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A Convenient Method of Synthesizing Protected α-Amino-γ-butyrolactones

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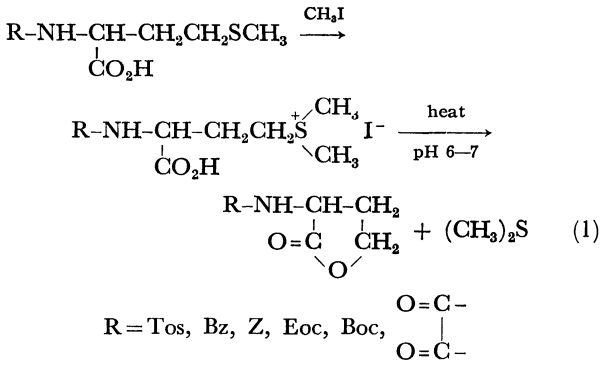
α-Amino-γ-butyrolactone (homoserine lactone) is a key intermediate in the synthesis of amino acids, especially γ-substituted α-amino acids, such as cystathionine,[1,2] homolanthionine,[2] canaline,[3] canavanine,[4] phosphinothricin,[5] and selenium analogs of methionine and homocysteine.[6] Suitable synthetic methods for the preparation of an optically-active α-amino-γ-butyrolactone are, therefore, of importance in connection with the synthesis of such types of amino acids and of peptides containing a homoserine.

The known method for the preparation of an optically-pure *N*-protected α-amino-γ-butyrolactone involves a two-step sequence in which *N*-tosyl-glutamine is converted into *N*-tosyl-α,γ-diaminobutyric acid with potassium hypobromite, followed by diazotization.[1] However, the amino-protecting group in this method is limited to an acid-stable group, such as the tosyl and benzoyl groups.

It was reported previously, in connection with studies of the determination of amino acid sequences in peptides containing methionine, that a methionine residue is transformed into an α-amino-γ-butyrolactone residue by treatment with methyl iodide or cyanogen bromide, followed by hydrolysis.[7]

We will report in this paper the application of the above procedure on a preparative scale to the widely-used, optically-active α-amino-γ-butyrolactones, suitably protected for further elaboration in the synthesis. Thus, readily-available, optically-active *N*-acyl-methionines, such as *N*-benzyloxycarbonyl(Z)-, *N*-tosyl(Tos)-, *N*-benzoyl(Bz)-, and *N*-ethoxycarbonyl(Eoc)-methionine, were treated with methyl iodide in a mixture of acetic acid and formic acid to form sulfonium salts; they were then hydrolyzed under reflux at pH 6—7. The resulting *N*-acyl-α-amino-γ-hydroxybutyric acids were converted into the corresponding lactones with hydrogen chloride. The unreacted *N*-acyl-methionines were extracted out with a sodium bicarbonate solution; optically-pure *N*-acyl-α-amino-γ-butyrolactones are thus obtained in good yields (Eq. (1)).

The *N*-*t*-butyloxycarbonyl (Boc) derivative, in which the Boc-group was cleaved by formic acid, was methylated in acetic acid without the use of formic acid, but the yield was rather low because the cleavage of the Boc-group occurred during the hydrolysis.



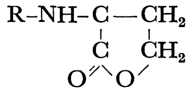
(1)

Bis-amide was obtained analogously from oxalyl bis-methionine. No appreciable racemization occurred during the procedure. The specific rotations of the derivatives synthesized above agreed with those of the derivatives which were obtained by the acylation of commercially-available optically-pure homoserine and by subsequent lactonization. The results are shown in Table 1.

Experimental

General Procedure. A solution of acyl-L-methionine

1) K. Jost and J. Rudinger, *Collect. Czech. Chem. Commun.*, **32**, 2485 (1967).
2) J. A. Stekol, *J. Biol. Chem.*, **173**, 153 (1948).
3) M. Kitagawa, *J. Agr. Chem. Soc. Jap.*, **12**, 871 (1936).
4) M. Kitagawa and T. Tomiyama, *J. Biochem.* (Tokyo), **11**, 265 (1929).
5) W. A. König and H. Zähner, *Helv. Chim. Acta*, **55**, 224 (1972).
6) E. P. Painter, *J. Amer. Chem. Soc.*, **69**, 232 (1947).
7) J. Bremner, *Biochem. J.*, **47**, 538 (1950).

Table 1.  (L-series)

R	Yield (%)	Mp (°C)	$[\alpha]^{25}_{D}$ (c 1, MeOH)	Anal. (%) Calcd C	H	N	Found C	H	N
C_6H_5CO–	73	137—139	−29.0°	64.38	5.40	6.83	64.14	5.39	6.78
$CH_3C_6H_4SO_2$–	92	130—133	+8.0°	51.76	5.13	5.49	51.60	5.17	5.51
C_2H_5OCO–	81	88—89	−34.8°	48.55	6.40	8.09	48.35	6.46	8.12
$C_6H_5CH_2OCO$–	80	126—127	−30.5°	61.27	5.57	5.96	61.48	5.65	6.08
$(CH_3)_3COCO$–	29	125.5—126.5	−27.6°	53.72	7.51	6.96	53.68	7.47	6.95
O=C–[a)] O=C–	45	298—303	−25.0°[b)]	46.88	4.72	10.93	45.94	4.75	10.81

a) This was not recrystallized. b) c 1, N NaOH.

(1 mol) in a mixture of acetic acid (300 ml), 80% formic acid (600 ml), and methyl iodide (110 ml) was allowed to stand in a dark place at room temperature for 10 hr. (In the case of Boc-L-methionine, formic acid was not used, and the mixture was allowed to stand for 48 hr). The mixture was then concentrated under reduced pressure below 40°C. The resulting oil was triturated with dry ether and dissolved in a N sodium hydroxide solution (1000 ml). The mixture was heated at 90°C with stirring for 3 hr. During the course of the reaction, the reaction mixture was kept at pH 6—7 by the addition of N sodium hydroxide. After cooling, the crystals which had appeared were collected by filtration, washed well with water, and dried. Recrystallization from ethyl acetate–petroleum ether gave an optically-pure *N*-acyl-α-amino-γ-butyrolactone. The mother liquor was adjusted to pH 2—3 with N hydrochloric acid and then allowed to stand at room temperature for 1 hr. The product was extracted with ethyl acetate, and the extract was washed with 4% sodium bicarbonate, N ammonia, and water, and dried over magnesium sulfate. The solvent was removed *in vacuo* and the crystals thus obtained were recrystallized from ethyl acetate–petroleum ether to afford an optically-pure *N*-acyl-α-amino-γ-butyrolacetone. The oxalyl derivative could not be recrystallized because of its low solubility in various solvents.