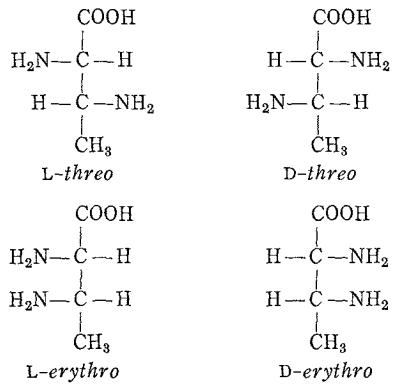
Communications to the editor

SYNTHESIS OF THE FOUR ISOMERS OF α,β-DIAMINOBUTYRIC ACID

Sir:

The incidence of α,β-diaminobutyric acid in the amphomycin group of antibiotics has been firmly established[1]. Aspartocin yielded α,β-diaminobutyric acid in the L-*threo* and D-*erythro* forms on hydrolysis[2]. Similarly these two forms have been isolated and identified from hydrolysates of amphomycin[3]. Since no synthetic route to the α,β-diaminobutyric acids has been recorded, we wish to communicate the synthesis of all four isomers (Fig. 1).

Fig. 1. Isomers of α,β-diaminobutyric acid (FISCHER projections)



We are currently engaged in syntheses of actinomycin analogs with substituted lactone oxygens. Replacement of the lactone oxygen by -NH- has recently been accomplished in a synthesis of actinomycin D lactam[4]. For this synthesis L-*threo*-α,β-diaminobutyric acid was required to replace L-threonine. A synthetic route to the L-*threo* isomer was developed and also used in preparations of the other three isomers. The rotations and melting points of the four isomers and their N^{α}-tosyl derivatives are recorded in Table 1.

L-*threo*-α,β-Diaminobutyric acid was prepared by a sequence of reactions using L-threonine as the starting material. Tosylation under SCHOTTEN-BAUMANN conditions gave *N*-tosyl-L-threonine, which was converted to the methyl ester by the action of diazomethane. Reaction with tosyl chloride in the presence of pyridine gave *N,O*-ditosyl-L-threonine methyl ester. Treatment of the *N,O*-ditosyl compound with ammonia-saturated methanol followed by hydrolysis in 6 N HCl afforded, after several recrystallizations from water, N^{α}-tosyl-L-*threo*-α,β-diaminobutyric acid in yields of 20~30 %. Its configuration was established by NMR data and by conversion to *N*-tosyl-L-threonine through treatment with nitrous acid which is known to proceed with retention of configuration[5].

Table 1. Physical characteristics of the isomers of α,β-diaminobutyric acid and their N^{α}-tosyl derivatives [a]

		Tos-Dbu-OH		H-Dbu-OH[b] × HCl	
		mp	$[\alpha]_D^{20}$ [c]	mp	$[\alpha]_D^{20}$ [c]
Threo	L	233~235°C	+28.2°	239~240°C	+39.3°
	D	231~232°C	−28.1°	225~226°C	−38.1°
Erythro	L	275~276°C	+47.1°	202~204°C	+10.3°
	D	271~272°C	−49.4°	200~202°C	−11.0°

a) Correct elemental analyses were obtained for all compounds
b) Refers to monohydrate
c) *c* 1, 6 N HCl

It was expected that the ammonolysis would proceed by a S_N2 type mechanism to yield the L-*erythro* isomer. Since only the L-*threo* isomer was isolated in pure form and racemic mixtures were also isolable a S_N1 mechanism seems not to be operative. A probable explanation of the observed phenomena is that the reaction is proceeding by two pathways. Firstly, the sulphonamide moiety is influencing the steric course of the reaction causing a double inversion of the β center *via* aziridine formation[6], therefore giving the pure L-*threo* isomer. Secondly, α,β-elimination gives the unsaturated compound, 1-*N*-tosylamino-2-methylacrylic acid methyl ester, followed by addition of ammonia to yield optically inactive racemic mixtures.

Removal of the tosyl group was effected by the action of sodium in liquid ammonia.

The residue was dissolved in ethanol/water and the pH of the solution adjusted to 2~3 with hydrochloric acid. On neutralization with pyridine L-*threo*-α, β-diaminobutyric acid monohydrochloride crystallized. The NMR spectrum in 2 N DCl was consistent with previously reported data[2,3] of material isolated from natural sources (H_α-H_β coupling constant 3.6 Hz, doublet at 4.6 ppm).

The D-*threo* isomer was prepared in a similar manner to that described above using D-threonine as starting material. The NMR in 2 N DCl was in agreement with the *threo* configuration, *i. e.* H_α-H_β coupling constant 3.6 Hz centered at 4.6 ppm.

In order to synthesize the *erythro* compounds, L- and D-allothreonine were prepared according to the method of ELLIOTT[7]. The same route, from the appropriate allothreonine isomer, as that decribed above was adopted in the two syntheses*. Experimental details of these syntheses and preparations of protected derivatives for use in peptide synthesis will be reported elsewhere.

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* NMR data of *erythro* isomers ; H_α-H_β coupling constant 6.6 Hz, doublet at 4.5 ppm.
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