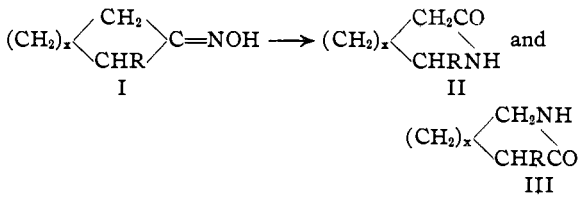
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Beckmann Rearrangement of Certain 2-Alkyl Cyclopentanone and Cyclohexanone Oximes[1,2]

BY JOHN G. HILDEBRAND, JR.,[3] AND MARSTON TAYLOR BOGERT

In the Beckmann rearrangement of 2-alkyl cyclanone oximes the formation of two structural isomers is possible,



It is of some importance, therefore, to discover which course this transformation takes.

The experiments recorded in the present paper concerned only the 2-methyl-, 2-ethyl- and 2-*n*-propylcyclopentanones, and 2-methylcyclohexanone. They indicated that the product in every case was that represented by (II). No evidence was obtained of the formation of any of the isomer (III).

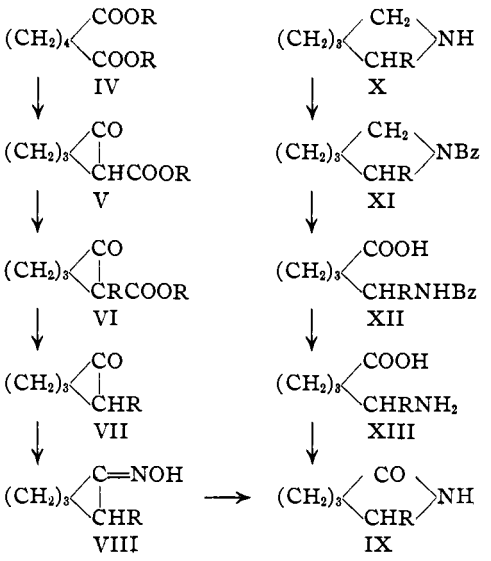
The steps followed in gathering this evidence are shown in the accompanying Flow Sheet.

In the cyclopentanone series (IV–XIII), ethyl adipate (IV), in toluene solution, was treated with sodium and dilute acetic acid. The carbethoxycyclopentanone (V) so obtained was in turn converted into its sodio derivative and alkylated in benzene suspension, giving (VI). Hydrolysis of this with dilute hydrochloric acid yielded (VII), whose oxime (VIII) was then rearranged, by the action of sulfuric acid, to (IX).

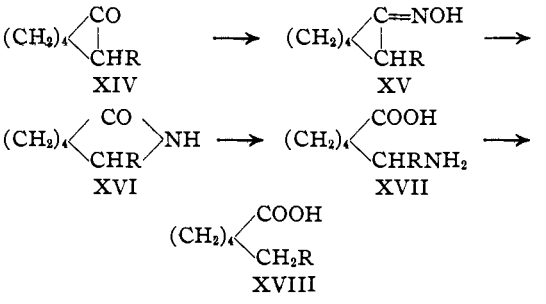
All of these lactams (IX) were proved by analysis to be isomeric with the corresponding alpha-alkyl homopiperidinic lactams (III) synthesized by Aschan,[4] but melted 20–30° higher. In further support of our conclusion concerning the constitution of (IX), benzoylhomoconic acid (XII) was prepared, by the oxidation of benzoylconiine (XI), and hydrolyzed to homoconic acid (XIII). The latter, when heated a few degrees above its m. p., yielded a lactam identical with that formed by the rearrangement of 2-*n*-propylcyclopentanone oxime.

FLOW SHEET

CYCLOPENTANONES



CYCLOHEXANONES



This rearrangement of the 2-alkylcyclopentanone oximes may occasionally prove of service for the preparation of amino acids not easily obtainable by other methods.

In the cyclohexanone series (XIV–XVIII), the product (XVI) obtained by the rearrangement of 2-methylcyclohexanone oxime (XV), on hydrolysis yielded an amino acid (XVII) which, when heated in a sealed tube with concentrated hydriodic acid, gave enanthic (XVIII) (identified by its *p*-phenylphenacyl ester) and unchanged initial amino acid.

The only 2-alkylcyclanone oxime hitherto sub-

(1) Based upon the dissertation submitted by J. G. Hildebrand, Jr., May, 1933, for the Ph.D. degree, under the Faculty of Pure Science, Columbia University, New York, N. Y., to which dissertation the reader is referred for further experimental details and literature citations.

(2) Presented in abstract before the Division of Organic Chemistry, at the St. Petersburg (Fla.) Meeting of the American Chemical Society, March 27, 1934.

(3) Lydia C. Roberts Fellow at Columbia University, 1929–1930 and 1931–1932.

(4) (a) Aschan, *Ber.*, **23**, 3692 (1890); (b) **24**, 2443 (1891).

jected to this transformation was this same 2-methylcyclohexanone oxime, which yielded a lactam, m. p. 90–91°, not identified by Wallach[5] at the time, but which we have now shown to possess the constitution (XVI). He showed also that the action of dilute sulfuric acid upon 4-methylcyclohexanone oxime converted it into the lactam of 4-methyl-6-aminopentane-1-carboxylic acid.

Acknowledgments.—Our grateful thanks are tendered to the trustees of the Joseph Henry Fund of the National Academy of Sciences for financial assistance in meeting the expense of the analytical work necessary to complete this investigation. We are also under obligations to Dr. I. Gubelmann, at the time Vice President of the Newport Company, Carrollville, Wisconsin, for a generous supply of cyclohexanone.

Experimental

Unless otherwise stated, all melting points determined by us are corrected and were taken while the temperature was being raised at the rate of 3° per minute.

2-Carbethoxycyclopentanone (V) was prepared from ethyl adipate and sodium, by the Dieckmann[6] process, with a number of improvements in experimental details, including the use of a specially designed expansible mechanical stirrer, which improved considerably the efficiency of the reaction.

2-Alkyl-2-carbethoxycyclopentanones (VI).—The sodio derivative of the ester (V) was alkylated in the usual way.[6g,7] The methyl and ethyl derivatives obtained agreed in properties with those recorded by other investigators,[7] except that we found the corrected melting points of their semicarbazones slightly higher: 2-methyl, m. p. 153–154°, literature 152–153°; 2-ethyl, m. p. 148.5–149.5°, literature 148–149°.

The 2-*n*-propyl derivative apparently has not been described hitherto. It formed a colorless liquid, b. p. 136.5–138° at 28 mm.; yield, 85.6%.

Anal. of semicarbazone, m. p. 160–161°. Calcd. for $C_{12}H_{21}O_3N_3$: C, 56.42; H, 8.29. Found: C, 56.21; H, 8.10.

2-Alkylcyclopentanones (VII).—The alkylated esters (VI), when hydrolyzed with concentrated hydrochloric acid, yielded the corresponding 2-alkylcyclopentanones, all of which were known previously, as well as their semicarbazones. Our products were checked by the melting points and analyses of the semicarbazones.

The oximes, prepared in the customary way from these three 2-alkylcyclopentanones and from 2-methylcyclohexanone, have been reported before, with the exception of the **2-*n*-propylcyclopentanone oxime,** which was obtained in 88% yield, b. p. 116–117.5° at 7 mm., 120–121.5° at 13 mm.

Anal. Calcd. for $C_8H_{15}ON$: C, 68.01; H, 10.71. Found: C, 68.27; H, 10.80.

Rearrangement of the Oximes.—The most satisfactory procedure for the transformation of the oximes was found to be the carefully controlled heating of a solution of the oxime in sulfuric acid of the proper strength and concentration, for the rearrangement is a function of both the strength of acid and the temperature used.

The cyclopentanone oximes proved to be much more readily transformed by sulfuric acid, and their sulfuric acid solutions more sensitive to oxidation at temperatures above normal, than the cyclohexanone oximes. Hence, weaker acids were found preferable for the former. A comparison of the yields of lactams, depending upon the strength of acid used, is shown below for the oximes studied.

PERCENTAGE YIELDS OF LACTAMS

	H_2SO_4, %				
Oxime	75	80	85	90	96.4
2-Me-cyclopent.	76	63	61		
2-Et-cyclopent.		60			
2-*n*-Pr-cyclopent.		59			
Cyclohex.	80	87	89	95	97
2-Me-cyclohex.			88	93	97

Wallach[8] and Ruzicka[9] have both employed sulfuric acid to accomplish such rearrangements, but did not work out the careful control of temperature, strength of acid and duration of heating required to obtain the yields recorded above. In the case of cyclohexanone oxime, for example, the yield of lactam reported by Wallach[8b] was 60%, by Ruzicka[9] 66%.

6-Methyl-2-piperidone (IX).—The following will illustrate our method of effecting this rearrangement.

A solution of 10 g. of 2-methylcyclopentanone oxime in 15 cc. of sulfuric acid of the proper strength (in this case, 75%) was placed in a dropping funnel at the top of a specially designed hollow mechanical stirrer inserted in a flask containing 5 cc. of sulfuric acid of the same strength (see figure). The flask was heated to approximately 108°, the stirrer placed in operation, and the oxime solution run in very slowly. When all had been added, the flask was allowed to cool to room temperature, the contents rinsed into a small beaker with an equal volume of water, 2 g. of animal charcoal added and the mixture filtered. The filtrate was made alkaline to litmus with strong (40–50%) sodium hydroxide solution. Ammonia was evolved during this neutralization, probably originating from ammonium sulfate formed by hydrolysis of some of the oxime by the sulfuric acid, for small amounts of the ketone were isolated among the products of the reaction.

The faintly alkaline filtrate was diluted to 215 cc. and extracted for five hours with chloroform in a Palkin[10] continuous extractor. The chloroform extract was filtered,

(5) Wallach, *Ann.*, **346**, 252 (1906).

(6) (a) Dieckmann, *Ber.*, **27**, 103 (1894); (b) Wislicenus and Schwanhauser, *Ann.*, **297**, 112 (1897); (c) Bouveault, *Bull. soc. chim.*, [3] **21**, 1019 (1899); (d) Dieckmann, *Ann.*, **317**, 27 (1901); (e) Bouveault and Locquin, *Bull. soc. chim.*, [4] **3**, 437 (1908); (f) Dobson, Ferns and Perkin, *J. Chem. Soc.*, **95**, 2015 (1909); (g) Van Ryselberge, *Bull. sci. acad. roy. Belg.*, [5] **12**, 171 (1920); (h) Cornubert and Borrel, *Bull. soc. chim.*, [4] **47**, 301 (1930); (i) Drake and Bronitsky, THIS JOURNAL, **52**, 3715 (1930).

(7) Case and Reid, *ibid.*, **50**, 3062 (1928).

(8) (a) Wallach, *Ann.*, **309**, 1 (1899); (b) **312**, 171 (1900).

(9) Ruzicka, *Helv. Chim. Acta*, **4**, 472 (1921).

(10) Palkin, Murray and Watkins, *Ind. Eng. Chem.*, **17**, 613 (1925).

the solvent removed and the residue distilled at 28 mm. pressure.

The first fraction (b. p. 80–140°) (1.6 g.) contained approximately 0.7 g. of 2-methylcyclopentanone, 0.5 g. of the lactam, and a small quantity of unidentified material.

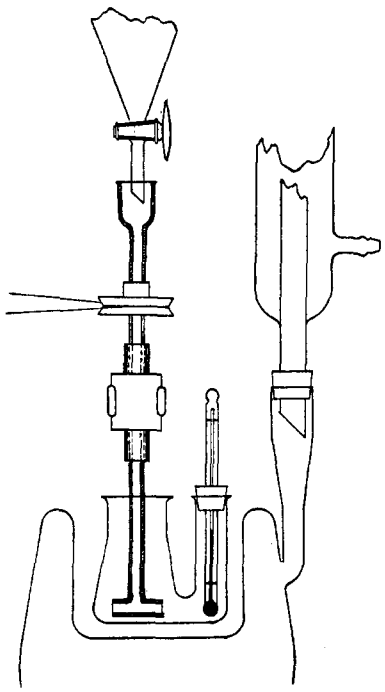


Fig. 1.

The second fraction (b. p. 140–148°) (7.1 g.) crystallized as it cooled and melted at 87.2–88°. Hydrolyzed under pressure with hydrochloric acid (20%), it gave a difficultly crystallizable compound which exhibited the properties of an amino acid hydrochloride. Dissolved in water, the solution shaken with silver oxide, filtered, the filtrate treated with hydrogen sulfide, again filtered and the filtrate concentrated at 100°, there was obtained a crystalline compound which rapidly lost water at 100°, with regeneration of the original lactam (m. p. 88–89°).

6-Ethyl-2-piperidone, prepared similarly, melted at 88.5–89.6° (corr.).

Anal. Calcd. for $C_7H_{13}ON$: C, 66.09; H, 10.31. Found: C, 66.48; H, 10.30.

Its behavior with hydrochloric acid, etc., was like that of the 6-methyl homolog.

6-*n*-Propyl-2-piperidone, m. p. 91.5–92.4°.

Anal. Calcd. for $C_8H_{15}ON$: C, 68.01; H, 10.71. Found: C, 68.35; H, 10.60.

Like its methyl and ethyl homologs, it could be hydrolyzed by hydrochloric acid to an amino acid hydrochloride, the amino acid from which lost water readily at 100°, with regeneration of the original piperidone.

That this compound actually possessed the structure assigned (IX), and not that of the isomeric alpha-*n*-propylhomopiperidinic lactam (III) synthesized by Aschan,[4] was proved by the synthesis of our product also through the steps stated in the introductory portion of this paper.

This independent synthesis involved the preparation of homoconic acid (XIII), essentially as described by Schotten[11] and by Baum,[12] through oxidation of benzoylconiine (XI) with potassium permanganate to benzoylhomoconic acid (XII) and hydrolysis of the latter with concentrated hydrochloric acid in a sealed tube. Our product melted at 156–158.5° (corr.). Baum[12] reported a melting point of 158°. Heated for fifteen minutes at about 165°, it lost water, with formation of a lactam, apparently identical (mixed m. p., etc,) with the propylpiperidone we obtained by the rearrangement of 2-*n*-propylcyclopentanone oxime.

Anal. (of the lactam) Calcd. for $C_8H_{15}ON$: C, 68.01; H, 10.71. Found: C, 68.30; H, 10.53.

5-Aminohexane-1-carboxylic Lactam (XVI).—Prepared from 2-methylcyclohexanone oxime, this lactam separated from ligroin in small colorless crystals, m. p. 90.5–91.5°. Wallach,[5] by a similar reaction, apparently obtained the same product and gave its m. p. as 90–91°, but did not identify it.

Anal. of our product. Calcd. for $C_7H_{13}ON$: C, 66.09; H, 10.31. Found: C, 66.34; H, 10.56.

5-Aminohexane-1-carboxylic acid (XVII) was prepared from the above lactam in the same way as the amino acid from 6-methyl-2-piperidone; yield, practically that calculated. It formed small colorless crystals (from water), m. p. 196–197.5° (corr.); and was best purified by solution in hot 96% ethanol, cooling, and precipitating by addition of anhydrous ether.

Anal. Calcd. for $C_7H_{15}O_2N$: C, 57.87; H, 10.40. Found: C, 58.24; H, 10.90.

Hexane-1-carboxylic Acid (Enanthic Acid) (XVIII).—The deamination of the above acid was accomplished by the method of Kwisda,[13] using 96% hydriodic acid under pressure, and the product was identified as enanthic acid, through its *p*-phenylphenacyl ester, following the procedure of Drake and Bronitsky.[6i]

Summary

1. The rearrangement of 2-alkyl cyclopentanone and cyclohexanone oximes by sulfuric acid, yields in the former case 6-alkyl-2-piperidones; and in the latter, the corresponding lactams of 5-amino-5-alkylpentane-1-carboxylic acid.

2. The constitution of the piperidones was established by proving that the transformation product of 2-*n*-propylcyclopentanone oxime was identical with the lactam of homoconic acid.

3. The structure of the lactam resulting from the rearrangement of 2-methylcyclohexanone oxime was ascertained by hydrolysis to the corresponding amino acid and production of enanthic acid therefrom by deamination.

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(11) Schotten, *Ber.*, **17**, 2548 (1884).
(12) Baum, *ibid.*, **19**, 500 (1886).
(13) Kwisda, *Monatsh.*, **12**, 419 (1891).