5 percent yield for the hydrogenation phase.

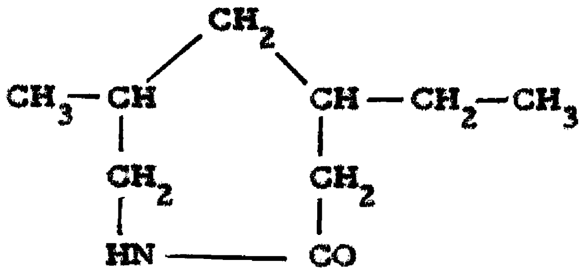
Preparation of 3-Methyl-5-Ethylcyclohexanone Oxime



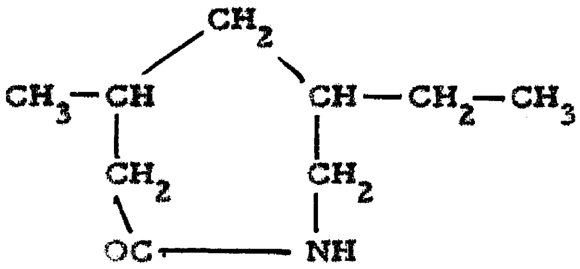
Two hundred and fifty-eight grams, 1.84 moles, of 3-methyl-5-ethylcyclohexanone dissolved in 1 liter of isopropyl alcohol was mixed with 399.5 g., 2.76 moles, of hydroxylamine hydrochloride, 148 g., 3.68 moles, of sodium hydroxide and 500 g., 3.68 moles, of sodium acetate trihydrate dissolved in 1.5 liters of water. The mixture was heated thirty minutes on the steam bath and allowed to stand overnight. The following day the mixture was again heated for thirty minutes on a steam bath and allowed to stand overnight. The isopropyl alcohol layer was separated and the water layer extracted with three 150 ml. portions of ether. The combined extracts were washed with 100 ml. of saturated salt solution, dried over sodium sulfate and the solvent was removed through a Vigreux column.

The residue contained water and was therefore further dried by adding benzene and removing the water by azeotropic distillation. Fractionation of the residue gave 240 g. of a viscous product (84 percent of theoretical amount) boiling at 129.5-134° C./15 mm. (reported boiling point 127-128° C./11 mm. [11]).

The Beckmann Rearrangement of 3-Methyl-5-Ethylcyclohexanone Oxime



and



Two hundred and forty grams of sulfuric acid (96.5 percent) was placed in a beaker equipped with a stirrer, thermometer and dropping funnel. The sulfuric acid was heated to 110° C. and the temperature was maintained between 110 and 115° C. by the slow addition of 120 g. of 3-methyl-5-ethylcyclohexanone oxime from the dropping funnel. After the complete addition of the oxime, which required one and one-half hours, the reaction mixture was heated for fifteen minutes between 110 and 115° C.

Two of the above reaction mixtures were combined, cooled to 10° C. and poured onto ice sufficient to dilute to 2 liters. The mixture was extracted with five 250 ml. portions of chloroform, washed three times with 50 ml. of 10 percent sodium carbonate and dried over anhydrous sodium sulfate and anhydrous magnesium sulfate. The solvent was removed by distillation. Distillation of the residue from a Claisen flask gave 179.5 g. of slightly yellow product (74.8 percent of the theoretical amount) boiling at 170 - 171.5° C./17-18 mm. The product solidified on cooling to room temperature.

Preliminary Solubility Studies of Dialkyl Substituted ϵ-Caprolactam Mixtures

The approximate solubilities of various mixtures of the lactam obtained by Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime were determined in a number of solvents in an attempt to find a suitable solvent for isolation of the pure isomeric lactams.

1. In a preliminary Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime a lactam mixture crystallized on pouring the reaction mixture onto ice. This lactam mixture was recrystallized from water to give the following fractions:

i m.p. 75-84° C.
ii m.p. 78-78.5° C.
iii m.p. 86-93° C.

The acid filtrate remaining after filtration of the original lactam crystals was extracted with chloroform. The chloroform extracts were washed with sodium carbonate solution and dried over anhydrous sodium sulfate. The residue remaining on evaporation of the chloroform was recrystallized from "hexane" to give the following fractions:

iv m.p. 76-78° C.

v m.p. 90-92° C.

The solubilities of fractions i, ii, iii, iv, and v were determined by dissolving a known weight of solid in a known volume of solvent and allowing crystallization to occur at the designated temperature. Crystallization was allowed to proceed overnight for the solubility determinations at room temperature and for one hour for the determinations at ice-bath temperature. The crystallized solid was then filtered and dried. The difference between the weight of the crystallized solid and the weight of the solid originally taken was used to estimate the solubility. The results are summarized in Table VI.

2. Solubilities were determined on a lactam mixture boiling at 175-176.3° C./15 mm. which was obtained by rearrangement of 3-methyl-5-ethylcyclohexanone oxime. All the product in this case was isolated by chloroform extraction followed by distillation. The solubilities are recorded in Table VII and were determined in a manner identical to the methods just described.

TABLE VI

APPROXIMATE SOLUBILITY OF MIXTURES OF METHYL ETHYL SUBSTITUTED ϵ-CAPROLACTAMS

Solvent	Lactam Fraction	Solubility in Grams per 100 Milliliters of Solvent	
		Room Temperature	Ice-bath Temperature
Water	v	1.4 g.	1.4 g.
Water	i	1.6 g.	1.6 g.
Ethyl acetate	i	v.s.	33. g.
Ethyl acetate	iii	v.s.	11. g.

TABLE VII

APPROXIMATE SOLUBILITY OF A DISTILLED MIXTURE OF METHYL ETHYL SUBSTITUTED ϵ-CAPROLACTAMS

Solvent	Solubility in Grams per 100 Milliliters of Solvent	
	Room Temperature	Ice-bath Temperature
Water	2.6 g.	2.3 g.
Ethyl acetate	v.s.	29. g.
Hexane	7.4 g.	5.8 g.

3. Fractional crystallization of the lactam mixture described in (1.) using hexane as the solvent, gave pure Lactam A, m.p. 105.8-106.2° C., and several mixtures of lower melting point. The solubility of the lowest melting lactam mixture, m.p. 73-79.5° C., obtained from the fractional crystallization was determined in various solvents. The results are recorded in Table VIII.

Subsequently it was found that separation could be accomplished more conveniently by extraction of the original lactam mixture with cold ethyl acetate and recrystallization of the various residues and extractives from hexane.

TABLE VIII

APPROXIMATE SOLUBILITY OF THE LOWEST MELTING MIXTURE OF METHYL ETHYL SUBSTITUTED ϵ-CAPROLACTAMS REMAINING AFTER ISOLATION OF SOME PURE LACTAM A

Solvent	Solubility in Grams per 100 Milliliters of Solvent	
	Room Temperature	Ice-bath Temperature
Acetonitrile	v.s.	33 g.
Heptane	22 g.	-
Ethylene dichloride	-	45 g.
Ethyl bromide	-	41 g.

Method for Separation of Isomeric Lactams Resulting From the Beckmann Rearrangement of 3-Methyl-5-Ethylcyclohexanone Oxime

The distilled mixture of lactams resulting from the rearrangement of 3-methyl-5-ethylcyclohexanone oxime was dissolved in half its weight of ethyl acetate and transferred to a beaker. The mixture was cooled in an ice-bath to crystallize the lactams. This preliminary operation was performed to give the solid a crystalline character better suited for the subsequent operations. This operation was not necessary when separating mixtures that were already in a satisfactory form, such as mixtures of lactams resulting from fractional crystallizations.

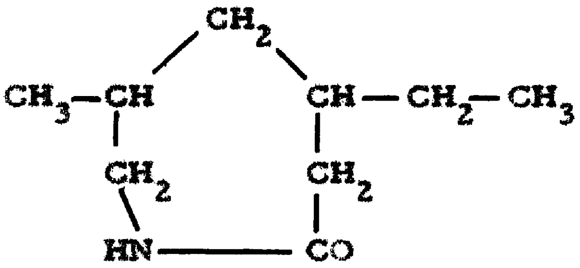
The mixture of lactams was extracted with several portions of ethyl acetate cooled to 0° C. The solid was stirred intermittently with the solvent for five minutes and then filtered by suction.

The melting points of the residues and the extractives were used as the criteria of the progress of the separation. The amount of solvent for each extraction was adjusted so that after all extractions, approximately one-third of the weight of the original material remained. The residue at this point melted over a considerable range but did not melt completely until the temperature had risen to at least 90° C. This was found satisfactory for purification by recrystallization.

Four to six recrystallizations of the residue from "hexane" (from petroleum) gave isomer A, m.p. 105.8-106.2° C.

Anal.: Calc'd for $C_9H_{17}ON$: C, 69.64; H, 11.04; N, 9.0.

Found: C, 69.65; H, 11.00; N, 8.9 (Kjeldahl).

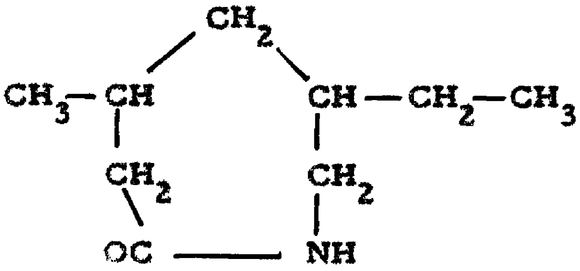


The ethyl acetate solutions from the extractions were evaporated to dryness and if necessary reextracted with ethyl acetate so that the extractive obtained by evaporation of the solvent melted above 73° C. In a few cases the extractive was recrystallized once from "hexane" in order to obtain the desired melting point.

The appropriate extractives were combined and recrystallized at least twelve times from "hexane" to give isomer B, m.p. 100.3-101.3° C.

Anal.: Calc'd for $C_9H_{17}ON$: C, 69.64; H, 11.04; N, 9.02.

Found: C, 69.58; H, 11.00; N, 9.10.



As an example, 179.5 g. of distilled lactams were dissolved in 100 ml. of ethyl acetate and cooled in an ice-bath to crystallize. This mixture was extracted with 350 ml. of cold ethyl acetate to leave 101.5 g. of residue m.p. 70-83.5° C. This residue was further extracted with 150 ml. of cold ethyl acetate to leave 54.5 g. of residue m.p. 82-96.0° C. Four recrystallizations of this residue from "hexane" gave 25.5 g. of isomer A, m.p. 105.8-106.2° C.

The ethyl acetate solutions from above were evaporated to dryness and the residual material extracted again independently with cold ethyl acetate. The ethyl acetate solutions from these second extractions were evaporated to dryness and the extractives recrystallised once from "hexane." By similar treatment of the extractives from the second extractions, more crystals were obtained. The combined crystals weighed 59.6 g.

and had an approximate melting point of 75 to 87° C. This material was recrystallized twelve times from "hexane" to give 9.1 g. of isomer B, m.p. 100.3-101.3° C.

Conversion of the Lactam of 3-Ethyl-5-Methyl-6-Aminohexanoic Acid to Ethyl 3-Ethyl-5-Methylhexanoate and Other Products

The method as described here was essentially the same as already described in this thesis for the nitrous acid treatment of ϵ-caprolactam.

Twenty grams, 0.13 mole, of the lactam of 3-ethyl-5-methyl-6-aminohexanoic acid, isomer A, was hydrolyzed by refluxing for one hour with the calculated amount of hydrochloric acid (11 ml. of concentrated hydrochloric acid diluted to 36 ml. with water). After evaporation of the solvent under vacuum on a steam bath, there remained a colorless viscous oil. A solution of 13.4 g., 0.19 mole, of sodium nitrite dissolved in 32 ml. of water was added to the oil over thirty minutes. A vigorous exothermic reaction took place with considerable foaming. After the sodium nitrite solution had been added the solution was made acid to Congo red by addition of dilute hydrochloric acid (one volume of concentrated hydrochloric acid to one volume of water). The organic upper layer turned green. The reaction mixture was heated for one hour on a steam bath. The mixture was cooled, extracted with chloroform and the chloroform extracts were dried over anhydrous sodium sulfate. The chloroform was removed by distillation on a steam bath. The residue was dissolved in 100 ml. of absolute ethyl alcohol and was hydrogenated on a low pressure Burgess-Parr hydrogenator using 0.1 g. of platinum oxide catalyst. Only a 0.5 lb. hydrogen pressure drop was observed. Based on experiences in the degradation of ϵ-caprolactam a pressure drop of about 2 lbs. was anticipated at this point.

The platinum was filtered and the mixture of acids was esterified by refluxing their alcoholic solution for twelve hours after addition of 5 ml. of concentrated sulfuric acid. The mixture was cooled in an ice-bath and was neutralized with a concentrated solution of sodium carbonate. The sodium sulfate was filtered and the filtrate was diluted with chloroform until two layers formed and the aqueous layer was extracted with chloroform. The chloroform extracts were washed twice with cold saturated sodium chloride solution and were dried over anhydrous sodium sulfate. The solvent was removed by distillation under vacuum on a steam bath. Fractionation of the residue through a one foot Vigreux column of 8 mm. diameter gave the following fractions:

I	0.4 g.	below 44° C./0.7 mm.
II	2.5 g.	51° C./1.4 mm. - 59° C./1.9 mm.
III	1.0 g.	59-87.5° C./1.9 mm.
IV	2.6 g.	87.5-97.5° C./1.9 mm.
V	1.1 g.	97.5-108° C./2 mm.
VI	2.1 g.	108-113° C./2 mm.

The residue left in the distillation flask weighed 2.7 g.

<u>Fraction I</u> was forerun and was not further investigated.

<u>Fraction II</u>, n_d^{25} 1.4288, which should be the saturated fatty ester, gave positive bromine and Baeyer tests for unsaturation. Two and three-tenths grams of Fraction II was dissolved in 5 ml. of acetic acid and was hydrogenated on the low pressure hydrogenator using platinum oxide catalyst. There was observed a 0.5 lb. hydrogen pressure drop in one hour. The platinum was filtered and the solvent was removed by distillation. Distillation of the residue through a small Claisen flask with Vigreux side arm gave 0.1 g. of forerun, and 1.6 g. of ethyl 3-ethyl-5-methylhexanoate boiling at 50-58° C./1 mm., n_d^{28} 1.4185 (n_d^{20} 1.4218, n_d^{25} 1.4198, see preparation of ethyl 3-ethyl-5-methylhexanoate).

Anal.: Saponification equivalent Calc'd for $C_{11}H_{22}O_2$: 186.3.

Found: 186.1.

The S-benzyl thiuronium salt (107) was prepared, and recrystallized from aqueous alcohol, m.p. 148.6-148.8° C.; no depression of the melting point was observed when mixed with an authentic sample (see preparation of ethyl 3-ethyl-5-methylhexanoate); a depression of the melting point was observed when mixed with the S-benzyl thiuronium salt of the isomeric 3,5-dimethylheptanoic acid (see preparation of ethyl 3,5-dimethylheptanoate).

Anal.: Calc'd for $C_{17}H_{28}O_2N_2S$: N, 8.6.

Found: N, 8.4 (Kjeldahl).

The p-toluidide was prepared (108, 109) by interaction of the ester with the magnesium bromide derivative of p-toluidine and was recrystallized from aqueous alcohol, m.p. 56.8-57.8° C.; no depression of the melting point was observed when mixed with an authentic sample (see preparation of ethyl 3-ethyl-5-methylhexanoate); a large melting point depression was observed when mixed with the p-toluidide of the isomeric ethyl 3,5-dimethylheptanoate (see preparation of ethyl 3,5-dimethylheptanoate).

Anal.: Calc'd for $C_{16}H_{25}ON$: N, 5.7.

Found: N, 5.6 (Kjeldahl).

Fraction III was apparently a mixture of the compounds obtained in Fractions II and IV and was not further investigated.

Fraction IV gave a strong Beilstein test for halogen and a positive sodium fusion test for halogen. By analogy to the results obtained by degradation of ϵ-caprolactam this fraction was tentatively identified as consisting predominately of ethyl 3-ethyl-5-methyl-6-chlorohexanoate. The position of the chlorine was not rigorously established.

The potassium salt of the acid obtained by acid hydrolysis of the ester followed by neutralization with potassium hydroxide was converted into the S-benzyl thiuronium salt by interaction with S-benzyl thiuronium chloride (107). The S-benzyl thiuronium salt obtained in this manner was recrystallized from ethyl acetate and melted at 153-154.5° C.

Anal.: Calc'd for $C_{17}H_{27}O_2N_2SCl$: N, 7.8; S, 8.9; Cl, 9.9.

Found: N, 7.5 (Kjeldahl); S, 8.9, 9.0; Cl, 9.7, 9.9.

The potassium salt of the acid obtained by saponification of the ester with alcoholic potassium hydroxide was converted into the S-benzyl thiuronium salt which was recrystallized from ethyl acetate, m.p. 146-147.5° C. The S-benzyl thiuronium salt prepared in the same manner from Fraction V melted at

146-147.5° C. Comparison of the melting points of the two S-benzyl thiuronium salts prepared from Fraction IV indicated apparently that saponification of the ester led to some hydrolysis of the chloro substituent.

Fraction V gave a positive Beilstein test for halogen and was probably a mixture of the compounds obtained in Fractions IV and VI. The S-benzyl thiuronium salt was prepared, m.p. 146-147.5° C.

Anal.: Calc'd for $C_{17}H_{27}O_2N_2SCl$: N, 7.8.
Calc'd for $C_{17}H_{28}O_3N_2S$: N, 8.2.
Found: N, 8.0 (Kjeldahl).

Fraction VI gave a slight Beilstein test for halogen. By analogy to the results obtained by degradation of ϵ-caprolactam this fraction was tentatively identified as consisting predominately of ethyl 3-ethyl-5-methyl-6-hydroxyhexanoate. The position of the hydroxyl group was not rigorously established.

The potassium salt of the acid obtained by saponification of the ester with alcoholic potassium hydroxide was converted into the S-benzyl thiuronium salt which was recrystallized from ethyl acetate, m.p. 128.8-129.4° C.

Anal.: Calc'd for $C_{17}H_{28}O_3N_2S$: N, 8.2; S, 9.4.

Found: N, 8.4 (Kjeldahl); S, 9.4, 9.6.

Conversion of the Lactam of 3,5-Dimethyl-6-Aminoheptanoic Acid to Ethyl 3,5-Dimethylheptanoate and Other Products

Ten grams of the lactam of 3,5-dimethyl-6-aminoheptanoic acid was degraded in an analogous manner to that described for the isomeric lactam of 3-ethyl-5-methyl-6-aminohexanoic acid. After hydrolysis with the calculated amount of hydrochloric acid and evaporation of the solvent there remained a colorless viscous oil. After treatment of this oil with 6.7 g., 0.1 mole, of sodium nitrite dissolved in 16 ml. of water the crude product was hydrogenated and esterified as already described. On distillation of the mixture of esters the following fractions were obtained:

I	0.1 g.	forerun
II	2.0 g.	66.5-69.5° C./2.9 mm.
III	0.2 g.	69.5-89° C./3 mm.
IV	1.2 g.	89-109° C./3 mm.
V	2.3 g.	109-122° C./3 mm.

and 1.7 g. of black residue remained in the distillation flask.

Fraction II, n_d^{29} 1.4244, gave positive bromine and Baeyer tests for unsaturation. One and seven-tenths grams of Fraction

II was dissolved in 5 ml. of acetic acid and was hydrogenated on the low pressure hydrogenator using platinum oxide catalyst. There was observed a 0.1 lb. pressure drop. The platinum was filtered and the solvent was removed by distillation. Distillation of the residue through a small Claisen flask with Vigreux side arm gave 1.2 g. of ethyl 3,5-dimethylheptanoate boiling at 50-54° C./1 mm., n_d^{28} 1.4191 (n_d^{20} 1.4218, n_d^{25} 1.4199, see preparation of ethyl 3,5-dimethylheptanoate).

Anal.: Saponification equivalent Calc'd for $C_{11}H_{22}O_2$: 186.3.
Found: 184.5.

The S-benzyl thiuronium salt (107) was prepared and recrystallized from aqueous alcohol, m.p. 139.6-140.6° C.; no depression of the melting point was observed when mixed with an authentic sample (see preparation of ethyl 3,5-dimethylheptanoate); when mixed with the S-benzyl thiuronium salt of the isomeric 3-ethyl-5-methylhexanoic acid (see preparation of ethyl 3-ethyl-5-methylhexanoate) a depression of the melting point of the higher melting isomer was observed.

Anal.: Calc'd for $C_{17}H_{28}O_2N_2S$: N, 8.6.
Found: N, 8.5 (Kjeldahl).

The p-toluidide was prepared (108, 109) by interaction of the ester with the magnesium bromide derivative of p-toluidine and was recrystallized from aqueous alcohol, m.p. 62.3-64.3° C.; no depression of the melting point was observed when mixed with an authentic sample (see preparation of ethyl 3,5-dimethylheptanoate); a large melting point depression was observed when mixed with the p-toluidide of the isomeric ethyl 3-ethyl-5-methylhexanoate (see preparation of ethyl 3-ethyl-5-methylhexanoate).

Anal.: Calc'd for $C_{16}H_{25}ON$: N, 5.7.

Found: N, 5.7 (Kjeldahl).

Fraction III was an intermediate fraction and was not further investigated.

Fractions IV and V gave strong Beilstein tests for halogen and by analogy to the degradation of the lactam of 3-ethyl-5-methyl-6-aminohexanoic acid probably consisted of the analogous chloro and hydroxy esters. These fractions were not further investigated.

Preparation of Ethyl Isobutyl Ketone

$$CH_3-CH_2-CO-CH_2-CH-(CH_3)_2$$

Method A: Catalytically over Thorium Oxide (89)

The apparatus and method for preparing ethyl isobutyl ketone was essentially the same as described for the preparation of methyl benzyl ketone in Organic Syntheses (89).

Three hundred and four grams, 4 moles, of practical grade propionic acid and 104 g., 1 mole, of technical grade isovaleric acid were mixed and added from a dropping funnel at a rate of sixteen drops per minute to a hot tube containing thorium oxide deposited on pea-size porous plate. The temperature of the tube was maintained between 400 and 450° C. Simultaneously a slow stream of carbon dioxide or nitrogen was passed through the tube to keep the gases in motion. The entire solution was run through in twelve hours. After all the solution had been added, 10 ml. of propionic acid was used to rinse out the funnel and it was passed through the reaction tube to facilitate the removal of the product. The hot gases were condensed in a long tube filled with glass beads and the condensate collected in an Erlenmeyer flask of appropriate size.

The condensate consisted of two layers. Both layers were treated with a 300 g. mixture of ice and water and were rendered alkaline to litmus with a slight excess of 50 percent sodium hydroxide solution. The oil was separated and the aqueous layer extracted with two 50 ml. portions of benzene. The extracts were combined with the oil and dried over anhydrous sodium sulfate. The solvent was removed by distillation. Fractionation of the residue gave 46.3 g. of product (41 percent of the theoretical amount based on isovaleric acid) boiling at 132 - 133° C. (reported boiling point, 135° C. [110]; 136-137° C. [111]). <u>Note:</u> When the ethyl isobutyl ketone was prepared using a two-to-one ratio of propionic acid to isovaleric acid, the percentage yield was reduced to 18 percent.

Method B: Cadmium Dialkyl Method (90-95)

A five liter, three-necked flask was fitted with a Hershberg stirrer, condenser, and Y-tube. The condenser was fitted with a drying tube filled with soda lime. One opening of the Y-tube was used for introduction of nitrogen. The other opening of the Y-tube was used for the addition of reagents.

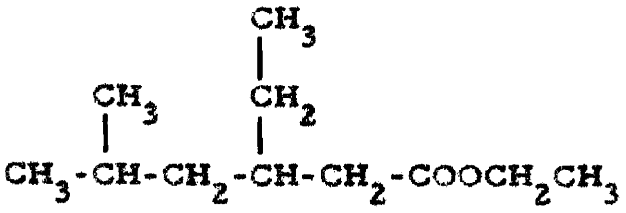
A solution of ethyl magnesium bromide was prepared in the flask by the usual method using 218 g., 2 moles, of Eastman practical grade ethyl bromide, 49 g., 2 moles, of magnesium turnings and one liter of diethyl ether dried over sodium.

One hundred and eighty-three grams, 1 mole, of anhydrous cadmium chloride, dried at 110° C. overnight, was added to the Grignard reagent over forty-five minutes under a nitrogen atmosphere. The reaction mixture was cooled in an ice-bath during the addition. The mixture was refluxed for one hour at which time the test for Grignard reagent with Michler's ketone was negative. The reaction mixture at this point was thick with solid and stirring was difficult and remained so up to the hydrolysis step. The ether was distilled off and replaced with an equal volume of benzene.

One hundred and twenty grams, 1 mole, of isovaleryl chloride previously prepared from isovaleric acid and thionyl chloride by the usual procedure (112) (b. 114 - 115° C., prepared in 50 percent yield) was introduced into the reaction mixture from a dropping funnel during forty-five minutes with no external cooling. The mixture was refluxed for one and one-half hours and then allowed to stand overnight.

Hydrolysis was accomplished by pouring onto 1.5 liters of dilute sulfuric acid (one part concentrated sulfuric acid to three parts of water). The organic layer was separated and the aqueous layer extracted with two 100 ml. portions of benzene. The solvent was removed by distillation. Fractionation of the residue gave 53 g. of the product, b.p. 132-133° C. (46.5 percent of the theoretical amount based on isovaleryl chloride).

Preparation of Ethyl 3-Ethyl-5-Methylhexanoate (96, 113)



$$CH_3\text{-}\overset{\substack{CH_3\\|}}{C}H\text{-}CH_2\text{-}\overset{\substack{CH_3\\|\\CH_2\\|}}{C}H\text{-}CH_2\text{-}COOCH_2CH_3$$

Thirty-nine and three-tenths grams, 0.6 mole, of 30 mesh zinc (Baker's C.P.) previously cleaned by the procedure of Fieser and Johnson (114) was placed in a two liter, three-necked flask fitted with a stirrer, dropping funnel and condenser. A drying tube filled with calcium chloride was fitted to the top of the condenser. A mixture of 57 g., 0.5 mole, of ethyl isobutyl ketone, 83.5 g., 0.5 mole, of ethyl bromoacetate (Eastman white label), 200 ml. of benzene and 170 ml. of toluene (96) both dried over sodium was added over a period of one hour. Heat was applied at the beginning of the addition to insure that the reaction had started. Continued vigorous interaction was regulated by the rate of addition of the reagent mixture. The mixture was finally refluxed for four hours, cooled and hydrolyzed by pouring into 400 ml. of 10 percent sulfuric acid. The organic layer was separated and the aqueous layer was extracted with three 50 ml. portions of benzene. The combined organic layers were washed successively with 50 ml. of cold 5 percent sulfuric acid, 50 ml. of cold 10 percent sodium carbonate, 50 ml. of cold water and dried over anhydrous sodium sulfate.

The sodium sulfate was filtered and the filtrate refluxed four hours with 85 g., 0.6 mole, of phosphorus pentoxide (97).[1] The mixture was cooled and the solution decanted. The residue was rinsed with benzene and the benzene decanted and combined with the first solution. The solvent was removed by distillation. Distillation of the residue gave 39.7 g. of unsaturated ester (43.2 percent of the theoretical amount) boiling at 103-106° C./19-20 mm.

Twenty-nine and eight-tenths grams of the unsaturated ester was hydrogenated[2] on the Parr low pressure hydrogenator

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[1] In the Reformatsky reaction dehydration was not effected using acetic anhydride as the dehydrating agent.

[2] The intermediate unsaturated esters in the preparation of ethyl 3-ethyl-5-methylhexanoate could not be hydrogenated in ethyl alcohol by low pressure hydrogenation with platinum oxide catalyst. Partial hydrogenation was effected using 1,360 p.s.i. of hydrogen, 60° C. temperature, ethyl alcohol solvent and Raney nickel as catalyst (99). Cope and Hancock (98) have used high pressure, high temperature hydrogenation for reduction of a similar unsaturated ester. It is interesting to note that the unsaturated esters obtained in preparation of ethyl 3,5-dimethylhexanoate by the same method could be hydrogenation in four hours using low hydrogen pressure, ethyl alcohol as solvent, and platinum oxide catalyst.

using an equal volume of acetic acid as solvent and 0.2 g. of platinum oxide as catalyst. The platinum was filtered off and the solvent removed by distillation. Distillation of the residue through a small Claisen flask with Vigreux side arm gave 26.4 g. of product (88 percent of the theoretical amount) boiling at 85-87° C./17 mm.

Redistillation of the product through a small diameter, one foot tall, heated Vigreux column gave 20.7 g. of product boiling at 62.0-64.0° C./4.2 mm., n_d^{20} 1.4218, n_d^{25} 1.4198, d_4^{20} 0.867.

Anal.: Calc'd for $C_{11}H_{22}O_2$: C, 70.9; H, 11.9; saponification equivalent, 186.3; MR, 54.53.

Found: C, 70.7; H, 12.0; saponification equivalent, 183.3; MR, 54.58.

Six and three-tenths grams of material boiling at 64.0-65.0° C./ 4.2 mm. was also obtained by further distillation and was not further investigated.

The S-benzyl thiuronium salt (107) of 3-ethyl-5-methylhexanoic acid was prepared and recrystallized from aqueous alcohol, m.p. 148.6-149.1° C. Mixtures of this salt with the S-benzyl thiuronium salt of the isomeric 3,5-dimethylheptanoic acid (see preparation of ethyl 3,5-dimethylheptanoate) showed melting points intermediate between the melting points of the two pure salts.

Anal.: Calc'd for $C_{17}H_{28}O_2N_2S$: N, 8.6.

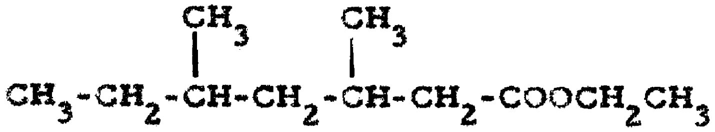
Found: N, 8.4 (Kjeldahl).

The p-toluidide was prepared (108, 109) by interaction of the ester with the magnesium bromide derivative of p-toluidine and was recrystallized from aqueous alcohol, m.p. 58.8-60.3° C. Mixtures of this derivative with the p-toluidide of 3,5-dimethylheptanoic acid (see preparation of ethyl 3,5-dimethylheptanoate) showed melting point depressions at least ten degrees below the lower melting isomer.

Anal.: Calc'd for $C_{16}H_{25}ON$: N, 5.7.

Found: N, 5.5 (Kjeldahl).

Preparation of Ethyl 3,5-Dimethylheptanoate (96, 113)



$$CH_3-CH_2-\overset{\overset{CH_3}{|}}{C}H-CH_2-\overset{\overset{CH_3}{|}}{C}H-CH_2-COOCH_2CH_3$$

4-Methyl-2-Hexanone

This intermediate was prepared by alkylation of ethyl acetoacetate with secondary butyl bromide and ketonic hydrolysis of the alkylation product following the procedure of Marvel and Hager (100). The product was obtained in 24.4 percent yield, b.p. 138-140.5° C./749 mm. (reported b.p. 139-142° C. [100]).

Ethyl 3,5-Dimethylheptanoate

This compound was prepared by essentially the same procedure used for the synthesis of the isomeric ethyl 3-ethyl-5-methylhexanoate.

The Reformatsky reaction was carried out with 39.3 g., 0.6 mole, of zinc, 57 g., 0.5 mole, of 4-methyl-2-hexanone, 83.5 g., 0.5 mole of ethyl bromoacetate, 200 ml. of benzene and 170 ml. of toluene.

The hydroxy ester was dehydrated with phosphorus pentoxide as previously described. Distillation of the resulting mixture of unsaturated esters gave the following fractions:

I	14.2 g.	forerun
II	20.7 g.	98-102° C./18 mm.
III	8.1 g..	100.5-108° C./16 mm.

Fraction I was not further investigated.

Fraction II was hydrogenated as already described using acetic acid solvent and platinum oxide catalyst. The platinum was filtered and the solvent removed by distillation. Distillation of the residue gave the following fractions:

A	10.1 g.	86-91.5° C./15 mm.
B	8.1 g.	89-94.0° C./17 mm.

Fraction III was treated identically to Fraction II and gave on distillation:

C	4.8 g.	87-90.5° C./16 mm.

p-Toluidides were prepared (108, 109) of Fractions A, B, and C and all melted at 64-65° C. Melting points of mixtures of the various toluidides showed no depression. Fractions A, B, and C were therefore combined and refractionated to give

17.8 g. of ethyl 3,5-dimethylheptanoate boiling at 59.5-61.0° C./ 2.6 mm., n_d^{20} 1.4218, n_d^{25} 1.4199, d_4^{20} 0.867.

Anal.: Calc'd for $C_{11}H_{22}O_2$: C, 70.9; H, 11.9; saponification equivalent, 186.3; MR, 54.53.

Found: C, 70.7; H, 12.0; saponification equivalent, 185.3; MR, 54.58.

The S-benzyl thiuronium salt (107) of 3,5-dimethylheptanoic acid was prepared and recrystallized from aqueous alcohol, m.p. 141.2-141.7° C. Mixtures of this salt with the S-benzyl thiuronium salt of the isomeric 3-ethyl-5-methylhexanoic acid (see preparation of ethyl 3-ethyl-5-methylhexanoate) showed melting points intermediate between the melting points of the two pure salts.

Anal.: Calc'd for $C_{17}H_{28}O_2N_2S$: N, 8.6.

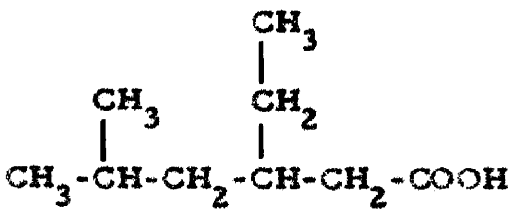
Found: N, 8.7 (Kjeldahl).

The p-toluidide was prepared (108, 109) by interaction of the ester with the magnesium bromide derivative of p-toluidine and was recrystallized from aqueous alcohol, m.p. 65.8-66.8° C. Mixtures of this derivative with the p-toluidide of 3-ethyl-5-methylhexanoic acid (see preparation of ethyl 3-ethyl-5-methylhexanoate) showed melting point depressions at least ten degrees below the lower melting isomer.

Anal.: Calc'd for $C_{16}H_{25}ON$: N, 5.7.

Found: N, 5.4 (Kjeldahl).

Preparation of 3-Ethyl-5-Methylhexanoic Acid



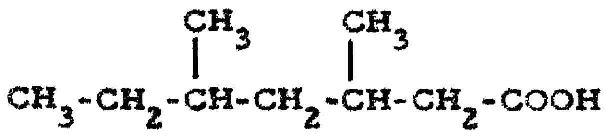
$$CH_3-\underset{}{CH}(CH_3)-CH_2-CH(CH_2CH_3)-CH_2-COOH$$

Five grams of ethyl 3-ethyl-5-methylhexanoate was saponified by refluxing for two and one-half hours with a solution of 3 g. of potassium hydroxide dissolved in 30 ml. of water and 10 ml. of alcohol. The reaction mixture was cooled and was made acid to Congo red by addition of dilute hydrochloric acid. The mixture was extracted with ether and the ether extracts were dried over anhydrous sodium sulfate. The sodium sulfate was filtered and the solvent was removed by distillation. Fractionation of the residue through a small Claisen flask with Vigreux side arm gave 0.6 g. of forerun boiling below 86° C./ 0.6 mm., and 3.0 g. of product boiling at 86-90° C./0.6 mm., n_d^{20} 1.4321, n_d^{25} 1.4301, d_4^{20} 0.907.

Anal.: Calc'd for $C_9H_{18}O_2$: C, 68.31; H, 11.47; neutralization equivalent, 158.2; MR, 45.30.

Found: C, 68.07, 68.00; H, 11.51, 11.43; neutralization equivalent, 156.2; MR, 45.25.

Preparation of 3,5-Dimethylheptanoic Acid



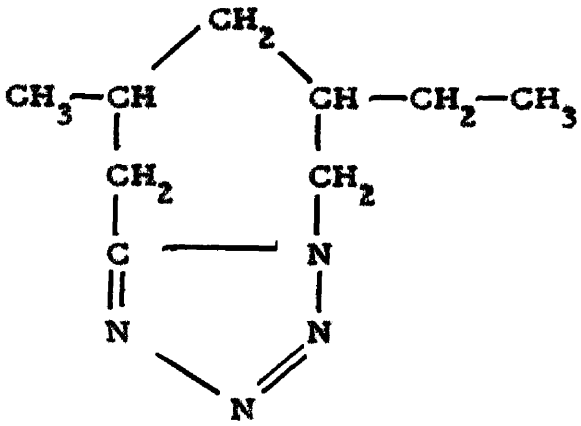
$$CH_3-CH_2-\overset{\overset{CH_3}{|}}{CH}-CH_2-\overset{\overset{CH_3}{|}}{CH}-CH_2-COOH$$

Five grams of ethyl 3,5-dimethylheptanoate was saponified with a solution of 3 g. of potassium hydroxide dissolved in 30 ml. of water and 10 ml. of alcohol. The crude material was isolated as previously described for the preparation of 3-ethyl-5-methylhexanoic acid and on fractionation gave 0.6 g. of forerun boiling below 87° C./0.7 mm., and 3.0 g. of product boiling at 87-90° C./0.7 mm., n_d^{20} 1.4319, n_d^{25} 1.4300, d_4^{20} 0.906.

Anal.: Calc'd for $C_9H_{18}O_2$: C, 68.31; H, 11.47; neutralization equivalent, 158.2; MR, 45.30.

Found: C, 68.20, 68.00; H, 11.43, 11.53; neutralization equivalent, 156.4; MR, 45.26.

Preparation of 7-Methyl-9-Ethyl-1,5-Pentamethylenetetrazole (101)



A 250 ml. three-necked flask was equipped with a stirrer and condenser. A small Erlenmeyer flask was attached to the third opening by means of large diameter rubber tubing slipped over the opening. The apparatus was dried in a hot room and protected from moisture by a calcium chloride tube attached to the top of the condenser. Five grams, 0.032 mole, of the lactam of 3,5-dimethyl-6-aminoheptanoic acid and 45 ml. of benzene were placed in the flask and stirred to effect solution. Seven and one-half grams, 0.037 mole, of phosphorus pentachloride was weighed quickly into the Erlenmeyer flask and attached to the apparatus. The phosphorus pentachloride was added to the reaction flask in small portions. During this addition the mixture was kept at room temperature by occasional cooling in an ice-bath. The reaction mixture was stirred until the phosphorus pentachloride had gone into solution.

The Erlenmeyer flask and rubber tubing attachment was then replaced with a dropping funnel and 50 ml. of a 10 percent solution of hydrazoic acid in benzene was added to the reaction mixture during one-half hour. During the addition of hydrazoic acid the mixture became warm and some hydrogen chloride was evolved. The reaction was kept at room temperature by intermittently cooling it with an ice-bath. The mixture was refluxed three hours during which operation much hydrogen chloride was evolved. It was allowed to stand overnight and then refluxed three hours longer until hydrogen chloride evolution had ceased. During the refluxing period solid precipitated from the reaction mixture.

The reaction mixture was cooled to 10° C. A solid that separated was filtered off and recrystallized from water to give 1.0 g. of colorless crystals melting at 91.8-95.8° C. This material which presumably was a mixture of lactam and tetrazole was not further investigated.

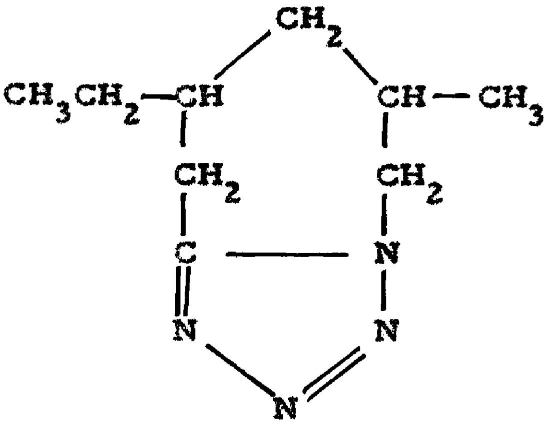
The benzene mother liquor was evaporated to dryness under vacuum on the steam bath. The residue was a dark colored viscous oil. The oil was poured onto ice and allowed to crystallize in the refrigerator. The water was decanted and the semisolid mass extracted three times with boiling "hexane." On cooling the "hexane" solution deposited 0.5 g. of product melting at 76-77.5° C. The product recrystallized from hexane melted at 79.5-80.5° C.

Anal.: Calc'd for $C_9H_{16}N_4$: C, 59.97; H, 8.95; N, 31.09.
Found: C, 60.00, 59.97; H, 8.90, 9.10; N, 31.13, 31.20.

Mixture melting points of this tetrazole with the isomeric 7-ethyl-9-methyl-1,5-pentamethylenetetrazole (see following preparation) showed melting points intermediate between the melting points of the two pure tetrazoles.

Harvill, Roberts, and Herbst (1) described a methyl ethyl pentamethylenetetrazole which had been obtained by the interaction of 3-methyl-5-ethylcyclohexanone oxime with sodium azide and chlorosulfonic acid. Their compound could have been either of the isomeric tetrazoles described in this and the following preparation. An authentic sample obtained from the above authors melted at 85.1-86.6° C. A mixture melting point determination with the tetrazole described in this preparation showed a depression of the higher melting tetrazole. Therefore, their tetrazole was not 7-methyl-9-ethyl-1,5-pentamethylenetetrazole.

Preparation of 7-Ethyl-9-Methyl-1,5-Pentamethylenetetrazole (101)



Five grams, 0.032 mole, of the lactam of 3-ethyl-5-methyl-6-aminohexanoic acid dissolved in 45 ml. of benzene was treated with 7.5 g., 0.37 mole, of phosphorus pentachloride and 50 ml. of a 10 percent solution of hydrazoic acid in benzene as previously described for the isomeric lactam of 3,5-dimethyl-6-aminoheptanoic acid.

A solid that separated on cooling the reaction mixture to 10° C. was filtered off and recrystallized from water to give 0.4 g. of colorless crystals melting at 87.6-89.1° C. This material which presumably was tetrazole containing a slight amount of lactam was not further investigated.

The product was isolated as previously described for the preparation of 7-methyl-9-ethyl-1,5-pentamethylenetetrazole. Recrystallization from hexane gave 0.1 g. of product, m.p. 87.2-88.2° C.

Anal.: Calc'd for $C_9H_{16}N_4$: C, 59.97; H, 8.95; N, 31.09.
Found: C, 59.92, 59.96; H, 8.95, 9.14; N, 31.30, 31.28.

Mixture melting points of this tetrazole with the isomeric 7-methyl-9-ethyl-1,5-pentamethylenetetrazole (see previous preparation) showed melting points intermediate between the melting points of the two pure tetrazoles.

A sample of the methyl ethyl pentamethylenetetrazole prepared by Harvill, Roberts, and Herbst (1) (see previous preparation) melted at 85.1-86.6° C. A mixed melting point determination with the tetrazole described in this preparation showed no depression. Therefore, their tetrazole was 7-ethyl-9-methyl-1,5-pentamethylenetetrazole.

SUMMARY

1. A study has been made of the degradation of ϵ-caprolactam to ethyl caproate. The other main products from the degradation have been identified as ethyl ϵ-chlorocaproate and ethyl ϵ-hydroxycaproate.

2. The Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime has been shown to give a mixture of the two structurally isomeric lactams. The lactams have been separated by solvent extraction and fractional crystallization and their structures have been established by conversion to ethyl 3-ethyl-5-methylhexanoate or to ethyl 3,5-dimethylheptanoate.

3. The new esters, ethyl 3-ethyl-5-methylhexanoate and ethyl 3,5-dimethylheptanoate, have been unequivocally synthesized by a Reformatsky reaction and have been characterized by physical constants and preparation of derivatives.

4. The two isomeric lactams, prepared by the Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime, have been converted into their respective methyl ethyl 1,5-pentamethylene-

tetrazoles. The position of the alkyl substituents in 7-methyl-9-ethyl-1,5-pentamethylenetetrazole and in 7-ethyl-9-methyl-1,5-pentamethylenetetrazole has now been established. The methyl ethyl 1,5-pentamethylenetetrazole prepared by Harvill, Roberts, and Herbst (1), whose structure had not been established, has been shown to be 7-ethyl-9-methyl-1,5-pentamethylenetetrazole by comparison with the two new tetrazoles of known structure.

5. A brief investigation has been made of the nitrosation and decomposition of the nitroso compound of ethyl ϵ-carboethoxyaminocaproate.

6. The new ϵ-iodocaproic acid has been prepared and characterized by analysis.

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