A Novel Synthesis of β-Hydroxyvaline

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Received February 5, 1971

The synthesis of β-hydroxyvaline from ethyl β,β-dimethylacrylate through 1,2-di(ethoxycarbonyl)-3,3-dimethylaziridine as intermediate shows a new way of preparation of this amino acid.

La synthèse de la β-hydroxyvaline à partir du β,β-diméthylacrylate d'éthyle en passant par le diéthoxycarbonyl-1,2 diméthyl-3,3 aziridine comme intermédiaire, illustre une nouvelle méthode de synthèse de cet acide aminé.

Canadian Journal of Chemistry, 49, 2610 (1971)

Until now several methods have been used to synthesize β-hydroxyvaline (1–7). However in none of these methods was 1,2-di(ethoxycarbonyl)-3,3-dimethylaziridine (**3**) used as intermediate.

The objective of our work was the preparation of such an aziridine. The opening of this aziridine with different reagents could be a general method for the synthesis of different derivatives of valine. The hydrolysis of these derivatives will lead to the corresponding amino acids. This note shows that the synthesis of such an aziridine is possible and the opening of the aziridine ring leads to the β-hydroxyvaline. Thus by following the method similar to that described by Lwowski and Maricich (8) the reaction of ethyl β,β-dimethylacrylate with *N*-(*p*-nitrobenzenesulfonoxy)urethan in the presence of triethylamine permitted the formation of the aziridine **3**, b.p. 110–115/0.1 mm Hg (dec.), yield 14% (see Scheme 1). Opening of the aziridine **3** with acetic acid gave ethyl 3-acetoxy-2-(ethoxycarbonylamino)-3-methylbutanoate (**4**), b.p. 115 ± 5°/0.09 mm Hg, yield 25%, and ethyl 2-(ethoxycarbonylamino)-3-methyl-3-butenoate (**5**) b.p. 90–100°/0.09 mm Hg, yield 28%. Compounds **4** and **5** were separated by chromatography. Alkaline hydrolysis of **4** with aqueous potassium hydroxide followed by elution on Rexyn 101 H gave β-hydroxyvaline (**6**), m.p. 221–223° (lit. 226–227° (5)), yield 10%.

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The synthesis of penicillamine using the novel method described herein is presently under active investigation in our laboratory.

Experimental

Solutions were concentrated under reduced pressure using a rotary evaporator and a water bath at a temperature of 40° and less. Reaction mixtures and products were examined by t.l.c. using silica gel GF-254, hexane–ether (50:50 v/v), and spray of 50% sulfuric acid in ethanol followed by heating at 200 °C. Melting and boiling points were uncorrected.

The i.r. spectra were recorded on a Beckman model IR-8 double beam spectrometer. The n.m.r. spectra were recorded on a Varian A-60 spectrometer. Mass spectra were done on a Hitachi–Perkin–Elmer model RMU 6-D. Elemental analyses were performed by Midwest Microlab Inc., Indianapolis, Indiana.

Ethyl β,β-Dimethylacrylate (1)

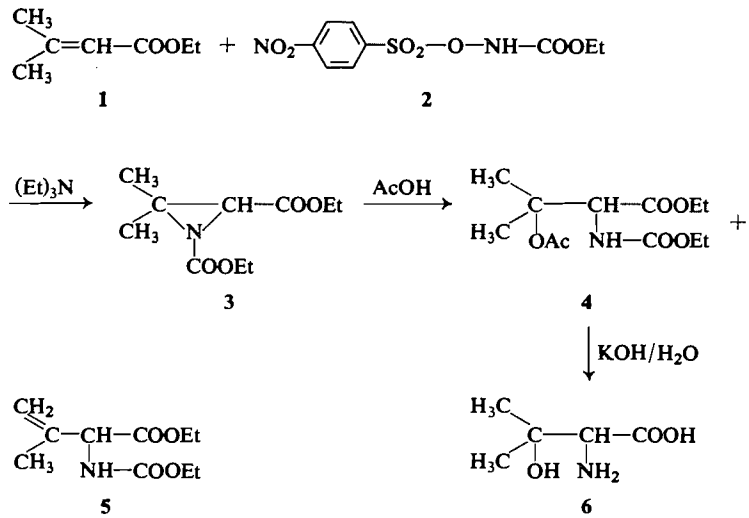
Product **1** was obtained from β,β-dimethyl acrylic acid by the method described by Moureu and Chovin (9); b.p. 152–153 °C (lit. (9) 153 °C).

N-(p-Nitrobenzenesulfonoxy)urethan (2)

Product **2** was prepared from *N*-hydroxyurethan and *p*-nitrobenzenesulfonyl chloride as described by Lwowski and Maricich (8); m.p. 114 °C (lit. (8) 116.4–116.8 °C).

1,2-Di(ethoxycarbonyl)-3,3-dimethylaziridine (3)

To a solution of 4.28 g (0.030 mol) of **1** and of 8.705 g (0.030 mol) of **2** in dichloromethane (100 ml) was added with stirring over a period of 1 h a solution of 3.33 g (0.033 mol) of triethylamine in dichloromethane (20 ml). After the mixture was stirred for 3 h, it was poured into ether (1000 ml). Triethylammonium *p*-nitrobenzenesulfonate was eliminated by filtration and the solution concentrated under reduced pressure. The oily residue was chromatographed on silica gel with hexane–ether



SCHEME 1

(90:10 v/v) as eluant to give the pure aziridine **3**; yield 0.89 g (14%), t.l.c. R_f 0.50; b.p. 110–115°/0.10 mm Hg (dec.); i.r. bands ($CHCl_3$) at 1720, 1382, and 1370 cm^{-1}; τ(CCl_4) 8.76 and 8.74 (6H, triplet), 8.71 and 8.69 (6H, singlet), 7.17 (1H, singlet), 5.91 and 5.96 (4H, quadruplet); mass spectra *m/e* 215.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.79; H, 7.96. Found: C, 55.51; H, 7.84.

Ethyl 3-Acetoxy-2-(ethoxycarbonylamino)-3-methylbutanoate (4) and Ethyl 2-(Ethoxycarbonylamino)-3-methyl-3-butenoate (5)

Compound **3**, (4.80 g, 0.022 mol), was added slowly during 3 h to glacial acetic acid (35 ml) at reflux. Once the addition finished the acetic acid was removed *in vacuo*, ether (200 ml) was added, the solution was dried over K_2CO_3, filtered, and evaporated. The oily residue was chromatographed on silica gel and eluted with hexane–ether (90:10 v/v) to obtain products **4** and **5**.

Product **4**, 1.720 g (28%); t.l.c. R_f 0.40; b.p. 115 ± 5°/0.09 mm Hg; i.r. bands (CCl_4) at 3460, 1745, 1730, and 1510 cm^{-1}; τ (CCl_4) 8.71 and 8.77 (6H, triplet), 8.47 and 8.53 (6H, singlet), 8.09 (3H, singlet), 5.83 and 5.93 (4H, quadruplet), 5.51 (1H, doublet), and 4.23 (1H, doublet).

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.35; H, 7.68. Found: C, 52.76; H, 7.97.

Product **5**, 1.19 g (25%); t.l.c. R_f 0.50; b.p. 90–100°/0.09 mm Hg; i.r. bands (CCl_4) at 3460, 1730, 1650, and 1500 cm^{-1}; τ (CCl_4) 8.73 and 8.77 (6H, triplet), 8.23 (3H, singlet), 5.83 and 5.93 (4H, quadruplet), 5.35 (1H, doublet), 5.05 (2H, multiplet), 4.43 (1H, doublet); mass spectra *m/e* 215.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.79; H, 7.96. Found: C, 55.62; H, 7.68.

β-Hydroxyvaline (6)

Compound **4**, (1.720 g, 0.0062 mol), was added to 25 ml of an aqueous solution of 1.00 *N* potassium hydroxide and heated at reflux for 18 h. The solution was concentrated *in vacuo* and passed on Rexyn 101H (10 g) and eluted with water. After evaporation of the water the yellow residue was crystallized in methanol to give β-hydroxyvaline 75 mg (10%), m.p. 221–223° (lit. (5) 226–227°); i.r. bands (Nujol) at 3200, 1670, 1600, and 1560 cm^{-1}; τ (D_2O) 8.53 and 8.73 (6H, singlet), 6.38 (1H, singlet) 6.15 (4.6H, DHO singlet).

Anal. Calcd. for $C_5H_{11}NO_3$: C, 45.03; H, 8.25. Found: C, 44.91; H, 7.94.

We thank the National Research Council of Canada for financial support.

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