[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KENTUCKY]

THE BECKMANN REARRANGEMENT OF SOME HETEROCYCLIC KETOXIMES

CHARLES BARKENBUS, JOHANNES F. DIEHL, AND GEORGE R. VOGEL

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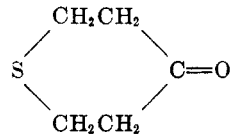
The recent work of Horning and Stromberg (1) has shown that polyphosphoric acid is an excellent reagent for the Beckmann rearrangement of ketoximes. Since this rearrangement works well with cyclohexanone oxime, a study of the activity of several heterocylic ketoximes under the same conditions has been made. Several ketoximes of some substituted piperidones have been subjected to the Beckmann rearrangement (2) but only 2,2,6,6-tetramethyl-1,4-piperidone oxime gave a lactam. Acetyl chloride was used as a catalyst and the yield was small. No other examples of heterocylic ketoximes having undergone this rearrangement could be found in the literature.

In this work the ketoximes of three types of heterocylic ketones, namely, tetrahydro-1,4-thiapyrone (I), tetrahydro-1,4-pyrone (II), and 1-methyl-1,4-piperidone (III) have been subjected to the Beckmann rearrangement using polyphosphoric acid as a catalyst.



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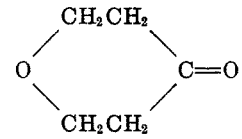

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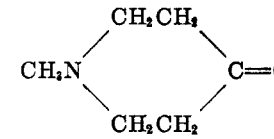
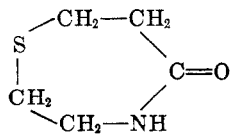


III

The particular oximes used were tetrahydro-1,4-thiapyrone oxime (IV), 2,6-diphenyltetrahydro-1,4-thiapyrone oxime (V), 1,1-dioxytetrahydro-1,4-thiapyrone oxime (VI), 2,6-dimethyltetrahydro-1,4-pyrone oxime (VII), and 1-methyl-1,4-piperidone oxime (VIII). These particular oximes were chosen because of their availability or relative ease of synthesis.

The conditions used by Horning and Stromberg (1) for the rearrangement of cyclohexanone were used in every case except that the lactams were extracted from the resulting acid solution by continuous extraction with chloroform over a period of 24 hours. Excellent yields of the corresponding lactams of ketoximes IV, V, and VII were obtained. These lactams are 1-thia-5-keto-4-azacycloheptane (IX), 1-thia-2,7-diphenyl-5-keto-4-azacycloheptane (X), and 1-oxa-2,7-dimethyl-5-keto-4-azacycloheptane.



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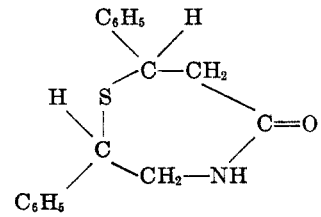

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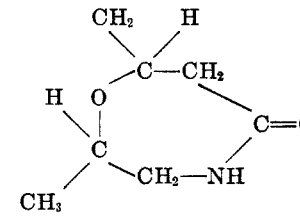

XI

TABLE I

LACTAMS

Lactam	M.P., °C	Yield, %	Analysis			
			Calc'd		Found	
			N	S	N	S
1-Thia-5-keto-4-azacycloheptane	115	85	10.69		10.57	
1 - Thia - 2,7 - diphenyl - 5 - keto - 4 - azacycloheptane	191–192	75		11.31		11.12
1 - Oxa - 2,7 - dimethyl - 5 - keto - 4 - azacycloheptane	126–127	70	9.78		9.50	

When oxime VI was used nothing could be extracted from the acid solution. No apparent decomposition took place during the rearrangement which would indicate that the lactam was probably formed, but was so soluble in water that it was not extractable with chloroform. No attempt was made to extract the neutralized water solution. Oxime VIII gave an intractible oil. Data concerning the lactams are listed in Table I.

In addition to the above ketoximes an attempt was made to prepare the oxime of 2,6-dimethyl-3-carbomethoxytetrahydro-1,4-thiapyrone. This β-ketoester is very resistive to hydrolysis and it was thought that it might form a stable oxime instead of reverting to an isoxazalone. However no product could be isolated except the unchanged β-ketoester.

The lactams were characterized by hydrolyzing them to the corresponding

TABLE II

AMINO ACIDS

Amino Acid	M.P., °C.	Yield, %	IpH	pK₁	pK₂	3,5-Dinitrobenzamides		Analysis			
						M.P., °C.	N.E.	Calc'd		Found	
								N	S	N	S
3 - (2 - Aminoethylmercapto)propanoic acid·HCl.	199 dec.	73.0						9.38		9.28	
3 - (2 - Aminoethylmercapto)propanoic acid	121–125	86.0	6.9	4.2	9.6	144	338	7.56		7.65	
3 - Phenyl - 3 - (1 - phenyl - 2 - aminoethylmercapto)-propanoic acid·HCl.	205–206 dec.	61.0							9.48		9.54
3 - Phenyl - 3 - (1 - phenyl - 2 - aminoethylmercapto)-propanoic acid	212–215 dec.	63.0	5.9	2.4	9.3	175–177	487		10.63		10.72
3 - (1 - Methyl - 2 - aminoethoxy)butanoic acid·HCl.	125–126	60.0						7.16		7.31	
3 - (1 - Methyl - 2 - aminoethoxy)butanoic acid.	189–191 dec.	68.0	6.8	3.8	9.9		350	8.69		8.43	

amino acids which in turn were converted to their hydrochlorides and 2,4-dinitrobenzoates. Electrometric titration of these acids established their pK values. The data for these amino acids are collected in Table II.

EXPERIMENTAL

Tetrahydro-1,4-thiapyrone oxime (IV). A mixture of the tetrahydro-1,4-thiapyrone (3) (20 g., 0.17 mole), 20 g. (0.30 mole) of hydroxylamine hydrochloride, and 40 g. (0.31 mole) of sodium acetate trihydrate in 200 ml. of water and 80 ml. of 95% alcohol was refluxed for three hours. One hundred ml. of solvent was distilled off and the residue chilled in an ice-bath to effect crystallization of the oxime. The crude oxime after filtration and drying in a vacuum desiccator over potassium hydroxide weighed approximately 20 g. (85–90%) and the melting point varied from 70–80°. Purification was effected by crystallization from a mixture of chloroform and Skellysolve A at −20° with a slight loss of material. The melting point of the pure oxime was 84–85°. The figures mentioned for the weight, yield and melting point of the crude oxime refer to a range of values obtained from several runs. The ketone, if impure, gives an oily oxime which is very difficult to crystallize.

2,6-Diphenyltetrahydro-1,4-thiapyrone oxime (V). A solution of 5 g. (0.019 mole) of 2,6-diphenyltetrahydro-1,4-thiapyrone (4) and 2.5 g. (0.036 mole) of hydroxylamine hydrochloride in 5 ml. of pyridine and 50 ml. of 95% alcohol was refluxed for two hours. Then 40 ml. of solvent was distilled off and 100 ml. of water was added to the residue. A white precipitate was formed which was filtered off, washed with 250 ml. of water, and air-dried. The dry solid was dissolved in chloroform, filtered, and the oxime precipitated by adding Skellysolve B to the solution. The crude oxime was crystallized two more times from this same solvent pair. Yield 4.35 g. (82%), m.p. 180°.

Anal. Calc'd for $C_{17}H_{17}NOS$: S, 11.31. Found: S, 11.14.

1,1-Dioxytetrahydro-1,4-thiapyrone oxime (VI). Tetrahydro-1,4-thiapyrone (10 g., 0.086 mole) was dissolved in 25 ml. of acetone in an Erlenmeyer flask and 25 ml. (0.22 mole) of 30% hydrogen peroxide was added in portions with shaking and cooling of the reaction mixture. After all the hydrogen peroxide had been added, the reaction mixture was shaken until it no longer evolved heat. Then it was allowed to stand for at least 24 hours. The mixture then was evaporated to dryness on a steam-bath under a current of air. The crude sulfone which remained as residue was dissolved in 200 ml. of water, 10 g. (0.144 mole) of hydroxylamine hydrochloride and 20 g. (0.147 mole) of sodium acetate trihydrate were added, and the mixture was refluxed for two hours. The solvent was removed by evaporation and the residue was extracted repeatedly with hot acetone. The extracts were evaporated to dryness and the oxime was recrystallized from methanol. The yield was 11 g. (80%) and the purified product melted with decomposition at 197.8°.

Anal. Calc'd for $C_5H_9NO_3S$: S, 19.53. Found: S, 19.59.

2,6-Dimethyltetrahydro-1,4-pyrone oxime (VII). Dehydroacetic acid was converted to 2,6-dimethyl-1,4-pyrone (5) which in turn was reduced to 2,6-dimethyltetrahydro-1,4-pyrone (6). The oxime was made from this ketone by the method of Borsche (7). The over-all yields were approximately those given in the literature.

1-Methyl-1,4-piperidone oxime (VIII). Dicarbomethoxyethylmethylamine, prepared by adding monomethylamine to methyl acrylate (8), was condensed to 1-methyl-1,4-piperidone with sodium (9). The oxime was made from this ketone by the method of Dickerman (2). The over-all yields were approximately those reported.

Preparation of the lactams. The method of Horning (1) was followed. In a 125-ml. Erlenmeyer flask was placed 2 g. (0.007 mole) of the oxime and 60 g. of polyphosphoric acid. The flask then was immersed in an oil-bath which previously had been heated to 115°. After the reaction mixture had reached 115° it was kept at this temperature for 15 minutes with constant stirring. The viscous liquid then was poured with stirring onto 200 g. of ice and the mixture was stirred until all had dissolved. This solution was extracted with chloroform in a continuous extractor for 24 hours. The chloroform solution was evaporated to about 10 ml.,

treated with charcoal and then, while keeping the solution near its boiling point, Skellysolve B was added drop by drop until a cloudiness developed. Then it was cooled and placed in a chest at −20° for 24 hours. The resulting crystals were filtered off and recrystallized from the same solvent pair.

The crude lactam obtained from 2,6-diphenyltetrahydro-1,4-thiapyrone oxime was insoluble in the acid solution and the thick viscous material was separated from the dilute acid by decantation. This material was soluble in pyridine from which it was precipitated as an amorphous solid by the addition of water. This solid was then crystallized from the above solvent pair.

Hydrolysis of the lactams to amino acid hydrochlorides. The lactam (2 g.) was refluxed for 4 hours with 10 ml. of concentrated hydrochloric acid and 15 ml. of water using an oil-bath heated to approximately 145°. The mixture was evaporated to dryness under reduced pressure. Then 50 ml. of water was added and again the mixture was evaporated to dryness. The white hydrochloride of the amino acid which remained was recyrstallized from methyl alcohol. The free amino acids were obtained by shaking a water solution of the hydrochlorides with silver oxide. After removing the silver chloride the silver salt was decomposed with hydrogen sulfide. Upon removal of the silver sulfide the solution was evaporated to dryness and the residue was crystallized from methyl alcohol.

The hydrochloride of 3-(1-methyl-2-amino ethoxy)butanoic acid failed to crystallize. It was made into the silver salt and the water solution of this salt was extracted several times with chloroform to remove unchanged lactam. The free amino acid was obtained on evaporating the water solution after removing the silver with hydrogen sulfide. The free amino acid was then converted to its hydrochloride.

SUMMARY

It has been shown that certain heterocyclic ketoximes undergo the Beckmann rearrangement in a manner similar to cyclohexanone oxime in the presence of polyphosphoric acid. Tetrahydro-1,4-thiapyrone oxime, 2,6-diphenyltetrahydro-1,4-thiapyrone oxime, and 2,6-dimethyltetrahydro-1,4-pyrone oxime rearrange smoothly to their corresponding lactams. These lactams were hydrolyzed to interesting amino acids which were characterized. 1-Methyl-1,4-piperidone oxime failed to give the expected lactam.

LEXINGTON, KENTUCKY

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