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A STUDY OF THE STRUCTURE OF SOME CYCLIC AMIDES AND RELATED TETRAZOLES[1]

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The treatment of alkylcyclohexanone oximes with sodium azide and chlorosulfonic acid has been shown to lead through ring expansion and a second cyclization to alkylpentamethylenetetrazoles (1). When this reaction was applied to unsymmetrically substituted cyclohexanone oximes (I), structurally isomeric pentamethylenetetrazoles (II and III) could result depending upon the extent of 1–2 or 1–6 bond rupture occurring in the cyclohexanone oxime ring. When the reaction was applied to 3,5-dialkylcyclohexanone oximes, pure dialkylpentamethylenetetrazoles were isolated, but no attempt was made to determine the position of the substituents in the products (1). It has been the purpose of this investigation to determine the position of the substituents in such dialkylpentamethylenetetrazoles.

The initial stage of tetrazole formation from the cyclohexanone oximes was assumed to be similar to the Beckmann rearrangement; at some point after ring expansion but before completion of the rearrangement by amide formation, the addition of the azide group caused tetrazole formation (1). Although amides do not react directly with hydrazoic acid or sodium azide to form tetrazoles, this conversion may be accomplished indirectly if the amide is first allowed to react with phosphorus pentachloride. The imide chloride so formed reacts readily with hydrazoic acid to form a tetrazole (2–4). It appeared feasible to accomplish stepwise conversion of cyclohexanone oximes to pentamethylenetetrazoles by first rearranging the oxime and determining the structure of the cyclic amides (IV and V) formed, and second, converting the cyclic amides into pentamethylenetetrazoles by way of their imide chlorides. This procedure has now been employed to establish the position of the substituents in 7-methyl-9-ethylpentamethylenetetrazole (II)[3] and its isomer, 7-ethyl-9-methylpentamethylenetetrazole (III) and to establish the identity of the methylethylpentamethylenetetrazole described by Harvill, *et al.* (1).

Since the structures of the pentamethylenetetrazoles would depend on knowledge of the structures of the lactams, a satisfactory method of converting the lactams into saturated aliphatic acids or other easily identifiable compounds was essential. The conversion of the parent ϵ-caprolactam into *n*-caproic acid was reinvestigated for this purpose. Attempts to reduce ϵ-caprolactam or ϵ-amino-

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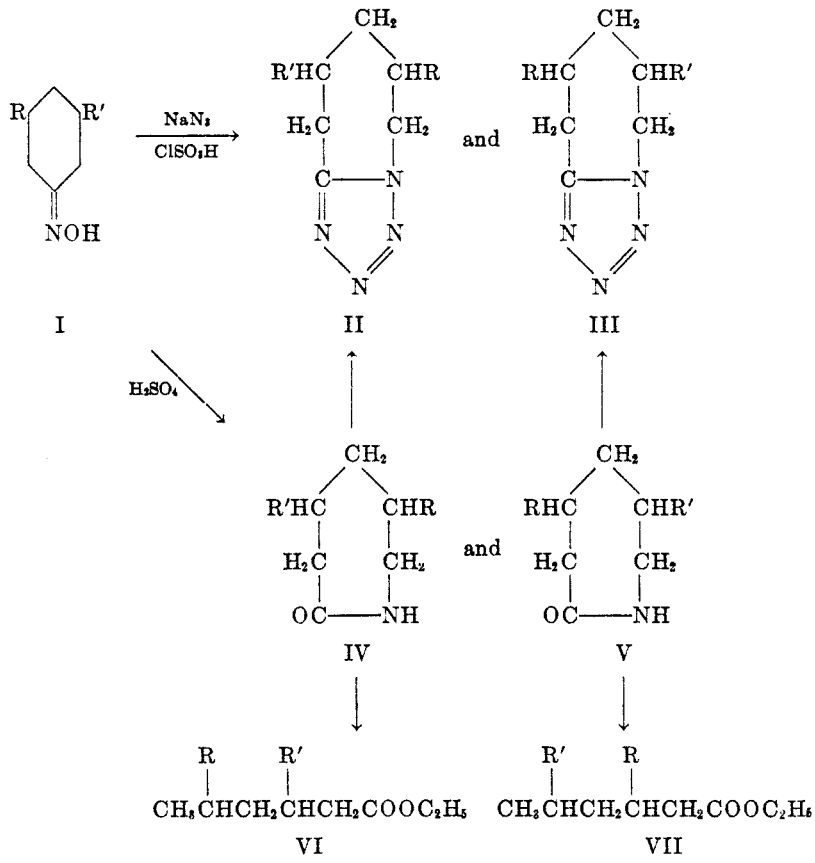
[3] The numbering of the pentamethylenetetrazole system employed by Harvill, *et al.*, (1) is retained.



R = Ethyl; R′ = Methyl

caproic acid with hydriodic acid by an adaptation of the method of Kwisda (5) showed little promise. Other routes involved the reaction of nitrous acid with either the lactam or the corresponding amino acid. Wallach (6, 7) had investigated the action of nitrous acid on several alkyl-substituted ϵ-aminocaproic acids and found unsaturated and hydroxy acids among the products. Helferich and Malkomes (8) studied the interaction of sodium nitrite and ϵ-aminocaproic acid hydrochloride and reported a 20% yield of an hexenoic acid along with a small quantity of a lactone and large amounts of unidentified high-boiling materials. These results are not surprising in view of the more recent studies of Whitmore and Langlois (9) on the action of nitrous acid on *n*-butylamine in the presence of hydrochloric acid; straight chain butenes, butyl alcohols, and butyl chlorides resulted. After some preliminary studies the procedure of Helferich and Malkomes was adopted since it gave the best yields of unsaturated acids.

One other sequence of reactions for the conversion of ϵ-caprolactam to ethyl caproate was investigated. The lactam was hydrolyzed and esterified; the ethyl ϵ-aminocaproate was converted successively into ethyl ϵ-carbethoxyamino-

caproate (VIII), and the N-nitroso derivative (IX) (10). Using conditions similar to those employed by Bollinger, *et al.* (11) for the decomposition of N-nitroso-N-cyclohexylurethan, the base-catalyzed decomposition of ethyl N-nitroso-ε-carbethoxyaminocaproate (IX) was studied. After hydrogenation of the mixture of products obtained from the decomposition reaction, crude ethyl caproate (VI, R = R′ = H) was isolated in 10% yield, The low yield of ester, particularly from the over-all point of view, discouraged further examination of this procedure. However, the results indicated that esterification at some stage of the transformation of the lactams to saturated acids was desirable to minimize losses through polymerization of unsaturated and hydroxy acids.

$$\underset{\text{VIII}}{C_2H_5OOCNH(CH_2)_5COOC_2H_5} \xrightarrow{HNO_2} \underset{\text{IX}}{C_2H_5OOCN(NO)(CH_2)_5COOC_2H_5} \xrightarrow[\text{Followed by hydrogenation}]{K_2CO_3 \text{ in } CH_3OH} \text{VI, R = R' = H}$$

The procedure adopted for structural studies involved hydrolysis of the lactams to the ε-aminocaproic acids which upon treatment with nitrous acid gave a mixture of chloro, hydroxy, and unsaturated acids. After hydrogenation and esterification of the mixture, the ethyl esters of the acids were separated by fractional distillation. Starting with ε-caprolactam pure ethyl caproate was isolated in 20–25% yield in this way. Ethyl ε-chloro- and ethyl ε-hydroxycaproate were also isolated from the reaction mixture. Recently Huisgen and Reinertshofer (12) reported comparable results from studies of the base-catalyzed decomposition of N-nitroso-ε-caprolactam in alcoholic solutions. The possibility of converting the moderately large amount of ethyl ε-hydroxycaproate obtained in our studies into ethyl caproate by treatment with phosphorus and iodine and subsequent reduction of the ε-iodocaproic acid was also studied. However, it did not seem useful to extend the procedure to the alkyl substituted hydroxycaproic acids, nor did the possibility of converting esters of the alkyl substituted chlorocaproic acids to the corresponding alkylcaproic acids appear to lend stronger support to the conclusions concerning the structures of the parent lactams.

Structural studies were undertaken with 3-methyl-5-ethylcyclohexanone oxime (I). Beckmann rearrangement of the oxime mixture was accomplished with sulfuric acid and led to a mixture of cyclic amides (IV and V). It might be pointed out that the original oxime mixture could contain as many as eight isomers grouped as four pairs of optical isomers due to various combinations of *cis* and *trans* arrangements of the alkyl groups and *syn* and *anti* configurations of the oximino group.[4] Each of the stereoisomeric oximes could give a different rearrangement product. The latter would fall into two groups of structural isomers with a *cis* and a *trans* racemate in each group. By fractional crystallization and fractional extraction techniques two pure methyl ethyl caprolactams, lactam A,

[4] It should be noted that 3,5-dimethylcyclohexanone has been found to have the *cis* configuration (13, 14) when prepared by the same methods used in this investigation for the preparation of 3-methyl-5-ethylcyclohexanone. It would seem reasonable to assume that we were not confronted with a mixture of isomers of maximum complexity.

m.p. 105.5–106°, and lactam B, m.p. 100–101°, were separated from the mixture. Lactam A was identified as 4-ethyl-6-methyl-2-ketohexamethylenimine (V) by degradation according to the scheme outlined above and isolation of ethyl 3-ethyl-5-methylhexanoate (VII). Similarly, lactam B was identified as 4-methyl-6-ethyl-2-ketohexamethylenimine (IV) by degradation to an unsaturated acid which was hydrogenated and isolated as ethyl 3,5-dimethylheptanoate (VI). The two saturated esters were identified by comparison with synthetic samples of the respective compounds that had been prepared by unequivocal methods. Two higher-boiling fractions were isolated as esters after degradation of lactam A. These were identified as a chloro ester and a hydroxy ester by analysis of their S-benzylthiouronium salts. Analogy to the results obtained with ϵ-caprolactam suggested that these were the ethyl esters of 6-chloro- and 6-hydroxy-3-ethyl-5-methylhexanoic acid, but these structures have not been established by synthesis.

The two isomeric esters, ethyl 3-ethyl-5-methylhexanoate and ethyl 3,5-dimethylheptanoate, were prepared by Reformatsky reactions between ethyl bromoacetate and the appropriate ketones, followed by dehydration of the hydroxy ester and hydrogenation of the resulting unsaturated ester. The new esters were characterized by analysis as such and in the form of free acids, *p*-toluidides and S-benzylthiouronium salts. The ketones required for the syntheses were prepared by standard reactions. Ethyl isobutyl ketone was prepared both by pyrolysis of a mixture of propionic and isovaleric acids over thorium oxide catalyst and by interaction of diethylcadmium and isovaleryl chloride. The better over-all yield based on isovaleric acid and the simplicity of the catalytic process commend it. 4-Methyl-2-hexanone was prepared by alkylation of ethyl acetoacetate with *sec.*-butyl bromide followed by ketonic hydrolysis of the product (15).

The pure lactams, A and B, were converted into the respective pentamethylenetetrazoles by treatment first with phosphorus pentachloride and then with hydrazoic acid in benzene solution. The intermediate cyclic imide chlorides were not isolated. From lactam A (V) was obtained 7-ethyl-9-methylpentamethylenetetrazole (III) which proved to be identical with the product described by Harvill, *et al.* (1) and obtained by them through interaction of 3-methyl-5-ethylcyclohexanone oxime, sodium azide, and chlorosulfonic acid. Mixture melting points of III and the product of Harvill, *et al.* showed no depression. The isomeric structure previously assigned arbitrarily to their product by these authors is incorrect. From lactam B (IV) 7-methyl-9-ethylpentamethylenetetrazole (II) was obtained by the same sequence of reactions. Mixtures of II and III showed melting points between those of the pure components; admixture of II also depressed the melting point of the product of Harvill, *et al.*

EXPERIMENTAL[5, 6]

ϵ-*Caprolactam* was prepared from cyclohexanone oxime by a modification of the procedure of Marvel and Eck (16). So that the heat of the reaction could be more easily dissipated,

[5] All melting points are corrected.

[6] Kjeldahl nitrogen determinations were done in this laboratory. All other analyses were done by Micro-Tech Laboratories, Skokie, Ill.

the oxime was added in small portions to a large volume of warm sulfuric acid. For instance, 200 g. of concentrated sulfuric acid was heated to about 105° and 100 g. of cyclohexanone oxime was added in very small portions with stirring at such a rate that the temperature of the reaction mixture did not exceed 130°. A temperature of at least 105° appears to be critical for the rapid initiation of the rearrangement. The lactam was isolated as described by Marvel and Eck (16).

Decomposition of ethyl N-nitroso-ε-carbethoxyaminocaproate. Ethyl N-nitroso-ε-carbethoxyaminocaproate (21 g., crude), prepared according to Adamson and Kenner (10), was added slowly to a suspension of 0.05 g. of finely powdered anhydrous potassium carbonate in 12 ml. of methanol (previously dried over potassium carbonate). Cooling in an ice-bath was necessary to control the exothermic reaction. Gas evolution was observed for three hours. After standing overnight at room temperature the mixture was boiled under reflux for an hour, cooled, filtered, diluted with 100 ml. of ethanol and subjected to hydrogenation at 50 p.s.i. hydrogen pressure in the presence of platinum oxide catalyst. The pressure drop indicated the uptake of about 0.035 mole of hydrogen. After removal of the solvent, the residue was distilled under reduced pressure and the following fractions were collected: (i) 1.4 g., b.p. 66–99° at 16 mm.; (ii) 3.7 g., b.p. 99–110° at 16 mm.; (iii) 7.1 g., b.p. 110–165° at 16 mm.; (iv) 1.9 g., b.p. 190–198° at 16 mm.; (v) 2 g. residue. Although the fractions were not rigorously identified, the experiences of Bollinger, *et al.* (11) with N-nitroso-N-cyclohexylurethan and of Huisgen and Reinertshofter (12) with N-nitroso-ε-caprolactam suggest that (i) is largely ethyl caproate; (ii) is chiefly ethyl ε-methoxycaproate, reported b.p. 94–95° at 15 mm. (17); and (iii) is mostly ethyl ε-hydroxycaproate, reported b.p. 135° at 15 mm. (18). This procedure was not studied further due to the many steps involved and the small over-all yield of saturated ester.

Degradation of ε-caprolactam. A solution of 23 g. (0.33 mole) of sodium nitrite in 40 ml. of water was added slowly during one hour to the crude ε-aminocaproic acid hydrochloride (8) obtained by hydrolysis of 25 g. (0.22 mole) of ε-caprolactam. The vigorous, exothermic reaction was controlled by intermittent cooling in an ice-bath. After standing three hours at room temperature the mixture was made acid to Congo Red with sulfuric acid, heated for an hour on a steam-bath, cooled, and extracted with five 50-ml. portions of chloroform. After drying the combined chloroform extracts over sodium sulfate, the solvent was removed by distillation through a column. The residue was taken up in 150 ml. of absolute ethanol and reduced at 50 p.s.i. hydrogen pressure in the presence of platinum oxide catalyst. The mixture of saturated and substituted acids then was esterified by boiling under reflux for 12 hours after adding an equal volume of absolute ethanol and 5 ml. of concentrated sulfuric acid. After neutralization of the acid and removal of the salts the mixture of esters was fractionated under reduced pressure through a Vigreux column. The following fractions were collected and identified: (i) 1.8 g., b.p. 57–58° at 13 mm., n_D^{20} 1.4072, reported for ethyl caproate n_D^{20} 1.4076 (19); (ii) 2.8 g., b.p. 66–72° at 1 mm., $n_D^{20.5}$ 1.4379, positive Beilstein test for halogen, reported for ethyl ε-chlorocaproate b.p. 106° at 14 mm., n_D^{18} 1.4398 (20); (iii) 1.1 g., b.p. 72–91° at 1 mm., intermediate; (iv) 4.6 g., b.p. 91–95° at 1 mm., n_D^{20} 1.4360, hydrazide, m.p. 115–116.5°, reported for ethyl ε-hydroxycaproate b.p. 104–106° at 4 mm., n_D^{25} 1.4381, hydrazide, m.p. 114–115° (21).

ε-Iodocaproic acid. A mixture of 1.25 g. (0.04 mole) of red phosphorus, 15.4 g. (0.096 mole) of ethyl ε-hydroxycaproate (18), and 15.3 g. (0.06 mole) of iodine was heated on a steam-bath under reflux for five hours. The cooled mixture was diluted with 100 ml. of ether, filtered, washed first with excess 10% sodium bisulfite solution, then with water, and dried over calcium chloride. After evaporating the solvent, the residue was stirred for four hours at room temperature with 100 ml. of 10% sodium hydroxide solution. The unsaponified layer was separated and the product was precipitated from the aqueous alkaline solution by acidification to Congo Red. The crude product was washed by suspension in water and recrystallized from aqueous ethanol, yield 10 g. (43%), m.p. 42.5–44°. The same product was obtained from ethyl ε-hydroxycaproate isolated after degradation of ε-caprolactam.

Anal. Calc'd for $C_6H_{11}IO_2$: I, 52.4. Found: I, 52.4, 52.7.

Reduction of ε-iodocaproic acid. To a suspension of 2.6 g. (0.04 g.-atom) of 30 mesh zinc (previously cleaned by washing with dilute acid, water, and ethanol) and 2.4 g. (0.01 mole) of ε-iodocaproic acid in 15 ml. of 95% ethanol, 5 ml. of concentrated hydrochloric acid was added dropwise during 15 minutes. The mixture was refluxed for 20 minutes, allowed to stand for four hours, and then treated with a second 5-ml. portion of concentrated hydrochloric acid. After boiling for half an hour under reflux all the zinc had dissolved. The reaction mixture was steam-distilled, the distillate extracted with three 10-ml. portions of ether, the ether evaporated on a steam-bath, and the residue taken up in 20 ml. of benzene. Fractionation of this solution gave 0.6 g. (43%) of ethyl caproate, n_D^{20} 1.4080.

Methylethyl-2-ketohexamethylenimine (IV and V). 3-Methyl-5-ethylcyclohexanone (1) was converted into its oxime by treatment with hydroxylamine hydrochloride in aqueous isopropyl alcohol solution in the presence of sodium hydroxide and sodium acetate (1). The oxime was obtained in 84% yield as a viscous liquid, b.p. 129–134° at 15 mm., reported b.p. 127–128° at 11 mm. (1).

In a beaker equipped with a stirrer, thermometer, and dropping-funnel 240 g. of concentrated sulfuric acid was heated to 110°. The temperature was maintained at 110–115° by the dropwise addition, with stirring, of 120 g. of 3-methyl-5-ethylcyclohexanone oxime during an hour and a half. Two such reaction mixtures were combined, cooled to 10° and poured onto sufficient ice to dilute to about 2 l. The aqueous solution was extracted with five 250-ml. portions of chloroform, and the extracts combined and washed with three 50-ml. portions of 10% sodium carbonate solution and then dried over magnesium sulfate. After removal of the solvent distillation of the residue gave 180 g. (75%) of pale yellow product, b.p. 170–171.5° at 17–18 mm. The product solidified on cooling to room temperature.

Separation of the isomeric lactams (IV and V). The crude lactam mixture (180 g.) was dissolved in 100 ml. of hot ethyl acetate and crystallized by cooling thoroughly in an ice-bath. Extraction of the resulting solids with 350 ml. of ice-cold ethyl acetate left 102 g. of solids, m.p. 70–84°. A second extraction with 150 ml. of ice-cold ethyl acetate left a residue of 54 g., m.p. 82–96°. Four recrystallizations of this residue from hexane gave 26 g. of lactam A (V), m.p. 105.5–106°.[7]

Anal. Calc'd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0.
Found: C, 69.7; H, 11.0; N, 8.9 (Kjeldahl).

Each ethyl acetate solution from above was evaporated to dryness and the solid residue again was extracted with ice-cold ethyl acetate. The ethyl acetate solutions from the second series of extractions were evaporated to dryness separately and the extractives were recrystallized from hexane. If the extractives did not melt above 75° at this point, a third extraction with ice-cold ethyl acetate was resorted to. The extractives, m.p. 75–87°, were combined (about 60 g.) and recrystallized 12 times from hexane to give 9.1 g. of lactam B (IV), m.p. 100–101°; admixture of lactam A caused a large depression.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0.
Found: C, 69.6; H, 11.0; N, 9.1 (Kjeldahl).

Degradation of lactam A (V). Lactam A (20 g., 0.13 mole) was hydrolyzed by refluxing for an hour with 11 ml. of concentrated hydrochloric acid diluted to 36 ml. with water. Evaporation of the solvent under a vacuum on a steam-bath left the amino acid hydrochloride as a colorless, viscous syrup. A solution of 13.4 g. (0.19 mole) of sodium nitrite in 32 ml. of water was added to the hydrochloride during 30 minutes. A vigorous exothermic reaction took place with gas evolution. The mixture was acidified to Congo Red with hydrochloric acid and heated for an hour on a steam-bath, cooled, extracted with chloroform and the extracts dried over sodium sulfate. The residue remaining after evaporation of the chloroform on a steam-bath was dissolved in 100 ml. of absolute ethanol and reduced at 50 p.s.i. hydrogen

[7] It may be noted that simple fractional crystallization of the lactam mixture from hexane will give pure lactam A, but the isolation of lactam B from the remaining mixture then is more difficult.

pressure using 0.1 g. of platinum oxide catalyst. The drop in pressure indicated the absorption of only 0.005 mole of hydrogen. The solution was filtered and the mixture of acids was esterified by refluxing their ethanolic solution for 12 hours after addition of 5 ml. of concentrated sulfuric acid. After neutralization of the acid with sodium carbonate and removal of the inorganic salts, the filtrate was diluted with chloroform until two layers formed. The aqueous layer was again extraced with chloroform. The combined chloroform solutions were washed with cold, saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent by distillation, the residue was fractionated under reduced pressure using a Vigreux column. The following fractions were collected: (i) 2.5 g., b.p. 51–59° at 1.9 mm.; (ii) 1.0 g., b.p. 59–87° at 1.9 mm.; (iii) 2.6 g., b.p. 87–97° at 1.9 mm.; (iv) 1.1 g., b.p. 97–108° at 2 mm.; (v) 2.1 g., b.p. 108–113° at 2 mm.; (vi) 2.7 g. residue.

Fraction (i) gave positive tests for unsaturation. Hydrogenation was completed with 2.3 g. of this fraction dissolved in 5 ml. of glacial acetic acid at 50 p.s.i. hydrogen pressure with platinum oxide catalyst. After removal of the solvent, fractionation of the material gave 1.6 g. of ethyl 3-ethyl-5-methylhexanoate, b.p. 50–58° at 1 mm., n_D^{28} 1.4185 (for synthetic ethyl 3-ethyl-5-methylhexanoate n_D^{20} 1.4218 and n_D^{25} 1.4198 were found, see below).

Anal. Calc'd for $C_{11}H_{22}O_2$: Sapon. equiv., 186.3. Found: Sapon. equiv., 186.1.

S-Benzylthiouronium salt of the acid, m.p. 148.5–149°, recrystallized from aqueous ethanol. No depression of m.p. on admixture of an authentic sample (see below).

Anal. Calc'd for $C_{17}H_{28}N_2O_2S$: N, 8.6. Found: N, 8.4 (Kjeldahl).

p-Toluidide, m.p 57–58°, recrystallized from aqueous ethanol; no depression on admixture of an authentic sample (see below).

Anal. Calc'd for $C_{16}H_{25}NO$: N, 5.7. Found: N, 5.6 (Kjeldahl).

Fraction (ii) appeared to be a mixture of materials in (i) and (iii).

Fraction (iii) gave strong tests for halogen. By analogy with the results of degradation of ϵ-caprolactam this fraction was tentatively identified as chiefly ethyl 3-ethyl-5-methyl-6-chlorohexanoate, although the position of the chlorine was not rigorously established. After saponification of the ester with aqueous potassium hydroxide, the S-benzylthiouronium salt of the acid, m.p. 153–154.5°, recrystallized from ethyl acetate, was isolated.

Anal. Calc'd for $C_{17}H_{27}ClN_2O_2S$: Cl, 9.9; N, 7.8; S, 8.9.
Found: Cl, 9.7, 9.9; N, 7.5 (Kjeldahl); S, 8.9, 9.0.

Fraction (iv) was probably a mixture of (iii) and (v).

Fraction (v) gave only a very faint test for halogen. By analogy to the results of degradation of ϵ-caprolactam the material was tentatively identified as ethyl 3-ethyl-5-methyl-6-hydroxyhexanoate, although the position of the hydroxyl group is not definitely established. The composition of the S-benzylthiouronium salt, m.p. 129–129.5°, recrystallized from ethyl acetate, obtained after saponification of the ester indicated that the material was a hydroxy ester.

Anal. Calc'd for $C_{17}H_{28}N_2O_3S$: N, 8.2; S, 9.4.
Found: N, 8.4 (Kjeldahl); S, 9.4, 9.6.

Degradation of lactam B (IV). Lactam B (10 g.) was treated in a manner analogous to that described for the isomeric lactam A. After hydrolysis with hydrochloric acid the amino acid hydrochloride was obtained as a colorless, viscous syrup. The hydrochloride was treated with 6.7 g. (0.1 mole) of sodium nitrite in 16 ml. of water, and the crude acids obtained by chloroform extraction were hydrogenated and esterified as described for the isomers. Distillation of the mixture of esters under reduced pressure using a Vigreux column gave the following fractions: (i) 2.0 g., b.p. 66–69° at 2.9 mm.: (ii) 0.2 g., b.p. 70–89° at 3 mm.; (iii) 1.2 g., b.p. 89–109° at 3 mm.; (iv) 2.3 g., b.p. 109–122° at 3 mm.; (v) 1.7 g. residue.

Fraction (i) gave positive tests for unsaturation. Hydrogenation was completed with 1.7 g. of this material in 5 ml. of glacial acetic acid at 50 p.s.i. hydrogen pressure using platinum oxide catalyst. Fractionation of the material under reduced pressure using a Vigreux column gave 1.2 g., b.p. 50–54° at 1 mm., n_D^{28} 1.4191. The product was identical with synthetic ethyl 3,5-dimethylheptanoate, b.p. 59.5–61° at 2.4 mm., n_D^{20} 1.4218, n_D^{25} 1.4199 (see below).

Anal. Calc'd for $C_{11}H_{22}O_2$: Sapon. equiv., 186.3. Found: Sapon. equiv., 184.5.

S-Benzylthiouronium salt prepared after saponification of the ester, m.p. 140–141°, recrystallized from aqueous ethanol; no depression of m.p. on admixture of an authentic sample (see below).

Anal. Calc'd for $C_{17}H_{28}N_2O_2S$: N, 8.6. Found: N, 8.5 (Kjeldahl).

p-Toluidide prepared from the ester, m.p. 62–64°, recrystallized from aqueous alcohol; no depression on admixture of an authentic sample (see below).

Anal. Calc'd for $C_{16}H_{25}NO$: N, 5.7. Found: N, 5.7 (Kjeldahl).

The higher-boiling fractions were not further characterized.

Ethyl isobutyl ketone. Method A. A mixture of propionic and isovaleric acids in 4:1 molar ratio was passed over thorium oxide deposited on pea-sized porous plate chips heated to 450° essentially as described for the preparation of methyl benzyl ketone (22). Fractionation of the crude product gave 41% of ethyl isobutyl ketone, b.p. 132–133°, reported b.p. 135° (23). With a 2:1 molar ratio of the acids only 18% of ethyl isobutyl ketone was obtained. *Method* B. Ethyl isobutyl ketone, b.p. 132–133° was obtained in 47% yield from diethylcadmium and isovaleryl chloride by an adaptation of Cason's general method (24).

Preparation of unsaturated esters. The technique for the Reformatsky reaction recommended by Natelson and Gottfried (25) was used to prepare the β-hydroxy esters which were then dehydrated directly with phosphorus pentoxide[8] using the procedure suggested by Kon and Nargund (26). In this way ethyl isobutyl ketone and ethyl bromoacetate were condensed and the resulting hydroxy ester was dehydrated to form a mixture of the ethyl 3-ethyl-5-methylhexenoates, b.p. 103–106° at 19–20 mm., yield 43%. Likewise, 4-methyl-2-hexanone (15) and ethyl bromoacetate were condensed to form ethyl 3,5-dimethyl-3-hydroxyheptanoate from which a mixture of ethyl 3,5-dimethylheptenoates was obtained by dehydration. The latter was separated into two fractions, b.p. 98–102° at 18 mm., and b.p. 100–108° at 16 mm., combined yield 31%. Both fractions gave the same saturated ester and were not examined more closely.

Ethyl 3-ethyl-5-methylhexanoate (VII). A solution of 30 g. of the ethyl 3-ethyl-5-methylhexenoates in an equal volume of glacial acetic acid was reduced at 50 p.s.i. hydrogen pressure with 0.2 g. platinum oxide catalyst.[9] Fractionation of the solution of the saturated ester under reduced pressure gave 26 g. (88%) of ethyl 3-ethyl-5-methylhexanoate, b.p. 62–64° at 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; Sapon. equiv., 186.3; MR, 54.53.
Found: C, 70.7; H, 12.0; Sapon. equiv., 183.3; MR, 54.58.

3-Ethyl-5-methylhexanoic acid. Ethyl 3-ethyl-5-methylhexanoate (5 g.) was saponified by boiling under reflux for 2.5 hours with a solution of 3 g. of potassium hydroxide in 40 ml. of 70% ethanol. After cooling and acidifying the saponification mixture, the free acid was extracted with ether, and the ether extracts were dried over sodium sulfate and fractionated under reduced pressure. Yield, 3 g. of 3-ethyl-5-methylhexanoic acid. b.p. 86–90° at 0.6 mm., n_D^{20} 1.4321, n_D^{25} 1.4301, d_D^{20} 0.907.

Anal. Calc'd for $C_9H_{18}O_2$: C, 68.3; H, 11.5; Neut. equiv., 158.2; MR, 45.30.
Found: C, 68.1, 68.0; H, 11.5, 11.4; Neut. equiv., 156.2; MR, 45.25.

S-Benzylthiouronium salt, m.p. 148.5–149°, recrystallized from aqueous ethanol.

Anal. Calc'd for $C_{17}H_{28}N_2O_2S$: N, 8.6. Found: N, 8.4 (Kjeldahl).

p-Toluidide, m.p. 59–60.5°, recrystallized from aqueous ethanol.

Anal. Calc'd for $C_{16}H_{25}NO$: N, 5.7. Found: N, 5.5 (Kjeldahl).

Ethyl 3,5-dimethylheptanoate (VI). The mixed ethyl 3,5-dimethylheptenoates (29 g.) dissolved in an equal volume of glacial acetic acid were reduced at 50 p.s.i. hydrogen pres-

[8] An attempted dehydration with acetic anhydride appeared to result in formation of the acetate of the hydroxy ester.

[9] Hydrogenation in ethanol solution with platinum oxide catalyst was not successful; even at 1,350 p.s.i. with Raney nickel catalyst only partial hydrogenation was effected in alcoholic solution. Cope and Hancock (27) resorted to high pressure and high temperature to reduce a similarly substituted unsaturated ester.

sure with 0.2 g. of platinum oxide catalyst. Fractionation of the product gave 18 g. of ethyl 3,5-dimethylheptanoate, b.p. 59.5–61° at 2.6 mm., n_D^{20} 1.4218, n_D^{25} 1.4199, d_D^{20} 0.867.

Anal. Calc'd for $C_{11}H_{22}O_2$: C, 70.9; H, 11.9; Sapon. equiv., 186.3; MR, 54.35.

Found: C, 70.7; H, 12.0; Sapon. equiv., 185.3; MR, 54.58.

3,5-Dimethylheptanoic acid. Saponification of 5 g. of ethyl 3,5-dimethylheptanoate with 3 g. of potassium hydroxide in 40 ml. of 70% ethanol gave 3 g. of 3,5-dimethylheptanoic acid, b.p. 87–90° at 0.7 mm., n_D^{20} 1.4319, n_D^{25} 1.4300, d_D^{20} 0.906.

Anal. Calc'd for $C_9H_{18}O_2$: C, 68.3; H, 11.5; Neut. equiv., 158.2; MR, 45.30.

Found: C, 68.2, 68.0; H, 11.4, 11.5; Neut. equiv., 156.4; MR, 45.26.

S-Benzylthiouronium salt, m.p. 141–141.5°, recrystallized from aqueous ethanol.

Anal. Calc'd for $C_{17}H_{28}N_2O_2S$: N, 8.6. Found: N, 8.7 (Kjeldahl).

p-Toluidide, m.p. 66–67°, recrystallized from aqueous ethanol.

Anal. Calc'd for $C_{16}H_{25}NO$: N, 5.7. Found: N, 5.4 (Kjeldahl).

7-Methyl-9-ethylpentamethylenetetrazole (II). Following the previously described procedure (4), 5 g. (0.032 mole) of lactam B, 4-methyl-6-ethyl-2-ketohexamethylenimine (IV), was dissolved in 45 ml. of dry benzene. To the stirred solution 7.4 g. (0.037 mole) of phosphorus pentachloride was added in small portions with intermittent cooling to keep the mixture at room temperature. When the phosphorus pentachloride had dissolved, 50 ml. of 10% solution of hydrazoic acid[10] in benzene was added during half an hour with continued stirring and cooling. After standing at room temperature for several hours the mixture was boiled under reflux for six hours when hydrogen chloride evolution had ceased. On cooling about 1 g. of solid separated and was identified as a mixture of the lactam and tetrazole. The benzene mother liquor was evaporated leaving an oily residue that solidified partially on standing under water in the refrigerator. The crude material was extracted repeatedly with boiling hexane from which 0.5 g. of the tetrazole separated on cooling, m.p. 79.5–80.5° after several crystallizations from hexane.

Anal. Calc'd for $C_9H_{16}N_4$: C, 60.0; H, 8.9; N, 31.1.

Found: C, 60.0, 60.0; H, 8.9, 9.1; N, 31.1, 31.2.

7-Ethyl-9-methylpentamethylenetetrazole (III). Using the procedure described for the isomer (II), 5 g. (0.032 mole) of lactam A, 4-ethyl-6-methyl-2-ketohexamethylenimine (V), was treated with 7.5 g. (0.037 mole) of phosphorus pentachloride and 50 ml. of 10% solution of hydrazoic acid in benzene to give 0.5 g. of the tetrazole, m.p. 87–88°, after several crystallizations from hexane.

Anal. Calc'd for $C_9H_{16}N_4$: C, 60.0; H, 8.9; N, 31.1.

Found: C, 60.0, 59.9; H, 9.1, 9.0; N, 31.3, 31.3.

Mixtures of the two isomeric tetrazoles showed melting points between those of the pure compounds. The melting point of a sample of the methylethylpentamethylenetetrazole of Harville, *et al.* (1), m.p. 85–86.5°, was not depressed on admixture of III but was lowered on admixture of II.

SUMMARY

Beckmann rearrangement of 3-methyl-5-ethylcyclohexanone oxime has been shown to give a mixture of lactams from which the isomeric 4-methyl-6-ethyl- and 4-ethyl-6-methyl-2-ketohexamethylenimines could be separated. The structures of the isomeric lactams were established by their conversion to ethyl 3,5-dimethylheptanoate and ethyl 3-ethyl-5-methylhexanoate, respectively. The two isomeric esters were synthesized by unequivocal reactions from 4-methyl-2-hexanone and ethyl isobutyl ketone, respectively. The isomeric lactams were also converted into 7-methyl-9-ethyl- and 7-ethyl-9-methyl-pentamethylenetetrazole. The latter has been shown to be identical with the methylethylpentamethylene-

[10] All operations involving hydrazoic acid should be conducted in a hood with good ventilation.

tetrazole obtained by interaction of 3-methyl-5-ethylcyclohexanone oxime with sodium azide and chlorosulfonic acid.

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