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α-Aminosulfonopeptides as Possible Functional Analogs of Penicillin; Evidence for their Extreme Instability.

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Abstract: Sulfonopeptide analogs of acyl-D-Ala-D-Ala bearing an α-aminosulfonic acid moiety in the penultimate position have been synthesized using a Curtius rearrangement step. The sulfonopeptides were prepared and examined in aprotic solvents, but they proved to be exceedingly labile in protic solvents; for example, α-acylaminosulfonodipeptide **31** proved to be too unstable to isolate in pure form and its methyl ester, **34**, decomposed with a half-life of *ca.* 8 min in 50% methanol at pD=5 and at 25°C. A mechanistic study relating to the stability of the α-sulfonopeptides is delineated, including an analysis of the decomposition products in aqueous solution.

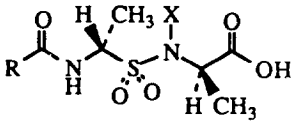
INTRODUCTION

This report covers the first synthesis of an internal α-aminosulfonamide analog (**1a**) of an acylalanylalanine. The latter species is an important unit in antibiotic chemistry since Strominger and Tiffer[1a] suggested that penicillin inhibited the transpeptidase involved in bacterial cell-wall synthesis by acting as a structural analog of the acyl-D-ala-D-ala terminus of nascent peptidoglycan strands. The structural similarity of penicillin to acyl-D-alanyl-D-alanine has been supported by molecular orbital calculations, which indicated a conformational analogy between penicillin and the tetrahedral transition state for the addition of the transpeptidase serine OH group to the penultimate carbonyl group of the D-ala-D-ala moiety.[2] In the past decades many details of this hypothesis have been verified experimentally; for example, the antibiotic-derived penicilloyl moiety and the substrate-derived acyl moiety are attached to the same site in the penicillin-binding proteins for a variety of genera of bacteria.[1]

Recently, some analogs of D-ala-D-ala in which the normal peptide linkage (-CO-NH-) was replaced by -CONHO- (aminoxy analogs) and -CO-NH-NH- (hydrazino analogs) have been examined for antibacterial activity[3]; these compounds are known to be active against *E. coli, Staphylococcus aureus, and Salmonella dublin.*[4] In addition, hippuryl DL-phenyllactate[5] and ester and thioester derivatives[6] of hippuric acid exhibited reactivities with respect to penicillin-sensitive enzymes similar to or better than those of the classical peptide substrate Ac_2-L-lys-D-ala-D-ala. Thus, modification of the peptide backbone has been rapidly developing in connection with searches for new biologically active peptides.[7] Based on this information on penicillin sensitive enzymes, it should be possible to design a modified acyl-D-ala-D-ala peptide to serve as an active-site-

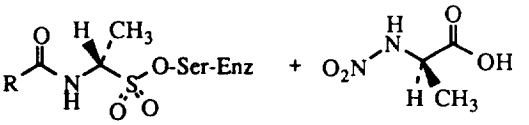
directed, enzyme-activated, irreversible inhibitor of the D-ala-D-ala transpeptidases; it presumably would have antibiotic activity.

In the present study the α-aminosulfonopeptide, **1b**, in which the penultimate amino acid unit of Ac-D-ala-D-ala was replaced with an α-aminoethanesulfonic acid residue, was designed as an inhibitor of the



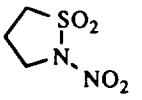
1 a: X = H
b: X = NO_2

penicillin-sensitive enzymes. Compound **1b** possesses a tetrahedral sulfur atom at the reaction center that may serve as a stable mimic of the corresponding tetrahedral carbon intermediates in transpeptidation. In addition, the nitro group[8] on the sulfonamide nitrogen atom is expected to enormously accelerate the rate of the acylation step in which the sulfonyl group will be bound to the enzyme in the form of a sulfonate ester of the serine residue (eq 1). Finally, sulfonate esters are considerably more stable to hydrolysis than esters based on carboxylic acids (in acyl enzymes)[9a]; that is, sulfonation of the DD-transpeptidases could be expected to lead to irreversible inhibition of the enzyme.



(1)

As examples of the latter principle, N-nitropropanesultam (**2**) rapidly inhibits the serine enzyme, α-chymotrypsin,[9c] and sultone **3** inhibits α-chymotrypsin in a rapid, stoichiometric reaction to form a catalytically inactive sulfonyl enzyme.[9b] A related design principle is apparent in **4**, a bicyclic ß-sultam analog of penicillin.[10]



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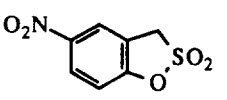

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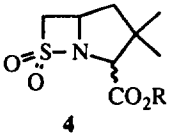

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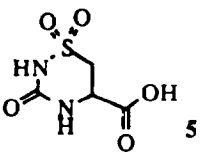
Simple sulfonamide groups are well known components of enzyme inhibitors; for example the sulfonamide derivatives **5** and **6** (designed as transition state analogs) are inhibitors of dihydroorotase[11a] and HIV-protease,[11b] respectively.



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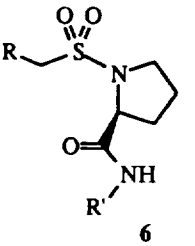

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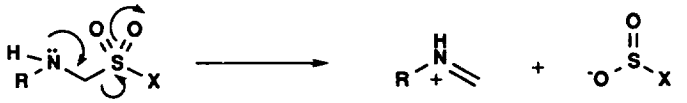
All early attempts to prepare sulfonodipeptides bearing an amino group *alpha* to an internal sulfonamide moiety, as in compound **1**, failed,[12,13,14] presumably because of the vigorous conditions usually required to activate sulfonic acid groups and the availability of a facile fragmentation pathway (eq 2).[15]

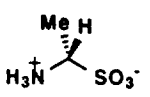


(2)

A successful synthesis of derivatives of α-acylaminosulfonoglycine and of phenylalanine analogs [and possibly of dipeptide analogs (*vide infra*)] was reported by Gilmore, *et al.*,[16] using a Curtius Rearrangement in the key step. By their route the activation and modification of the sulfonic acid group occurs early in the synthesis before the labile α-aminosulfonic acid moiety is introduced (Chart 1). However, these workers report that they were unable to synthesize alanine analogs.[16a] Since the thermal Curtius rearrangement is known to be extremely reliable for aliphatic, aromatic and heterocyclic azides of various sizes and complexity,[17] we reinvestigated the alanine case and by carefully controlling reaction condition were able to synthesize several α-aminosulfonoalanyl analogs of peptides, including an α-sulfono analog of the acylalanylalanines. Unfortunately, these compounds were quite labile in aqueous and protic media. In the course of these studies further evidence for the fragmentation mode shown in eq 2 was obtained.

RESULTS AND DISCUSSION

Sulfono Analogs of Amino Acids and Simple Derivatives. Sulfonoamino acids, *eg* **7**, are fairly stable compounds,[18,19] as are dipeptides in which the sulfonic acid group is at the terminus of the molecule, *eg* **8**[20]. At least the former exhibit antibiotic activity.[19] As reported above, however, attempts to convert α-aminosulfonic acids and related compounds into sulfonopeptides have failed.



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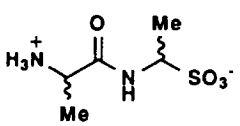

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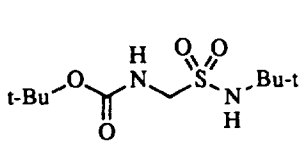
In preliminary work the attempted reaction of α-chloroethanesulfonamides with various nucleophiles (NH_3/ether, 25°C,1 h; NH_4OH, 25°C, 24 h; $NaNH_2$/liq NH_3, -30°C, 24 h; KNCO/EtOH, 100°C, 24 h; TMGA/CH_2Cl_2, reflux, 24 h) failed; unchanged starting material was obtained.[21] For an approach utilizing the hydrogenation of α-nitrosulfonamides, our preparation of a precursor compound, α-nitroethyl benzenesulfone, from the reaction of benzenesulfonyl chloride with nitroethane using the procedure of Seebach, et. al.[22] resulted in very low yields of product (5 - 10%), making this route unattractive.

The Curtius approach was used in the present study to prepare sulfonoglycine derivatives, *eg* **9**. The reactions of Gilmore and Lin[16] were repeated (*via* steps analogous to those outlined in Chart 1) utilizing the key compound **10**, with results similar to the reported ones[16] except that in the last step of the synthesis a mixture of **9** and **11** was obtained from which the latter, but not the former, could be obtained in a pure state.



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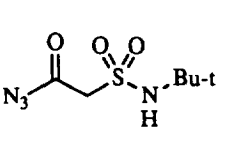

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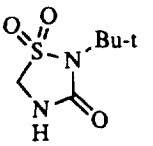

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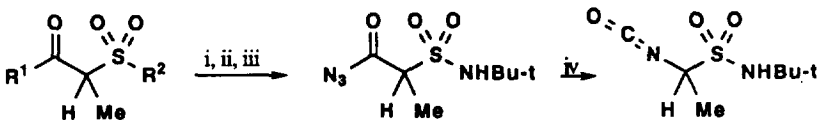
New physical data for the reaction intermediates in this synthesis are reported in the Experimental Section.

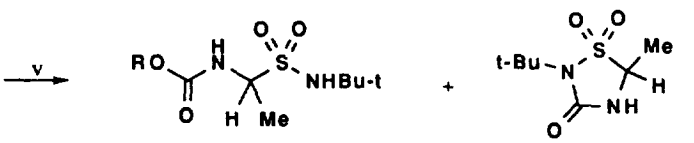
Attention was then shifted to the unknown sulfonoalanine analog (Chart 1). The key intermediate



12a R^1 = OEt, R^2 = Cl
12b R^1 = OEt, R^2 = t-BuNH
12c R^1 = $NHNH_2$, R^2 = t-BuNH

13

14



15a R = Me
15b R = t-Bu

16

i: t-butylamine, ii: N_2H_4, iii: HNO_2, iv: heat, v: ROH

Chart 1. The Synthesis of alanine-based α-amidosulfonamides.

13 was obtained as a crystalline solid in high yield by the treatment of ethyl 2-(chlorosulfonyl)propionate (**12a**)[23] with t-butylamine followed by hydrazinolysis and diazotization. Refluxing **13** in benzene for 1.5 h produced only sulfonohydantoin **16**. A solution of acyl azide **13** in benzene preheated for a few minutes prior to the addition of tert-butyl alcohol produced sulfonohydantoin **16**, but not the desired sulfonamide (**15**). The use of excess t-butyl alcohol gave acetaldehyde as a major product (with a trace of **16**), and extraction of the product mixture with aqueous base at pH 8 afforded tert-butylamine. These results suggested that the rate of intramolecular cyclization is faster than the intermolecular reaction of the isocyanate with a bulky alcohol.[24] The reaction of **13** with methanol, a less hindered alcohol, was attempted using a variety of solvents. Isocyanate **14** was detected under several reaction conditions (Table 1). Its formation was greatly influenced by the nature of the solvent and the amount of alcohol used. When **13** was refluxed in CH_2Cl_2 in the absence of alcohol, the isocyanate **14** was detected in low yield; in ether, only the sulfonohydantoin **16** was formed. When 2-4 equivalents of methanol were present, the reaction afforded ca. 75% of the isocyanate; prolonged refluxing resulted in the cyclization of **14** (to **16**) without any detectable formation of **15a**. With 64 equiv. of

Table 1. Products from the Curtius Rearrangement of Azide **13**[a].

Solvent	ROH (equiv)	Temp (°C)	Time (h)	Reactants and Products (%)[a] 13	14	15a	16
CH_2Cl_2		40	2	43	22	0	35
Et_2O		35	4	30	0	0	70
CH_2Cl_2	MeOH (2)	40	4	15	75	0	10
CH_2Cl_2	MeOH (2)	40	8	5	0	0	95
CH_2Cl_2	MeOH (64)	40	10	0	0	80	20
C_6H_6	t-BuOH (2)	80	1.5				>90
MeOH		65	1	0	0	<5[b]	<5[b]

[a] 400 MHz NMR analysis. [b]Detected in trace amounts.

MeOH in CH_2Cl_2, the reaction mixture produced (on refluxing for 10 h) the desired carbamate **15a** in 80% yield (+ 20% of **16**). The use of greater excesses of MeOH led to many decomposition products and only traces of compounds **15** and **16**. It thus appears that the reaction of the isocyanate with alcohols is a relatively slow one. Interestingly, the solvolysis product, the methyl ester of 2-(N-t-butylsulfamyl)propanoic acid was not formed in these reactions.

Decomposition of Methyl N-(N-tert-butylsulfamyl-1-ethyl)carbamate (15a) in aqueous media. *The* thermal decompositions of acyl azide **13** with more than 64 equiv of methanol in CH_2Cl_2 led to a complex set of decomposition products including acetaldehyde. Carbamate **15a** was stable in non-polar organic solvents such as chloroform and ether; no decomposition was observed after 7 days at 25°C. However, the compound rapidly decomposed in aqueous solutions. In a D_2O-CD_3OD solution (50/50 v/v), no decomposition was noted after 30 min (25°C), but complete decomposition was observed after 96 h. The half-lives of **15a** at 25°C at pD = 2 and 5 in D_2O-CD_3OD mixtures (50/50 v/v)) were approximately 3 min and 20 min, respectively.

The decomposition of **15a** in neutral D_2O had a half-life of approximately 20 min. Analysis of the products revealed the reaction pathway outlined in Chart 2; after 1 h at 25°C, methyl N-(1-hydroxyethyl)carbamate (**19**) was observed as the major product (ca. 90%). It was characterized by direct comparison with an adduct produced from the reaction of acetaldehyde with methyl carbamate in D_2O. After the solution was allowed to stand for 24 h at 25°C, the signals of acetaldehyde, methyl carbamate (**20**), 1-hydroxyethanesulfonate ion (**22**) and N-carbomethoxy-1-aminoethanesulfonate ion (**23**) appeared and increased with time at the expense of the signals of **19**. After 36 h, compounds **20**, **22** and **23** remained in a molar ratio of ca 3:3:4 and a trace of acetaldehyde was detected. Thus, the sulfonamide **15a** appears to produce carbamate **19** *via* imine intermediate **17** (see eq 1). The alcohol, **19**, establishes an equilibrium with methyl carbamate (**20**) and acetaldehyde; then, acetaldehyde reacts with bisulfite ion (**21**) to yield **22**. In a similar way, the reaction of imine **17** with bisulfite ion produces compound **23**.

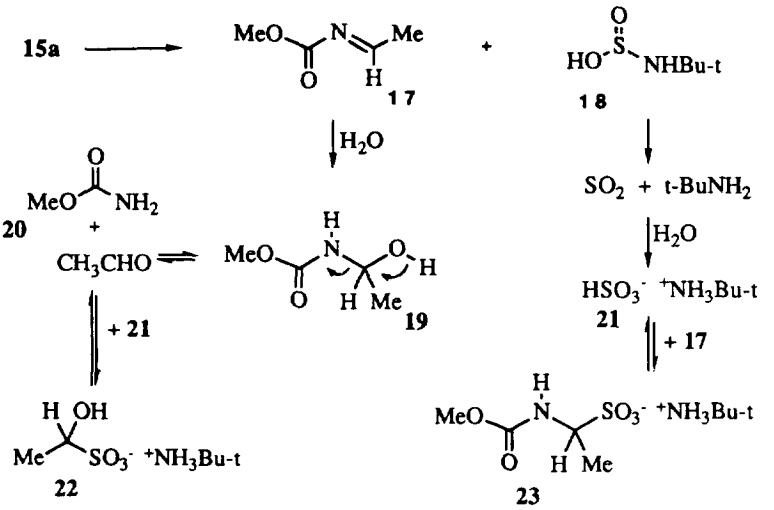
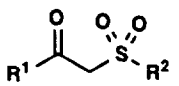
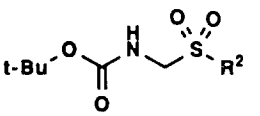
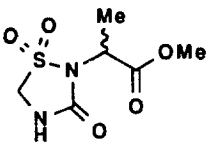


Chart. 2. Decomposition of sulfonoalanine derivative **15a** in water

Sulfonoglycylalanines. A preliminary study of the synthesis of carbamates of sulfonoglycylalanine (*eg*, **25**) was next addressed. Intermediates **24a-d** were involved in a sequence similar to that used for the simpler analogs (Chart 1) and the ala-ala analog (Chart 3). However, pure products could not be isolated from the thermal decomposition of azide **24d**. Therefore, azide **24d** was converted into ester **24e** by brief exposure to diazomethane. The decomposition of azide **24e** in toluene led to sulfonohydantoin **26**; the decomposition in the







24 **a**: R^1 = OEt, R^2 = Cl
b: R^1 = OEt, R^2 = $NHCHCH_3CO_2H$
c: R^1 = $NHNH_2$, R^2 = $NHCHCH_3CO_2H$
d: R^1 = N_3, R^2 = $NHCHCH_3CO_2H$
e: R^1 = N_3, R^2 = $NHCHCH_3CO_2CH_3$

25: R^2 = $NHCHCH_3CO_2CH_3$ **26**

presence of t-butanol led to mixtures of **25** and **26**, and other decomposition products. Gilmore and Lin reported the synthesis of the t-butyl alanate esters corresponding to **24b, c** and **25**, but experimental procedures were not provided and the physical data reported were limited to refractive indices, optical rotations, and one melting point.[16a] The synthesis of **24b** and the t-butyl esters corresponding to **24b, c**, and **25** were reported in the Ph.D. thesis of H.-J. Lin with characterization of the products;[25] our data for these compounds differ significantly, however. For **24b** we observe signals in the ^{1}H-NMR spectrum ($CDCl_3$) for the methine

hydrogen at 4.38 ppm (p, J=7.2Hz) [a value of 4.34-4.19 was found for the analogous methine hydrogen of compound **27**] and for the —CH_2SO_2— group at δ4.11 (AB quartet); the multiplicity of this signal is consistent with the presence of a chiral center in the molecule. Lin, however, reported 3.85 ppm for the methine hydrogen and 4.17 for the CH_2SO_2 group as a singlet; singlets for that grouping in compounds **24b** & **c** were also reported. The compounds isolated by Lin apparently have different backbone structures than ours.

Sulfonoalanylalanines. Attention was then directed to the sulfono analog of D-Ala-D-Ala, compound **31** (Chart 3). The condensation of sulfonyl chloride **12a** with alanine using either organic bases or an aqueous basic solution led to low yields (5-35%) of compound **27** in a brown-colored mixture that was difficult to purify. The difficulty in the coupling of **12a** with alanine was successfully overcome through use of N,O-bis-trimethylsilylalanine[26] (prepared *in situ* from the p-toluenesulfonic acid salt of alanine and hexamethyldisilazane in the absence of base); compound **27** was obtained in the form of a clear oil (as a diastereomeric mixture) in almost quantitative yield. To our knowledge, this is the first example of the coupling of sulfonyl chlorides with amino acids in the absence of bases (which can cause side reactions). Subsequent treatment of **27** with excess hydrazine in ethanol yielded hydrazinium salt **28**. The conversion of **28** into propionyl azide **29** was carried out with 2 equiv of sodium nitrite in a cold, aqueous ether mixture at pH 1-2. The crude extract concentrated below 5°C afforded practically pure azide **29** as a viscous oil (52% yield); the azide was relatively stable in $CDCl_3$ solution (no decomposition after 24 h at 0°C).

Azide **29** was subjected to thermal decomposition in ether in an attempt to produce sulfohydantoin **35**, by analogy to the rapid cyclization noted for the conversion of the monomer azide **13** to compound **16**; however, decomposition occurred to produce a complex mixture of white precipitates. In the presence of methanol, 10% of the desired sulfonopeptide, **31**, was formed; it was identified by conversion with diazomethane into methyl carbamate **34**.

The latter compound was also prepared *via* intermediates **29**, **32** and **33**: the carboxylic acid group of **29** was esterified with excess diazomethane (0°C, 1 min) to yield **32** as a white solid (strong absorptions at 2148, 1744 and 1711 cm^{-1} for the characteristic azide and carbonyl groups). Attempts to synthesize the cyclic sulfohydantoin **36** by heating **32** in CH_2Cl_2 or ether in the absence of methanol led to complete decomposition analogous to decomposition occurring in the thermal decomposition of **29**. However, the isocyanate intermediate **33** could be detected (NMR) during the thermal decomposition in the presence of methanol. Refluxing a solution of **32** and 16 equivalents of methanol in CH_2Cl_2 afforded isocyanate **33** and unchanged acyl azide **32** in a 60/35 ratio, accompanied by a trace of methyl carbamate **34** (NMR analysis). In order to prepare sulfohydantoin **36**, pyridine (3 equiv) was added to a solution of isocyanate **33** in $CDCl_3$ at -50°C, and the solution was allowed to warm to 25°C. The NMR spectrum showed signals [d 4.79 (m, 1H, CHCO), 4.67, 4.62 (q, 1H, $CHSO_2$), 3.78 (s, 3H, OMe), 1.77, 1.76 (d, 3H, Me), 1.67, 1.65 (d, 3H, Me)] attributable to compound **36** as a diastereomeric mixture. The structure of this compound was assigned as sulfonohydantoin **36** because the signal of the methine proton next to the sulfonyl group at 4.67 and 4.62 ppm had a similar shift to that of the methine proton [quartet, 4.63 ppm] of **16**. However, attempted isolation by evaporation of the solvent *in vacuo* (25 °C) led to complete decomposition [compound **16** was more stable; 3 months at room temperature were required for complete decomposition (Note: methyl carbamate **15a** was stable under those conditions)].

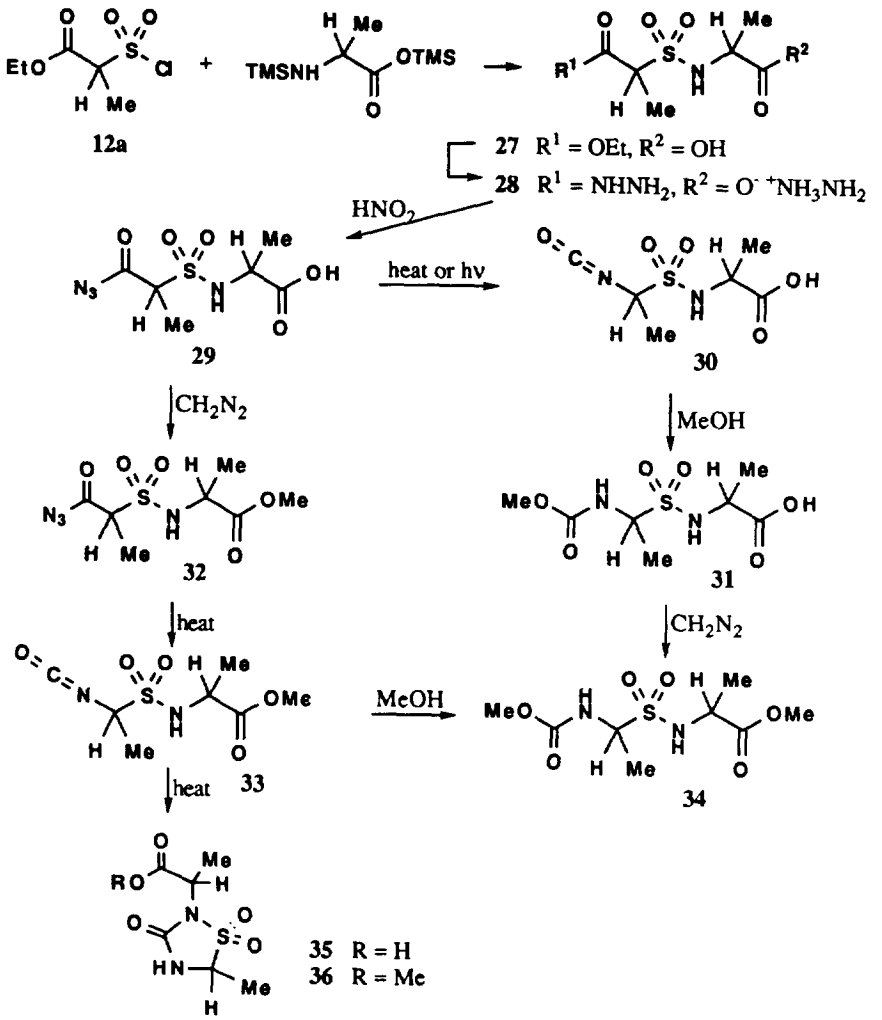


Chart 3. Synthesis of an α-aminosulfonoala-ala dipeptide.

The desired carbamate **34** was prepared using the conditions used for the synthesis of **15a** (compound 32+64 equiv. of methanol, 10 h reflux in CH_2Cl_2); a practically pure product (more than 90% by NMR analysis) with none of cyclic sulfohydantoin **36** was obtained. The diastereomeric mixture was partially separated by short column chromatography on silica gel to yield **34** in 37% yield; a long stay on silica gel resulted in the decomposition of the product. Sulfonodipeptide **34** was stable in non-polar organic solvents such as chloroform, but labile in protic solvents. At 25°C in a mixture of D_2O-CD_3OD (50/50 v/v) at pD 5, the half-life was approximately 8 min; at pD 9, the compound was completely decomposed in 5 min. The results of these studies indicate that the intermediate isocyanate **33** was readily formed in the thermally induced Curtius

rearrangement, and that intramolecular cyclization was considerably retarded compared to that of the simple tert-butylsulfonyl isocyanate, compound **14**.

Of particular interest to us was the preparation of sulfonopeptide **31** bearing a free carboxyl group at the C-terminal alanine residue. This compound was only detected (NMR) in very low yields (5-20%) in the thermally induced Curtius rearrangement of **29** under various reaction conditions; it decomposed during purification attempts. An alternative approach, the photolytic decomposition of carbonyl azides was then examined.[27] A 2% methanolic CH_2Cl_2 solution of **29** in a quartz tube was irradiated for 15 min in a Rayonet Reactor using 2537 A° lamps. The NMR spectrum of the crude mixture concentrated *in vacuo* below 5°C showed approximately 50% of the desired carbamate **31** accompanied by an uninterpretable mixture of by-products (with a typical thiol odor). Attempted purification of **31** met with failure due to its instability; complete decomposition occurred even in the aprotic solvent $CDCl_3$within 4 days at 25 °C. When an initial reaction mixture containing carbamate **31** was treated with diazomethane (0°C for 1 min), compound **34** identical to that obtained from the thermal decomposition of compound **32** in methanol was formed.

The sulfonodipeptides (*eg*, **31** & **34**) are considerably less stable than their amino acid analogs (*eg*, **15a**); this instability may be a consequence of the greater range of intramolecular interactions available to the former compounds.

Thermal Decomposition of 1-(Azidocarbonyl)ethanesulfonyl-DL-alanine (29). Attempted Curtius rearrangements of azide **29** always produced white precipitates and acetaldehyde either in the presence or absence of methanol under various reaction conditions (25 - 60°C). To locate the labile linkages in compound **29**, the decomposition of acyl azide **29** in $CDCl_3$ was followed by NMR spectroscopy at 25°C (Chart 4). A white precipitate accumulated with time; at the half life (12 h), the NMR spectrum of the $CDCl_3$ phase showed only acetaldehyde with unchanged acyl azide **29**. The white precipitates were collected, dried *in vacuo* and analyzed (NMR, D_2O); acetaldehyde, its bisulfite addition product (**22**), 1-aminoethanesulfonic acid (**38**), N-carbamyl-DL-alanine (**37**) and alanine were detected (in a molar ratio of *ca* 10:15:20:35:20). N-Carbamylalanine **37** (a major product) was probably formed *via* an intramolecular cyclization (pathway a) [note that the sulfonohydantoins are common products in the azide decompositions (see above)]. Alanine and the sulfono analog of alanine (**38**) are obtained from the hydrolysis of the isocyanate (pathway b). These results indicate that acyl azide **29**, with a free carboxyl group, decomposes to produce isocyanate **30** even at room temperature; the isocyanate subsequently decomposes, 64% *via* path a and 34% via path b (based on the product ratio of carbamoylalanine **37** to alanine).

Summary. α-Aminosulfono analogs of acylalanylalanine have been synthesized (apparently for the first time). They can be observed in non-polar organic solvents such as chloroform and ether but are too unstable to isolate or to be used in bio-assays in aqueous media. The dipeptide analogs were much more labile in aqueous systems than the simple α-aminosulfonamide **15a**. Analyses of the decomposition products indicates that the C-S bond of α-aminosulfonopeptides, and the sulfonohydantoins derived from them, are extremely labile in protic solvents.

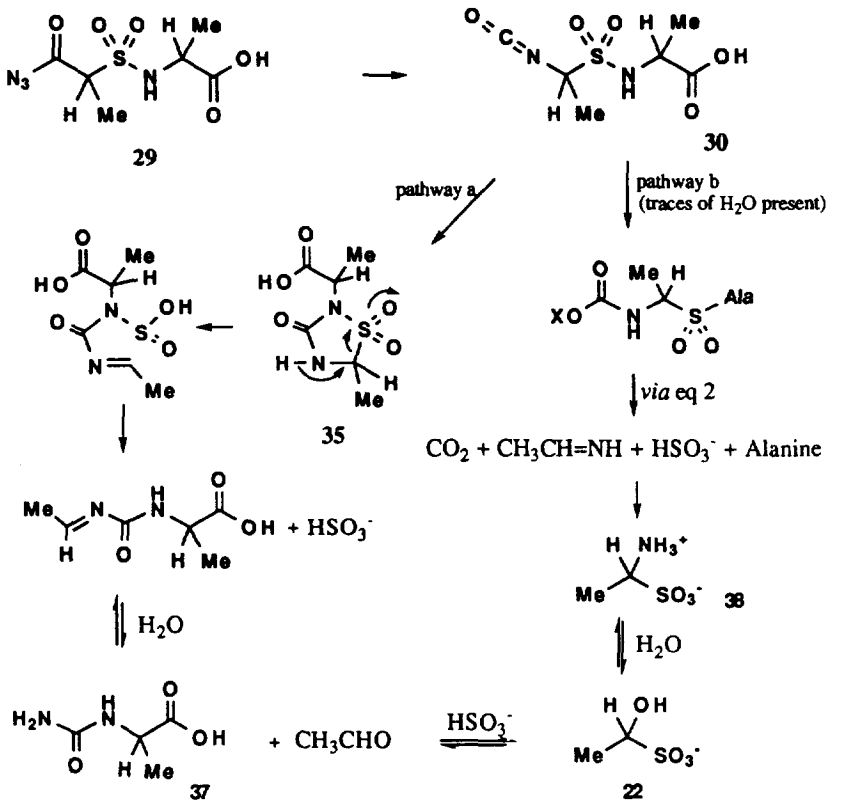


Chart 4. Products formed in the decomposition of acyl azide **29**.

Experimental Section

General Methods. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Proton magnetic resonance spectra were measured on a XL-400 instrument. Data are reported in ppm from internal tetramethylsilane for ^1H NMR, or from sodium 3-(trimethylsilyl) propionate (TSP) when using D_2O as solvent. A Beckman Model 4500 pH meter was used to measure pH (pD) values. Low and high resolution or exact mass measurements were recorded on a VG Instrument 70-S Mass spectrometer operating at an electron impact ionizing potential of 70 eV. Data are reported as the mass to charge ratio (m/e) of the observed ion, where M^+ refers to the molecular ion, followed by the intensity of the ions relative to the largest peak assigned as 100%. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Baker fluorescent glass-backed TLC plate were used for analyses of reactions. Column chromatography was conducted using Merck silica gel 60 (70-230 mesh). Diethyl ether was distilled from benzophenone ketyl under N_2 and CH_2Cl_2 was distilled from calcium hydride before use. All other solvents and reagents were used as received from commercial sources.

The Synthesis of an α-Aminosulfonoglycine. The following compounds were prepared essentially by the procedures of Gilmore and Lin.[16] Only compounds for which new physical data was measured are listed. ***N-tert-Butylsulfamylacetic Acid Hydrazide***: ^{1}H NMR ($(CD_3)_2SO$) δ 3.81 (s, 2H), 1.27 (s, 9H) [lit.[16a] δ 3.8 (s, 2H), 1.3 (t, 3H, CH_3)]. ***N-tert-Butylsulfamylacetyl Azide (10)***: ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 2H), 1.40 (s, 9H); IR ($CDCl_3$) 2132, 1719, 1337, and 1149 cm^{-1}. ***tert.-Butyl N-(tert.-Butylsulfamylmethyl) carbamate*** (9): ^{1}H NMR ($CDCl_3$) δ 4.40 (d, 2H, J=7.0Hz), 1.47 (s, 9H), 1.39 (s, 9H); ^{1}H NMR ($(CD_3)_2SO$) δ 4.24 (d, 2H, J=7.1Hz), 1.46(s, 9H), 1.31(s, 9H); IR (KBr) 1695, 1367, and 1135 cm^{-1} (lit:[16] Note: the two sets of spectral data reported[16a & 16b] differ).

Ethyl 2-(N-*tert*-Butylsulfamyl)propionate (12b). To a cooled solution (0°C) of 3.6 g (50 mmol) of *tert*-butylamine in 40 mL of CH_2Cl_2 was added dropwise 5.0 g (25 mmol) of ethyl 2-(chlorosulfonyl)propionate (**12a**)[23] over a period of 15 min, then the mixture was further stirred at 25°C for 1 h. The mixture was washed with water, with saturated aqueous NaCl, and the orgaic extract was dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 3.2 g (54%) of a crude solid which was further purified by recrystallization from ether to yield 2.5 g (42%) of the product as a white solid: mp 76-78°C; IR ($CHCl_3$) 2981, 1736, 1330 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.54 (br s, 1H), 4.26 (q, J=7.2 Hz, 2H), 3.95 (q, J=7.2 Hz, 1H), 1.64 (d, J=7.2 Hz, 3H), 1.40 (s, 9H), 1.32 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_9H_{19}NO_4S$: C, 45.55; H, 8.07. Found: C, 45.87; H, 7.85.

2-(N-*tert*-Butylsulfamyl)propionic Acid Hydrazide (12c). To a stirred solution of 1.5 g (6.3 mmol) of Ethyl 2-(N-tert-Butylsulfamyl)propionate (**12b**) in 7 mL of EtOH was added 0.43 g (12.6 mmol) of 95% hydrazine under N_2 and the mixture was allowed to stand for 12 h. Removal of volatile materials *in vacuo* gave 1.45 g (96%) of the product as a sticky solid which was used without further purification; IR ($CHCl_3$) 3410, 2980, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.7-4.5 (br s, 4H), 3.86 (q, J=7.2 Hz, 1H), 1.63 (d, J=7.2 Hz, 3H), 1.40 (s, 9H).

2-(N-*tert*-Butylsulfamyl)propionyl Azide (13). To a cooled solution (-5°C) of 0.18 g (0.8 mmol) of 2-(N-*tert*-Butylsulfamyl)propionic acid hydrazide (**12c**) in 1 mL of water and 5 mL of ether was added 0.13 mL (1.6 mmol) of conc HCl and 60 mg (0.87 mmol) of sodium nitrite in 0.5 mL of water. The mixture was stirred for 10 min at the same temperature, and then it was extracted with cold methylene chloride (5 mL x 3). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried over sodium sulfate, and evaporated to dryness *in vacuo* to afford 160 mg (86%) of crude solids, which were further purified by recrystallization from ether and petroleum ether at -20°C to give **13** as a white solid (115 mg, 62%); m.p. 40-45°C; IR ($CHCl_3$) 3340, 2146, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.43 (br s, 1H), 3.91 (q, J=7.2 Hz, 1H), 1.64 (d, J=7.2 Hz, 3H), 1.41 (s, 9H).

1-(Methoxycarbonylamino)ethanesulfonic Acid N-*tert*-butylamide (15a). To a solution of 0.12 g (0.51 mmol) of azide **13** in 70 mL of CH_2Cl_2 was added 1.38 mL of anhydrous methanol (34.1 mmol) under N_2 and the mixture was refluxed for 10 h. After removal of the solvent *in vacuo* , the crude product (110 mg) contained the title compound **15a** and sulfonohydantoin **16** in a molar ratio of *ca.* 4:1 (NMR analysis). Recrystallization from ether afforded 53 mg (43%) of **15a** as a white sold: mp 99°C (dec.); IR ($CHCl_3$) 2978, 1730, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.44 (br d, 1H), 4.93 (m, 1H), 4.23 (br s, 1H), 3.72 (s, 3H), 1.56 (d, J=6.4 Hz, 3H), 1.39 (s, 9H); MS (EI, 70 eV), m/e (relative intensity) 159 (8), 102 (95), 70 (9), 64 (8). Anal. Calcd for $C_8H_{18}N_2O_4S$: C, 40.32; H, 7.61; N, 11.76. Found: C, 40.21; H, 7.31; N, 11.69.

An intermediate in the reaction above, 1-(N-*tert*-butylsulfamyl)ethyl isocyanate (**14**), was characterized as follows: to a solution of 10 mg of azide **13** in 5 mL of CH_2Cl_2 was added *ca* 3 mg of methanol under N_2 and the mixture was refluxed for 4 h. After removal of the solvent *in vacuo*, the residue showed **14**, **16** and unchanged azide **13** in a molar ratio of 7.5:1.0:1.5 (NMR analysis): IR ($CDCl_3$) 2244 , 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (br s, 1H), 4.42 (q, J=6.8 Hz, 1H), 1.67 (d, J=6.8 Hz, 3H), 1.41 (s, 9H). When a solution of **14** in $CDCl_3$ (0.5 mL) was treated with a drop of methanol, the corresponding carbamate **15a** was obtained in 25 min at 25°C.

When the reaction was repeated without methanol, the reaction mixture showed **16**, **14** and **13** in a molar ratio of 0.15:0.51:0.34 (NMR analysis).

2-*tert*-Butyl-5-methyl-1,2,4-thiadiazolin-3-one-1,1-Dioxide (16). A solution of 80 mg (0.34 mmol) of **13** in 40 mL of CH_2Cl_2 was refluxed under N_2 for 10 h. After removal of the solvent *in vacuo*, the NMR spectrum of the crude product indicated an almost quantitative yield of the title compound. Further purification was accomplished by recrystallization from ether and petroleum ether to afford 59 mg (84%) of a white solid: mp 96-97°C; IR ($CHCl_3$) 3419, 1734, 1337 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.43 (br s, 1H), 4.63 (dq, J=6.4, 1.2 Hz, 1H), 1.64 (s, 9H), 1.60 (d, J=6.4 Hz, 3H). Anal. Calcd for $C_7H_{14}N_2O_3S$: C, 40.76; H, 6.84. Found: C, 41.02; H, 7.02.

Sulfonoglycylalanine Synthesis [(general procedures analogous to those of Chart 3 (and ref. 16a) were followed)]. **Compound 24b**: mp. 66.0-66.5°C; ^1H NMR ($CDCl_3$) δ 5.97 (br d, 1H, J=8.5 Hz), 4.38 (dq, 1H, J=7.2 Hz, 8.5 Hz), 4.27 (q, 2H, J=7.2 Hz), 4.11 (AB q, 2H, Δδ 0.1 ppm, J=15.2 Hz), 1.56 (d, 3H, J=7.2 Hz), 1.32 (t, 3H, J=7.2 Hz) (lit: see text); IR (KBr) 3333, 1739, 1721, 1346, 1132 cm^{-1}. Anal. Calcd for $C_7H_{13}N_1O_6S_1$: C, 35.14; H, 5.38; N, 5,85. Found: C, 35.06; H, 5.31; N, 5.78. **Compound 24c**: pasty solid (lit.[25] viscous syrup); ^1H NMR ($(CD_3)_2SO$) δ 3.81 (AB q, 2H, Δδ 0.25 ppm, J=13.2 Hz), 3.60 (q, 1H, J=7.2 Hz), 1.25 (d, 3H, J=7.2 Hz) [(lit. 4.06 (s, 2H), 3.73 (q, 1H), 1.47 (d, 3H)]. **Compound 24d**: liquid (lit.[25] liq.); ^1H NMR ($CDCl_3$) δ 5.82 (br d, 1H, J=8.4 Hz), 4.33 (m, 1H, J=7.2 Hz), 4.13 (AB q, 2H, Δδ 0.1 ppm, J=14.8 Hz), 1.54 (d, 3H, J=7.2 Hz). **Compound 24e**: liquid ^1H NMR ($CDCl_3$) δ 5.37 (br d, 1H, J=8.5 Hz), 4.31 (dq, 1H, J=7.2, 8.5 Hz), 4.10 (AB q, 2H, Δδ 0.13 ppm, J=15.2 Hz) 3.79 (s, 3H), 1.51 (d, 3H, J=7.2 Hz); IR (neat) 2149, 1739, 1714, 1345, 1139 cm^{-1}. **Compound 26**: ^1H NMR ($CDCl_3$) δ 5.97 (br s, 1H), 4.65 (q, 1H, J=7.5Hz), 4.66 (d, 2H, J=1.6 Hz), 3.79 (s, 3H), 1.77 (d, 3H, J=7.5 Hz); IR (KBr) 3211, 1750, 1731, 1334, 1165 cm^{-1}. Anal. Calcd for $C_6H_{10}N_2O_5S_1$: C 32.43; H, 4.54; N, 12.61. Found: C, 32.41; H, 4.13; N, 12.55.

N-(1-Carboethoxyethanesulfonyl)-DL-alanine (27). To a suspension of 1.0 g (3.8 mmol) of the p-toluenesulfonate salt[26] of DL-alanine in 10 mL of CH_2Cl_2 was added 0.81 mL (3.8 mmol) of hexamethyldisilazane under N_2 and the mixture was stirred at 25°C for 30 min. To the reaction mixture was added 0.77 g (3.8 mmol) of sulfonyl chloride **12a**[23] in one portion and the mixture was stirred for 4 h. After filtration through celite, the filtrate was diluted with ethyl acetate, washed with saturated aqueous NaCl and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 0.87 g (93%) of a 1:1 mixture of diastereomers in the form of a clear, thick oil, essentially pure by ^1H NMR analysis, which was used in the subsequent steps without further purification. A pure sample was prepared by extracting a solution of the mixture in 5% $NaHCO_3$ with ethyl acetate, acidifying the aqueous phase with 1N HCl; IR (neat) 3284, 1737, 1333, 1139 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43, 5.32 (2 br d, 2x1H, NH), 4.34-4.19 (2 m, 2x3H, NCHCO and CH_2O), 4.06,

4.01 (2 q, J=7.2 Hz, 2x1H, CHS), 1.62, 1.61 (2 d, J=7.2 Hz, 2x3H, CH_3CHS), 1.52, 1.51 (2 d, J=7.2 Hz, 2x3H, $NCHCH_3$), 1.30, 1.29 (2 t, 2x3H); MS (EI, 70 eV), m/e (relative intensity) 210 (5), 209 (8), 208 (100); MS (CI, NH_3), m/e (relative intensity) 271 ($M + NH_4^+$, 100), 254 ($M + H^+$, 5), 225 (10), 208 (10), 90 (16); MS (HRCI) mol wt calcd for $C_8H_{19}N_2O_6S$ ($M + NH_4^+$) 271.0964, found 271.0969.

1-(Hydrazinocarbonyl)ethanesulfonyl-DL-alanine Hydrazine Salt (28). To a solution of 1.36 g (5.4 mmol) of **27** in 10 mL of ethanol was added 2.1 g (43 mmol) of hydrazine monohydrate at 25°C under N_2 and the mixture was allowed to stand overnight. Removal of volatile materials *in vacuo* gave 1.39 g (95%) of a thick clear oil. The residue was dissolved in 3 mL of water, washed with ether (5 mL x 3) and evaporated to dryness to afford **28** as a white solid (1.07 g, 73%), essentially pure (NMR analysis) (used without further purification); IR (KBr) 3570-2347, 1672, 1592 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.9-4.1 (br signal, 2x9H), 3.88 (2 q, 2x1H, CHS), 3.65, 3.56 (2 q, J = 7.2 Hz, 2x1H, NCHCO), 1.37, 1.32 (2 d, J=7.2 Hz, 2x3H, CH_3CHS), 1.25, 1.24 (2 d, J=7.2 Hz, 2x3H, $NCHCH_3$).

1-(Azidocarbonyl)ethanesulfonyl-DL-Alanine (29). To a cooled solution (-5°C) of 0.37 g (1.4 mmol) of hydrazide **28** in 1.5 mL of water and 7 mL of ether was added slowly 0.45 mL (5.5 mmol) of conc HCl and 190 mg (2.9 mmol) of sodium nitrite in 1 mL of water in that sequence. Afters stirring at the cited temperature for 10 min, the mixture was extracted with cold CH_2Cl_2 (5 mL x 3). The combined extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated to dryness at 0°C *in vacuo* to afford 190 mg (52%) of a 1/1 mixture of diastereomers as a clear, thick oil, essentially pure by ^1H NMR analysis, which was used without further purification; IR ($CDCl_3$) 3368-2500, 2147, 1713, 1344, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.49, 5.44 (2 br d, 2x1H, NH), 4.31 (2 m, 2x1H, NCHCO), 4.05, 3.98 (2 q, J=7.2 Hz, 2x1H, CHS), 1.66, 1.65 (2 d, J=7.2 Hz, 2x3H, CH_3CHS), 1.56, 1.55 (2 d, J=7.2 Hz, 2x3H, $NCHCH_3$). Compound **29** in $CDCl_3$ exhibited a half-life of 12 hr at 25°C (NMR analysis).

Methyl 1-(Azidocarbonyl)ethanesulfonyl-D,L-alaninate (32). A cooled solution (0°C) of 190 mg (0.70 mmol) of azide **29** in 2 mL of ether was added excess diazomethane in ether. The mixture was swirled in darkness for 1 min (longer exposures led to the methylation of the sulfonamide moiety) and then evaporated to dryness *in vacuo* to afford a 1/1 mixture of diastereomers in the form of a white solid (180 mg, 95%), essentially pure (^1H NMR analysis), which was used without further purification; IR ($CDCl_3$) 2148, 1744, 1711 cm^{-1}; ^1H NMR δ 5.47, 5.42 (2 br d, 2x1H, NH), 4.26 (2 m, 2x1H, NCHCO), 4.05, 3.96 (2 q, J=7.2 Hz, 2x1H, CHS), 3.80, 3.79 (2 s, 2x3H, OMe), 1.65, 1.64 (2 d, J=7.2 Hz, 2x3H, CH_3CHS), 1.50, 1.49 (2 d, 2x3H, $NCHCH_3$).

Methyl 1-(Methoxycarbonylamino)ethanesulfonyl-DL-alaninate (34). To a solution of 140 mg (0.50 mmol) of **32** in 80 mL of CH_2Cl_2 was added 1.4 mL (32 mmol) of methanol under N_2, and the mixture was refluxed for 10 h. The crude mixture (130 mg, 97%) obtained by removal of the solvent *in vacuo* showed almost pure diastereomeric carbamate **34** with a trace of decomposed materials (NMR analysis). Short column chromatography on silica gel (3:2 hexane/ethyl acetate) gave 50 mg (37%) of a thick oil which partially separated the diastereomers: IR ($CDCl_3$) 3350, 1735, 1509 cm^{-1}. High-Rf diastereomer: ^1H NMR ($CDCl_3$) δ 5.4 (br d, 1H, NH), 5.22 (br d, 1H, NH), 4.98 (br m, 1H, CHS), 4.16 (qt, 1H, NCHCO, J=7.2 Hz), 3.79 (s, 3H, OCH_3), 3.70 (s, 3H, CH_3OCON), 1.59 (d, J=6.8 Hz, 3H, CH_3CHS), 1.48 (d, J = 7.2 Hz, 3H, CH_3CHNH). (Decoupling at d 4.98 caused a doublet at 1.48 to collapse to a singlet. D_2O exchange caused the broad multiplet at d 4.98 to generate a clear quartet.). Low-Rf diastereomer: ^1H NMR ($CDCl_3$) δ 5.45 (br d,

1H, NH), 5.20 (br d, 1H, NH), 4.98 (br m, 1H, $CHSO_2$), 4.16 (qt, J=7.2 Hz, 3H, NCHCO), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, CH_3OCON), 1.56 (d, J = 6.8 Hz, 3H, $\underline{CH_3}CHSO_2$), 1.46 (d, J = 7.2 Hz, 3H, $\underline{CH_3}CHNH$). MS (EI, 70 eV), m/e (relative intensity) 194 (1), 102 (64), 70 (22), 64 (30); MS (CI, NH_3), m/e (relative intensity) 286 (M+ NH_4^+), 205 (12), 130 (13), 104 (100); MS (HRCI) mol wt calcd for $C_8H_{16}N_2O_6S$ ($M+NH_4^+$) 286.1073, found 286.1080. Anal. Calcd for $C_8H_{16}N_2O_6S$: C, 35.82; H, 6.01. Found: C, 36.12; H, 6.25.

1-(Methoxycarbonylamino)ethanesulfonyl)-DL-alanine (31). Using a modified procedure of McManus, *et al.*,[28] a solution of 10 mg (3.5×10^{-2} mmol) of azide **29** in 2% methanolic CH_2Cl_2 (5 mL) in a quartz test tube carefully flushed with N_2 was irradiated for 15 min in a Rayonet Reactor (2537 A° lamps). The crude mixture obtained by removal of the solvent *in vacuo* showed the desired product **31** as the 1/1 mixture of diastereomer *ca.* 50% yield with a four uninterpretable peaks (typical thiol odor) by the ratio of NMR integration of peaks; ^1H NMR ($CDCl_3$) δ 5.01 (2 br m, 2x1H, $CH_3\underline{CH}SO_2$), 4.21 (2 m, 2x1H, $CH_3\underline{CH}NH$), 3.73, 3.70 (2 s, 2x3H, OCH_3), 1.59, 1.57 (2 d, J=6.8 Hz, 2x3H, $\underline{CH_3}CHSO_2$), 1.52, 1.50 (2 d, J=7.2 Hz, 2x3H, $\underline{CH_3}CHNH$). Compound **31** in this reaction mixture in $CDCl_3$ was completely decomposed in 4 days of standing at 25°C. Treatment of the reaction mixture with diazomethane at 0°C for 1 min gave **34**, identical to the product obtained from the thermal decomposition of ester **32**.

Stability of 2-*tert*-Butyl-5-methyl-1,2,4-thiadiazolin-3-one-1,1-Dioxide (16). Compound **16** (3 mg) was dissolved in a solution of 0.1 mL of CD_3OD and 0.3 ml of $CDCl_3$ at 25°C and NMR spectra were run at intervals. No decomposition was observed 24 h after standing at 25 °C; a trace of decomposition was noted after 13 days.

Decomposition of 1-(Methoxycarbonylamino)ethanesulfonic Acid N-*tert*-butylamide (15a). Samples of **15a** (2 mg) were dissolved in a mixture of 0.2 mL of D_2O and 0.2 mL of CD_3OD at 25°C and the solutions were adjusted to *ca.* pH 2, pH 5 with 1N DCl in D_2O, respectively. At pH 2, the decomposition was found to have a half-life of *ca.* 3 min at 25°C. At pH 5, the decomposition was found to have a half-life of approximately 20 min at 25°C. A third sample of Compound **15a** (2 mg) was dissolved in a mixture of 0.2 ml of D_2O and 0.2 ml of CD_3OD. No decomposition was observed within 30 min at 25°C (NMR analysis); ^1H NMR δ 4.87 (q, 1H), 3.68 (s, 3H), 1.51 (d, 3H), 1.33 (s, 9H). The mixture was completely decomposed 5 days after standing at room temperature. Final ^1H NMR δ 4.96 (q, 1H), 3.67 (s, 3H), 1.38 (d, 3H), 1.33 (s, 9H). The solution of decomposition mixture was evaporated to dryness *in vacuo*, and the residue was dissolved in D_2O. The NMR spectrum showed only one singlet at 1.37 ppm; basification of the solution with sodium bicarbonate and extraction with $CDCl_3$ yielded *tert*-butylamine. A fourth sample of **15a** (2 mg) was dissolved in 0.4 mL of D_2O; decomposition was examined by NMR at regular intervals at 25°C. Compound **15a** decomposed with a half-life of *ca.* 20 min. After standing for 1 h, the NMR spectrum showed methyl N-(1-hydroxyethyl)carbamate (**19**) (vide infra) as a major product (>90%); the carbamate **19** disappeared completely after 36 h at 25°C. In the decomposition mixture, methyl carbamate (**20**), 1-hydroxyethanesulfonate (**22**)[18] and 1-(N-carbomethoxy)aminoethanesulfonate (**23**) (vide infra) were detected in a molar ratio of 3:3:4; a trace of acetaldehyde remained. 1-Hydroxycarbamate **19** was obtained in ca 30% as equilibrium mixture by standing the mixture of acetaldehyde and methyl carbamate in D_2O at 25°C for 1 week: ^1H NMR (D_2O): δ 5.28 (q, 1H), 3.66 (s, 3H), 1.34 (d, 3H); 1-(N-carbomethoxy)aminoethanesulfonic acid (**23**) was prepared by the procedure of Frankel and Moses.[13a]

Decomposition of Methyl 1-(Methoxycarbonylamino)ethanesulfonyl-DL-alaninate (34). Compound **34** (0.2 mg) in 0.5 mL of $CDCl_3$ showed no decomposition after 10 days at 25°C. The following compounds were added to similar solutions at 25°C (observations in parentheses): one equivalent of acetic acid (no dec. in 3 days); one equiv of pyridine (no dec. in 3 days); 5 equiv of acetic anhydride (no dec. in 1.5 h); 5 equiv of trifluoroacetic anhydride (complete dec. in 1.5 h). A sample of **34** (3 mg) was dissolved in a mixture of 0.3 mL of CD_3OD and 0.1 mL of D_2O; no decomposition was observed during 30 min at 25°C. This solution was adjusted to *ca.* pH 8 with sodium bicarbonate in D_2O; it showed complete decomposition of **31** in 3 days at room temperature. A sample of **31** (3 mg) was dissolved in 0.2 mL of D_2O and 0.2 mL of CD_3OD and the solution was adjusted to *ca.* pH 9.5 with potassium carbonate in D_2O; complete decomposition occurred in 5 min. A similarly constituted solution adjusted to pH 5 showed decomposition with a half-life of *ca.* 8 min at 25°C.

Thermal Decomposition of 1-(Azidocarbonyl)ethanesulfonyl-DL-alanine (29). Compound **29**, as a solid (15 mg), was placed under vacuum (10^{-2} Torr) and allowed to decompose over a period of 4 days at 25°C. The product was extracted with $CDCl_3$ and the insoluble fraction was dissolved in 0.5 ml of D_2O. The NMR spectrum of the $CDCl_3$ solution showed only two compounds: acetaldehyde and unchanged starting material in a ratio of 2:3. The NMR spectrum of the D_2O solution (*ca.* pH 1.5) showed five compounds: acetaldehyde, 1-hydroxyethanesulfonic acid (**22**) [δ 4.57 (q, 1H), 1.49 (d, 3H)], 1-aminoethanesulfonic acid (**38**) [δ 4.32 (q, 1H), 1.59 (d, 3H)], N-carbamyl-DL-alanine (**37**) [δ 4.19 (q, 1H), 1.38 (d, 3H)], and alanine [δ 4.01 (q, 1H), 1.47 (d, 3H)] in a ratio of *ca.* 10:15:20:35:20 (the decomposed products were identified by direct comparisons with authentic samples by NMR). Essentially the same product mixture was obtained from the decomposition of compound **29** (20 mg) in $CDCl_3$ (0.5 mL) at 25°C for 2 days.

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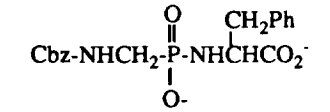

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