# α-Oximinoketones. VI. Synthesis of Alkyl 5-Cyano-2-oximinovalerates and DL-Lysine from 2,6-Diacyloximinocyclohexanones[1]

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An improved version of the previous synthesis of lysine from cyclohexanone[1] gave the yields indicated in the following four steps: (1) nitrosation of cyclohexanone to 2,6-dioximinocyclohexanone (75%); (2) acetylation of 2,6-diacetoximinocyclohexanone (76%); (3) cleavage with sodium ethoxide in ethanol to ethyl 5-cyano-2-oximinovalerate (88%); and hydrogenation to DL-lysine (57%). The overall yield was 29%. A study of the "second order" Beckmann rearrangement in alcohols (step 3) was made, and the mechanistic implications of the results are discussed. The key to improved yields in this step was the discovery that alkyl 5-cyano-2-oximinovalerates are resistant to further rearrangement by acylating agents and base.

The previous paper in this series[1] described the synthesis of DL-lysine in 20% over-all yield from cyclohexanone by the three-step sequence shown below:
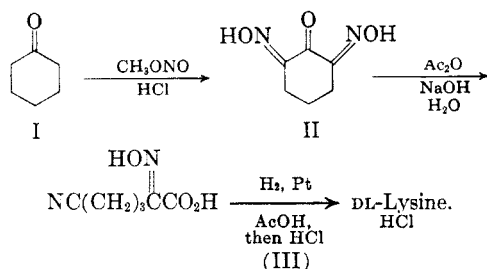

The over-all yield was the result of yields of 75% in step I, 62% in step II, and 43% in step III. In contrast to 5-cyano-2-oximinovaleric acid, its ethyl ester was reduced to lysine in 57% yield. However, a rather low yield on esterification of the acid (61%) reduced the over-all yield in step III to 35%. Thus the over-all conversion to lysine by proceeding through the ester was actually a little poorer than when the acid was hydrogenated. It was obvious, therefore, that a substantial improvement in the over-all lysine process would be realized if an ester of 5-cyano-2-oximinovaleric acid instead of the free acid could be obtained in step II. It should be noted also that although the yield in the partial "second order" Beckmann rearrangement (step II) was fairly good, it was attained by using only half the amount of acetic anhydride theoretically necessary for the desired single cleavage, which necessitated recovery and recycling of a considerable portion of the 2,6-dioximinocyclohexanone charged to the reaction.

In attempting to devise a method for obtaining an ester of 5-cyano-2-oximinovaleric acid instead of the free acid in step II, it was pertinent to reconsider the mechanism of the second order Beckmann re-

arrangement of α-oximino ketones.[3] It has been suggested previously[4] that this rearrangement involves acylation of the oxime; the concurrent departure of the acylate anion and shift of an electron pair from a position between the carbonyl carbon and the oxime carbon to a position between the latter carbon and the nitrogen, thus cleaving the carbon — carbon bond and forming a nitrile and an oxocarbonium cation; and finally combination of the cation with solvent or with the anion which initiated the rearrangement:
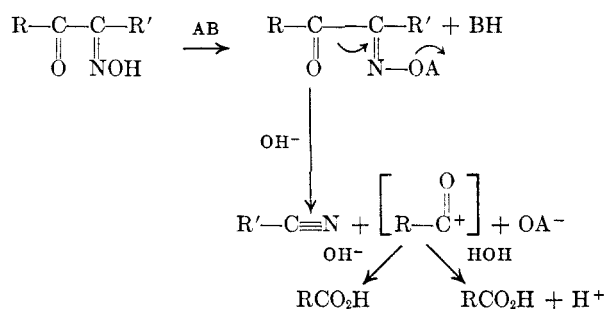
It is equally possible on the basis of previous work to regard the final two steps as concerted, that is, to assume that in the rearrangement the acylated α-oximino ketone is attacked at the carbonyl carbon by the anion of the base as the acylate ion departs. In fact, attack by the anion might even be regarded as the initiating step in the rearrangement:
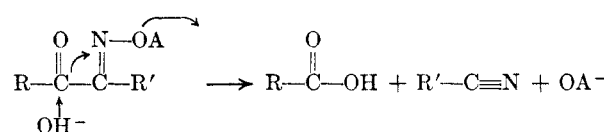
This view appears to be that held by Green and Saville.[5] Whatever the exact sequence of the last two steps, it was grasped that on the basis of this

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(1) Paper V of this series: A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *J. Org. Chem.*, in press.
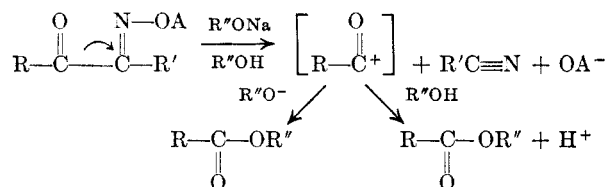
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(3) Helpful discussion of this mechanism with R. Miller, E. R. Gilmont, B. R. Franko, and H. Stange of this laboratory is gratefully acknowledged.
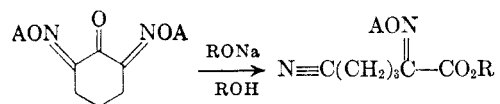
(4) A. F. Ferris, *J. Org. Chem.*, in press.

(5) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

mechanism the treatment of a preformed α-acyloximino ketone with a solution of a metal alkoxide in an alcohol should give an ester product in the second order rearrangement:

$$\begin{array}{c} \overset{O}{\underset{\parallel}{R-C}}-\overset{N-OA}{\underset{\parallel}{C}}-R' \xrightarrow[R''OH]{R''ONa} \left[\overset{O}{\underset{\parallel}{R-\overset{+}{C}}} \right] + R'C\equiv N + OA^- \\ R''O^- \swarrow \qquad \searrow R''OH \\ \underset{\underset{O}{\parallel}}{R-C-OR''} \qquad \underset{\underset{O}{\parallel}}{R-C-OR''} + H^+ \end{array}$$

This concept applied to a 2,6-diacyloximinocyclohexanone should give the acyl derivative of the desired ester in step II;

$$\underset{AON}{\diagup}\overset{O}{\underset{\parallel}{\diagup}}\underset{NOA}{\diagdown} \xrightarrow[ROH]{RONa} N\equiv C(CH_2)_3\overset{O}{\underset{\parallel}{C}}-CO_2R$$

It was expected that a deficiency of alkoxide would have to be used to avoid attack on the alkyl 5-cyano-2-acyloximinovalerate, just as it had been necessary to use a deficiency of acylating agent in the earlier preparation of 5-cyano-2-oximino-valeric acid.[1]

The first 2,6-diacyloximinocyclohexanone was prepared by Borsche[6] by treating 2,6-dioximino-cyclohexanone with benzoyl chloride in the presence of pyridine. Repeating this preparation gave 2,6-dibenzoyloximinocyclohexanone in 47% yield. The melting point of this compound, 186–187°, was considerably higher than that reported by Borsche, 170–172°, but it seems probable that our material was the same as his, since our melting point was taken on a Fisher-Johns block while his was almost certainly taken in a capillary. A more practical acylated product was prepared by treating 2,6-dioximinocyclohexanone with a 3:1 excess of acetic anhydride containing a catalytic amount of mineral acid. A 76% yield of 2,6-diacet-oximinocyclohexanone, m.p. 177.5–178.5°, was obtained.

When 2,6 - diacetoximinocyclohexanone was treated with a solution of sodium ethoxide in ethanol the result was in part that which had been expected, and in part unexpected. The product was an ethyl ester, but it was ethyl 5-cyano-2-oximinovalerate, not the expected ethyl 5-cyano-2 acetoximinovaler-ate. The acetyl group which should have been on the α-oximino group had been removed by solvoly-sis. Further, it soon became apparent that the use of a deficiency of base was not necessary, since ethyl 5-cyano-2-oximinovalerate was obtained in very good yield (88%) when the equivalent amount or even an excess of base was used. The failure of ethyl 5-cyano-2-acetoximinovalerate to be cleaved might be explained by assuming that the rearrange-ment did not have time to take place because of very

rapid solvolysis, but this seems very unlikely in view of the fact that oxime esters normally rear-range very rapidly and exothermically in the pres-ence of base.[4,7] Further, when 2,6-diacetoximino-cyclohexanone was treated with a suspension of an equivalent of sodium methoxide in benzene, methyl 5-cyano-2-acetoximinovalerate, a stable and readily isolable compound, was obtained in 62% yield. In contrast, attempts to dissolve 5-cyano-2-oximinovaleric acid in acetic anhydride, even in the absence of base, led to rapid rearrangement.[1] Even more vigorous rearrangement occurred in the presence of base, when the ammonium salt of 5-cyano-2-oximinovaleric acid was added to acetic anhydride. Ethyl 5-cyano-2-oximinovalerate has been shown[1,8] to dissolve without decomposition in acetic anhydride prior to hydrogenation. It must be concluded that ethyl 5-cyano-2-acetoximi-novalerate is solvolyzed in ethanol because, like the acetates of syn-benzoin oxime and syn-benzil monoxime,[7] it has very little tendency to undergo rearrangement.

The fact that an acylated α-oximino ester, pre-sumably in the anti configuration since it is de-rived from a material in which both oxime groups appear to be anti to the carbonyl,[1] fails to be cleaved under conditions which lead to rapid cleavage of acylated α-oximino acids and ketones is a most striking one. At the present time this behavior must be listed with the similar behavior of the acetates of syn-benzoin oxime and syn-benzil monoxime as not capable of ready interpretation from the stand-point of mechanism. From a synthetic point of view, the stability of ethyl 5-cyano-2-oximinovalerate is most useful, since it permits the cleavage of 2,6-diacetoximinocyclohexanone in good yield with-out the necessity for recycling starting material.

Some additional experiments directed toward extending the synthesis were only partially suc-cessful. A solution of sodium hydroxide in ethanol could be substituted for the solution of sodium ethoxide, but the yield of ethyl 5-cyano-2-oximino-valerate was reduced to 72%. 2,6-Dibenzoyloxim-inocyclohexanone was cleaved also by sodium ethoxide in ethanol, but the yield was only 60%.

None of the experiments thus far discussed shed any light on the sequence of events in the second order rearrangement: that is, they did not indicate whether the reaction was initiated by departure of the acylate anion, by attack of the base anion, or by a concerted attack and departure. Experi-ments with a variety of weaker bases did provide an indication of the probable sequence. Weak bases were found to be catalysts for the rearrangement in series of qualitative experiments wherein suspen-sions of 2,6-diacetoximinocyclohexanone in ethanol

(6) W. Borsche, Wallach Fest., 301 (1909); Chem. Abstr., 5, 883 (1911).

(7) A. H. Blatt and R. P. Barnes, J. Am. Chem. Soc., 56, 1148 (1934).

(8) P. Olynyk, D. B. Camp, A. M. Griffith, S. Woislowski, and R. W. Helmkamp, J. Org. Chem., 13, 465 (1948).

were treated with various bases, and a rapid rise in temperature was taken as an indication of reaction. By this means sodium acetate, sodium cyanide, sodium carbonate, and several amines were shown to be catalysts for the reaction. In a quantitative experiment it was found that when 2,6-diacetoximinocyclohexanone was slurried in ethanol and treated with excess sodium acetate there was obtained in very good yield a mixture of ethyl 5-cyano-2-oximinovalerate and ethyl 5-cyano-2-acetoximinovalerate in about equal amounts. With excess diethylamine or n-butylamine in ethanol the only product was ethyl 5-cyano-2-oximinovalerate in yields of 76% and 79% respectively. Similarly, when 2,6-diacetoximinocyclohexanone was slurried in isopropanol and treated with n-butylamine, isopropyl 5-cyano-2-oximinovalerate was obtained in 83% yield. The infrared spectra of the ester products from the amine-catalyzed reactions indicated that they contained traces of amides. Attempts to prepare the amides in quantity by treating 2,6-diacetoximinocyclohexanone in dioxane with diethylamine and n-butylamine gave only tars. The fact that an ester was obtained when 2,6-diacetoximinocyclohexanone was cleaved with sodium acetate in ethanol might be explained on the basis of initiation of the rearrangement by base attack on the carbonyl carbon, since it is possible to postulate that an intermediate mixed anhydride was obtained and then reacted with solvent to give the observed product. The similar result with amines, however, seems to be explainable only on the assumption that the first step of the reaction was the departure of the acylate anion and shift of the electron pair, and that this was followed by reaction of the oxocarbonium ion formed by the cleavage with the alcohol solvent. Since there appears to be no noteworthy difference between the amine-catalyzed, the alkoxide-catalyzed, and the hydroxide-catalyzed reactions, it seems reasonable to suppose that all second order Beckmann rearrangements follow this sequence.

On the basis of the work described in this paper, the preferred route to lysine is a four-step combination of reactions reported herein and in the previous paper,[1] including nitrosation of cyclohexanone with methyl nitrite (75%), acetylation of 2,6-dioximinocyclohexanone with acetic anhydride (76%), cleavage of 2,6-diacetoximinocyclohexanone with sodium ethoxide in ethanol (88%), and reduction of ethyl 5-cyano-2-oximinovalerate by catalytic hydrogenation (57%). This sequence gave an over-all yield of 29%, better than the 20% of the first sequence, and had the additional advantage of not requiring recycle of 2,6-dioximinocyclohexanone.

EXPERIMENTAL[9]

2,6-Dibenzoyloximinocyclohexanone. To a stirred solution of 56.0 g. (0.40 mole) of benzoyl chloride and 24.0 g. (0.30

mole) of pyridine in 200 ml. of benzene was added 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone over 15 min. The temperature rose from 26 to 41°. The mixture was held at 45–50° by application of heat for 30 min., then was cooled to 20°. A solid precipitated and was recovered by suction filtration. The filter cake was washed with benzene and alcohol and was dried *in vacuo.* There was obtained 17.0 g. (47%) of 2,6-dibenzoyloximinocyclohexanone, m.p. 186–187°.

Anal. Calcd. for $C_{20}H_{16}O_5N_2$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.92; H, 4.70; N, 7.65.

2,6-Diacetoximinocyclohexanone. To a stirred solution of 1 ml. of concentrated sulfuric acid in 612 g. (6 moles) of acetic anhydride was added portionwise 156 g. (1 mole) of 2,6-dioximinocyclohexanone. The addition required 45 min. The temperature rose from 27 to 55°, and then was held at 50–55° by external cooling. After addition was complete, the temperature was held at 50° for 30 min. by application of heat. The reaction mixture was cooled to 25°, and the precipitate which formed was recovered by filtration, washed with three 200-ml. portions of benzene, and dried. The lemon yellow crystals of 2,6-diacetoximinocyclohexanone amounted to 183 g. (76%), m.p. 177.5–178.5° dec.

Anal. Calcd. for $C_{10}H_{12}O_5N_2$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.96; H, 5.13; N, 11.64.

Ethyl 5-cyano-2-oximinovalerate. (a) *From 2,6-dibenzoyloximinocyclohexanone and sodium ethoxide in ethanol.* A solution of 0.6 g. (0.025 g.-atom) of sodium in 100 ml. of absolute ethanol was prepared. A slurry of 8.5 g. (0.0233 mole) of 2,6-dibenzoyloximinocyclohexanone in 150 ml. of absolute ethanol was prepared, and the sodium ethoxide solution was added to the slurry with cooling to maintain the temperature at 20–30°. Addition required 15 min., and stirring was continued for an additional 30 min. The excess alcohol was distilled off at reduced pressure and at a temperature not exceeding 50°. The residue was taken up in 50 ml. of hot carbon tetrachloride and filtered to remove solid which failed to dissolve. After drying, the insoluble solid weighed 3.0 g. (theory for sodium benzoate, 3.6 g.). Solid crystallized from the carbon tetrachloride filtrate on cooling and was recovered by filtration and dried. There was obtained 2.8 g. (60%) of ethyl 5-cyano-2-oximinovalerate, m.p. 72–74°. (Lit.,[10] m.p. 74°.)

(b) *From 2,6-diacetoximinocyclohexanone and sodium ethoxide in ethanol.* A solution of sodium ethoxide in ethanol was prepared by dissolving 11.5 g. (0.50 g.-atom) of sodium in 500 ml. of absolute ethanol. This solution was cooled to 20°, and a slurry of 120.0 g. (0.50 mole) of 2,6-diacetoximinocyclohexanone in 500 ml. of absolute ethanol was added, the temperature being held at 20–30° by external cooling. After the addition was complete and there was no further tendency for the temperature of the reaction mixture to rise, the alcohol was evaporated at reduced pressure at 40–50°. The resulting slurry was taken up in 1000 ml. of ether, and the mixture was filtered to remove solid which failed to dissolve. The filter cake was washed with 100 ml. of ether, and the filtrate and washings were combined and washed with 500 ml. of saturated sodium bicarbonate solution. The ether solution was dried over anhydrous magnesium sulfate, stirred with decolorizing charcoal, and filtered. The ether was evaporated under reduced pressure, and the residue was dried *in vacuo.* There was obtained 81.0 g. (88%) of ethyl 5-cyano-2-oximinovalerate, m.p. 74–75°.

(c) *From 2,6-diacetoximinocyclohexanone and diethylamine in ethanol.* In 300 ml. of absolute ethanol was slurried 24.0 g. (0.10 mole) of 2,6-diacetoximinocyclohexanone. With vigorous stirring, 24.0 g. (0.33 mole) of diethylamine was added, the temperature being held at 20–30° by external cooling. The clear brown solution obtained was evaporated under

(9) All melting points are uncorrected.

(10) E. Fischer and F. Weigert, *Ber.,* **35**, 3772 (1902).

reduced pressure on a hot water bath, and the residue was taken up in 300 ml. of ether. The ether solution was washed with 150 ml. of saturated sodium bicarbonate solution, treated with decolorizing charcoal, and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure to leave 14.0 g. (76%) of ethyl 5-cyano-2-oximino-valerate, m.p. 73°.

(d) *From 2,6-diacetoximinocyclohexanone and n-butylamine in ethanol.* With vigorous stirring 14.6 g. (0.20 mole) of *n*-butylamine was added to a slurry of 24.0 g. (0.10 mole) of 2,6-diacetoximinocyclohexanone in 200 ml. of absolute ethanol. The temperature rose rapidly from 25 to 55° during the addition of the first few ml. of the amine, then dropped off slowly as the rest was added. After addition was complete, the resulting clear solution was evaporated under reduced pressure on a hot water bath. The residue was taken up in 500 ml. of ether, and the ether solution was washed with dilute hydrochloric acid and saturated sodium bicarbonate solution. It was then treated with decolorizing charcoal and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure left 14.5 g. (79%) of ethyl 5-cyano-2-oximinovalerate, m.p. 70°. The infrared spectrum of this material showed that it contained a trace of amide.

Methyl 2-acetoximino-5-cyanovalerate. A mixture of 800 ml. of dry benzene, 120 g. (0.5 mole) of 2,6-diacetoximinocyclo-hexanone, and 27 g. (0.5 mole) of sodium methoxide was stirred vigorously. In 1 hr. the temperature rose from 27 to 65°. The mixture was cooled to 45°, and the temperature rose in 15 min. to 51°. The mixture was cooled to 40°, and no further increase in temperature occurred. A test with pH paper showed that the mixture was neutral, and it was cooled to room temperature and filtered. After drying the filter cake weighed 40 g. (theory for sodium acetate, 41 g.). The benzene was evaporated at reduced pressure at 50°, and the residue was held under vacuum for 24 hr. to insure removal of all volatile material. There remained 66 g. (62%) of methyl 2-acetoximino-5-cyanovalerate, a brown oil. After standing for several days the oil partially crystallized. The mixture of liquid and solid was recrystallized from a mixture of equal volumes of ethyl acetate and cyclohexane to give 33 g. (31%) of white crystalline methyl 2-acetoximino-5-

cyanovalerate, m.p. 48°. The infrared spectrum of this solid was essentially identical to that of the oil.

Anal. Calcd. for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.73; N, 13.50.

Action of sodium acetate in ethanol on 2,6-diacetoximino-cyclohexanone. With vigorous stirring 5.0 g. (0.0610 mole) of anhydrous sodium acetate was added to a slurry of 10.0 g. (0.0416 mole) of 2,6-diacetoximinocyclohexanone in 30 ml. of absolute ethanol. The temperature rose rapidly to 80°, then dropped slowly. After standing an hour the mixture was heated to 60° under reduced pressure to evaporate the ethanol. The residue was taken up in 100 ml. of ether, and the solid which failed to dissolve was removed by filtration. The filtrate was washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure to leave 7.8 g. of white solid, m.p. 50–56°. Comparison of the infrared spectrum of this material with those of ethyl 5-cyano-2-oximinovalerate and methyl 2-acetoximino-5-cyanovalerate indicated that this material was composed of about equal amounts of ethyl 5-cyano-2-oximinovalerate (theory, 7.7 g.) and ethyl 2-acetoximino-2-cyanovalerate (theory, 9.4 g.).

Isopropyl 5-cyano-2-oximinovalerate from 2,6-diacetox-iminocyclohexanone and n-butylamine in isopropanol. The procedure described for the analogous reaction in ethanol was followed using an equal volume of isopropanol. There was obtained 16.5 g. (83%) of isopropyl 5-cyano-2-oximino-valerate, a brownish oil. After standing several days the oil crystallized. A portion of the solid was recrystallized from a 5:1 cyclohexane–ethyl acetate mixture to give white crystals of isopropyl 5-cyano-2-oximinovalerate, m.p. 55–56°.

Anal. Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.14. Found: C, 54.43; H, 7.24; N, 14.09.

PRINCETON, N. J.

The Five Monocarboxylic Acids of Phenanthrene[1,2]

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The syntheses, melting points, ultraviolet and infrared spectra of the five monocarboxylic acids of phenanthrene are reported.

During a study of the synthesis and properties of alkylphenanthrenes it was found that many of the best synthetic routes to these hydrocarbons involve substitution reactions on phenanthrene or a partially hydrogenated phenanthrene. Such reactions frequently produce mixtures of isomers and it is necessary for identification to convert the substitution products to known structures. The monocarboxylic acids of phenanthrenes are a logical set of reference structures, as many functional groups can be converted readily to the carboxylic acid group.

Although syntheses and melting points of the five isomeric phenanthrene monocarboxylic acids have been reported,[4-18] examination of the literature

(1) Taken in part from the dissertation submitted by D. D. Neiswender in partial fulfillment of the requirements for the Ph.D. degree at The Pennsylvania State University.

(2) Presented in part before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, California, April, 1958.

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(4) L. F. Fieser, *J. Am. Chem. Soc.* **54**, 4110 (1932).

(5) J. R. Dice and P. A. Smith, *J. Org. Chem.* **14**, 179 (1949).