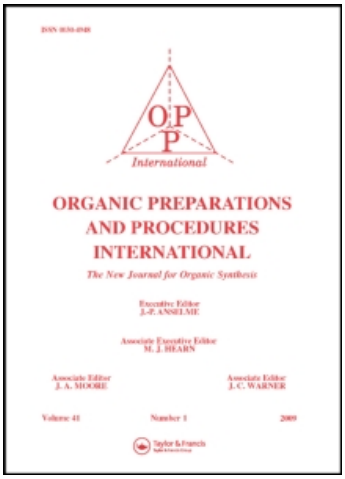

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GLYCYLGLYCOLIC ACID

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GLYCYLGLYCOLIC ACID

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Schröder and Lübke[2] reported that the simple depsipeptide prototype glycylglycolic acid was an oil, in contrast to the high-melting zwitterionic peptide analog glycylglycine, and behaved more as an amino acid ester than a peptide derivative. Such a drastic alteration in physical character is inexplicable on the basis of the stated structure of the compound. It was of interest, therefore, to synthesize glycylglycolic acid in order to ascertain the actual nature of this substance.

Treatment of benzyloxycarbonylglycylglycolic acid pentamethylbenzyl ester[3-5] with hydrogen bromide in acetic acid resulted in rapid cleavage of the protecting groups and formation of glycylglycolic acid hydrobromide. Neutralization of the product with aqueous ammonia gave glycylglycolic acid as a crystalline solid with typically zwitterionic properties. The structure of the compound was established by elementary and quantitative amino acid analyses, infrared and proton magnetic resonance spectroscopy, and thin-layer chromatography.

A possible explanation of the behaviour reported by Schröder and Lübke[2] is that crystallization of glycylglycolic acid hydrochloride from *ethanol*-ether resulted in extensive esterification. The corresponding hydrobromide was found to be sparingly soluble in ethanol, and prolonged boiling with

the solvent was necessary to effect solution. The hydrobromide, however, is readily crystallized from *methanol*-ether.

Experimental[6]

Glycylglycolic acid Benzyloxycarbonylglycylglycolic acid pentamethylbenzyl ester[3-5] (1.3 g) was treated with 2N hydrogen bromide in acetic acid (12 ml) for 30 minutes at room temperature. Dilution with ether precipitated glycylglycolic acid hydrobromide, which was washed with ether and dried *in vacuo* (603 mg; 94%). The compound was crystallized from methanol-ether, m.p. 198.5 - 200° dec.; ν_{max} 1760 (depsipeptide ester CO), 1745 (shoulder, CO_2H), 1580 and 1550 cm^{-1} (NH_3^+ deformation bands).

Anal. Calcd. for $C_4H_8BrNO_4$: C, 22.4; H, 3.7; N, 6.5; Br, 37.4.

Found: C, 22.4; H, 3.9; N, 6.4; Br, 37.4.

A solution of the hydrobromide (341 mg) in a little water was brought to pH 7.0 by addition of 1N ammonium hydroxide. Glycylglycolic acid separated on addition of ethanol. The product was washed with ethanol and ether (yield, 198 mg; 94%), and recrystallized from aqueous ethanol, m.p. 166 - 167° with prior charring.

Anal. Calcd. for $C_4H_7NO_4$: C, 36.1; H, 5.2; N, 10.4.

Found: C, 35.9; H, 5.4; N, 10.6.

The infrared spectrum had a strong ester carbonyl band at 1750 cm^{-1}, and a very intense broad band comprising two peaks at 1600 and 1545 cm^{-1} representing ionized carboxyl and NH_3^+ deformation absorptions, respectively. There was a weak band at 2110 cm^{-1}, characteristic of many zwitterionic substances.

The compound was homogeneous by thin-layer chromatography on Silica-gel G in several solvent systems. Plates were developed with ninhydrin, and in each case a bright yellow spot was obtained indicative of the amino acid ester moiety, R_f 0.15 (phenol - water, 3:1), 0.55 (sec-butanol - formic

acid - water, 15:3:2), 0.40 (n-propanol - water, 7:3), and 0.25 (n-butanol - acetic acid - water, 3:1:1).

A sample of the depsipeptide was hydrolysed in 6N HCl at 110° *in vacuo* for 24 hours. Amino acid analysis of the hydrolysate gave the glycine content as 7.9 mmole/g (calcd. 7.5 mmole/g).

The proton magnetic resonance spectrum in D_2O solution consisted of two singlets with τ values of 5.43 and 6.00, corresponding to the glycolyl and glycyl methylene protons, respectively.

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References

1. Abbreviations for protecting groups are:- Z, benzyloxycarbonyl; PMB, pentamethylbenzyl.
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6. The microanalyses were carried out by the Australian Microanalytical Service, Melbourne. Melting points are uncorrected. Infrared spectra were obtained with KBr disks.

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