

replaced by 300 ml. of ether and water was added. The aqueous layers were extracted thoroughly with ether. The combined ethereal solutions were dried and then evaporated. The resulting residues were then fractionally crystallized from petroleum ether (b.p. 60–90°) to give recovered  $\beta$ -hydroxy ester and/or benzophenone. Since the  $\beta$ -hydroxy ester is only slightly soluble in this solvent, it crystallizes first, reduction of the solvent volume and cooling being required for recovery of the ketone. In each case the identities of the  $\beta$ -hydroxy ester and ketone were verified by comparison of their infrared spectra with those of the respective authentic substances.

In a repetition of Experiment 2, Table II, involving  $\beta$ -hydroxy ester I and one equivalent of sodium amide, the ammonia was replaced by ether at the end of 4 hr. and the ethereal suspension, without being neutralized, was filtered through a fritted-glass funnel. Benzophenone (86%) was obtained from the ethereal filtrate in the usual manner following acidification with aqueous hydrochloric acid. The solid on the funnel was shown not to contain a benzophenone-sodium amide addition complex by its noninflammability, and by the fact that its acidification produced no benzophenone.

*Cleavage of  $\beta$ -hydroxy ester I by sodium ethoxide.* To a solution of 0.0008 mole of sodium ethoxide in 50 ml. of absolute ethanol was added 2.0 g. (0.007 mole) of  $\beta$ -hydroxy ester I. The mixture was allowed to stand at room temperature with occasional shaking for 48 hr. when complete solution was achieved. The solution was poured with stirring into a solution of 5 ml. of concd. hydrochloric acid and 25 ml. of water. Much (50 ml.) of the solvent was removed, and the residue

extracted with ether. There was isolated 2.6 g. (85%) of the 2,4-dinitrophenylhydrazone of benzophenone, m.p. 236–238°, reported<sup>19</sup> m.p. 238°.

In a blank experiment with  $\beta$ -hydroxy ester I and absolute ethanol, essentially complete recovery of this compound was realized.

*Attempted condensation of malonic ester and benzophenone by lithium amide.* To a stirred suspension of 0.1 mole of lithium amide in 400 ml. of anhydrous liquid ammonia was added 16 g. (0.1 mole) of diethyl malonate in an equal volume of ether. The suspension was stirred for 5 min. and 18.2 g. (0.1 mole) of benzophenone in 40 ml. of anhydrous ether was added. After stirring for 1 hr. the suspension was inversely neutralized with ammonium chloride. The ammonia was replaced by 300 ml. of ether. The combined ethereal solution was then evaporated. The resulting residue was vacuum distilled to give 14.8 g. (92%) of recovered diethyl malonate, b.p. 94–98° at 18 mm, reported<sup>20</sup> b.p. 88–89° at 13 mm. Also, 15.9 g. (88%) of benzophenone was recovered, b.p. 186–189° at 15 mm. The benzophenone reaction, after solidification, was crystallized from petroleum ether (b.p. 60–90°) to give crystals of the ketone, m.p. 46–47°.

Repetition of this reaction, but using 2, 3 or 4 equivalents of lithium amide, gave comparable recoveries of the ketone and diester in each case.

DURHAM, N. C.

(19) N. R. Campbell, *Analyst*, **61**, 393 (1936).

(20) H. Reitter and A. Weindel, *Ber.*, **40**, 3361 (1907).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT CENTER OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

## $\alpha$ -Oximinoketones. VII. Synthesis of Alkyl 5-Cyano-2-oximinovalerates and DL-Lysine from 2,6-Dioximinocyclohexanone<sup>1</sup>

ARTHUR F. FERRIS, GRANNIS S. JOHNSON,<sup>2</sup> FRANCIS E. GOULD, AND HUGO STANGE

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DL-Lysine monohydrochloride has been prepared in 63% over-all yield from cyclohexanone by a three-step synthesis which involves: (1) nitrosation of cyclohexanone to give 2,6-dioximinocyclohexanone (75%), (2) reaction of 2,6-dioximinocyclohexanone in ethanolic sodium ethoxide with acetic anhydride to give ethyl 5-cyano-2-oximinovalerate (92%), and (3) hydrogenation of ethyl 5-cyano-2-oximinovalerate over Raney nickel in acetic anhydride containing a basic co-catalyst followed by hydrolysis with hydrochloric acid to give DL-lysine monohydrochloride (92%). Discovery that ethanol could be used as solvent for step (2) and Raney nickel as catalyst for step (3) more than doubled the overall yield obtained in previous versions of this synthesis.<sup>3,4</sup>

In two previous papers<sup>3,4</sup> the two similar syntheses of DL-lysine from cyclohexanone outlined below as routes (A) and (B) (p. 1303) were described.

In both syntheses the key reaction was the "partial cleavage" of 2,6-dioximinocyclohexanone to 5-cyano-2-oximinovaleric acid or a derivative. It is readily apparent that conversion of cyclohexanone to lysine *via* this key reaction offers an

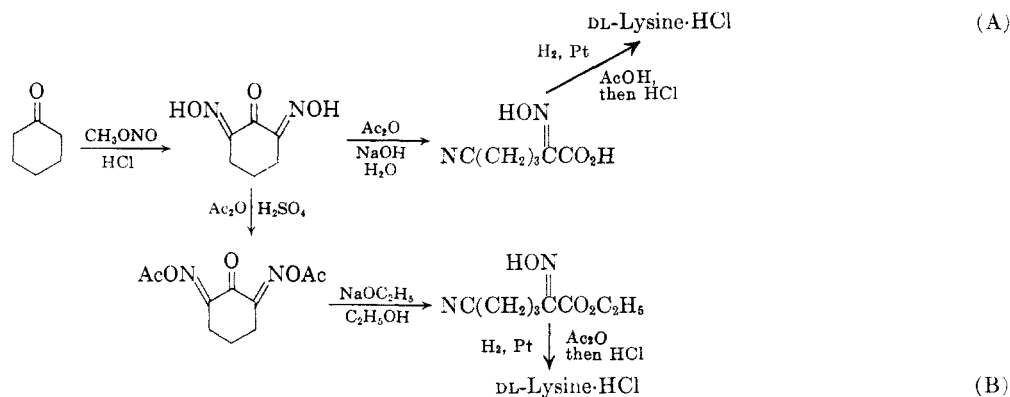
extremely facile synthesis of this important amino acid, quite possibly more direct than any previously reported. Neither of the previous versions of this synthesis realized its full potential, however, since both suffered from unsatisfactory yields in the steps following the relatively satisfactory initial nitrosation (75% yield). Thus in the first version of the synthesis (route A),<sup>3</sup> the yield in the partial cleavage step was 62% and in the reduction step only 43%, giving an over-all yield of 20%. In the second version (route B),<sup>4</sup> the excellent 88% yield of the partial cleavage was in part offset by the necessity for introducing a separate acylation step (76% yield), so that the over-all conversion of 2,6-dioximinocyclohexanone to ethyl 5-cyano-2-oximinovalerate was 67%.

(1) A preliminary account of this work appeared in *Chem. & Ind. (London)*, 996 (1959).

(2) Present address: General Aniline and Film Corp., Linden, N. J.

(3) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *J. Org. Chem.*, **25**, 492 (1960).

(4) A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, **25**, 496 (1960).

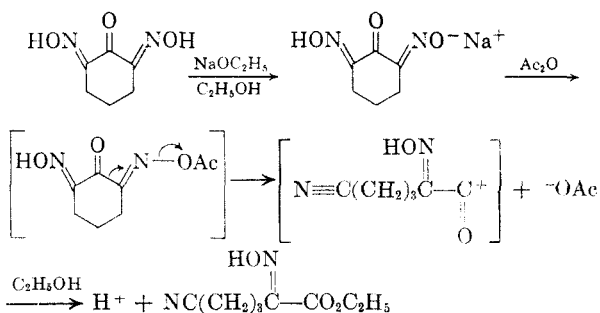


Again the reduction step was the least satisfactory, a yield of only 57% being obtained. Although in simplicity and over-all yield (29%) this version probably compares favorably with most reported lysine syntheses, it still did not constitute the superior method which was the goal of this work. The attainment of high yields in the partial cleavage and reduction steps, which would afford such a superior method, was ample incentive for further study of these reactions.

In the course of an examination of the partial cleavage reaction, it was found that high yields could be obtained and isolation of a 2,6-diacetyloximinocyclohexanone avoided by a very simple expedient: When 2,6-dioximinocyclohexanone was added to an alcohol containing an equivalent or a little more of strong base, a monosalt appeared to be formed. A completely clear solution was not obtained, but the solid dioxime seemed to go into solution and another solid appeared to come out. When the slurry thus obtained was treated with about an equivalent of acetic or propionic anhydride, very high yields of alkyl 5-cyano-2-oximinovalerates were obtained. Because of its convenience, the combination of sodium ethoxide in ethanol with acetic anhydride as acylating agent was the subject of the most study, and eventually yields as high as 92% were obtained consistently with this system. A number of other combinations of alcohol and strong base also gave good yields with acetic anhydride as acylating agent, including sodium methoxide, magnesium methoxide, and benzyltrimethylammonium hydroxide in methanol, sodium and potassium hydroxide in ethanol, sodium isopropoxide in isopropyl alcohol, and sodium benzyolate in benzyl alcohol. In essence, then, it was found that an alcohol could be used instead of water as the solvent for the second order Beckmann rearrangement, with the difference that an ester instead of a carboxylic acid product was obtained. From the standpoint of the lysine synthesis, this was a tremendously important difference, since, unlike 5-cyano-2-oximinovaleric acid, the alkyl 5-cyano-2-oximinovalerates are not cleaved further by acylating agent and base.<sup>4</sup> Thus the use of an alcohol as solvent for the cleav-

age step retained the simplicity of that step in route A, but avoided the secondary cleavage to glutaronitrile which reduced the yield of 5-cyano-2-oximinovaleric acid in A.

The success of the second order Beckmann rearrangement in alcohols was at first surprising. In typical experiments the mole ratio of alcohol hydroxyl to oxime hydroxyl ranged from 12:1 to 70:1, yet the acid anhydride reacted with the oxime hydroxyl exclusively. It seemed logical to explain this striking selectivity on the basis of ionization of the oxime, since the oxime anion would be expected to be much more effective in attacking the anhydride than the neutral alcohol molecule.<sup>5</sup> Evidence substantiating this hypothesis was obtained when 2,6-dioximinocyclohexanone was slurried in alcohols containing weak bases like pyridine and *n*-butylamine and treated with an equivalent of acetic anhydride. Under these conditions yields of oximino ester were very poor. This is the expected result, since the neutral oxime hydroxyl has no particular advantage over the neutral alcohol hydroxyl in reactivity toward the anhydride. On the basis of all these data, the probable course of the successful reaction with strong base is that shown below:



Interestingly, acid chlorides were much less selective than anhydrides in reacting with the oxime anion in preference to the alcohol. When used in conjunction with sodium ethoxide in ethanol, equivalent amounts of acetyl chloride, benzoyl chloride, and benzenesulfonyl chloride

(5) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1956, p. 300.

gave only 20–40% yields of ethyl 5-cyano-2-oximinovaleate, and substantial amounts of unchanged 2,6-dioximinocyclohexanone were recovered. It is possible that the poor performance of the acid chlorides is the result of their tendency to react, at least in part, by an  $S_N1$  mechanism. A situation where reaction with the alcohol by such a mechanism competed with nucleophilic attack by the oxime anion would be expected to give the observed result, namely some selectivity in favor of the oxime anion but not the complete selectivity observed with anhydride where  $S_N2$  attack is the only path of reaction.<sup>5</sup>

An effort was made to simplify the preparation of alkyl 5-cyano-2-oximinovaleates still further by preparing 2,6-dioximinocyclohexanone in an alcohol and carrying out the cleavage in the same solvent without isolating the dioxime. Since base is necessary for the cleavage reaction, a base-catalyzed nitrosation<sup>6</sup> was obviously most convenient. When a solution of cyclohexanone in ethanol containing slightly more than an equivalent of sodium ethoxide was treated with ethyl nitrite<sup>6</sup> and then with acetic anhydride, a 50% yield of ethyl 5-cyano-2-oximinovaleate was obtained. When the nitrosation was carried out in ethanol but in the presence of a catalytic amount of hydrochloric acid, and then enough sodium ethoxide was added to neutralize the acid and convert the 2,6-dioximinocyclohexanone to the monosodium salt, treatment with acetic anhydride gave a 64% yield of ethyl 5-cyano-2-oximinovaleate. Neither of these yields is quite as good as the 69% over-all yield obtained by isolating 2,6-dioximinocyclohexanone and then cleaving it in ethanolic sodium ethoxide with acetic anhydride. It should be noted, however, that the simpler processes were not studied in as much detail as the route involving isolation of 2,6-dioximinocyclohexanone.

When the cleavage step had been improved as described above, the only unsatisfactory yield remaining was that in the critical reduction step. An extended search was made in an effort to find a catalyst-solvent system which would permit hydrogenation of ethyl 5-cyano-2-oximinovaleate to lysine without the side reactions which apparently were responsible for the low yields obtained in earlier work.<sup>3,4</sup> In the course of this search the combination of Raney nickel and acetic anhydride was tried. Although Adkins' classic work on catalytic hydrogenation<sup>7</sup> states that this combination cannot be used, recent work<sup>8–10</sup>

has indicated that use of this catalyst-solvent system, particularly with the addition of sodium acetate or other weak base,<sup>8,9</sup> enables oximes to be hydrogenated in good yield to acetylated primary amines. The use of the combination of a Raney metal catalyst and an acid anhydride solvent in the hydrogenation of nitriles does not appear to have been reported. Surprisingly, this combination proved to be strikingly more effective in the reduction of ethyl 5-cyano-2-oximinovaleate than the apparently very similar platinum-acetic anhydride system. At 50 p.s.i. and 50°, and with sodium acetate as co-catalyst, hydrogenation usually was complete in about two hours, and lysine monohydrochloride was isolated in 92% yield after hydrolysis of the reaction mixture with hydrochloric acid. With a platinum catalyst, temperatures above 25° led to difficulty, and hydrogenation at 25° and 50 p.s.i. required eight hours and resulted in a yield of only 57%. Further study showed that even more rapid hydrogenation, complete in fifteen minutes, and equally good yields were obtained when strong bases such as sodium hydroxide, potassium hydroxide, or benzyltrimethylammonium hydroxide were used as co-catalysts. Very poor yields of lysine were obtained when no basic co-catalyst was used. The strong base co-catalysts had the additional advantage that the catalyst recovered after their use was as active as fresh catalyst, and could be re-used repeatedly. With a sodium acetate co-catalyst, the activity of the Raney nickel diminished markedly after each use, and was too low to be of practical use after three or four cycles. The platinum catalyst, by way of comparison, was completely inactive after a single use.

When the reaction mixture was worked up by evaporating excess acetic anhydride and the acetic acid formed in the reduction and by precipitating the co-catalyst from the resulting sirup by the addition of ethyl acetate and ether, the previously uncharacterized ethyl ester of *N,N'*-diacetyllysine was obtained in 98% yield. The somewhat lower yield obtained when lysine was isolated as the monohydrochloride was probably the result of mechanical losses in the crystallization step. The ethyl ester of *N,N'*-diacetyllysine was obtained as a viscous sirup which partially crystallized on long standing.

With the completion of the work reported here, the synthesis of lysine from cyclohexanone *via* 2,6-dioximinocyclohexanone reached its final form. The preferred route includes nitrosation of cyclohexanone with methyl nitrite to give 2,6-dioximinocyclohexanone (75%), partial cleavage of 2,6-dioximinocyclohexanone in ethanolic sodium ethoxide with acetic anhydride to give ethyl 5-cyano-2-oximinovaleate (92%), and hydrogenation of ethyl 5-cyano-2-oximinovaleate in acetic anhydride over Raney nickel with a basic co-catalyst

(6) O. Touster, *Org. Reactions*, **7**, 350 (1953).

(7) H. Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, Wis., 1937.

(8) S. I. Lur'e, G. A. Ravdel, and E. S. Chaman, *Zhur. Obshchei Khim.*, **22**, 2011 (1952); *J. Gen. Chem. U.S.S.R. (Eng. Transl.)*, **22**, 2065 (1952).

(9) M. Vignau, *Bull. soc. chim. France*, 638 (1952).

(10) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **9**, 23 (1955).

(92%). The over-all yield is 63%. With a slight penalty in yield the first two steps can be combined and the isolation of 2,6-dioximinocyclohexanone avoided. In either variation, this sequence of reactions offers probably the simplest and most direct chemical synthesis of lysine presently available.

#### EXPERIMENTAL<sup>11</sup>

*Methyl 5-cyano-2-oximinovalerate.* (1) *From sodium methoxide in methanol.* A solution of sodium methoxide in methanol was prepared by dissolving 5.0 g. (0.22 g.-atom) of sodium in 250 ml. of absolute methanol. To this solution was added 31.2 g. (0.20 mole) of 2,6-dioximinocyclohexanone,<sup>3</sup> and the mixture was stirred until most of the dioxime had dissolved. Then 22.0 g. (0.22 mole) of acetic anhydride was added dropwise, the temperature being held at 20–30° by external cooling. When addition was complete, the methanol was evaporated under reduced pressure. The residue was taken up in 500 ml. of ether, and the solid which failed to dissolve (sodium acetate) was removed by filtration. The filtrate was stirred with activated charcoal for an hour and dried over anhydrous magnesium sulfate. Removal of solids and evaporation of solvent under reduced pressure left 25.0 g. (74%) of liquid methyl 5-cyano-2-oximinovalerate,  $n_D^{25}$  1.4779. On long standing this material crystallized to a solid, m.p. 61.5–62°.

*Anal.* Calcd. for  $C_7H_{10}O_3N_2$ : C, 49.39; H, 5.92; N, 16.46. Found: C, 49.08; H, 5.95; N, 16.50.

(2) *From magnesium methoxide in methanol.* To a solution of 1.2 g. (0.05 g.-atom) of magnesium metal in 300 ml. of methanol was added 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone. While the temperature was maintained at 20–30° by external cooling, 10.2 g. (0.10 mole) of acetic anhydride was added. When addition was complete the cooling bath was removed, and the temperature rose to 40°. After the mixture had cooled to room temperature the solvent was evaporated under reduced pressure, and the residue was taken up in 500 ml. of ether. The solid which failed to dissolve was removed by filtration, and the filtrate was washed with 300 ml. of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether left 11.0 g. (65%) of liquid methyl 5-cyano-2-oximinovalerate. The infrared spectrum of this liquid was identical with that of an authentic sample of methyl 5-cyano-2-oximinovalerate.

(3) *From benzyltrimethylammonium hydroxide in methanol.* To a solution of 8.3 g. (0.05 mole) of benzyltrimethylammonium hydroxide in 300 ml. of methanol was added 7.8 g. (0.05 mole) of 2,6-dioximinocyclohexanone. Most but not all of the solid dissolved on stirring. While the temperature was maintained at 20–30° by external cooling 5.1 g. (0.05 mole) of acetic anhydride was added. The reaction mixture was worked up as described under (2) to give 5.0 g. (59%) of liquid methyl 5-cyano-2-oximinovalerate. The infrared spectrum of this sample was identical with that of an authentic sample.

*Ethyl 5-cyano-2-oximinovalerate.* (1) *From sodium ethoxide in ethanol.* To a solution of 13.8 g. (0.60 g.-atom) of sodium in 750 ml. of absolute ethanol was added 78.0 g. (0.50 mole) of 2,6-dioximinocyclohexanone. To the resulting slurry was added 61.0 g. (0.60 mole) of acetic anhydride over 30 min., the temperature being held at 20–30° by external cooling. The solvent was evaporated under reduced pressure at 60–70°, and the resulting semisolid mass was taken up in 1000 ml. of ether. The solid which failed to dissolve was removed by filtration, and the ether solution was washed with 1000 ml. of saturated sodium bicarbonate solution. After drying over magnesium sulfate, the ether was evaporated to leave

85.0 g. (92%) of solid ethyl 5-cyano-2-oximinovalerate. A portion of the material was recrystallized from carbon tetrachloride to give a white solid, m.p. 73°. A mixture of this solid and authentic ethyl 5-cyano-2-oximinovalerate<sup>3</sup> melted at 73°.

(2) *From potassium hydroxide in ethanol.* This reaction was carried out as described under methyl 5-cyano-2-oximinovalerate (2), using a solution of 5.6 g. (0.10 mole) of potassium hydroxide in 300 ml. of absolute ethanol, 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone, and 10.2 g. (0.10 mole) of acetic anhydride. There was obtained 12.0 g. (65%) of ethyl 5-cyano-2-oximinovalerate. The infrared spectrum of this sample was identical with that of an authentic sample.

*Isopropyl 5-cyano-2-oximinovalerate.* To 1000 ml. of isopropyl alcohol heated to 60° was added 13.0 g. (0.57 g.-atom) of sodium at 60–70°. When the sodium had dissolved, 78.0 g. (0.50 mole) of 2,6-dioximinocyclohexanone was added, and then, at 50–60°, 58.0 g. (0.57 mole) of acetic anhydride. When heat evolution had ceased, the solvent was evaporated under reduced pressure, and the residue was taken up in 1000 ml. of ether. The material which failed to dissolve was removed by filtration, and the filtrate was washed with 500 ml. of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether left 51.0 g. (51%) of isopropyl 5-cyano-2-oximinovalerate, an oil which crystallized on standing. Recrystallization of a portion of the material from 5:1 cyclohexane-ethyl acetate gave pure white crystals, m.p. 55–56°. The infrared spectrum of this material was identical with that of an authentic sample.<sup>4</sup>

*Benzyl 5-cyano-2-oximinovalerate.* To a solution of 2.3 g. (0.10 g.-atom) of sodium in 200 ml. of benzyl alcohol was added 15.6 g. (0.10 mole) of 2,6-dioximinocyclohexanone. The mixture was stirred until most of the solid had gone into solution, and then 10.9 g. (0.11 mole) of acetic anhydride was added, the temperature being held at 20–30°. After addition was complete the alcohol was evaporated under reduced pressure, and the residue was taken up in 1000 ml. of ether. The insoluble material was removed by filtration, and the filtrate was evaporated under reduced pressure. Since some product appeared to have remained in the insoluble solid, the filter cake was taken up in water, and the material which failed to dissolve was combined with the residue from the evaporation of the ether filtrate. This procedure gave a total of 14.0 g. (54%) of crude benzyl 5-cyano-2-oximinovalerate, m.p. 125–130°. A portion of the crude solid was recrystallized three times from benzene to give pure benzyl 5-cyano-2-oximinovalerate, m.p. 132–134°. The infrared spectra of the crude and recrystallized materials were identical.

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_3$ : C, 63.40; H, 5.73; N, 11.38; Found: C, 63.20; H, 5.52; N, 10.97.

*Ethyl 5-cyano-2-oximinovalerate by the one-step procedure.* (1) *Base-catalyzed nitrosation.* To a solution of 5.0 g. (0.22 g.-atom) of sodium in 300 ml. of absolute ethanol was added 19.6 g. (0.20 mole) of cyclohexanone. A separate ethyl nitrite generator was charged with 36.0 g. (0.52 mole) of sodium nitrite, 24.0 g. (0.52 mole) of ethanol, and 40 ml. of water, and was connected to the reactor by a tube leading below the liquid level in the reactor. With the generator at 25°, a solution of 40.0 g. (0.40 mole) of sulfuric acid in 40 ml. of water was added dropwise to the nitrite-ethanol solution, thereby generating ethyl nitrite, which passed over into the reactor. The reactor was stirred vigorously and was maintained at 30–40° by external cooling. When all the ethyl nitrite had been admitted, the reactor contents were stirred for an additional 30 min. Then while the temperature was maintained at 20–30°, 24.0 g. (0.24 mole) of acetic anhydride was added dropwise. When addition was complete volatile materials were evaporated under reduced pressure, and the residue was taken up in 500 ml. of ether. The material which failed to dissolve was removed by filtration, and the filtrate was washed with saturated sodium bicarbonate

(11) All melting points are uncorrected.

solution, decolorized with activated charcoal, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 18.0 g. (50%) of crude ethyl 5-cyano-2-oximinovalerate. Recrystallization of a portion of this material from carbon tetrachloride gave pure ethyl 5-cyano-2-oximinovalerate, m.p. 73–74°. The infrared spectrum of this material was identical with that of an authentic sample.

(2) *Acid-catalyzed nitrosation.* Into a solution of 19.6 g. (0.20 mole) of cyclohexanone and 4 ml. of concd. hydrochloric acid in 150 ml. of absolute ethanol was passed 39.1 g. (0.52 mole) of ethyl nitrite generated as described in the preceding experiment. The reaction temperature was held at 30–40° by external cooling. The mixture was stirred for 30 min. after all the nitrite had been admitted, then a solution of 6.0 g. (0.25 g.-atom) of sodium in 150 ml. of absolute ethanol was added. The basic solution which resulted was held at 20–30° by external cooling while 22.0 g. (0.22 mole) of acetic anhydride was added. When addition was complete volatile materials were evaporated under reduced pressure, and the residue was taken up in 300 ml. of ether. The solid which failed to dissolve was removed by filtration, and the filtrate was washed with saturated sodium bicarbonate solution, decolorized with activated charcoal, and dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure to leave 23.0 g. (64%) of crude ethyl 5-cyano-2-oximinovalerate. A portion of this material was recrystallized from carbon tetrachloride to give pure ethyl 5-cyano-2-oximinovalerate, m.p. 73–74°. The infrared spectrum of this compound was identical with that of an authentic sample.

*DL-Lysine monohydrochloride.* (1) *Hydrogenation of ethyl 5-cyano-2-oximinovalerate over Raney nickel with sodium acetate co-catalyst.* A portion of Raney nickel<sup>11</sup> amounting to 3–5 g. was washed twice with 20-ml. portions of ethanol, then twice with 20-ml. portions of acetic anhydride. The washed catalyst and 6.0 g. of anhydrous sodium acetate were then added immediately to a solution of 18.4 g. (0.10 mole) of ethyl 5-cyano-2-oximinovalerate in 120 ml. of acetic anhydride. The resulting mixture was heated to 50° and shaken under hydrogen at an initial pressure of 50 p.s.i. The theoretical amount of hydrogen was taken up in about 2 hr. The catalyst was removed by filtration, and the filtrate was stirred with 80 ml. of water for several hours to decompose the acetic anhydride. Then 180 ml. of concd. hydrochloric acid was added, and the mixture was heated under reflux for 16 hr. The resulting solution was evaporated under reduced pressure to a sirupy mass. The mass was treated with two 50-ml. portions of concd. hydrochloric acid, and evaporated to a sirup after the addition of each portion. The final residue was taken up in 200 ml. of boiling 95% ethanol, and a solution of 10 ml. of pyridine in 20 ml. of ethanol was added. DL-Lysine monohydrochloride began to

precipitate almost immediately. To ensure complete precipitation the mixture was held at 5° for 24 hr. At the end of this time 15.6 g. (86%) of DL-lysine monohydrochloride, m.p. 262–264°, was recovered by filtration. Another 1.2 g. was recovered by concentration of the filtrate. The total yield was thus 16.8 g. (92%). The infrared spectrum of this product was identical with that of an authentic sample of DL-lysine monohydrochloride.

(2) *Hydrogenation of ethyl 5-cyano-2-oximinovalerate with benzyltrimethylammonium hydroxide co-catalyst.* A 2–3 g. portion of Raney nickel, washed as described under (1) above, was added along with 1.5 g. of benzyltrimethylammonium hydroxide to a solution of 9.2 g. (0.05 mole) of ethyl 5-cyano-2-oximinovalerate in 60 ml. of acetic anhydride. The resulting mixture was heated and shaken under hydrogen at an initial pressure of 50 p.s.i. until 50° was reached. At this point a vigorously exothermic reaction set in, which raised the temperature to 75° in a few minutes with external heating cut off. The theoretical amount of hydrogen was taken up in 15 min. The reaction mixture was worked up as described under (1) above, halving all quantities of reagents. There was obtained 8.0 g. (88%) of DL-lysine monohydrochloride. The infrared spectrum of this material was identical with that of an authentic sample.

*Ethyl ester of N,N'-diacetyllysine.* The procedure described under DL-lysine monohydrochloride (1) was followed, except that the sodium acetate was replaced by 3.0 g. of potassium hydroxide. Hydrogen uptake was complete in 15 min., the temperature rising from 50 to 70° during this time with no external heating. The catalyst was removed by filtration, and the acetic acid and acetic anhydride were evaporated from the filtrate under reduced pressure. The viscous sirupy residue was taken up in 100 ml. of ethyl acetate, and the solid which separated was removed by filtration. When 300 ml. of ether was added to the filtrate, it separated into two layers. The ether (upper) layer was separated, and the lower layer was taken up in 50 ml. of ethyl acetate. A small amount of solid separated and was removed by filtration. The filtrate was evaporated under reduced pressure to give 25.2 g. (98%) of sirupy but essentially pure ethyl ester of N,N'-diacetyllysine. The analysis given below was obtained on the sirupy material. On long standing the sirup partially crystallized.

*Anal.* Calcd. for C<sub>12</sub>H<sub>22</sub>O<sub>4</sub>N<sub>2</sub>: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.98; H, 8.57; N, 10.62.

*Acknowledgment.* The assistance of John E. Zarembo and his staff in carrying out the analyses reported herein and of Herman Adelman and his staff in obtaining and assisting in the interpretation of infrared spectra is gratefully acknowledged.

PRINCETON, N. J.

(11) Obtained in active form under water from the Raney Catalyst Co., Chattanooga, Tenn.