A NEW SYNTHESIS OF DL-γ-HYDROXY-ORNITHINE[1,2]

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ABSTRACT

A convenient synthesis of DL-hydroxy-ornithine is described. Starting from diethyl allylmalonate, it involves treatment with sulphuryl chloride followed by hydrolysis and distillation to give a 90% yield of 2,5-dichloro-4-valerolactone. Condensation of this with two equivalents of potassium phthalimide in dimethylformamide gives a quantitative yield of crude 2,5-diphthalimido-4-valerolactone. This lactone is converted quantitatively by acid hydrolysis to DL-γ-hydroxy-ornithine, isolated as the dihydrochloride of the corresponding 2,5-diamino-4-valerolactone. The over-all yield calculated from allyl chloride is 80%.

INTRODUCTION

2,5-Diamino-4-hydroxyvaleric acid (hydroxy-ornithine), a "non-natural" amino acid, was first synthesized in 1916 by Hammarsten (8), starting from allylhippuric acid. Other syntheses, developed by Traube, Johow, and Tepohl (13) in 1923, involved condensation between epichlorhydrin and diethyl malonate. In 1926, Tomita and Fukagawa (11) condensed 1-chloro-2-hydroxy-3-phthalimidopropane with diethyl phthalimidomalonate and in 1935, Tomita and Nakashima (12) reported on similar compounds. An attempt to synthesize hydroxy-ornithine from histidine by Langenbeck and Hutschenreuter (9) in 1929 has proved to be unsuccessful. Finally, Dey (3), in 1937, published a synthesis in which 1,2-epoxy-3-phthalimidopropane was condensed with diethyl malonate.

However, these various condensations led to extremely low yields of hydroxy-ornithine and consequently are not suitable for the preparation of substantial quantities of this amino acid. The need for a readily available intermediate thus became obvious.

The 2,5-dichloro- or 2,5-dibromo-valerolactones, which can be readily obtained (5), were first considered as possible starting materials. However, treatment of these lactones with ammonia favored cyclization to hydroxy-proline (5).

It was therefore decided to investigate the condensation of these 2,5-dihalogenated-4-valerolactones with potassium phthalimide.

Diethyl allylmalonate (III) was prepared in a 91% yield by condensation of allyl chloride (I) and diethyl malonate (II). Treatment of diethyl allylmalonate (III) with sulphuryl chloride or addition and substitution of bromine to the unsaturated free acid (IV) in chloroform, followed in both cases by acid hydrolysis and vacuum distillation, gave respectively a 90% yield of the 2,5-dichloro-4-valerolactone (V) and a 73% yield of the dibromo derivative (VI) (based on

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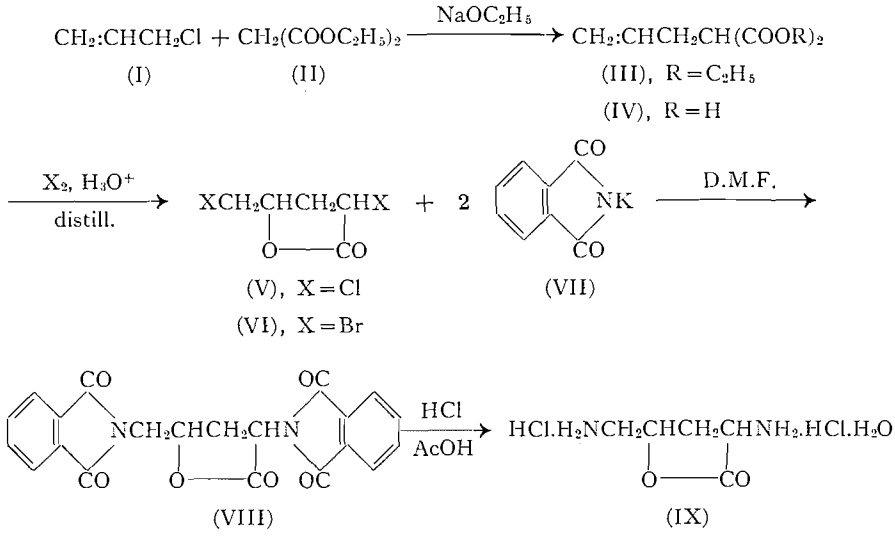
allylmalonic acid, itself obtainable in 82% yield by saponification of the corresponding diester).



The next step involved condensation of the dihalogenated lactones with two equivalents of potassium phthalimide (VII). Dimethylformamide (D.M.F.) was successfully used as a solvent for this reaction while other solvents like toluene or xylene (7) did not lead to a homogeneous product. In this manner, the two lactones led to a quantitative yield of crude 2,5-diphthalimido-4-valerolactone (VIII) which is virtually insoluble and which was best purified with little lost by treatment with activated charcoal in a large volume of glacial acetic acid.

The hydrolysis of the 2,5-diphthalimido-4-valerolactone (VIII) with a mixture of glacial acetic acid and concentrated hydrochloric acid gave a nearly quantitative yield of hydroxy-ornithine isolated as 2,5-diamino-4-valerolactone dihydrochloride monohydrate (IX).

The over-all yield of hydroxy-ornithine through the dichlorolactone amounted to 80% based on allyl chloride.

EXPERIMENTAL*

Diethyl Allylmalonate (III)

Using the method of Conrad and Bischoff (2), 153 gm. of allyl chloride (I) and 641 gm. of diethyl malonate (II) were condensed to give diethyl allylmalonate (III). Yield: 364 gm. (91%), b.p. 71–73° (1.5 mm.), n_D^{20}: 1.430. (Lit.: b.p. 93° (6 mm.) (4), n_D: 1.433 (6) or n_D^{20}: 1.430 (7).)

2,5-Dichloro-4-valerolactone (V)

Diethyl allylmalonate (III) (169.3 gm.) was treated with sulphuryl chloride (243 gm.), then hydrolyzed and vacuum distilled to give 2,5-dichloro-4-

**Melting points are uncorrected.*

valerolactone (V) as described by Gaudry and Godin (5). Yield: 129.1 gm. (90.5%), b.p. 118–121° (2 mm.), n_D^{20}: 1.495. (Lit.: b.p. 159–161° (13 mm.) (10), $n_D^{24.6}$: 1.496 (1).) Anal. Calc. for $C_5H_6O_2Cl_2$: Cl, 42.0. Found: Cl, 41.6.

Allylmalonic Acid (IV)

Saponification of 100 gm. of diethyl allylmalonate (III) by sodium hydroxide, followed by acidification, gave allylmalonic acid (IV). Yield: 58.8 gm. (82%), m.p. 103°. (Lit.: m.p. 103° (2).)

2,5-Dibromo-4-valerolactone (VI)

Allylmalonic acid (IV) (58.8 gm.) was treated with bromine (163 gm.) as described by Gaudry and Godin (5). The yield of 2,5-dibromo-4-valerolactone (VI) was 83.3 gm. (73%), b.p. 156–157° (4 mm.), n_D^{20}: 1.557. (Lit.: b.p. 150–151° (3 mm.), n_D^{20}: 1.555 (7).) Anal. Calc. for $C_5H_6O_2Br_2$: Br, 62.0. Found: Br, 62.1.

2,5-Diphthalimido-4-valerolactone (VIII)

2,5-Dichloro-4-valerolactone (V) (106.9 gm., 0.63 mole) was added dropwise, at room temperature, to a mechanically stirred suspension of potassium phthalimide (VII) (262 gm., 1.41 moles) in dimethylformamide (800 ml.). The mixture was then heated to about 100° for six hours. The liquid was slowly poured into four liters of water with vigorous stirring, the cold suspension filtered, and the residue washed thoroughly with water–ethanol mixture (4:1) and dried at 105° for several hours. The amorphous material thus obtained was sufficiently pure for use in the next step. Yield of crude product: 252 gm. Recrystallization from a large volume of glacial acetic acid gave crystals, m.p. 263°. (Lit.: m.p. 260° (3).) Anal. Calc. for $C_{21}H_{14}N_2O_6$: N, 7.18. Found: N, 7.24.

2,5-Diamino-4-valerolactone Dihydrochloride Monohydrate (IX)

A mixture of glacial acetic acid (350 ml.), concentrated hydrochloric acid (700 ml.), and 2,5-diphthalimido-4-valerolactone (VIII) (70.0 gm., 0.18 mole) was heated under reflux for 24 hr. The rather insoluble compound dissolved gradually as the hydrolysis proceeded. The filtrate was evaporated to dryness under reduced pressure after the phthalic acid had been removed from the cold solution. The residue was dissolved in water and the solution was decolorized with Norit, concentrated to a small volume, and precipitated by the addition of ethanol. Recrystallization from water–ethanol mixture gave the monohydrate of the 2,5-diamino-4-valerolactone dihydrochloride (IX). Yield: 38.8 gm. (98%), m.p. 239°. (Lit.: m.p. 239–240° (13).) Anal. Calc. for $C_5H_{10}O_2N_2.2HCl.H_2O$: N, 12.68; Cl, 32.05. Found: N, 12.68; Cl, 31.80.

The dihydrochloride when filtered through a column of a strongly basic resin (Permutit S-1) apparently gave the monohydrochloride, which could not be isolated. However, a chloride determination on an aliquot from the eluate gave a figure roughly equivalent to one half of the total chloride content of the dihydrochloride. The monopicrate, obtained by treating the eluate with one equivalent of picric acid, had a sharp melting point of 180° instead of 185–190° as reported by Hammarsten (8).

The 2,5-diamino-4-valerolactone, being a weak base, migrated toward the cathode when submitted to paper electrophoresis in a buffer solution of pH 8.6. The 2,5-diamino-4-valerolactone had a R_f value of about 0.24 on circular chromatograms in 80% pyridine – 20% water system, while in phenol saturated with water the R_f value for a one-dimensional chromatogram was around 0.10.

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