was found to have b.p. 85–90° (0.1 mm.) and n_D^{23} 1.4420. Passage of anhydrous hydrogen chloride into an ether solution of this ester deposited the *hydrochloride* of *dimethyl* DL-*aspartate*, which crystallized from ethanol–ethyl acetate as slightly hygroscopic, colorless, hard prism clusters, m.p. 115–116.5°, undepressed on admixture with an authentic specimen prepared from DL-aspartic acid.

Anal. Calcd. for $C_6H_{11}O_4N \cdot HCl$ (197.63): C, 36.46; H, 6.12; N, 7.09. Found: C, 36.67; H, 6.17; N, 7.10.

Acknowledgment. We are deeply grateful to Dr. F. E. King, F.R.S., British Celanese Ltd., for supplying a generous comparison sample of *L*(−)-baikiain and to Professor Joseph H. Burckhalter for giving much helpful advice and encouragement during the course of this work. We also wish to thank the University of Kansas for providing a grant from the General Research Fund and the General Aniline and Film Corp. for furnishing *cis*-2-butene-1,4-diol.

LAWRENCE, KAN.

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

α-Oximinoketones. V. The Synthesis of 5-Cyano-2-oximinovaleric Acid and DL-Lysine from 2,6-Dioximinocyclohexanone[1]

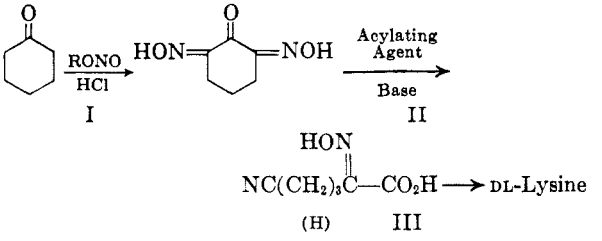
ARTHUR F. FERRIS, GRANNIS S. JOHNSON,[2] FRANCIS E. GOULD, AND HAROLD K. LATOURETTE

Received September 4, 1959

A new three-step synthesis which gives DL-lysine monohydrochloride in 20% overall yield from cyclohexanone has been developed. The reaction sequence is: (1) conversion of cyclohexanone to 2,6-dioximinocyclohexanone by the action of methyl nitrite, (2) partial cleavage of 2,6-dioximinocyclohexanone to 5-cyano-2-oximinovaleric acid by the action of acylating agent and aqueous base, and (3) reduction of 5-cyano-2-oximinovaleric acid to DL-lysine by catalytic hydrogenation.

The importance of L-lysine as an essential amino acid in the diet of man and some higher animals and its relative scarcity in most of the common cereal proteins have led to many attempts to prepare this amino acid synthetically. Perhaps the largest number of published syntheses have proceeded from ε-caprolactam (most commonly prepared by Beckmann rearrangement of cyclohexanone oxime).[3] Other favorite starting materials have been malonic ester[4–6] or its derivative, acetamidomalonic ester.[7,8] Several elegant syntheses have been based on oxygen-containing heterocyclic materials such as acrolein dimer (3,4-dihydro-2H-pyran-2-carboxaldehyde)[9] or furfural.[10–12]

The need for a better method of preparing DL-lysine than any of those described has led to an extended effort in this laboratory to realize the deceptively simple three-step synthesis shown in equation form below:



This research is described in this and the next two papers of this series.

The preparation of 2,6-dioximinocyclohexanone (Step I) was described first by Borsche[13] and has been studied more recently by Treibs and coworkers.[14] The reduction of the ethyl ester of 5-cyano-2-oximinovaleric acid has been carried out successfully,[4–6] so that it seemed logical to believe that step III could be made to succeed. The critical step thus appeared to be II, which may be described as a partial "second order" Beckmann rearrangement, wherein it was desired to bring about rearrangement at one oxime group but not at the

(1) A preliminary account of this and the next two papers in this series was published in *Chem. & Ind. (London)*, 996 (1959).

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

(3) R. J. Wineman, E. T. Hsu, and C. E. Anagnostopoulos, *J. Am. Chem. Soc.*, **80**, 6233 (1958); W. C. Francis, J. R. Thornton, J. C. Werner, and T. R. Hopkins, *J. Am. Chem. Soc.*, **80**, 6238 (1958). Previous work is summarized in these papers.

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

(5) H. Borsook, C. L. Deasy, A. J. Haagen-Smit, G. Keighley, and P. H. Lowy, *J. Biol. Chem.*, **176**, 1383 (1948).

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

(7) M. Servigne and E. Szarvasi, *Compt. rend.*, **238**, 1595 (1954).

(8) D. T. Warner and O. A. Moe, *J. Am. Chem. Soc.*, **70**, 2763, 3918 (1940).

(9) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5280 (1951).

(10) A. O. Rogers, R. D. Emmick, L. W. Tyran, L. B. Phillips, A. A. Levine, and N. D. Scott, *J. Am. Chem. Soc.*, **71**, 1837 (1949).

(11) R. Gaudry, *Can. J. Research*, **26B**, 387 (1948).

(12) H. Conroy, U. S. Patents **2,786,848** and **2,786,850**, March 26, 1957; H. Conroy and W. J. Paleveda, U. S. Patent **2,786,849**, March 26, 1957.

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

(14) A. Treibs and D. Dinelli, *Ann.*, **517**, 152 (1935); A. Treibs and A. Kuhn, *Chem. Ber.*, **90**, 1691 (1957).

other. Although the second order Beckmann rearrangement is well enough known to be discussed in several general references[15-17] and to have been the subject of at least one careful study,[18] no record was found of any attempt to carry out the reaction only once in a system capable of reacting twice. The fact that the intermediate α-oximino acid should react further to give a nitrile, carbon dioxide, and water under acylating conditions is well documented.[19] In addition, at the time that this work was undertaken, it was not completely certain that aliphatic and cycloaliphatic α-oximino ketones existed completely in the *anti* form, an essential feature of the proposed synthesis.[18] However, the work of Taylor[20] on the metal complexes of α-oximino ketones made it appear reasonable to assume before experiments were undertaken that 2,6-dioximinocyclohexanone existed in the *anti* form.

As expected, step I of the synthesis presented no serious problems. The treatment of cyclohexanone with methyl nitrite in the presence of hydrochloric acid, a modification[21] of the Borsche[13] synthesis, gave 2,6-dioximinocyclohexanone consistently in about 75% yield.

Before serious study of step II was undertaken, preliminary experiments were carried out to establish with certainty the configuration of 2,6-dioximinocyclohexanone. 2-Oximinocyclohexanone was prepared from 2-carbethoxycyclohexanone[22] by the method of Geissman and Schlatter,[23] and it was subjected to the second order Beckmann rearrangement. The action of benzenesulfonyl chloride and aqueous base gave a 71% yield of 5-cyanovaleric acid, identified by hydrolysis to adipic acid. Very recently Murakami and Tokura[24] have shown that 2-oximino-1-tetralone is cleaved by thionyl chloride in liquid sulfur dioxide to *o*-(2-cyanoethyl)benzoic acid, but unfortunately the results of their work had not been published at the time that our preliminary experiments were carried out. In a second experiment, 2,6-dioximinocyclohexanone was treated with three equivalents of benzenesulfonyl chloride and base, and a 50% yield of glutaronitrile was obtained. (Borsche[25] tentatively identified glutaronitrile as one of the products obtained by the action of base on 2,6-dibenzoyloximinocyclohexanone.) The fact that these reactions all give nitriles and not isonitriles[18] indicated that 2,6-dioximinocyclohexanone and the other cyclic α-oximino ketones possess the desired *anti* configuration. This left little doubt that the proposed synthesis was feasible, and the key problem then became the question of stopping the rearrangement at the desired intermediate point.

Two major lines of approach to the problem of partial rearrangement were taken: The first consisted of attempting to induce a chemical difference between the two oximino groups so that one would react and the other would not; the second consisted of using a deficiency of acylating agent in the rearrangement, accepting the necessity of recovering and recycling a considerable amount of starting material, and hoping thus to save a considerable portion of the intermediate 5-cyano-2-oximinovaleric acid from attack. All attempts to use the first approach failed. Although simple α-oximino ketones can be alkylated easily,[26] only tars were obtained in experiments designed to produce monoalkyl derivatives of 2,6-dioximinocyclohexanone. Tarry products were obtained likewise in efforts to reduce the dioxime to 2-amino-6-oximinocyclohexanone or derivatives thereof.

The second approach proved to be more fruitful. When 2,6-dioximinocyclohexanone was dissolved in aqueous base and treated with a deficiency of acylating agent, 5-cyano-2-oximinovaleric acid was formed. The most difficult problem in connection with this step was that of finding a method of isolation for the very water soluble product. The first successful method of isolation was based on the observation of Aymaretto[27] that complexes of α-oximino acids with copper, nickel, or cobalt ions were soluble in base but insoluble in dilute acids. Thus, in working up the reaction mixtures from the partial rearrangement (or, probably better, partial cleavage[28]) the solutions were acidified, the unchanged 2,6-dioximinocyclohexanone which precipitated was removed by filtration, and a solution of nickel sulfate was added to precipitate the nickel complex of 5-cyano-2-oximinovaleric acid. Some acylating agents were considerably more effective in the partial cleavage reaction than others, the best being acetic anhydride, which gave yields of nickel complex as high as 68% (based on 2,6-dioximinocyclohexanone not recovered). The best yield obtained with benzenesulfonyl chloride was only 35%, and with phosphorus oxychloride 15%. Free 5-cyano-2-oximinovaleric acid was obtained

(15) A. H. Blatt, *Chem. Revs.*, **12**, 218 (1933).
(16) V. Migrdichian, *Org. Synthesis*, **Vol. 1**, Reinhold Publishing Corp., New York, 1957, p. 376.
(17) E. F. Degering, *An Outline of Organic Nitrogen Compounds*, University Lithoprinters, Ypsilanti, Mich., 1950, p. 184.
(18) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934).
(19) R. E. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, J. Wiley and Sons, Inc., New York, 1953, p. 598.
(20) T. W. J. Taylor and E. K. Ewbank, *J. Chem. Soc.*, 2818 (1926); T. W. J. Taylor, *J. Chem. Soc.*, 2018 (1931).
(21) O. Touster, *Org. Reactions*, **7**, 351 (1953).
(22) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, *Org. Syntheses*, **Coll. Vol. II**, 531 (1943).
(23) T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).
(24) D. Murakami and N. Tokura, *Bull. Chem. Soc. Japan*, **31**, 1044 (1958). We are indebted to Dr. Tokura for sending us a copy of this publication.
(25) Ref. 13, p. 305.
(26) A. F. Ferris, *J. Org. Chem.*, **24**, 1726 (1959).
(27) M. Aymaretto, *Gazz. chim. ital.*, **57**, 648 (1927).
(28) A. F. Ferris, *J. Org. Chem.*, **25**, 12 (1960).

from the nickel complex by treating a solution of the complex in aqueous base with dimethylglyoxime, removing the precipitated nickel dimethylglyoxime by filtration, evaporating the filtrate under reduced pressure, treating the residue with ethanolic hydrochloric acid, removing sodium chloride by filtration, evaporating the filtrate, and recrystallizing the crude acid from chloroform. The yield of pure 5-cyano-2-oximinovaleric acid obtained by this technique was 57% based on nickel complex; hence, the overall yield based on 2,6-dioximinocyclohexanone was 38%.

The yield of step II was improved considerably by the development of better techniques of isolation. The best method was based on saturating the acidified reaction mixture with an inorganic salt and then extracting with a normally water soluble solvent. When isopropanol was used as the solvent the crude extract contained some inorganic salt and had to be purified further by extraction with ether. Pure 5-cyano-2-oximinovaleric acid was precipitated from the ether solution by the addition of hexane or chloroform. The yield of partial cleavage product from 2,6-dioximinocyclohexanone was 62% with this recovery system. A similar system based on ethyl acetate as the extracting solvent gave a somewhat poorer yield, 53%.

In view of the report[6] that catalytic hydrogenation of ethyl 5-cyano-2-oximinovalerate to DL-lysine proceeds readily, serious difficulty had not been anticipated in step III of the proposed synthesis. In actual fact, however, finding a combination of catalyst and solvent which would bring about the hydrogenation of 5-cyano-2-oximinovaleric acid to lysine proved very difficult. As had been anticipated, acetic anhydride, the solvent used[6] in the reduction of the ethyl ester, could not be used because it rearranged the acid to glutaronitrile, carbon dioxide being evolved. A number of other catalyst-solvent systems commonly used in the hydrogenation of nitriles and/or oximes[29,30] were tried without success, including platinum and palladium-on-charcoal in ethanolic hydrochloric acid, and Raney nickel and precious metal catalysts in ethanolic ammonia. The nickel complex of 5-cyano-2-oximinovaleric acid was found to be soluble in ethanolic ammonia, and attempts were made to hydrogenate it in the presence of a variety of catalysts, all without success. In most of these failures hydrogen was taken up—in many instances the theoretical amount—but in no case was the product lysine. Although the nature of the products was not investigated, it seemed probable that the failures could be attributed to the condensation reactions leading to secondary amines which are well known complications[29,30] in many reductions of nitriles to primary amines.

(29) H. Adkins and R. L. Shriner in H. Gilman, *Organic Chemistry*, Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, 1943, p. 809.

(30) Ref. 19, p. 658.

It was ultimately found that the combination of platinum (from *in situ* reduction of platinum oxide) as catalyst and acetic acid as solvent led to uptake of the theoretical amount of hydrogen and to isolation of lysine as the monohydrochloride upon treating the reaction mixture with hydrochloric acid. The classic technique of Eck and Marvel[31] was used in the isolation of the DL-lysine monohydrochloride. A study of the reduction ultimately raised the yield of DL-lysine monohydrochloride to 43%. At this point in the development of the new lysine synthesis, the overall yield of lysine from cyclohexanone was 20%.

Since the hydrogenation of the ethyl ester of 5-cyano-2-oximinovaleric acid had been reported[6] to proceed in much better yield (73%) than that obtained in this study with the acid, conversion of the acid to the ester followed by hydrogenation of the ester seemed to offer an opportunity to improve the over-all yield of the process. Because of the ease with which the acid is decomposed in acidic media, conventional esterification techniques could not be used. However, by adding a little thionyl chloride to a solution of the acid in ethanol and allowing the mixture to stand at room temperature for a few days,[32] ethyl 5-cyano-2-oximinovalerate was prepared in 61% yield. When hydrogenated in acetic anhydride in the presence of platinum this material was reduced, and DL-lysine monohydrochloride was obtained upon hydrolysis of the reaction mixture with hydrochloric acid. However, even in an extended series of experiments it was never possible to duplicate the reported yield of 73%.[6] A number of variations involving changes in amount of solvent and catalyst gave yields consistently in the range of 50–57%. Thus, by proceeding through the ester the yield of lysine from 5-cyano-2-oximinovaleric acid was 35%, and over-all from cyclohexanone, 16%. The route involving hydrogenation of the acid is to be preferred, since it gave a better over-all yield of lysine in fewer steps.

EXPERIMENTAL[33,34]

2,6-Dioximinocyclohexanone. To a solution of 491 g. (5.00 moles) of cyclohexanone in 2500 ml. of ether was added 100 ml. of concentrated hydrochloric acid. The solution was cooled to 10°, and nitrogen was passed slowly through it for 10–15 min. Then, with nitrogen flow continuing, methyl nitrite was passed in slowly from an external generator. The methyl nitrite was generated by adding a solution of 320 ml. (5.75 moles) of concentrated sulfuric acid in 575 ml. of water dropwise to a mixture of 845 g. (11.25 moles) of sodium nitrite, 400 g. (12.50 moles) of methanol, and 750 ml. of water. The temperature was maintained at 5–15° by ex-

(31) J. C. Eck and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. II,** 374 (1943).

(32) K. Freudenberg and W. Jakob, *Ber.*, **74,** 1001 (1941).

(33) All melting points are uncorrected.

(34) Most of the microanalyses were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

ternal cooling while the methyl nitrite was passed in over about 5 hr. A yellow solid precipitated as the reaction proceeded. When all the methyl nitrite had been added the cooling bath was removed, and the mixture was allowed to warm to about 25°. Any tendency for the temperature to rise above this point was controlled by intermittent cooling. After 3 hr. at 25° the hydrochloric acid was neutralized by the addition of 100 ml. of pyridine. (If the product was to be used within a few days for the next step of the reaction, neutralization was not necessary.) The yellow solid product was recovered by suction filtration, and was washed on the filter with 500 ml. of acetone. It was sucked as dry as possible, and then was dried further in a vacuum desiccator. There was obtained 612 g. (78%) of yellowish brown 2,6-dioximinocyclohexanone, pure enough for use in the next step of the reaction. For an analytical sample, a portion of the crude product was recrystallized four times from 2:1 methanol-water. The final product was a mass of fine yellow needles which showed no definite melting point, but charred slowly in the range of 160–200° when heated in a capillary.

Anal. Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.95. Found: C, 46.22; H, 5.17; N, 17.77.

5-Cyano-2-oximinovaleric acid. To a solution of 200 g. (5.0 moles) of sodium hydroxide in 2000 ml. of water was added 156.1 g. (1.0 mole) of 2,6-dioximinocyclohexanone. The temperature was held at 20–25° while the oxime dissolved to give an orange-brown solution. With vigorous stirring 51.1 g. (0.5 mole) of acetic anhydride was added over 30 min., the temperature being held at 20–30°. After stirring for 1 hr., a solution of 150 ml. of concentrated sulfuric acid in 150 ml. of water was added slowly, the temperature being held at 20–25°. Unchanged 2,6-dioximinocyclohexanone precipitated and was recovered by filtration, washed with two 100-ml. portions of water, and dried. Recovered 2,6-dioximinocyclohexanone amounted to 88.5 g. The filtrate, amounting to 2530 ml., was saturated with sodium sulfate and extracted once with 1000 ml. of isopropanol and once with 500 ml. The combined isopropanol solution was concentrated *in vacuo* at 50° to a slurry. The slurry was extracted with four 400-ml. portions of ether, the ether solution was dried, and the ether was evaporated at reduced pressure. There was obtained 42.0 g. of 5-cyano-2-oximinovaleric acid, m.p. 105° dec., a 54% yield based on acetic anhydride and a 62% yield based on 2,6-dioximinocyclohexanone not recovered. A portion of this material was recrystallized by being taken up in hot ethyl acetate (5 ml./g. solid) and precipitated by addition of two volumes of a 3:1 hexane-chloroform mixture. The recrystallized acid melted at 109–110° dec.

Anal. Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.95; neut. equiv., 156.1. Found: C, 46.44; H, 4.92; N, 17.94; neut. equiv., 155.1.

Ethyl 5-cyano-2-oximinovalerate. To a solution of 31.0 g. (0.20 mole) of 5-cyano-2-oximinovaleric acid in 400 ml. of absolute ethanol was added 5.5 g. (0.046 mole) of thionyl chloride. The mixture was allowed to stand at room temperature. Each day a 1 ml. aliquot was removed, diluted with water, and titrated with 0.1*N* sodium hydroxide. When the acidity remained constant (9 days) the ethanol was removed by distillation at reduced pressure at 40–50°. The solid residue was recrystallized twice from carbon tetrachloride to give 20.0 g. (61%) of pure ethyl 5-cyano-2-oximinovalerate, m.p. 74–75°, (lit.,[4] m.p. 74°).

Reduction of 5-cyano-2-oximinovaleric acid. In a solution of 7.8 g. (0.10 mole) of 5-cyano-2-oximinovaleric acid in 100 ml. of glacial acetic acid was suspended 0.6 g. of platinum oxide (Adams' catalyst), and the mixture was shaken at room temperature with hydrogen at 50 p.s.i. After 8 hr. the theoretical amount of hydrogen had been taken up. The catalyst was filtered from the reaction mixture, and the acetic acid was evaporated under reduced pressure at 40–50°. The residue was treated with 25 ml. of concentrated hydrochloric acid, and the excess was evaporated under reduced pressure. This treatment was repeated, and after evaporation to dryness there remained 7.9 g. of solid. This was taken up in 100 ml. of boiling 95% ethanol, and a solution of 10 ml. of pyridine in 10 ml. of 95% ethanol was added. A white solid separated slowly. After several days standing the solid was recovered by filtration and dried. It amounted to 3.9 g. (43%) of DL-lysine monohydrochloride, m.p. 258–262°. The infrared spectrum of this product was identical with that of an authentic sample of DL-lysine monohydrochloride.

Reduction of ethyl 5-cyano-2-oximinovalerate. In a solution of 36.8 g. (0.20 mole) of ethyl 5-cyano-2-oximinovalerate in 200 ml. of acetic anhydride was suspended 3.0 g. of platinum oxide, and the mixture was shaken at room temperature with hydrogen at 50 p.s.i. In about 8 hr. the theoretical amount of hydrogen was taken up. The catalyst was filtered from the reaction mixture and washed with 25 ml. of acetic anhydride. The filtrate was heated with 300 ml. of water at 50°, and the mixture was stirred until it became homogeneous. Then 450 ml. of concentrated hydrochloric acid was added, and the resulting solution was heated under reflux for 16 hr. The water and hydrochloric acid were evaporated at reduced pressure at 50–60°. The resulting sirup was treated twice with 100-ml. portions of concentrated hydrochloric acid, evaporating to a sirup after each treatment. The final sirup was dissolved in 200 ml. of boiling 95% ethanol. The solution was cooled to room temperature and 800 ml. of ether was added. A white precipitate of DL-lysine dihydrochloride formed. The supernatant liquid was decanted, and the solid was dissolved in 850 ml. of hot absolute ethanol. To the hot solution was added 48 ml. of pyridine in 100 ml. of hot ethanol. A white solid precipitated at once. The solution was held for 16 hr. at 5° to complete the precipitation, then the solid was recovered by filtration and dried. It amounted to 21.0 g. (57%) of DL-lysine monohydrochloride, m.p. 256–260°. Its infrared spectrum was identical with that of an authentic sample of DL-lysine monohydrochloride.

Acknowledgment. The authors gratefully acknowledge the assistance of Otmer H. Huffman in carrying out many of the experiments herein described, of Duane K. Chapman and Herman Adelman in taking and helping to interpret infrared spectra, and of Raymond Annino and his associates in carrying out a number of analyses.

PRINCETON, N. J.