Beckmann Rearrangements in Alicyclic Systems. III. 2,2-Dimethylcycloalkanone Oximes[1,2]

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Received January 15, 1962

The Beckmann rearrangement of 2,2-dimethylcyclopentanone, cyclohexanone, and cycloheptanone oximes has been examined. With either phosphorus pentachloride or thionyl chloride these oximes were cleaved to unsaturated nitriles. Only in the rearrangement of 2,2-dimethylcyclohexanone oxime on treatment with benzenesulfonyl chloride or thionyl chloride was the lactam expected from normal rearrangement obtained. With polyphosphoric acid, the oximes rearranged to α,β-unsaturated ketones; 2,2-dimethylcyclopentanone oxime gave 3-methyl-2-cyclohexenone, 2,2-dimethylcyclohexanone oxime gave a mixture of 2-isopropyl-2-cyclopentenone and 2-isopropylidene cyclopentanone, and 2,2-dimethylcycloheptanone oxime yielded a mixture of 2-isopropyl-2-cyclohexenone and 2-isopropylidene cyclohexanone. In the last case the product of polyphosphoric acid rearrangement was the saturated amide, 7-methyloctanamide. The unsaturated nitriles were shown to cyclize under conditions similar to those use in the polyphosphoric acid oxime rearrangements to the α,β-unsaturated ketones.

In several previous reports, the rearrangements of a series of spiroketoximes[3] and 2,2-diphenylcycloalkanone oximes[4] have been described. Polyphosphoric acid rearrangements of these oximes resulted in the formation of products usually not encountered in Beckmann rearrangements. For example, heating the oxime of spiro[4.5]decanone-1 at 125° for ten minutes did not yield the substituted lactam nor did this reaction result in the formation of the unsaturated nitrile from oxime fragmentation. Rather Δ^9-octalone-1, an α,β-unsaturated ketone, was formed in high yield. Alternately, the attempted rearrangement of the oxime using phosphorus pentachloride cleaved the oxime to 4-(1'-cyclohexenyl)butyronitrile. Heating the unsaturated nitrile under the conditions utilized in the rearrangement in polyphosphoric acid resulted in the formation of the α,β-unsaturated ketone. Extensions of rearrangements of this type have been reported in which the spiro-substituted alicyclic ring has been replaced by *gem*-diphenyl groups. In this latter study,[4] the size of the cycloalkyl ring was shown to affect markedly the products of the oxime rearrangements.

In view of these results, it was of interest to extend further the study of abnormal rearrangements under a variety of catalytic conditions using simple 2,2-dialkyl-substituted cycloalkanone oximes. It was anticipated that additional information concerning the effect of varied substituents and varied ring size would assist in the elucidation of the scope and limitations of these unusual rearrangements. The study reported here was undertaken to examine specifically the rearrangement characteristics of 2,2-dimethylcyclopentanone, 2,2-dimethylcyclohexanone, and 2,2-dimethylcycloheptanone oximes under a variety of rearrangement conditions.

The syntheses of the ketones followed previously reported routes.[5-7] All of the ketones were oximated in high yield using pyridine–ethanol mixtures, and only one pure oxime was formed from each ketone. The configuration with the hydroxyl *trans* to the *gem*-dimethyl group was anticipated for each on steric grounds and is substantiated by the products of the rearrangement.

Rearrangement of the Oximes.—The rearrangement of 2,2-dimethylcyclohexanone oxime was studied most extensively. On treatment of this oxime with phosphorus pentachloride an almost quantitative yield of 6-methyl-5-heptenonitrile was obtained. The cyano group was distinguished by its infrared absorption and the compound was identified by hydrolysis to the unsaturated acid followed by reduction to the saturated acid and conversion of the acid to the known 6-methylheptanamide. The position of the double bond was determined by ozonolysis to give as one of the products acetone, identified by comparison of its dinitrophenylhydrazone with an authentic sample. Using thionyl chloride considerable tarring of the reaction mixture occurred. By chromatography over alumina, the lactam, 2-keto-7,7-dimethylhexamethyleneimine was obtained. The unsaturated nitrile although present was not isolated from the remaining viscous black resin. A more suitable catalyst for the preparation of the lactam, although still contaminated with an appreciable amount of the unsaturated nitrile, was found when

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[1] This work was supported by a Frederick Gardner Cottrell grant from the Research Corporation and grants #B-2239 and B-3628 from the Department of Health, Education, and Welfare, Public Health Service.

[2] This work was presented in part at the 136th National American Chemical Society Meeting, Atlantic City, New Jersey, 1959.

[3] (a) R. K. Hill and R. T. Conley, *Chem. Ind.* (London), 1314 (1956); (b) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960); (c) R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

[4] R. T. Conley and B. E. Nowak, *ibid.*, **27**, 1965 (1962).

[5] R. T. Conley, *Rec. trav. chim.*, **81**, 198 (1962).

[6] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 2753 (1954).

[7] P. D. Bartlett and A. Bavley, *ibid.*, **60**, 2416 (1938).

benzenesulfonyl chloride and sodium hydroxide were employed to effect the rearrangement. 6-Methyl-5-heptenonitrile was isolated from the crude yellow reaction product in 27% yield while the lactam could be obtained in 54% yield by chromatographic techniques.

Since the lactam could be obtained effectively from both thionyl chloride and benzenesulfonyl chloride treatment of the oxime, it was anticipated that this product would also be found among the products of polyphosphoric acid rearrangement of the oxime. However, rearrangement with polyphosphoric acid resulted in the formation in high yield of two α,β-unsaturated ketones, 2-isopropyl-2-cyclopentenone and 2-isopropylidenecyclopentanone. These ketones were characterized by their infrared spectra, ultraviolet spectra, and the formation of 2,4-dinitrophenylhydrazone derivatives, identical in all respects with authentic samples.

The oxime of 2,2-dimethylcyclopentanone behaved in an analogous manner. Phosphorus pentachloride transformed the oxime almost quantitatively to 5-methyl-4-hexenonitrile. The identity of the nitrile was established by ozonolysis to acetone. The carbon skeleton of the nitrile was established by hydrolysis to the corresponding acid which took up one mole of hydrogen on catalytic hydrogenation with Adams' catalyst to yield 5-methylhexanoic acid, identified by conversion to the known 5-methylhexanamide. Polyphosphoric acid rearranged the oxime in low yield to 3-methyl-2-cyclohexenone. No other products could be isolated from the reaction product mixture by column chromatography. The ketone was identified by its characteristic infrared spectrum, ultraviolet spectrum, and scarlet 2,4-dinitrophenylhydrazone whose identity was confirmed by mixed melting point with a synthetic sample.

Similarly, the rearrangement of 2,2-dimethylcycloheptanone oxime using thionyl chloride produced a high yield of 7-methyl-6-octenonitrile which was characterized by conversion to the known unsaturated amide. The structure was confirmed, as well, by ozonolysis and reduction to the known saturated amide. Polyphosphoric acid rearrangement of the oxime resulted in the formation in low yield of two ketones which were homologous to those obtained from the rearrangement of 2,2-dimethylcyclohexanone oxime, namely, 2-isopropyl-2-cyclohexenone and 2-isopropylidene cyclohexanone. These ketones were characterized by their typical infrared and ultraviolet spectra and previously described 2,4-dinitrophenylhydrazone derivatives. In contrast, however, the major product of the rearrangement was found to be 7-methyloctanamide. The identity of the amide was established by mixed melting point determinations with both the unsaturated amide, obtained from the thionyl chloride oxime cleavage product, and its reduction product. The former depressed on melting the mixture while the latter showed no depression.

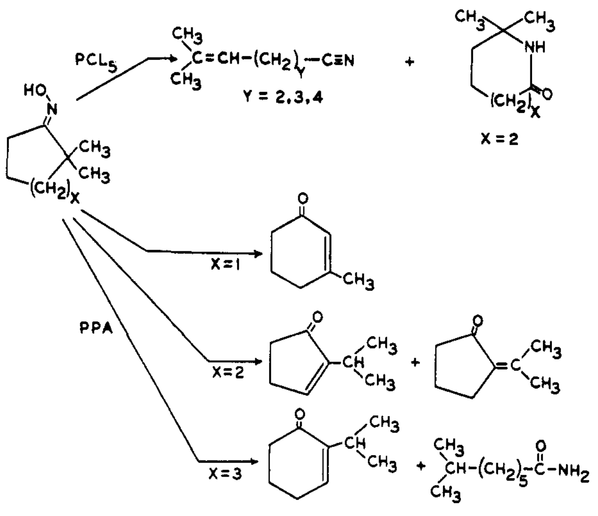

Figure 1

A reasonable mechanism for these reactions is illustrated for 2,2-dimethylcyclohexanone oxime in Fig. 1. As in all Beckmann rearrangements, the reaction is initiated by protonation or esterification of the oxime hydroxyl. Dissociation of the N—O bond to form the azacyclopropene intermediate or transition state followed by collapse of this transition state in the normal rearrangement would be expected to yield the lactam. Competing with this process, the stabilization imparted to a positive charge located on the α-carbon might be expected to promote dissociation of the intermediate to the nitrile and carbonium ion fragments. Loss of a proton from this ion forms the unsaturated nitrile.

Since the rearrangement products formed are markedly dependent upon the environment, this mechanism seems most suitable since the processes described by which the nitrile and lactam are produced would be expected to be sensitive to the environmental effects imparted to the system by both the catalyst and solvent systems. In contrast to the two primary products of oxime rearrangement, under appropriate conditions it might be expected that the unsaturated nitrile might react further. In earlier studies the hydration of the cleaved fragment was described[8]; however, the relationship of the nitrile with the double bond if suitable could result in cyclization to an initial α,β-unsaturated imine.[4] On hydrolysis, the formation of the ketone would be expected. In further confirmation of the correctness of initial unsaturated nitrile formation, the unsaturated nitriles obtained from the thionyl chloride or phosphorus pentachloride rearrangements were cyclized in hot polyphosphoric acid (rearrangement conditions) to produce the α,β-unsaturated ketones. The

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[8] (a) R. T. Conley and F. A. Mikulski, *Tetrahedron*, **5**, 90 (1958); (b) R. T. Conley and F. A. Mikulski, *J. Org. Chem.*, **24**, 97 (1959).

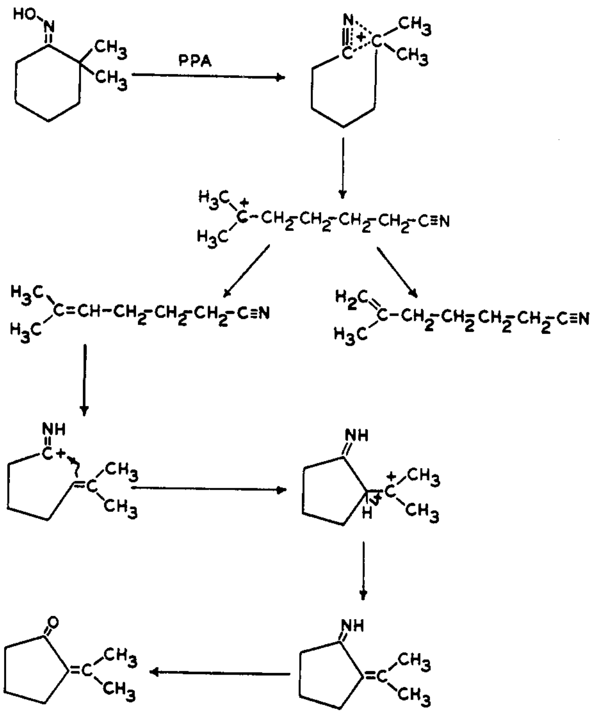

Figure 2

possibility of initial hydration to the amide has been excluded previously.[9] This is even more reasonable if examples reported earlier[3,4] are considered together with the present results. Examples of four-membered ring formation are noticeably absent in these studies.[10] Further, those reactions resulting in seven-membered ring formation usually give minor amounts of α,β-unsaturated ketones[3b] or none at all.[3c] Therefore, it is consistent to propose the rather ready cyclizations of the unsaturated nitriles as an independent, medium-induced process which stems from the oxime cleavage product.

These studies also cast some doubt on the validity of the accepted classification of normal and abnormal Beckmann rearrangement[11] or analogous classifications.[12] Since the cleavage process is apparently dependent upon the structural characteristics of the oximino compound involved and the catalyst-solvent system as they affect the stability and direction of collapse of the transition state, it would seem far more realistic to incorporate these ideas into a single mechanistic description of the reaction which includes such oxime behavior as observed in the Neber reaction[13,14] and the Wolff aromatization[15] of oximes.

It should also be noted that in each case where the unsaturated nitrile cyclizations in polyphosphoric acid are not particularly favorable—for example, in those cases where double bond migration to an *exo* position to a six-membered ring or to a less stable chain position is required prior to cyclization—an unusual product for Beckmann rearrangements has been observed repeatedly. In these cases, a saturated amide has been isolated as the major reaction product. In this study, this amide was the major reaction product from the polyphosphoric acid-catalyzed rearrangement of 2,2-dimethylcycloheptanone oxime. Isolation of an amide under these conditions is not surprising; however, the amide should have been unsaturated. The manner by which this product arises is presently under study.

Experimental

All melting points were taken using the capillary method and are uncorrected. The infrared spectra used for comparison were recorded using a Baird, Model AB-2, or a Beckman IR-4 recording spectrophotometer with sodium chloride optics. The ultraviolet spectra were obtained using a Beckman DK-2A recording spectrophotometer. All ultraviolet spectra were determined on samples in ethanol solution. All vapor phase chromatographic data were collected using a Perkin-Elmer, Model 154-C, Vapor Fractometer equipped with a Perkin-Elmer *R*-column (Ucon polyglycol LB-550-X).

Reactants.—2,2-dimethylcyclopentanone was prepared by the pinacol rearrangement of 1-(1′-hydroxycyclobutyl)dimethylcarbinol.[5] Additional quantities were obtained by the oxidation of 2,2-dimethylcyclohexanone to 2,2-dimethyladipic acid using nitric acid followed by barium oxide cyclization to the ketone[6] and by the pinacol rearrangement of *cis*-1,2-dihydroxy-1,2-dimethylcyclopentane.[7] 2,2-Dimethylcyclohexanone was obtained by the pinacol rearrangement of 1-(1′-hydroxycyclopentyl)dimethylcarbinol.[16] In similar fashion 2,2-dimethylcycloheptanone was isolated from the acid catalyzed rearrangement of 1-(1′-hydroxycyclohexyl)dimethylcarbinol.[17] All oximes were prepared by the method described by Cram.[6]

Beckmann Rearrangements. I. 2,2-Dimethylcyclopentanone Oxime. (a) With Phosphorus Pentachloride.—To a mixture of 2.2 g. of phosphorus pentachloride and 32 ml. of anhydrous ether, 1.00 g. (0.0076 mole) of 2,2-dimethylcyclopentanone oxime was added in small portions over a 15-min. period. During the addition the reaction vessel was cooled in an ice bath. After the addition of the oxime, the ice was allowed to melt and the mixture slowly warmed to room temperature. After 24 hr., the ether was evaporated and 50 ml. of water added to the residual oil. The aqueous solution was extracted five times with 25-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 0.80 g. (94%) of light yellow 5-methyl-4-hexenonitrile. The infrared spectrum of the oil indicated the characteristic

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[9] R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957).

[10] It should be noted that the ketones isolated from unsaturated nitrile cyclization are the same as those obtained from the corresponding unsaturated acid cyclizations by polyphosphoric acid. See ref. 18b. Similar results have also been observed in correlative studies of the Schmidt reaction; see R. T. Conley and B. E. Nowak, *ibid.*, **26**, 692 (1961).

[11] A. H. Blatt, *Chem. Rev.*, **12**, 215 (1933).

[12] (a) A. F. Ferris, *J. Org. Chem.*, **24**, 580 (1959); (b) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

[13] For examples see: (a) P. W. Neber and A. V. Friedholshein, *Ann.*, **449**, 109 (1926); (b) P. W. Neber and A. Uber, *ibid.*, **467**, 52 (1928); (c) P. W. Neber and A. Burgard, *ibid.*, **493**, 281 (1932).

[14] For a discussion of the mechanism see: D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33, 38 (1953).

[15] For examples see: (a) F. W. Semmler, *Ber.*, **25**, 3352 (1892); (b) L. Wolff, *Ann.*, **322**, 351 (1902); (c) G. Schroeter, *Ber.*, **63**, 1308 (1930); (d) A. Hardy, E. R. Ward, and L. A. Day, *J. Chem. Soc.*, 1979 (1956); (e) H. E. Zaugg, M. Freifelder, and B. W. Horrom, *J. Org. Chem.*, **15**, 1197 (1950); M. V. Blatt, *Experentia*, **13**, 70 (1957).

[16] R. Kuhn and A. Winterstein, *Ber.*, **67**, 354 (1934).

[17] H. Meerwein and J. Schafer, *J. prakt. Chem.*, **104**, 289 (1922).

nitrile absorption at 4.45 μ. The nitrile was purified by chromatography over an alumina column in ether. Fractions 3–12 were combined and evaporated to give 0.68 g. (80%) of pure 5-methyl-4-hexenonitrile, b.p. 89–91°/8 mm.

Anal. Calcd. for $C_7H_{11}N$: C, 77.63; H, 9.89; N, 12.49. Found: C, 77.60; H, 9.87; N, 12.59.

Hydrolysis of 5-Methyl-4-hexenonitrile.—A mixture of 0.30 g. of 5-methyl-4-hexenonitrile, 1 g. of potassium hydroxide, 5 ml. of water, and 5 ml. of 95% ethanol was heated at reflux for 16 hr. The ethanol was evaporated *in vacuo* and an equal volume of water added to the residual solution. The mixture was extracted once with 10 ml. of ether to remove unchanged nitrile. The aqueous solution was cooled and acidified with cold 10% hydrochloric acid. The mixture was extracted five times with 10-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 0.24 g. of a crude yellow oil. The oil was transferred to a single bulb micro still and a few drops of 5-methyl-4-hexenoic acid distilled for combustion analysis at 98–100°/5 mm., $n^{20}D$ 1.4462 (lit.[18a] b.p. 98–99°/5 mm., $n^{20}D$ 1.4470).

Anal. Calcd. for $C_7H_{12}O_2$: C, 66.38; H, 9.22. Found: C, 66.22; H, 9.22.

Ozonolysis of 5-Methyl-4-hexenoic Acid.—A solution of 0.08 g. of 5-methyl-4-hexenoic acid in 15 ml. of glacial acetic acid was ozonized with a stream of oxygen containing 4% ozone. Water (10 ml.) was added and oxygen bubbled through the solution for 10 min. The solution was made alkaline with dilute sodium hydroxide and extracted three times with 10-ml. portions of ether. The ether extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and treated with 2,4-dinitrophenylhydrazine reagent, yielding acetone 2,4-dinitrophenylhydrazone, m.p. 124.5–126°, undepressed by mixing with an authentic sample.

Reduction of 5-Methyl-4-hexenoic Acid.—A mixture of 0.08 g. of 5-methyl-4-hexenoic acid, 0.010 g. of platinum oxide (Adams' catalyst), and 20 ml. absolute ethanol was hydrogenated at 60 p.s.i.g. for 5 hr. The apparatus was vented and the solution filtered and evaporated. The crude acid was taken up in 40 ml. of benzene. The volume was reduced to 20 ml. by distillation to be sure the benzene solution was dry. Oxalyl chloride (0.1 ml.) was added and the mixture refluxed for 1 hr. on a steam bath. On cooling, the benzene was evaporated *in vacuo*. The residue was dissolved in anhydrous benzene, cooled, and treated with anhydrous ammonia. After 20 min., the benzene solution was evaporated to dryness and the light brown solid residue recrystallized from ethyl acetate–petroleum ether to give 0.04 g. of 5-methylhexanamide, m.p. 104–104.5° (lit.[19] 103.5–104°).

(b) **Using Polyphosphoric Acid.**—A mixture of 2.00 g. (0.015 mole) of 2,2-dimethylcyclopentanone oxime and 27 g. of polyphosphoric acid was heated with manual stirring at 125–130°. After 12 min., the contents of the reaction vessel were hydrolyzed over crushed ice. The aqueous mixture was made alkaline with 10% sodium hydroxide. The odor of ammonia was detectable above the alkaline solution. The mixture was extracted four times with 50-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a black semisolid tar. Column chromagraphy of the viscous tar over a petroleum ether packed, alumina column resulted in the isolation of a single component. Fractions 7–13 were evaporated to yield 0.76 g. of a crude yellow oil which was identical in spectral properties to 3-methyl-2-cyclohexenone. The oil was distilled *in vacuo* to give 0.54 g. (32%) of the purified ketone, b.p. 69–73° /3 mm. (lit.[20] b.p. 68–71° /3 mm.), λ_{max} 224 mμ, log ε 4.12 (lit.[18b] λ_{max} 224 mμ, log. ε 4.13).

Anal. Calcd. for $C_7H_{10}O$: C, 76.95; H, 8.91. Found: C, 76.82; H, 8.70.

The 2,4-dinitrophenylhydrazone was prepared using the sulfuric acid–ethanol procedure, to give a deep red precipitate. After two recrystallizations from chloroform–methanol, scarlet plates were obtained, m.p. 180.5–181.5° (lit.[3b,18b] m.p. 178–179° and 181–182°, respectively), with no melting point depression on admixture with an authentic sample.

Cyclization of 5-Methyl-4-hexenonitrile in Polyphosphoric Acid.—A mixture of 0.30 g. of 5-methyl-4-hexenonitrile and 8.0 g. of polyphosphoric acid was heated at 125–130° for 20 min. The mixture was hydrolyzed and worked up as described previously. The crude products were treated with 2,4-dinitrophenylhydrazine reagent directly to yield after three recrystallizations, 3-methyl-2-cyclohexenone 2,4-dinitrophenylhydrazone, m.p. 180–181.5° undepressed when mixed with an authentic sample.

II. 2,2-Dimethylcyclohexanone Oxime. (a) With Phosphorus Pentachloride.—To a mixture of 2.2 g. of phosphorus pentachloride and 32 ml. of anhydrous ether 1.00 g. (0.0071 mole) of 2,2-dimethylcyclohexanone oxime was added in small portions over a 15-min. period. The reaction mixture was mixed by swirling and maintained at 0° during the addition of the oxime by external cooling in an ice bath. The mixture was allowed to stand for 24 hr. at room temperature. The ether was evaporated and 50 ml. of water added to the residue. The aqueous solution was extracted five times with 25-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 0.86 g. (98%) of 6-methyl-5-heptenonitrile. The nitrile was characterized by its typical infrared absorption at 4.45 μ. The nitrile was purified by chromatography over alumina in ether. Freactions 2–15 were combined and evaporated to give 0.82 g. (94%) of pure 6-methyl-5-heptenonitrile, b.p. 93–95°/8 mm.

Anal. Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37. Found: C, 78.12; H, 10.61; N, 11.45.

Hydrolysis of 6-Methyl-5-heptenonitrile.—Using the procedure outlined previously for the hydrolysis of 5-methyl-4-hexenonitrile, 0.50 g. of the unsaturated nitrile was converted to the unsaturated acid which was purified by ether elution from an alumina column, 6-methyl-5-heptanoic acid (0.48 g.), $n^{20}D$ 1.4500, was obtained (lit.[18a] $n^{20}D$ 1.4502).

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.56; H, 9.95.

Ozonolysis of 6-Methyl-5-heptenoic Acid.—Using the ozonolysis procedure previously described, the unsaturated acid was ozonized to give, after the usual work-up, acetone 2,4-dinitrophenylhydrazone, m.p. 124–126°, undepressed by mixing with an authentic sample.

Reduction of 6-Methyl-5-heptenoic Acid.—Using the procedure described for the reduction of 5-methyl-4-hexenoic acid, 6-methyl-5-heptenoic acid was saturated with hydrogen. The crude acid was converted directly to the amide. After recrystallization from ethyl acetate–petroleum ether, the amide melted at 115–115.5° (lit.[19] m.p. 114°).

(b) **With Thionyl Chloride.**—To an ice-cold suspension of 3.00 g. (0.021 mole) of 2,2-dimethylcyclohexanone oxime in 40 ml. of anhydrous, thiophene-free benzene 3 ml. of freshly distilled thionyl chloride was added dropwise. After standing at room temperature for 24 hr., the benzene was evaporated in vacuo. Water (40 ml.) was added to the residual oil and the aqueous mixture extracted four times with 30-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 2.82 g. of a black viscous oil. The oil was chromatographed over alumina in chloroform solution. Fractions 5–12 on evaporation of the chloroform yielded 0.75 g. (24%) of a white crystalline solid, 2-keto-7,7-dimethylhexamethyleneimine, m.p. 90.5–91°, the melting point of which was unchanged after sublimation at reduced

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(18) (a) M. F. Ansell and S. S. Brown, *J. Chem. Soc.*, 1788 (1957); (b) M. F. Ansell and S. S. Brown, *ibid.*, 2955 (1958).

(19) P. A. Levene and C. H. Allen, *J. Biol. Chem.*, **27**, 433 (1916).

(20) C. S. Marvel and C. L. Levesque, *J. Am. Chem. Soc.*, **60**, 280 (1938).

pressure. The infrared spectrum in carbon tetrachloride indicated a sharp single N—H vibration at 2.95 μ and amide I band at 6.05 μ.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.01; H, 10.99; N, 9.87.

The residual material on the column was eluted with methanol. Concentration indicated a small amount of nitrile was also present by the weak 4.45 μ band in the infrared spectrum.

(c) **Using Benzenesulfonyl Chloride in Sodium Hydroxide.**—A mixture of 1.00 g. (0.0071 mole) of 2,2-dimethylcyclohexanone oxime, 1.10 g. of benzenesulfonyl chloride, 0.25 g. of sodium hydroxide, 20 ml. of acetone, and 5 ml. of water was heated at reflux for 4 hr. On cooling, the acetone was evaporated at reduced pressure. Water (20 ml.) was added and the mixture extracted five times with ether to yield a light yellow oil. Chromatographic separation of the oil using an ether-filled alumina column as previously described yielded two products:

6-Methyl-5-heptenonitrile.—Fractions 3–9, on evaporation of the ether eluents, yielded 0.23 g. (27%) of the unsaturated nitrile identical in all respects with the nitrile obtained using phosphorus pentachloride as the rearrangement catalyst.

2-Keto-7,7-dimethylhexamethyleneimine, fractions 19–24, on evaporation of the chloroform–ether eluents, yielded 0.54 g. (54%) of the lactam, m.p. 90–91°, undepressed on admixture with the lactam isolated in the thionyl chloride rearrangement mixture.

(d) **Using Polyphosphoric Acid.**—A well stirred mixture of 2.00 g. (0.014 mole) of 2,2-dimethylcyclohexanone oxime and 30.9 g. of polyphosphoric acid was slowly heated to 125–130°. After 10 min., the mixture was poured over crushed ice and the aqueous acid mixture made alkaline with cold 10% sodium hydroxide solution. The alkaline solution was extracted five times with 100-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a light red oil. The infrared spectrum of the oil was indicative of an α,β-unsaturated five-membered ring ketone with an intense carbonyl band at 5.90 μ and a 6.13 μ C=C stretching vibration of almost equal intensity. The oil was distilled *in vacuo* to give two distinct fractions. Each fraction was further purified by vapor phase chromatography for refractive index and ultraviolet analysis.

2-Isopropyl-2-cyclopentenone, b.p. 83–85°/24 mm. n^{20}_{D} 1.4720, λ_{max} 235 mμ, log ϵ 4.20 (lit.[18a] b.p. 84.5–85°/24 mm. n^{20}_{D} 1.4722, λ_{max} 235 mμ, log ϵ 4.24).

The 2,4-dinitrophenylhydrazone was prepared in the usual manner. After two recrystallizations from chloroform–methanol, the red needles melted at 203.5–204.5° (lit.[18b] m.p. 202–203°), undepressed by admixture with an authentic sample.

2-Isopropylidenecyclopentanone, b.p. 90–92°/24 mm. n^{20}_{D} 1.4851, λ_{max} 253.5 mμ, log ϵ 4.10 (lit.[18b] b.p. 91.5–92°/24 mm. n^{20}_{D} 1.4855, λ_{max} 255 mμ, log ϵ 4.10).

The 2,4-dinitrophenylhydrazone was prepared in the usual manner. After four recrystallizations from chloroform–methanol, the scarlet needles melted at 227.5–228° (lit.[18b] m.p. 226–227°), undepressed by admixture with an authentic sample.

In a second experiment, the ketonic mixture was separated by vapor phase chromatography. At 175°, a column pressure of 25 p.s.i.g. and a 45 ml. of helium flow per minute the retention time of 2-isopropyl-2-cyclopentenone was 8.9 min. and that of 2-isopropylidenecyclopentanone was found to be 12 min. The total ketonic fraction (1.61 g.) gave 43% of 2-isopropyl-2-cyclopentenone and 57% of 2-isopropylidenecyclopentanone, by peak area measurement, indicating a yield of 39% and 52% for each isomer, respectively.

Cyclization of 6-Methyl-5-heptenonitrile Using Polyphosphoric Acid.—A mixture of 0.50 g. of 6-methyl-5-heptenonitrile and 9.5 g. of polyphosphoric acid was heated at 125–130° for 15 min. The mixture was hydrolyzed and worked up as described previously for the Beckmann rearrangement of 2,2-dimethylcyclohexanone oxime. The red oil (0.42 g.) was analyzed chromatographically to indicate a 43% yield of 2-isopropyl-2-cyclopentenone and 51% of 2-isopropylidenecyclopentanone.

III. **2,2-Dimethylcycloheptanone Oxime.** (a) **With Thionyl Chloride.**—To a cooled suspension of 3.00 g. (0.019 mole) of 2,2-dimethylcycloheptanone oxime in 36 ml. of anhydrous, thiophene free benzene 3 ml. of freshly distilled thionyl chloride was added in a dropwise manner. The mixture was allowed to stand for 24 hr. at room temperature after which the benzene was evaporated *in vacuo*. Water (100 ml.) was added to the residual oil and the aqueous mixture extracted five times with 75-ml. portions of ether. The ether extracts were combined and dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 2.8 g. of crude products. The infrared spectrum indicated the only major product to be the unsaturated nitrile. The crude product mixture was distilled *in vacuo* to yield 2.47 g. (93%) of 7-methyl-6-octenonitrile, b.p. 99.5–101°/8 mm.

Anal. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.96; H, 11.17; N, 9.98.

Hydrolysis of 7-Methyl-6-octenonitrile.—Using the procedure outlined previously for the hydrolysis of 5-methyl-4-hexenonitrile, 1.50 g. of the unsaturated nitrile was converted to the unsaturated acid. The crude acid was distilled *in vacuo* to yield 1.41 g. of 7-methyl-6-octenoic acid, b.p. 100–102°/0.8 mm. n^{20}_{D} 1.4519 (lit.[18a] b.p. 99–101°/0.7 mm., n^{20}_{D} 1.4513).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.26; H, 10.49.

7-Methyl-6-octenamide.—7-Methyl-6-octenoic acid (0.82 g.) was treated in the cold with 1.0 g. of oxalyl chloride, slowly warmed to room temperature, then refluxed on a steam bath for 2 hr. The excess oxalyl chloride was evaporated at reduced pressure. The residue was taken up in 30 ml. of anhydrous benzene and treated in the cold with anhydrous ammonia. The excess benzene was evaporated after 20 min. to yield a light brown solid. The crude amide was recrystallized from ethyl acetate–petroleum ether to give 0.51 g. of 7-methyl-6-octenamide, m.p. 119–120°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.59; H, 11.18; N, 9.00.

Reduction of 7-Methyl-6-octenamide.—Using the procedure described for the reduction of 5-methyl-4-hexenoic acid, 7-methyl-6-octenamide was saturated with hydrogen. After recrystallization from ethyl acetate–petroleum ether, the amide melted at 106.5–107° (lit.[19] m.p. 106.5°).

Ozonolysis of 7-Methyl-6-octenoic Acid.—Using the ozonolysis procedure previously described the unsaturated acid was ozonized to give after the usual work up, acetone-2,4-dinitrophenylhydrazone, m.p. 124–126°, undepressed by mixing with an authentic sample.

(b) **Using Polyphosphoric Acid.**—A mixture of 5.00 g. (0.032 mole) of 2,2-dimethylcycloheptanone oxime and 65.0 g. of polyphosphoric acid was slowly heated to 125–130°. After 10 min., the mixture was poured over crushed ice and the aqueous mixture made alkaline with cold 10% sodium hydroxide solution. The alkaline solution was extracted four times with 200-ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 4.80 g. of a dark red viscous oil. Infrared examination of the crude product mixture indicated the product mixture contained both amide and ketone components. The mixture was chromatographed over 210 g. of alumina eluting first with ether followed by 1:1 ether–chloroform, then chloroform alone.

2-Isopropyl-2-cyclohexenone and 2-Isopropylidenecyclohexanone.—Fractions 8–21 were combined and evaporated to give 1.60 g. (36%) of a mixture of two α,β-unsaturated ketones. The ketonic mixture was separated by vapor phase chromatography. At 175°, a column pressure of 25 p.s.i.g. and a 45 ml./min. helium flow, the retention times of 2-isopropyl-2-cyclohexenone and 2-isopropylidenecyclohexanone were 9.3 min. and 13.2 min., respectively. The yields, determined by peak area measurements and adjusted on the basis of the total amount of the ketonic material, were 30.2% and 5.7% for the respective isomers. The refractive index, ultraviolet spectra, and the 2,4-dinitrophenylhydrazone derivatives of each ketone were obtained on pure samples by trapping the helium off-gas from the fractometer. Twenty successive trappings of 8-microliter samples were sufficient to obtain enough material for these determinations.

2-Isopropyl-2-cyclohexenone (30.2%), n^{20}_D 1.4769; λ_{max} 235 mμ, log. ϵ 4.20 (lit.[18b] n^{20}_D 1.4773; λ_{max} 235 mμ, log ϵ 3.82). The 2,4-dinitrophenylhydrazone derivative after two recrystallizations from chloroform–methanol was isolated as fine red needles, m.p. 186–187° (lit.[18b] 190–191°).

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 57.31; H, 5.77; N, 16.55. Found: C, 57.30; H, 5.92; N, 16.49.

2-Isopropylidenecyclohexanone (5.7%), n^{20}_D 1.4920; λ_{max} 254 mμ, log ϵ 4.02 (lit.[18b] n^{20}_D 1.4922; λ_{max} 254 mμ, log ϵ 3.80). The 2,4-dinitrophenylhydrazone derivative after two recrystallizations from chloroform–methanol was isolated as maroon needles, m.p. 181.5–182.5° (lit.[18b] m.p. 182–183°).

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 57.31; H, 5.77; N, 16.55. Found: C, 57.23; H, 5.64; N, 16.44.

7-Methyloctanamide.—Fractions 48–59 were combined and the chloroform was evaporated to yield 2.90 g. (57.2%) of 7-methyloctanamide which after a crystallization and sublimation (100° at 0.05 mm.) melted at 106.5–107.5° undepressed by admixture with an authentic sample prepared as previously described.

Reduction of the Ketonic Mixture.—A mixture of 0.50 g. of the crude ketonic mixture, isolated from the rearrangement, 0.1 g. of Raney nickel, and 10 ml. of 1,2-dichloroethane, was hydrogenated for 1.5 hr. at 60 p.s.i.g. The vessel was vented and the solution filtered and evaporated. The residue was treated with 2,4-dinitrophenyhydrazine reagent to give an orange precipitate. After two recrystallizations from chloroform–methanol, orange needles of 2-isopropylcyclohexanone 2,4-dinitrophenylhydrazone were obtained, m.p. 136.5–137°, undepressed by admixture with an authentic sample.

Cyclization of 7-Methyl-6-octenonitrile in Polyphosphoric Acid.—The unsaturated nitrile (1.00 g.) and 17 g. of polyphosphoric acid were heated at 125–130° for 10 min. The ketonic component was isolated as previously described and the mixture analyzed chromatographically to give 31.5% and 4.3% of 2-isopropyl-2-cyclohexenone and 2-isopropylidenecyclohexanone, respectively.

A General Route to Hydantoins

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Received November 3, 1961

A general method for preparing hydantoins directly from a variety of carbonyl derivatives is reported. In spite of the enhanced stability normally exhibited by such derivatives, the reaction appears to be equivalent to that observed with the parent carbonyl compounds. As such, it provides a useful extension to the general route to α-amino acids from carbonyl compounds *via* a hydantoin intermediate.

Hydantoins, because of their pronounced stability and availability from a variety of carbonyl compounds, find general utility as precursors of α-amino acids.[2,3] One limitation imposed on their use in this capacity stems from the fact that the carbonyl compound is not always readily accessible. Such is the case in the synthesis of tryptophan from 5-(3′-indolylmethyl)hydantoin, the parent 3-indoleacetaldehyde being difficult to prepare and handle because of its limited stability.[4,5]

Recently reported work on the synthesis of tryptophan[6] has demonstrated the feasibility of preparing 5-(3′-indolylmethyl)hydantoin from 3-indoleacetaldehyde semicarbazone, a stable and readily accessible derivative of 3-indoleacetaldehyde.[5] The demonstration of this reaction has prompted the examination of various other carbonyl derivatives as precursors of the corresponding hydantoins. It can now be reported that hydantoin formation has been observed with a sufficient variety of these derivatives to indicate the general nature of the reaction. Since carbonyl derivatives are inherently more stable than the parent carbonyl compounds, it is felt this provides a useful extension to the general method of preparing α-amino acids from carbonyl compounds *via* a hydantoin intermediate.

Types of carbonyl derivatives found to be operable include semicarbazones, thiosemicarbazones, oximes, azines, phenylhydrazones, imidazolidines, and azomethines. Indications are that these derivatives respond in an equivalent manner whether they are derived from an aldehyde or ketone. The reaction conditions used parallel closely those normally employed to prepare a hydantoin from a free carbonyl compound, namely—treatment of the particular carbonyl derivative with an excess of hydrogen cyanide and ammonium carbonate. A reasonable rate of reaction was observed in most cases operating under oxygen-free conditions at 100° under autogenous pressure. The addition of sodium bisulfite (two to two hundred molar per cent based on the carbonyl derivative) frequently improved the yield of hydantoin but was not es-

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