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SYNTHESIS OF 4-AMINO-2-HYDROXYBUTYRIC ACIDS

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1,3-Dipolar addition of the nitronic ester 1 to methyl acrylate and methyl crotonate afforded the corresponding adducts, 2 and 6, respectively. These were converted to the 4-amino-2-hydroxybutyric acids, 5 and 8.

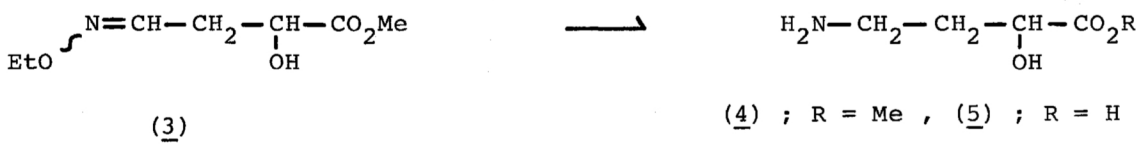
Recent investigation on the modification of antibiotics disclosed that acylation of kanamycin with L-4-amino-2-hydroxybutyric acid at the C-1 amino group of deoxystreptamine moiety improved the antibiotic activities ;[1] the acylated kanamycin inhibited some kanamycin resistant microorganisms including Pseudomonas species. This amino acid, 4-amino-2-hydroxybutyric acid, has been discovered as a constituent of an antibiotics, butyrosin,[2] and was synthesized[3] from 2-hydroxybutyrolactone.

In the course of our studies on 1,3-dipolar addition of nitronic esters, we have found nonconjugated nitronic esters regiospecifically reacted with α,β-unsaturated carbonyl compounds to give 5-substituted isoxazolidines.

This paper deals with a new synthesis of 4-amino-2-hydroxybutyric acids, (5) and (8), from the adducts of nitronic ester (1) to acrylic esters.

The nitronic ester (1) was prepared by the ethylation of sodium salt of nitromethane with triethyloxonium fluoroborate at 0°C and the ester was directly allowed to react with methyl acrylate. The cycloaddition reaction smoothly proceeded at -10°C

(1) + $CH_2=CHCO_2Me$ → (2) →



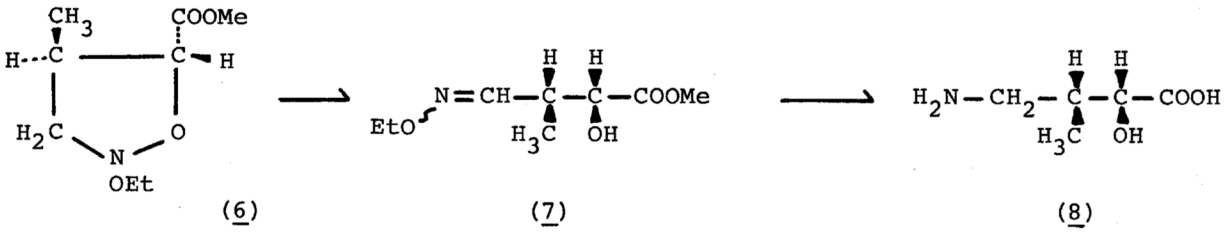
(3) →

$H_2N-CH_2-CH_2-CH(OH)-CO_2R$

(4) ; R = Me , (5) ; R = H

to yield a 1:1 adduct. The regiospecific formation of (2) was revealed from the NMR spectrum; the spectrum showed a double-doublet at 4.66 ppm assignable to the proton at C-5 besides a broad triplet at 3.60 ppm due to the methylene protons at C-3 of the isoxazolidine ring. The adduct (2) resisted hydrogenation on palladium or platinum oxide even in the presence of acid. Heating of (2) at 100°C afforded the ethoxyimino compound (3) in quantitative yield; $\nu_{max}(CCl_4)$: 3450,1735,1630 cm^{-1}. The compound (3) is a mixture of syn and anti isomers because the two triplets appear at 6.75 (J = 5 Hz) and 7.40 (J = 6 Hz) ppm due to EtO-N=C-H protons in the NMR spectrum. Catalytic hydrogenation of the ethoxyimino compound (3) with platinum oxide afforded methy 4-amino-2-hydroxybutyrate (4) in a good yield. Acid catalyzed hydrolysis of the methyl ester and subsequent purification by ion exchanger chromatography gave the desired hydroxyamino acid (5) ; mp 189-191°C(lit. 191-192°C). The NMR spectrum and Rf values of the paper chromatography under various solvent systems were identical with those of the authentic sample.[4)]

The nitronic ester (1) also reacted with methyl crotonate to give a cycloaddition product (6); $\delta(CCl_4)$: 1.33 (d,3H),2.5-3.5 (m,3H),4.3 (d,1H) ppm. An isomerization of (6) was effected by heating (6) at 100°C to give rise to the ethoxyimino compound (7), which was converted to 4-amino-2-hydroxy-3-methylbutyric acid (8); $\delta(D_2O)$: 1.05 (3H,d, J = 7 Hz),2.2 (1H,br.),3.05 (2H,d,J = 6 Hz),4.0 (1H,d,J = 4 Hz) ppm by hydrogenation followed by hydrolysis.



(6) (7) (8)

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4) The authors thank Dr. T. Naito, Bristol-Banyu Research Laboratories, for providing the authentic sample of 4-amino-2-hydroxybutyric acid.

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