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Synthesis of 4-Amino-2-hydroxybutanoic Acid and Its 3-Methyl Derivative

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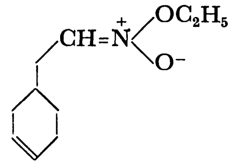
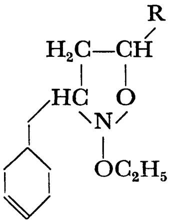
1,3-Dipolar addition of the nitronic ester (**3**) to methyl acrylate afforded regiospecifically the isoxzolidine (**4**), which produced the oxime ether (**7**) on heating. Reduction of **7** followed by hydrolysis gave the hydroxy amino acid (**6**), which is known to improve anitibiotic activities. The nitronic ester (**3**) also reacted regio- and stereospecifically with methyl crotonate to produce the adduct (**8**). Pyrolysis of (**8**) followed by reduction and hydrolysis gave the *erythro* hydroxy amino acid (**11**).

Recent investigation of the modification of antibiotics disclosed that acylation of kanamycin with L-4-amino-2-hydroxybutanoic acid (**6**) at the C-1 amino group of deoxystreptamine moiety improved the antibiotic activities;[1] the acylated kanamycin inhibited some kanamycin resistant microorganisms including *Psudomonas* species. This amino acid, 4-amino-2-hydroxybutanoic acid (**6**), was discovered as a constituent of an antibiotic butyrosin,[2] and had been synthesized[2] from 2-hydroxybutyrolactone in conjunction with the synthesis of deoxyeritadenine. In the course of studies on the new annelation reaction we have found that, whereas the nitronic ester (**1**) was not cyclized by intramolecular 1,3-dipolar cycloaddition of the nitronic ester group to the isolated double bond,[4] **1** was regiospecifically condensed to an acrylate or acrylonitrile to give isoxazolidines (**2a** and **2b**). The fuctionalities in the adduct (**2a**), an oxygen atom at α-position and a nitrogen atom at γ-position to the carboxy ester group indicate a new synthetic route to the 4-amino-2-hydroxybutanoic acid (**6**).

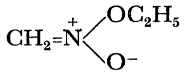

(**1**)

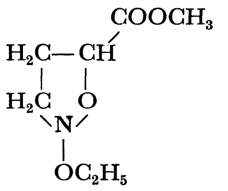

(**2a**; R=COOCH$_3$)
(**2b**; R=CN)

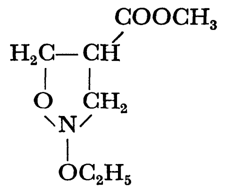
This paper deals with a new synthesis of 4-amino-2-hydroxybutanoic acid (**6**) and its 3-methyl derivative (**11**) from the adducts of the nitronic ester (**3**) with methyl acrylate and metyl crotonate.

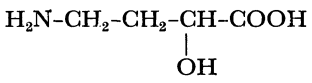
Many methods are known for the preparation of nitronic esters. The *O*-alkylation of sodium, potassium, or silver salts of nitroalkanes with alkyl halides has been examined extensively. The initial product is found to be nitronic esters, but they decompose easily to form oximes and carbonyl compounds. The ester (**3**) was thus prepared by the ethylation of sodium salt of nitromethane with triethyloxonium fluoroborate at 0 °C,[6] the ester being used for the reaction with methyl acrylate without purification. The cycloaddition reaction proceeded smoothly at −10 °C to yield a 1 : 1-adduct. Although two structures, (**4**) and (**5**), were considered feasible for the adduct, the NMR spectrum and TLC showed the exclusive formation of **4**. The spectrum showed a double-doublet at 4.66 assignable to the proton at C-5 besides other signals consistent with structure (**4**).

The isoxazolidine (**4**) was quantitatively converted into a mixture of *syn*- and *anti*-oxime ethers (**7**) on heating at 100 °C. The NMR spectrum of the mixture showed two signals with almost equal intensities at 7.40 and 6.75, which are assignable to protons attached to imino carbon atoms of *syn*- and *anti*-oxime ethers, respectively. Catalytic hydrogenation of the oxime ethers over platinum oxide afforded methyl 4-amino-2-hydroxybutanoate in a good yield. Acid catalyzed hydrolysis and purification by ion exchange chromatography afforded the hydroxy amino acid (**6**) in 37% overall yield from adduct (**4**). The NMR spectrum and R_f value in paper chromatography of the synthetic hydroxy amino acid (**6**) were identical with those of natural 4-amino-2-hydroxybutanoic acid.


(**3**)

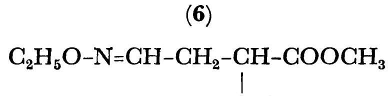

(**4**)


(**5**)



$$H_2N\text{-}CH_2\text{-}CH_2\text{-}\underset{\displaystyle OH}{CH}\text{-}COOH$$

(**6**)

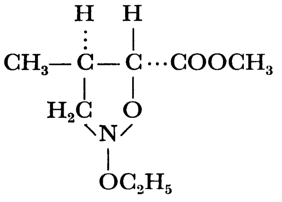


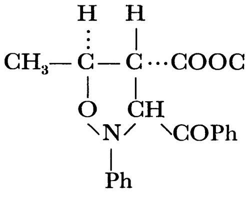
$$C_2H_5O\text{-}N{=}CH\text{-}CH_2\text{-}\underset{\displaystyle OH}{CH}\text{-}COOCH_3$$

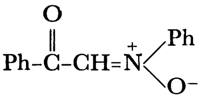
(**7**)

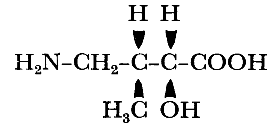
Regiospecificity of the 1,3-dipolar addition of the nitoronic ester (**3**) was also observed when **3** reacted with methyl crotonate. The structure of the cycloaddition product (**8**) was determined from the spectra, and the stereochemistry was assigned from the reaction mechanism. Huisgen *et al.*[7] reported that intermolecular cycloaddition of the nitrone (**9**) to methyl crotonate proceeds regiospecifically to give the isoxazolidine (**10**). The discrepancy in the regiospecificity of the two reactions would be explained in terms[8] o diffffference of electron distribution in the nitronic ester and the nitrone.

The isoxazolidine (**8**) was converted into the *erythro* hydroxy amino acid (**11**) in the same manner as described above. Isomerization of **8** to the corresponding oxime ether at 200 °C, followed by catalytic hydrogenation and hydrolysis yielded 4-amino-*erythro*-2-hydroxy-3-methylbutanoic acid (**11**).


(**8**)


(**10**)


(**9**)


(**11**)

Experimental

NMR spectra were obtained with a Hitachi H-60 instrument using TMS as an internal standard. All the infrared spectra were taken on a Hitachi EPI-S2 spectrophotometer. Melting points and boiling points are uncorrected.

Methyl 2-Ethoxy-5-isoxazolidinecarboxylate (4) and Methyl 4-Ethoxyimino-2-hydroxybutanoate (7). A 1.8 M solution of sodium ethoxide in ethanol (300 ml; 0.54 mol) was added to nitromethane (30 g ; 0.50 mol) with stirring at room temperature. The mixture was stirred for 20 min, and the solvent was removed with a suction pump at 40°. The resulting sodium salt of nitromethane was dried *in vacuo* for 3 h. To this was added dry dichloromethane (400 ml), and the suspension was cooled at −5 °C. A solution of triethyloxonium fluoroborate (100 g ; 0.53 mol) in dichloromethane (80 ml) was added to the suspension under nitrogen atmosphere during 5 min, and the mixture was stirred for 15 min at −5 °C. Freshly distilled methyl acrylate (46.8 g ; 0.55 mol) was added to the ethyl nitronate solution, and the reaction mixrure was allowed to stand at −15 °C overnight. The precipitates were filtered away, and the filtrate was evaporated. Distillation yielded **4** (8.1 g) ; bp 95—99 °C/10 Torr; ν_{max} (CCl_4) : 1735 cm^{-1} ; δ(CCl_4) : 1.20 (3H, t, J=6 Hz), 2.2—3.3 (2H, m), 3.60 (2H, t, J=5.5 Hz), 3.78 (3H, s), 3.90 (2H, q, J=6 Hz), and 4.66 (1H, dd, J=5 and 9 Hz ; m/e 175 (M^+), 146 (M^+-OCH_3), 130 ($M^+-OC_2H_5$), and 129 ($M^+-HOC_2H_5$). Found: m/e 175.083. Calcd for $C_7H_{13}NO_4$: 175.084. Another fraction with higher boiling point, 78.5 °C/4 Torr, was found to be the oxime ether (**7**) (19.5 g); δ(CCl_4) : 1.25 (3H, t, J=6 Hz), 2.5—3.4 (1H, m), 3.80 (3H, s), 4.05 (1H, q, J=6 Hz), 4.10 (1H, q, J=6 Hz), 4.40 (1H, t, J=6.5 Hz), 6.75 (1/2H, t, J=5 Hz), and 7.40 (1/2H, t, J=6 Hz). Found : C, 48.04 ; H, 7.19 ; N, 8.32%. Calcd for $C_7H_{13}NO_4$: C, 47.99 ; H, 7.19 ; N, 8.00%. The adduct (4) was quantitatively converted to the oxime ether (**7**) on heating at 100 ° for 1 h.

4-Amino-2-hydroxybutanoic Acid (6). The oxime ether (**7**) (2.0 g ; 11.4 mmol) was hydrogenated over platinum oxide (400 mg) in methanol (8 ml) in the presence of concentrated hydrochloric acid (1.3 ml). Crude methyl 4-amino-2-hydroxybutanoate (1.8 g) was heated with 6 M hydrochloric acid (20 ml) for 6 h. The product was adsorbed on a cation exchanger (Amberlite Type I CG 120) (13 g). Elution with water afforded the recovered methyl ester, and with 0.5% aqueous ammonia 4-amino-2-hydroxybutanoic acid (**6**) (469 mg ; 37% from **7**) ; mp 189—190 °C (lit,[1] 191—192 °C) ; δ(D_2O) : 2.08 (2H, m), 3.12 (2H, t), and 4.12 (1H, dd).

Methyl 2-Ethoxy-4-methyl-5-isoxazolinecarboxylate (8). The procedure was essentially the same as that for the preparation of **4**. Nitromethane (15 g) was converted to sodium salt, and treated with triethyloxonium fluoroborate (31 g) and methyl crotonate (17 ml). The mixture was allowed to stand at −15 °C overnight. Distillation afforded **8** (950 mg) ; bp 65—66 °C/0.9 Torr. The NMR spectrum of this material showed peaks at δ : 1.16 (3H, t), 1.33 (3H, d), 2.5—3.5 (3H, m), 3.7 (3H, s), and 4.3 (1H, d), and no others. Its TLC showed only one spot. Found : 189.098. Calcd for $C_8H_{15}NO_4$: 189.100.

*4-Amino-*erythro*-2-hydroxy-3-methylbutanonic Acid (11).* The isoxazolidine (**8**) was heated at 200 °C in a sealed tube for 10 min producing methyl 4-ethoxyimino-2-hydroxy-3-methylbutanoate in a quantitative yield ; ν_{max}(CCl_4) : 3500, 1735, and 1610 cm^{-1} ; δ(CCl_4) : 1.20 (3H, d), 1.20 (3H, t), 6.60 (1/3H, d), and 7.20 (2/3H, d). The oxime ether (317 mg ; 1.67 mmol) was hydrogenated over platinum oxide (60 mg) in methanol (5 ml) containing three drops of concentrated hydrochloric acid. The crude product was heated in 6M hydrochloric acid (20 ml), and the resulting mixture was chromatographed on a cation exchanger (Amberlite Type I CG 120) (13 g). Elution with 0.5% aqueous ammonia afforded **11** (176 mg) as a thick oil ; ν_{max} (KBr) : 3500 (br.), 1580 (br.), 1460, 1400, 1130, and 1060 cm^{-1}. Paper chromatography of this amino acid showed a single spot (water–butanol–acetic acid), and its NMR spectrum showed peaks at δ (D_2O) : 1.05 (3H, d, J=7Hz), 2.2 (1H, br.), 3.05 (2H, d, J=6 Hz), and 4.0 (1H, d, J=4 Hz). No other signals showing the presence of impurities were found in the spectrum. The amino acid was characterized as a N-phthaloyl derivative, which was prepared according to Nefken's method[9], and purified by chromatography on Sephadex LH 20. This phthaloyl derivative was an oil, showing one spot in its TLC. Its NMR spectrum exhibited peaks at δ : 1.15 (3H, d), 2.5 (1H, m), 4.15 (1H, d), 3.8 (2H, ABX), and 7.85 (5H, br.s), and no others. Found : 263.079. Calcd for $C_{13}H_{13}NO_5$: 263.081.

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