mole) of compound XIII reacted with 2.7 g. of phosphorus tribromide (0.03 equiv.) in 80 ml. of dry ether containing 0.56 ml. of pyridine for three hours at −30° and was allowed to stand overnight at room temperature. A spectroscopic examination of the bromide itself and of the two fractions obtained by partition between 95% methanol and petroleum either showed no absorption above 230 mμ even in high concentrations. This shows that no significant amount of spontaneous dehydrobromination had occurred. Seven grams of the crude bromide (XIV), obtained after decomposition of the reaction mixture with water, was dried *in vacuo* and dissolved in 250 ml. of acetone. Upon refluxing of this solution with 40 g. of anhydrous potassium carbonate for twelve hours and filtration, the residue of the acetone solution was taken up in 350 ml. of low boiling petroleum ether (40–60°) and extracted eight times with 35-ml. portions of 95% methanol. Evaporation of the petroleum ether layer yielded 2.44 g. of crude product which was purified by a succession of slow evaporative distillations and chromatographic separations on aluminum oxide. The purified end-product boiled at 48° ($10^{-2}$ mm.); $n^{27}D$ 1.5855 (extrapolated for $n^{20}D$ 1.590), λ max. 315 mμ, ε max. 22,000. This compound was very sensitive and unstable on standing.

*Anal.* Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72; $OCH_3$, 12.19. Found: C, 82.43; H, 8.88; $OCH_3$, 11.13.

**Acknowledgment.**—We wish to thank Mrs. Edith Rosen Kaplan and Miss Bernice Hamerman for their able and painstaking assistance.

## Summary

1. The preparation of an analog of vitamin A methyl ether, which differs from it by the absence of three methyl groups on the ring and by containing two triple bonds in the conjugated system, and of the corresponding analog of β-ionylideneethanol, the lower isoprenolog of vitamin A, is described.

2. The preparation of trisnor-dehydro-β-ionone and several other intermediates, especially that of the 3,4-epoxide of 1-cyclohexenyl-3 methyl-1-butyne is reported and the reaction of the latter with ethyl magnesium bromide is discussed.

NEW YORK 29, N. Y. RECEIVED JUNE 8, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

# Amino Acids. II. A New Synthesis of DL-Lysine[1]

BY DONALD T. WARNER AND OWEN A. MOE

DL-Lysine has been synthesized by the reduction of ethyl α-isonitroso-δ-cyanovalerate,[1a] by reduction and hydrolysis of ethyl α-carbethoxy-α-phthalimido-δ-cyanovalerate,[2] from benzoyl piperidine[3] through the intermediate ε-benzoylaminocaproic acid,[4,5] by action of hydrazoic acid[6] upon the proper cyclic ketone,[7] and by a multistep procedure using β-chloropropionaldehyde diethylacetal.[8] The present report describes a new synthesis of DL-lysine which involves γ-acetamido-γ,γ-dicarbethoxybutyraldehyde[9] as the key intermediate. A previous report[10] from this laboratory has demonstrated the usefulness of the phenylhydrazone of this aldehydo compound I in the synthesis of DL-tryptophan and DL-ornithine monohydrochloride.

The addition of liquid hydrogen cyanide to a solution of the aldehydo compound I in benzene yielded the cyanohydrin II. When the reaction mixture was cooled, crude II (m. p. 83.5–85°) was deposited as a white crystalline material in yields of approximately 80%. After recrystallization from benzene, the material was pure and melted at 86.5–87.5°.

However, it was not necessary to isolate the cyanohydrin II as a crystalline material. Either a benzene solution of the cyanohydrin or the crude oily product could be treated directly with acetic anhydride. Presumably, the acetate III was formed which on heating yielded the unsaturated nitrile IV. This was considered a probable course since reduction of the unsaturated nitrile IV in the presence of platinum oxide yielded the diacetamido compound V in approximately 50% yield based on the aldehydo compound I. The structure of V was proved by an unequivocal synthesis involving alkylation of ethyl acetamidomalonate by γ-chlorobutyronitrile followed by the catalytic reduction of the product in the presence of acetic anhydride.

Dehydration of the cyanohydrin, II, with phosphorus oxychloride presumably yielded compound IV directly since it was converted to compound V by reduction in the presence of platinum oxide and acetic anhydride. The pure diacetamido compound, V, was hydrolyzed by the action of acid to DL-lysine dihydrochloride in 77% yield. The over-all yield of DL-lysine dihydrochloride based on the cyanohydrin, II, was approximately 40%. The DL-lysine dihydrochloride was converted to the monohydrochloride and the dibenzoyl derivative in accordance with known procedures.

(1) Paper No. 91, Journal Series, General Mills, Inc., Research Department.

(1a) Fischer and Weigert, *Ber.*, **35**, 3772 (1902).

(2) Sörensen, *Compt. rend. trav. lab.* Carlsberg, **6**, 1 (1903).

(3) V. Braun, *Ber.*, **42**, 839 (1909).

(4) Eck and Marvel, *J. Biol. Chem.*, **106**, 387 (1934).

(5) Galat, THIS JOURNAL, **69**, 86 (1947).

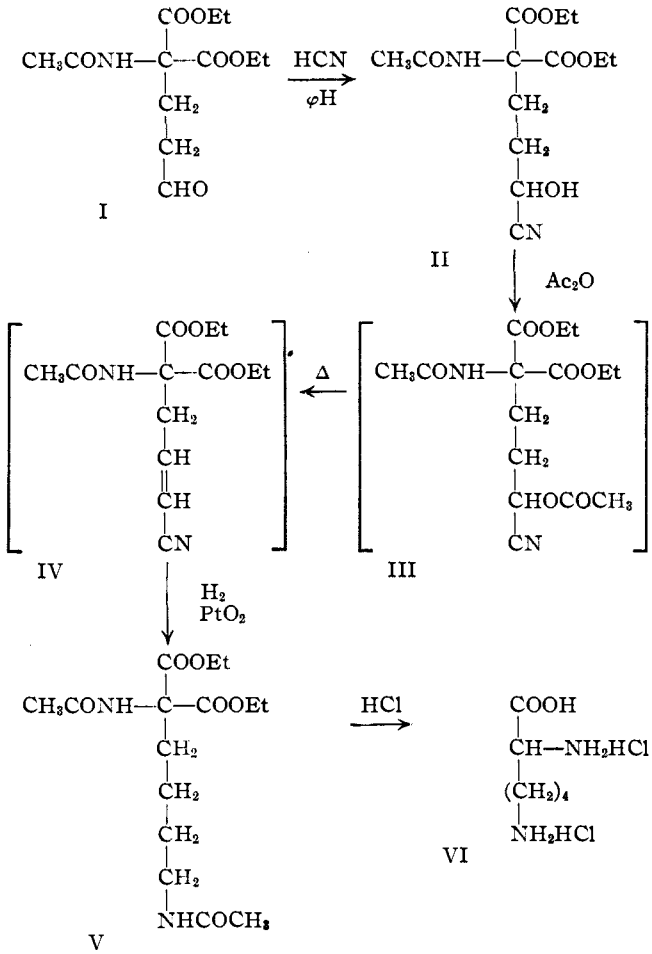
(6) Schmidt, *Ber.*, **57**, 704 (1924); **58**, 2413 (1925).

(7) Adamson, *J. Chem. Soc.*, 1564 (1939).

(8) Sugasawa, *J. Pharm. Soc. Japan*, **550**, 1044 (1927), from *Chem. Abst.*, **22**, 1572 (1928).

(9) Moe and Warner, THIS JOURNAL, **70**, 2763 (1948).

(10) Warner and Moe, THIS JOURNAL, **70**, 2765 (1948).




## Experimental[11]

**Preparation of the Cyanohydrin, II.—A.** An alcoholic solution (128 cc.) of the crude aldehydo compound I[9] (0.25 mole) was mixed with 14 cc. of liquid hydrogen cyanide at 0°. After complete mixing, 6 drops of 50% aqueous potassium hydroxide were added. The resulting reaction mixture was maintained at 5° for a period of forty-eight hours. After neutralization by the addition of 85% phosphoric acid (0.6 cc.), the mixture was concentrated *in vacuo*. A viscous, light yellow oil resulted.

**B.** The isolation of the crystalline cyanohydrin was accomplished in the following manner: A benzene solution (225 cc.) of the aldehydo compound (0.25 mole) was mixed with 17 cc. of liquid hydrogen cyanide at 5°. The temperature of the reaction mixture increased to 10°. Then the aqueous potassium hydroxide (6 drops of 50% solution) was added and the reaction mixture was placed in the refrigerator for ninety hours. After neutralization with 1 cc. of 85% phosphoric acid, the mixture was returned to the refrigerator overnight. The white crystalline product was collected by filtration and dried. The yield of the crude cyanohydrin II melting at 83.5–85° was 59.8 g. (approximately 80%).

An analytical sample was prepared by two crystallizations from benzene (m. p. 86.5–87.5°).

*Anal.* Calcd. for $C_{13}H_{20}O_6N_2$: C, 52.00; H, 6.71; N, 9.33. Found: C, 52.26; H, 6.72; N, 9.16.

**Preparation of the Diacetamido Compound, V.—A.** The viscous yellow oil (0.25 mole) obtained under **A.** above was mixed with 40 cc. of acetic anhydride and heated at 85° for one hour. The reaction mixture was concentrated *in vacuo* at 70°. The residual oil weighed 80 g. and it was mixed with 180 cc. of acetic anhydride and 3 g. of platinum oxide. The reduction was carried out at room temperature at 1250 pounds initial pressure. After twenty-one hours the reduction was complete and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* and the viscous residue thus obtained crystallized rapidly. Ether (250 cc.) was added and the mixture was macerated in order to remove some oily product. Filtration and drying yielded 46 g. of the crude diacetamido compound V melting at 123–128°. The product was suspended in ether (100 cc.) and macerated again. The solid was collected and dried. The yield of the diacetamido compound V was 44.9 g. (52% yield based on I) and melted at 127.5–130°.

An analytical sample was prepared by two crystallizations from benzene–alcohol (m. p. 132.5–133.5°).

*Anal.* Calcd. for $C_{15}H_{26}O_6N_2$: C, 54.51; H, 7.93; N, 8.48. Found: C, 54.28; H, 7.6; N, 8.78.

**B.** The cyanohydrin compound II (10 g., m. p. 86.5–87.5°) was dissolved in 15 cc. of benzene and 15 cc. of pyridine. Phosphorus oxychloride (7 cc.) was added, and the temperature of the reaction mixture increased rapidly to 50°. Cooling was necessary in order to maintain the temperature below 50°. The resulting reaction mixture was permitted to stand at room temperature overnight and then poured into iced hydrochloric acid. Benzene (100 cc.) was added and the benzene layer was collected, washed with water, sodium bicarbonate solution and water. After drying over anhydrous sodium sulfate, the benzene was removed by distillation *in vacuo* and the residual oil weighed 6.2 g. The oil was dissolved in 40 cc. of acetic anhydride at 20°. Platinum oxide (0.5 g.) was added, and the mixture was subjected to hydrogenation at room temperature and an initial pressure of 1300 pounds of hydrogen. When the reduction was complete, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residual oil was mixed with 200 cc. of ether and an immediate precipitate was obtained. The product was collected by filtration and dried *in vacuo*. Five grams melting at 128–130° was obtained. Recrystallization from benzene increased the melting point to 131.5–133°. No depression in the melting point was observed when mixed with the product obtained under **A.**

**C. Alkylation of Acetomidomalonate with γ-Chlorobutyronitrile.**—Ethyl acetamidomalonate (32.55 g.) was dissolved in 150 cc. of absolute ethanol containing 16.6 g. of γ-chlorobutyronitrile. Sodium iodide (0.35 g.) was added, and the solution was heated to the reflux temperature, when a solution of sodium ethoxide (3.45 g. of sodium and 100 cc. of absolute ethanol) was added dropwise with stirring over a ninety-minute period. The reaction mixture was refluxed for an additional twenty-four hours. After cooling, the precipitated sodium chloride was removed by filtration and the filtrate was concentrated *in vacuo* to remove excess ethanol. The residue was dissolved in 200 cc. of benzene and washed with four 50-cc. portions of saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the benzene was removed by distillation, yielding a viscous oil. The residual oil was distilled *in vacuo*. Considerable quantities of γ-chlorobutyronitrile and ethyl acetamidomalonate were collected in the first fraction. However, a substantial fraction (5.8 g.) was collected at 135–136° (0.04 mm.), $n^{25}D$ 1.4645.

The crude ethyl α-acetamido-α-carbethoxy-δ-cyanovalerate (2 g.) was dissolved in 15 cc. of acetic anhydride and reduced at room temperature and an initial pressure of 1300 pounds hydrogen in the presence of platinum oxide. When the reduction was complete, the catalyst was removed by filtration and the filtrate concentrated *in vacuo*

(11) The authors are indebted to James R. Kerns for the microanalyses.

to yield a residual oil. The addition of 50 cc. of ether yielded 0.7 g. of the crude reduction product melting at 90–115°. Recrystallization from absolute ethanol increased the melting point to 129–131.5°, and an additional recrystallization from benzene yielded the pure diacetamido compound IV melting at 132–133° and the melting point was not depressed when mixed with compounds under A and B.

*Anal.* Calcd. for $C_{15}H_{26}O_6N_2$: N, 8.48. Found: N, 8.58.

**Preparation of DL-Lysine Dihydrochloride.**—The purified diacetamido compound, V (33.6 g., m. p. 132–133°) was mixed with 200 cc. of concentrated hydrochloric acid. The resulting reaction mixture was refluxed for a period of eighteen hours. The resulting water-clear solution was concentrated *in vacuo* and a solid mass resulted. The residual solid was dissolved in 150 cc. of boiling 95% ethanol. After filtration the alcoholic solution was diluted with 50 cc. of ether and permitted to stand overnight. The white crystalline product was collected by filtration, washed with 80 cc. of ethanol–ether (50–50) solution, and dried *in vacuo*. The yield of DL-lysine dihydrochloride was 17.1 g. (77%) melting at 181–186° (dec.).

The dihydrochloride (2.9 g.) was converted to the monohydrochloride (m. p. 256–258° (dec.)). Mixed melting point with authentic sample (Eastman Kodak Co.) showed no depression.

*Anal.* Calcd. for $C_6H_{15}O_2N_2Cl$: C, 39.44; H, 8.27; N, 15.34; Cl, 19.4. Found: C, 39.13; H, 7.90; N, 15.67; Cl, 18.8.

Treatment of either the dihydrochloride or the monohydrochloride with an excess of benzoyl chloride yielded the dibenzoyl derivative melting at 145–146°. When mixed with an authentic sample of dibenzoyl-lysine, it melted at 145–146°.

*Anal.* Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.76; H, 6.27; N, 7.91. Found: C, 68.01; H, 6.14; N, 7.85.

The dipicrate was prepared and melted at 185–187° (dec.) after drying.

## Summary

1. A new synthesis of DL-lysine has been described.

2. An intermediate product, namely, ethyl α-carbethoxy-α-ε-diacetamidocaproate, has been prepared by three different synthetic routes.

MINNEAPOLIS 13, MINN. RECEIVED JUNE 10, 1948

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[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY, TULANE UNIVERSITY]

# Action of the Grignard Reagent on β-D-Glucose Pentaacetate

BY C. G. JEREMIAS[1] AND C. A. MACKENZIE

A number of authors have reported the formation of addition compounds between esters and Grignard reagents with the original ester being recovered on hydrolysis of the reaction product. Fischer[2] in 1912 claimed the formation of such products for glucose pentaacetate, acetobromoglucose, glucose tetraacetate and methyl tetraacetyl-β-D-glucoside when each compound was treated with methylmagnesium iodide. Analyses indicated addition compounds with the Grignard reagent and the ester combined in a 2:1 molar ratio. Hydrolysis of the products returned the original esters in good yields. In 1930 Fröschl and Zellner[3] reported similar results using methyl- and ethylmagnesium iodides. The 2:1 ratio resulted even when a large excess of the Grignard reagent was used. In all of the above work the reagents were mixed in a reaction vessel set in an ice-bath.

Different results were reported by Paal and Hörnstein.[4] They stated, without giving their experimental evidence, that the treatment of glucose pentaacetate with phenylmagnesium bromide resulted in the formation of a tertiary alcohol, diphenylmethylcarbinol. Hurd and Bonner,[5] have recently reported the same result for these reagents.

## Discussion

The purpose of the present work was to test the behavior of glucose pentaacetate toward various Grignard reagents in an effort to determine if tertiary alcohols were generally formed in such reactions or if the addition type compounds first described by Fischer and Hess were to be expected.

We have used Grignard reagents prepared from methyl iodide, *n*-butyl bromide and bromobenzene. Molar ratios of Grignard reagent to ester of 2:1 and 10:1 were employed. The reagents were mixed at 0–5° and 25–35°.

The reaction, in general, proceeded in a normal fashion, that is, tertiary alcohols were formed. In view of the fact there was a marked decrease in the yield of tertiary alcohol at the lower temperature, it seems possible that the 2:1 addition compounds might be obtained if the reaction temperature should be decreased further. At the temperatures used, however, we obtained no evidence for the formation of the previously described addition compounds.

Glucose was obtained in a good yield as a product of the reaction. In connection with the isolation of this product, it is of interest to note that the Grignard reagent did not add to the glucose pentaacetate by opening its ring structure. Reaction was with the acetate groups only.

## Experimental

The preparation of 5-methyl-5-nonanol, described below, is representative of the type of procedure employed.

Glucose pentaacetate (48.8 g., one eighth mole) was dissolved in 250 ml. of chloroform (1000 ml. of benzene or 2500 ml. of diethyl ether may be used in place of the chloroform). One quarter mole of *n*-butylmagnesium bromide (added as a solution of 0.5 *M* butylmagnesium bromide in ether) was placed in a three-liter three-neck flask. The

(1) Present address, Tennessee Eastman Corp., Kingsport, Tenn.
(2) Fischer and Hess, *Ber.*, **45**, 912 (1912).
(3) Fröschl and Zellner, *Monatsh.*, **55**, 25 (1930).
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(5) Hurd and Bonner, THIS JOURNAL, **67**, 1972 (1945).