The Base Cyclization of Vinylic Cysteine Sulfones

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Vinylic cysteine sulfones (**1a, b, c**) cyclize in dilute base under mild conditions to cyclic sulfone amino acids. In each case, two isomers (**2** and **3**) are produced. Nmr analysis shows that these differ in configuration at atom 5 and in ring conformation. The less soluble isomer (**2**) has the *R* configuration at 5 and a conformation with the carboxyl axial. The more soluble isomer (**3**) has the *S* configuration at 5, and a ring conformation with the carboxyl equatorial.

Recently, we have shown that *cis*-*S*-(1-propenyl)-L-cysteine *S*-oxides in dilute base cyclize in low yields to the two cyclic sulfoxide amino acids, cycloalliin (**5**) and a diastereomeric sulfoxide (**4**).[2] This reaction has been extended to the β-substituted vinyl cysteine sulfones. *cis*-*S*-(1-Propenyl)- (**1a**), *trans*-*S*-(1-butenyl)- (**1b**), and *cis*-*S*-(β-styryl)-L-cysteine *S*-dioxides (**1c**) cyclize in diluted base to cyclic sulfone amino acids. In each case, two isomers, **2** and **3**, are formed which are configurationally related to the sulfoxides **4** and **5**, respectively. The pairs of sulfones **2** and **3** differ in ring conformation and in the configuration at atom 5, the former having the *R* configuration at 5 and the latter, the *S* configuration. In each case, the configuration at 3 is *R* since they are derived from L-amino acids.[3] The ring conformations and the configurations at C-5 of cycloalliin (**5**) as the hydrochloride–hydrate in the solid state[4] and of the isomeric sulfoxide **4**[5] have recently been determined by X-ray diffraction.

The unsaturated sulfone amino acids (**1a, b, c**) were prepared by oxidation of the corresponding β-substituted vinyl cysteines with hydrogen peroxide in acetic acid at 50° or in acetic acid–trifluoroacetic acid at 10 and 25°. The configuration of the double bond in **1a** and **1c** was previously established as *cis*[2] by nmr methods, but the configuration of the 1-butenylcysteine and of its sulfone (**1b**) is believed to be *trans* from infrared evidence.

Cyclization of the unsaturated sulfones is accomplished by action of 2 *N* ammonium hydroxide or 0.2 *N* sodium hydroxide at room temperature for 3–5 days to give combined yields of the cyclic sulfones of 75–90%. Internal addition of the amino group to the double bond of the α,β-unsaturated sulfones is much smoother than the corresponding reaction with the sulfoxides since (+)- or (−)-*cis*-propenylcysteine sulfoxides give yields of only 25–30%[2] of cyclic compounds and the styrylcysteine sulfoxides do not cyclize at all under these conditions.[6] For each pair of isomers, the sulfone represented by **2** is much less soluble in water or aqueous ethanol than the isomer **3**, and the compounds are easily separable by fractional crystallization. The isomers also differ in their behavior to hydrochloric acid. The **3** isomers are conveniently isolated as the hydrochloride salts from the mother liquors, after crystallization of the **2** isomers which do not form stable crystalline hydrochlorides. In solubility behavior and salt-forming properties the sulfone isomers resemble the sulfoxides **4** and **5**.[2]

The structures and the configurations of the asymmetric carbon atom 5 of **2a** and **3a** (R = CH_3) were established by correlation with the corresponding sulfoxides of known configurations. Thus, permanganate oxidation of cycloalliin (**5**) yielded **3a** and a similar oxidation of **4** yielded **2a**. The two opposite chair conformations, at least in trifluoroacetic acid solvent, for these two isomeric sulfones **2a** and **3a** was shown by nmr spectra. The similar solubilities and salt-forming properties of the other pairs of isomers (R = C_2H_5 and C_6H_5) coupled with the fact that the conformational requirements of the ethyl and methyl groups are similar and that the phenyl group should have an even greater tendency[7] to assume an equatorial position suggest that the less soluble compounds **2b** (R = C_2H_5) and **2c** (R = phenyl) agree in configuration at C-5 and

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(2) J. F. Carson and L. E. Boggs, *J. Org. Chem.*, **31**, 2862 (1966).

(3) Although cysteine derivatives may undergo racemization in base, this is probably not a factor in our preparations. It has been established both by chemical degradation and by X-ray analysis that the cyclic sulfoxides **4** and **5** have the L configuration at C-3. By oxidation, these are converted into the sulfones **2a** and **3a**. The styryl-L-cysteine sulfoxides do not cyclize in base, but show no evidence of epimerization under these conditions. Presumably the sulfones would cyclize with preservation of the L configuration at C-3. Recently, we have cyclized 1-butenyl-L-cysteine sulfoxide in dilute base to the ethyl homologs of **4** and **5**, and these on oxidation yield the sulfones **2b** and **3b** (unpublished work). Unfortunately, the D line rotations of our sulfones, in contrast to the sulfoxides or the sulfides, are very small and are of no value as criteria of purity or for correlation of configuration.

(4) K. J. Palmer and K. S. Lee, *Acta Cryst.*, **20**, 790 (1966).

(5) K. J. Palmer, unpublished data.

(6) J. F. Carson and L. E. Boggs, *J. Org. Chem.*, **32**, 673 (1967).

(7) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 44.

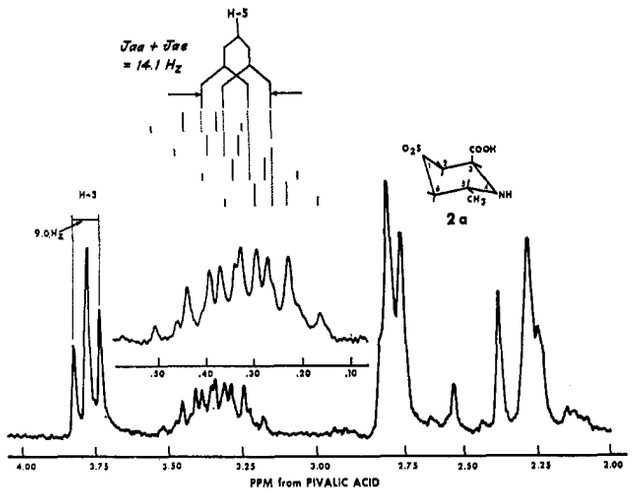


Figure 1.—Partial nmr spectrum of 3-(*R*)-carboxy-5-(*R*)-methyl-1,4-thiazane *S*-dioxide in trifluoroacetic acid–20% D_2O at 65° (pivalic acid, internal standard).

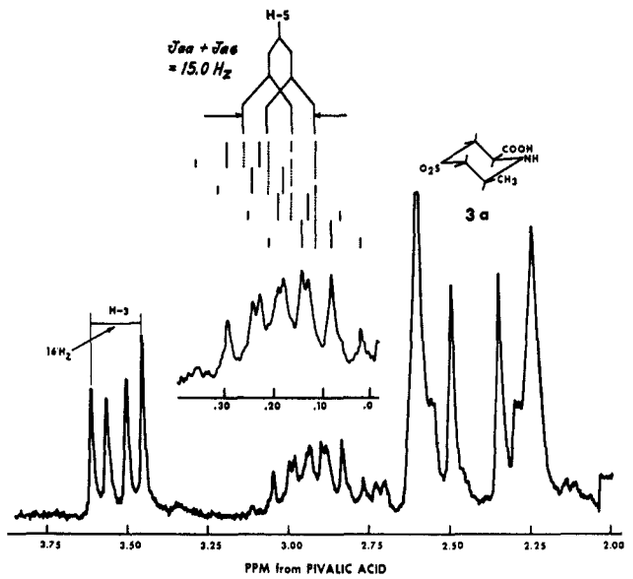


Figure 2.—Partial nmr spectrum of 3-(*R*)-carboxy-5-(*S*)-methyl-1,4-thiazane *S*-dioxide in trifluoroacetic acid–20% D_2O at 65° (pivalic acid, internal standard).

in conformation with **2a** and that the more soluble isomers **3b** and **3c** parallel **3a** in conformation and in configuration. This was confirmed by nmr spectra.

The 100-MHz nmr spectra of these sulfones did not permit a complete analysis of all the multiplets from the six ring protons and in particular the absorptions representing the H-2 protons could not be isolated from other resonances. In general, couplings of the protons at the asymmetric atoms C-3 and C-5 established both configuration of these atoms and ring conformations in the solvents used except for **2b** and **3b** where only the H-3 multiplet could be analyzed. This multiplet, representing the "X" part of an "ABX" system, appeared as a triplet except in one case where four lines were obtained. Although individual coupling constants in this system cannot be determined without an analysis of the "AB" portion, the separation of the outer lines of the "X" part which is equal to (J_{32} + $J_{32'}$) establishes whether a *trans* diaxial coupling is present or not.

Figure 1 shows the spectrum of **2a** in trifluoroacetic acid–20% D_2O with pivalic acid as an internal standard with a first-order analysis of the H-5 multiplet. The four protons at positions 2 and 6 are represented by a complex multiplet from 2.10 to 2.85 ppm downfield from pivalic acid. The methyl group resonance appeared as a doublet centered at 0.43 ppm coupled with H-5 ($J_{CH_3\text{-}5}$ = 6.8 Hz). The H-5 multiplet was centered at 3.37 ppm downfield from pivalic acid with the coupling, $J_{5\text{-}CH_3}$ = 6.7 Hz, appearing in the four overlapping quartets. The separation of 14.1 Hz between the outer lines of the "X" quartet establishes that the couplings between H-5 and the two 6 protons must include a diaxial coupling. The H-3 resonance appeared as a triplet centered at 3.77 ppm. The separation of the outer lines (9.0 Hz) almost certainly cannot include a diaxial coupling, particularly when compared with the separations obtained with **3a, b,** and **c** (see below). These data are consistent only with a conformation in which the carboxyl is axial and the methyl equatorial and therefore sulfone **2a** in trifluoroacetic acid has the same conformation as the corresponding sulfoxide (**4**) in the solid state.

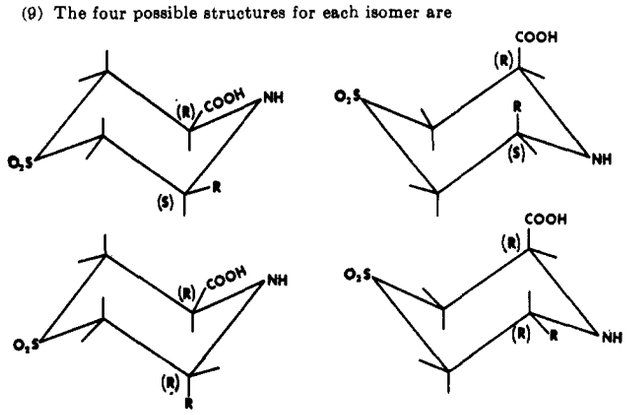
Figure 2 shows the nmr spectrum of **3a** determined under the same conditions as for **2a**. Again, the signal for the four protons at 2 and 6 occurred in a multiplet from 2.1 to 2.8 ppm which could not be analyzed. The signal for the methyl group appeared as a doublet centered at 0.32 ppm downfield from pivalic acid[8] with $J_{CH_3\text{-}5}$ = 6.5 Hz. As in the previous case, H-5 was represented by a multiplet centered at 2.95 ppm with the coupling $J_{5\text{-}CH_3}$ = 6.5 Hz appearing in the overlapping quartets. The separation of 15.0 Hz between the outer lines of the "X" quartet requires a diaxial coupling between H-5 and H-6. The proton at 3 gave rise to a quartet centered at 3.53 ppm from pivalic acid. The outer line separation, 16 Hz, must contain a diaxial coupling. Diaxial couplings at H-5 and H-3 require that both carboxyl and methyl groups be equatorial as in the corresponding sulfoxide.

For the remaining four compounds, the configuration at C-5 is not known by any chemical correlation. Therefore, four possible conformations[9] must be considered for each isomer although a conformation with both R and COOH axial is highly unlikely.

Figure 3 shows a portion of the nmr spectrum for the **2c** isomer (R = phenyl) in trifluoroacetic acid–D_2O at 65°. The signal for the 5 proton appeared as a quartet

(8) The chemical shift for the methyl group and its coupling with H-5 were determined in D_2O at 31.5°.

(9) The four possible structures for each isomer are



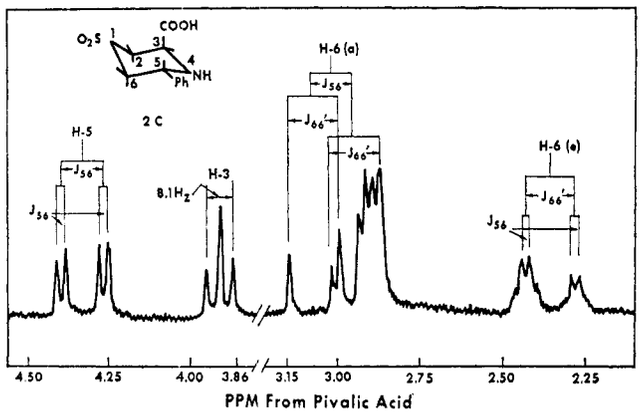


Figure 3.—Partial nmr spectrum of 3-(*R*)-carboxy-5-(*R*)-phenyl-1,4-thiazane *S*-dioxide in trifluoroacetic acid–20% D_2O at 65° (pivalic acid, internal standard).

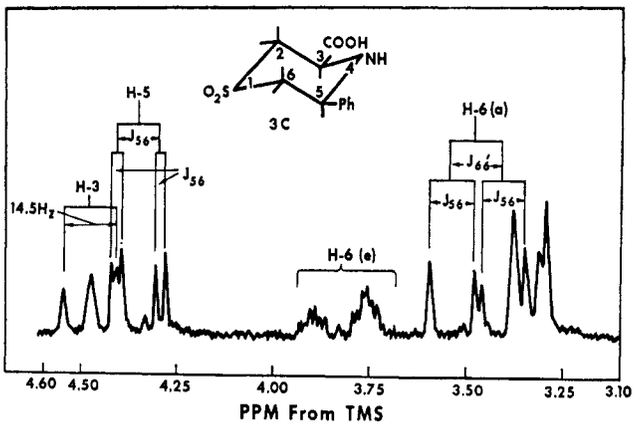


Figure 4.—Partial nmr spectrum of 3-(*R*)-carboxy-5-(*S*)-phenyl-1,4-thiazane *S*-dioxide in deuterated pyridine at 85° (tetramethylsilane, internal standard).

centered at 4.32 ppm downfield from pivalic acid. First-order approximation gave J_{56} = 12.8 (aa) and 2.6 Hz (ae). This assignment was confirmed by couplings observed for the protons at C-6. The 6 equatorial proton appeared as a quartet centered at 2.35 ppm yielding $J_{66'}$ = 15 Hz and J_{65} = 2.5 Hz (ea). The 6 axial proton also exhibited a quartet centered at 3.00 ppm with $J_{66'}$ = 14.9 Hz and J_{65} = 12.6 Hz (aa). The 3 proton appeared as a triplet centered at 3.92 ppm with an outer line separation of 8.1 Hz. This cannot include a diaxial coupling. These data establish that the carboxyl is axial and the phenyl equatorial and hence **2c** has the same ring conformation and configurations as **2a**.

The spectrum of **3c** in deuterated pyridine at 85° is shown in Figure 4. Positions were measured relative to TMS as an internal standard. H-5 and H-3 appeared as an overlapping quartet and triplet, respectively. The 5-proton quartet centered at 4.35 ppm gave by first-order approximation, J_{56} = 11.5 (aa) and 2.5 Hz (ae). The assignment was consistent with the appearance of the 6 axial proton as a quartet centered at 3.47 ppm with $J_{66'}$ = 12.5 Hz and J_{65} = 11.5 Hz (aa). The H-3 triplet centered at 4.48 ppm had an outer line separation of 14.5 Hz which must include a diaxial coupling. The 6 equatorial proton was represented by two multiplets at 3.77 and 3.90 ppm (presumably complicated by long-range coupling with the protons at 2). The data require that **3c** must have the same configuration at C-5 as **3a** and with approximately the same chair conformation. The assignment of these protons is not unequivocal. Thus, the quartet at 3.47 ppm assigned to H-6 (a) may very well represent H-2 (a), and the assignments of H-5 and H-3 may be reversed. In this case, there would still be the requirement of two diaxial couplings in agreement with the assigned conformation.

Isomers **2b** and **3b** (R = C_2H_5) gave complex spectra in trifluoroacetic acid–D_2O and only the 3 protons could be identified. H-3 of **2b** gave a triplet centered at 3.76 ppm downfield from pivalic acid very close to the chemical shift of the corresponding proton in the methyl homolog (**2a**). The separation of the outer lines, 9.0 Hz, indicates that a diaxial coupling is absent which restricts the conformation to two possibilities, one with the carboxyl axial and ethyl equatorial and the other with both carboxyl and ethyl groups axial. The former conformation is more likely, and **2b** therefore agrees with **2a** and **2c**. Similarly H-3 of **3b** appeared as a triplet centered at 3.58 ppm with an outer line separation of 15.5 Hz which must include a *trans* diaxial coupling and restricts the compound to two conformations: carboxyl and ethyl both equatorial and carboxyl equatorial and ethyl axial. The former conformation is certainly preferred which gives **3b** a conformation similar to **3a** and **3c**.

In Table I are listed the sums of the vicinal coupling constants. The values for ΣJ_{56} (14.0–15.4 Hz) are consistent with the interpretations and reflect the fact that in each case the substituent on C-5 is equatorial although the configurations of C-5 in the **2** and **3** series of sulfones are opposite. On the other hand, the values of ΣJ_{23} for the **2** series of sulfones are a consequence of an axial carboxyl and the higher values for the **3** series are due to the presence of an equatorial carboxyl although the configuration of C-3 is the same in each compound.

TABLE I
SUMS OF VICINAL COUPLING CONSTANTS

Isomer	ΣJ_{56}, Hz	ΣJ_{23}, Hz
2a	14.1	9.0
2b	...	9.0
2c	15.4	8.1
3a	15.0	16.0
3b	...	15.0
3c[a]	14.0	14.5

[a] Measured in deuteriopyridine at 85°, other compounds in TFA–20% D_2O at 65°.

Experimental Section

Infrared spectra were determined as potassium bromide disks in a Perkin-Elmer[10] Model 237 spectrophotometer. All nmr spectra were taken on a Varian Associates[10] HA-100 spectrometer.

cis-*S*-(1-Propenyl)-L-cysteine *S*-Dioxide (1a).—A solution of 7.0 g (0.0435 mol) of *cis*-*S*-(1-propenyl)-L-cysteine[2] in 440 ml of acetic acid containing 40 ml of 32.8% hydrogen peroxide (0.386 equiv) was kept for 7 hr at 50° and overnight at 25°. Concentration *in vacuo* to an oil and crystallization from 15 ml of water and 45 ml of ethanol yielded 3.76 g of lustrous micaceous plates. An additional 0.4 g was obtained from the mother liquor to give a combined yield of 49%. Recrystallization from aqueous ethanol gave the pure product: mp 153° dec; $[\alpha]^{26}D$ −0.7° (*c* 2, water);

(10) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

ir (KBr), 1125 cm^{-1} (sulfone), no absorption in sulfoxide region (1000–1060 cm^{-1}).

Anal. Calcd for $C_6H_{11}O_4NS$: C, 37.30; H, 5.74; N, 7.25. Found: C, 37.4; H, 5.79; N, 7.25.

cis-*S*-(β-**Styryl**)-L-**cysteine** *S*-**Dioxide** (1c).—To a suspension of 3.04 g (0.0136 mol) of *S*-(β-styryl)-L-cysteine[6] in 250 ml of acetic acid at +7°, there was added 40 ml of cold trifluoroacetic acid with stirring to give a complete solution. Hydrogen peroxide (32.9%, 14 ml, 0.135 equiv) was added at the rate of 2 ml/hr while the solution was maintained at 10°. The solution was then stirred for 8 hr at 25° and concentrated *in vacuo* to a white solid. The solid was stirred with 100 ml of ice–water, filtered, and washed again with cold water until the filtrate was neutral. A yield of 3.0 g (86%) of crystalline product was obtained. This was recrystallized from 360 ml of water to yield 2.36 g of pure sulfone: mp 159–160° dec; $[\alpha]^{25}D$ +38.0° (*c* 1.7, 2 *N* hydrochloric acid); ir (KBr) 1132 (sulfone), no absorption at 1000–1050 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.3; H, 5.21; N, 5.42.

Attempted oxidation with hydrogen peroxide in hot acetic acid (without trifluoroacetic acid) yielded only traces of sulfone, probably owing to insolubility in the reagent.

trans-*S*-(**1-Butenyl**)-L-**cysteine.**—Isomerization of *S*-crotyl-L-cysteine in dimethyl sulfoxide–potassium *t*-butoxide at room temperature resulted in incomplete reaction as observed by Müller and Virtanen,[11] but pure product could be isolated in low yield by several recrystallizations.

In a typical preparation, a solution of 10 g of crotylcysteine[11] in 650 ml of dimethyl sulfoxide containing 9 g of potassium *t*-butoxide was stirred for 39 hr at 25°. The turbid solution was poured into 1400 ml of ice–water containing 50 ml of acetic acid, and the resulting solution was poured through a column of Dowex 50 (H^+) (250 cm^3). The ion exchanger was washed thoroughly with water, and the amino acids were eluted with 1500 ml of 2 *N* ammonium hydroxide. Concentration of the ammoniacal solution *in vacuo* yielded a first crop of crystals, 3.78 g (*ca.* 75% 1-butenyl derivative). Two other fractions of lower purity were obtained to give a total yield of 7.0 g (over-all purity 60%). The first fraction was recrystallized twice more by concentration of ammoniacal solutions to give 1.2 g of pure 1-butenyl-L-cysteine: mp 173° dec; $[\alpha]^{25}D$ −53.6° (*c* 2.3, 2 *N* hydrochloric acid) (5 min, rapidly decreases owing to decomposition). The infrared was very similar to *S*-crotyl-L-cysteine except for an additional absorption at 950 cm^{-1}, in addition to 975 cm^{-1} (region of *trans* double bond) found in the crotyl derivative; uv max 222 mμ (ϵ_{max} 6640) (sh 238 mμ) water. Paper chromatography, rel R_f with respect to alanine = 5.70–5.76 (for crotyl cysteine, rel R_f = 5.22) with butanol–acetic acid–water (63:10:27) (20 hr).

trans-*S*-(**1-Butenyl**)-L-**cysteine** *S*-**Dioxide** (1b).—This was prepared in the same manner as the 1-propenyl derivative. From 3.0 g of 1-butenylcysteine, there was obtained 1.66 g (47%) of the sulfone. The compound was recrystallized from ethanol–water (3:1): mp 210–215° dec; $[\alpha]^{25}D$ +7.3° (*c* 2.2, water); ir (KBr), 1125 (sulfone), 965 cm^{-1} (*trans* double bond), no sulfoxide absorption.

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.56; H, 6.32; N, 6.76. Found: C, 40.8; H, 6.38; N, 6.85.

Cyclization of *cis*-*S*-(**1-Propenyl**)-L-**cysteine** *S*-**Dioxide** (1a) **to 2a and 3a.**—A solution of 3.49 g (0.0181 mol) of **1a** in 450 ml of oxygen-free 0.2 *N* sodium hydroxide was allowed to stand in the dark at 25° for 60 hr. The solution was then acidified with 25 ml of acetic acid and poured through a column of Dowex 50 (H^+) (250 cm^3). The ion exchanger was washed with 2 l. of water, and the amino acids were eluted with 1200 ml of 2.0 *N* ammonium hydroxide. The eluate, after decolorizing with carbon, was concentrated *in vacuo* to a white crystalline solid. This was suspended in 12 ml of hot water to which 24 ml of hot ethanol was added. The suspension after refrigeration for 2 days yielded 1.19 g (34%) of small prisms. This fraction was **2a**. The material in the mother liquor after removal of solvent was crystallized from 7 ml of water and 25 ml of ethanol to yield 0.587 g (16.8%) as tiny needles. This compound was **3a**. Crystallization of the mother liquor from more concentrated alcoholic solutions (80–90% ethanol) yielded three more fractions of **3a** totaling 1.37 g (39%).

(11) A. L. Müller and A. I. Virtanen, *Acta Chem. Scand.*, **20**, 1163 (1966).

The first fraction was recrystallized from water to yield 665 mg of pure **2a**, **3-(*R*)-carboxy-5-(*R*)-methyl-1,4-thiazane *S*-dioxide** as small prisms: mp 267 dec; $[\alpha]^{25}D$ ~0 (*c* 2, 2.5 *N* HCl); ir, 1130 and 1155, moderate absorption at 1023 cm^{-1}.[12]

Anal. Calcd for $C_6H_{11}NO_4S$: C, 37.30; H, 5.74; N, 7.25. Found: C, 37.50; H, 5.81; N, 7.27.

The mother liquor from the first fraction on adding ethanol yielded 450 mg of **2a** (ir indistinguishable from the recrystallized first fraction). The compound does not form a stable hydrochloride salt. Evaporation of hydrochloric acid solutions to dryness yielded only starting material.

The last four fractions **3a** had virtually identical infrared spectra but differed greatly in this respect from the first fraction. Recrystallization from 80–85% ethanol yielded pure **3a**, **3-(*R*)-carboxy-5-(*S*)-methyl-1,4-thiazane *S*-dioxide** as tiny needles: mp 261° dec; $[\alpha]^{25}D$ −4.0° (*c* 2; 2.5 *N* hydrochloric acid); ir, 1150 (sulfone), moderate absorption at 1020 cm^{-1}.[12]

Anal. Calcd for $C_6H_{11}O_4NS$: C, 37.30; H, 5.74; N, 7.25. Found: C, 37.3; H, 5.76; N, 7.27.

3a Hydrochloride.—A solution of 350 mg of **3a** in 35 ml of 2 *N* hydrochloric acid was concentrated *in vacuo* to *ca.* 5 ml when crystallization occurred. After refrigeration overnight, the crystals were filtered and washed with 4 ml of cold 3 *N* hydrochloric acid and dried *in vacuo* 48 hr, 162 mg of needles, mp 241° dec. The compound analyzed as the hydrochloride hydrate.

Anal. Calcd for $C_6H_{11}NO_4S \cdot HCl \cdot H_2O$: C, 29.09; H, 5.70; N, 5.66; Cl, 14.31. Found: C, 29.4; H, 5.59; N, 5.65; Cl, 14.2.

The mother liquor, on evaporation to dryness and crystallization from 2 ml of water +20 ml of acetone yielded 130 mg of blades, mp 241 dec, analyzing for the hemihydrochloride.

Anal. Calcd for $C_6H_{11}NO_4S \cdot 0.5HCl$: C, 34.1; H, 5.51; N, 6.69. Found: C, 34.08; H, 5.48; N, 6.62.

This compound was usually obtained by crystallization from aqueous acetone and the hydrochloride hydrate by crystallization from cold 3–4 *N* hydrochloric acid.

Oxidation of Cycloalliin (5) **to the Sulfone 3a.**—Oxidation with permanganate by the procedure of Barnsley, *et al.*,[13] gave consistently higher yields of cyclic sulfones than oxidation with hydrogen peroxide. A solution of 1.66 g (0.00716 mol) of cycloalliin hydrochloride hydrate in 100 ml of 0.5 *N* sulfuric acid was stirred at 20–22° while a solution of 900 mg of potassium permanganate in 100 ml of water was added dropwise over a 2-hr period. The solution was stirred for an additional 2 hr at 25°, and excess permanganate was destroyed by the addition of 4 ml of formic acid. The solution was clarified by filtration, and most of the sulfate was removed as barium sulfate on addition of 0.5 *N* barium hydroxide solution. The solution was then passed through a cation exchanger [Amberlite IR-120 (H^+)], and the amino acid was obtained by elution with ammonium hydroxide. A yield of 1.0 g (72%) of sulfone was obtained: $[\alpha]^{25}D$ −3.7° (*c* 2, 2.5 *N* hydrochloric acid). The compound was shown to be identical with **3a** by analysis and by ir and nmr spectroscopy.

Oxidation of Cycloalliin Isomer (4) **to the Sulfone 2a.**—This oxidation followed the previous procedure. From 600 mg (0.00339 mol) of **4**, permanganate oxidation yielded 296 mg (45%) of crystalline product (crystallized from water). Elemental analysis, $[\alpha]D$ ~0, and ir and nmr spectra showed the compound to be identical with **2a**.

Cyclization of *trans*-*S*-(**1-Butenyl**)-L-**cysteine** *S*-**Dioxide** (1b) **to 2b and 3b.**—A solution of 5 g (0.0241 mol) of the sulfone **1b** in 750 ml of 2 *N* ammonium hydroxide was allowed to stand for 5 days at room temperature and then concentrated *in vacuo* to *ca.* 35 ml. A first fraction of crystals was obtained, 792 mg (15.8%). The mother liquor was taken to dryness *in vacuo*, dissolved in 200 ml of hot water, and again concentrated *in vacuo* to 30 ml (crystallization). After refrigeration overnight, a second fraction was obtained, 700 mg (14%). These two fractions had very similar infrared spectra and were shown to be the **2b** isomer. This material was recrystallized by dissolving in 200 ml of 0.5 *N* ammonium hydroxide and conentrating *in vacuo* to *ca.* 25 ml, accompanied by crystallization, to yield 700 mg of **2b**, **3-(*R*)-carboxy-5-(*R*)-ethyl-1,4-thiazane *S*-dioxide**: mp 262° dec;

(12) Absorption at 1023 cm^{-1} ordinarily considered to be in the sulfoxide region is surprising since these compounds are believed to be free of sulfoxide. This absorption was not present in the uncyclized sulfone.

(13) E. A. Barnsley, A. E. R. Thomson, and L. Young, *Biochem. J.*, **90**, 588 (1964).

$[\alpha]^{25}D$ −13.4° (*c* 2.4, 2.5 *N* hydrochloric acid); ir, 1125 and 1135 (sulfone), weak at 1025 cm^{-1}.[12]

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.56; H, 6.32; N, 6.76. Found: C, 40.5; H, 6.24; N, 6.76.

The mother liquor yielded an additional 250 mg of **2b**. This compound did not form a stable hydrochloride salt.

The aqueous mother liquor, after removal of **2b**, was taken to dryness and crystallized from 80–90% ethanol to yield three fractions (total 1.81 g, 36%). Additional product was obtained by converting the mother liquor into the hydrochloride salt. Crystallization from 2 ml of water and 30 ml of acetone yielded 530 mg of a crystalline hemihydrochloride (9.7%). These last three fractions and the hydrochloride were shown to be substantially pure **3b** isomer. A part of these three fractions (1.23 g) was recrystallized from 20 ml of water to yield 851 mg as coarse rectangular plates of **3b**, **3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane *S*-dioxide**: mp 256° dec; ir, 1133 cm^{-1} (sulfone), no sulfoxide absorption.

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.56; H, 6.32; N, 6.76. Found: C, 40.6; H, 6.22; N, 6.80.

The hydrochloride was prepared from this fraction and shown to be identical with the salt previously isolated. A solution of 585 mg of **3b** in 30 ml of 2 *N* hydrochloric acid was concentrated *in vacuo* to dryness and crystallized from a solvent mixture of 1 ml of water and 25 ml of acetone to yield 600 mg of the hemihydrochloride of **3b**: mp 238° dec; $[\alpha]^{25}D$ −7.0° (*c* 2.1, 2 *N* hydrochloric acid).

Anal. Calcd for $C_7H_{13}NO_4S \cdot 0.5HCl$: C, 37.28; H, 6.03; N, 6.21; Cl, 7.86. Found: C, 36.9; H, 5.94; N, 6.09; Cl, 7.91.

Cyclization of *cis*-*S*-(β-Styryl)-L-cysteine *S*-Dioxide (1c) to 2c and 3c.—A solution of 2.17 g (0.00851 mol) of *cis*-*S*-(β-styryl)-L-cysteine *S*-dioxide (**1c**) in 400 ml of 2 *N* ammonium hydroxide (free of oxygen) was allowed to stand for 5 days at 25° under nitrogen, and the solution was then concentrated *in vacuo* to a white solid. This was digested with 100 ml of water at 80° for 5 min and refrigerated overnight. Filtration yielded 1.01 g (47%) of white solid (**2c**). The aqueous filtrate was reduced *in vacuo* to a dry solid which was stirred with 100 ml of methanol. Only a trace of material was insoluble. The methanol-soluble material tended to gel on concentration and could not be crystallized. It was converted into the hydrochloride by addition of hydrochloric acid, and the solution was concentrated *in vacuo* to a crystalline solid (hydrochloride of **3c**).

The first fraction (water and methanol insoluble) was purified by solution in 125 ml of normal ammonium hydroxide followed by concentration *in vacuo* to 40 ml, addition of 100 ml of water, and concentration again to 40 ml. A yield of 0.44 g of crystalline **2c**, **3-(*R*)-carboxy-5-(*R*)-phenyl-1,4-thiazane *S*-dioxide**, was obtained. Concentration of the mother liquor to 10 ml yielded a second crop, 0.424 g. The compound is rather insoluble in 2 *N* hydrochloric acid (<0.5%) but moderately soluble in 6 *N* acid. Removal of acid *in vacuo* yielded the starting material. The compound had mp 288° dec; $[\alpha]^{26}D$ +8.3° (*c* 2, 5 *N* hydrochloric acid); ir, 1140 (sulfone) and no absorption in 1000–1060-cm^{-1} region.

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.3; H, 5.12; N, 5.49.

The methanol-soluble fraction (hydrochloride) was dissolved in 50 ml of hot methanol and concentrated *in vacuo* to *ca.* 20 ml (crystallization). Acetone (20 ml) was added, and the mixture was crystallized overnight in the refrigerator. A yield of 848 mg (34%) of delicate needles was obtained. A second fraction was recovered by concentration of the mother liquor to 5 ml and addition of 20 ml of acetone, 294 mg (12%). The compound analyzed as the hydrochloride of **3c**, **3-(*R*)-carboxy-5-(*S*)-phenyl-1,4-thiazane *S*-dioxide**: mp 248° dec; $[\alpha]^{26}D$ −13.4° (*c* 1.3, *N* hydrochloric acid); ir, 1760 (unionized carboxyl) and 1110 and 1155 cm^{-1}, no absorption in the sulfoxide region.

Anal. Calcd for $C_{11}H_{13}NO_4S \cdot HCl$: C, 45.28; H, 4.84; Cl, 12.15. Found: C, 45.7; H, 4.91; Cl, 11.8.

Registry No.—**1a**, 17190-47-5; **1b**, 17190-48-6; **1c**, 7732-30-1; **2a**, 17190-58-8; **2b**, 17190-50-0; **2c**, 17190-51-1; **3a**, 17190-59-9; **3a** HCl, 17190-52-2; **3a** hemihydrochloride, 17190-53-3; **3b**, 17190-54-4; **3b** hemihydrochloride, 17190-55-5; **3c** hydrochloride, 17190-56-6; *trans*-5-(1-butenyl)-L-cysteine, 17190-57-7.

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3-Epiisotelekin from *Gaillardia Aristata* Pursh. and the Structure of Farinosin[1,2]

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The structure of a minor sesquiterpene lactone isolated from *Gaillardia aristata* Pursh. has been shown to be 3-epiisotelekin (**2a**). In the course of the structure proof evidence has been accumulated which requires revision of the structure of farinosin, a sesquiterpene lactone from *Encelia farinosa* Gray, to **13**.

As part of our systematic study of *Helenium* and related species we reported recently[1] the isolation and structure determination of the pseudoguaianolide spathulin (**1**) from a collection of *Gaillardia aristata* Pursh. made in Colorado. A minor constituent found in this species was an unidentified sesquiterpene lactone which we called aristalin.

In an effort to secure more aristalin for structure investigation, we have now examined a collection of *G. aristata* from Alberta, Canada. This resulted in the isolation of a new sesquiterpene lactone, shown to be 3-epiisotelekin (**2a**) by means of reactions which also led to the revision of the structure of farinosin, a lactone isolated by one of us recently from *Encelia farinosa* Gray.[6]

Gaillardia aristata Pursh., collected near Calgary, Alberta,[7] after the usual work-up[1] and chromatography over silicic acid afforded two crystalline compounds. One of them, mp 258–260°, was identical with spathulin in accordance with our previous report.[1] The second compound was not identical with aristalin, however, and must be formulated as 3-epiisotelekin (**2a**) for the following reasons.

(1) Constituents of Gaillardia Species. VI. Previous paper: W. Herz, S. Rajappa, M. V. Lakshmikantham, D. Raulais, and J. J. Schmid, *J. Org. Chem.*, **32**, 1042 (1967).

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(6) T. A. Geissman and R. Mukherjee, *J. Org. Chem.*, **33**, 656 (1968).

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