Sulfilimines.—The sulfilimines were prepared from the corresponding sulfide and chloramine-T: S,S-diphenyl-N-toluenesulfonylsulfilimine, mp 111–112°, lit.[23] 113°; S-methyl-S-phenyl-N-*p*-toluenesulfonylsulfilimine, mp 128–129°, lit.[23] mp 132°; S,S-dimethyl-N-*p*-toluenesulfonylsulfilimine, mp 158–159°, lit.[24] mp 157–158°.

Acknowledgment.—The authors wish to thank Professor R. W. Taft for some helpful comments.

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The Synthesis and Base-Catalyzed Cyclization of (+)- and (−)-*cis*-S-(1-propenyl)-L-cysteine Sulfoxides

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Received April 8, 1966

S-(2-propenyl)-L-cysteine (I) has been isomerized to *cis*-S-(1-propenyl)-L-cysteine (II). Oxidation of the latter with aqueous hydrogen peroxide yielded a mixture of diastereomeric sulfoxides which was separated into the (+)- and (−)-*cis*-S-(1-propenyl)-L-cysteine sulfoxides (III). These compounds are isomers of the corresponding (+)-*trans* amino acid found in *Allium cepa* (onions). Reaction of either of the diastereomeric *cis* amino acids (III) in aqueous base produced cycloalliin (3-methyl-1,4-thiazane-5-carboxylic acid 1-oxide) (VI) and a new isomeric cyclic sulfoxide amino acid IV with unknown chirality at the sulfur atom.

S-(1-propenyl)-L-cysteine sulfoxide has been isolated from the onion (*Allium cepa*) and has been shown to be the precursor of the lachrymatory properties which result from enzyme action.[2] Recently, we have shown that the double bond of this naturally occurring amino acid has the *trans* configuration.[3] In this paper we report the synthesis of the dextro- and levorotatory *cis*-S-(1-propenyl)-L-cysteine sulfoxides (III), which are isomers of the naturally occurring amino acid, and the study of their cyclization in base.

S-(2-propenyl)-L-cysteine (I) was isomerized to *cis*-S-(1-propenyl)-L-cysteine (II)[4] by reaction with potassium *t*-butoxide in dimethyl sulfoxide. Oxidation of II with hydrogen peroxide in water yielded a mixture of diastereomeric sulfoxides III which were separated into the dextro- and levorotatory sulfoxides by fractional crystallization. The (+) isomer, which is less soluble in aqueous ethanol, has $[\alpha]^{25}D$ +118.5 (water) and the (−) isomer, which accumulates in the mother liquor, has $[\alpha]^{25}D$ −106.6.[5] The two isomers were further characterized by the preparation of N-2.4-dinitrophenyl derivatives. Both of the sulfoxides give the lachrymatory effect and onion aroma when treated with the C-S lyase enzyme of *Albizzia lophanta*.[6] Like the *trans* amino acid, the new isomers are unstable to mineral acid and to base and are very sensitive in solution to atmospheric oxygen.

The naturally occurring *trans* isomer, in the presence of dilute ammonium hydroxide, cyclizes to cycloalliin[7] for which the structure VI [3-(*S*)-methyl-1,4-thiazane-5-(*R*)-carboxylic acid 1-(*S*)-oxide] was recently established by X-ray analyses.[8] Reaction of, the *cis* amino acids with aqueous base, however is more complex. Cycloalliin is formed in yields of 10–16% and an isomeric cyclic sulfoxide (IV) is isolated in 14–24% yield. In addition, at least two other unidentified ninhydrin-reacting components are produced.

The structure of IV as a 3-methyl-1,4-thiazane-5-carboxylic acid 1-oxide was established by Raney nickel desulfurization to yield N-isopropyl-L-alanine which is also obtained on desulfurization of cycloalliin. Reduction of IV with hydriodic acid yielded the sulfide V (Figure 1), the structure of which was confirmed by nmr spectra.

The sulfide V differs from the corresponding sulfide VII obtained by reduction of cycloalliin only in the configuration of the C-methyl atom. Palmer and Lee[8] have recently shown by X-ray analyses that crystalline cycloalliin hydrochloride hydrate has the chair conformation with the sulfoxide oxygen axial and *trans* to the methyl and carboxyl groups which are equatorial. Since the carbon atom bearing the methyl group has the (*S*) configuration in cycloalliin (VI) it must have the (*R*) configuration in the isomeric sulfoxide IV and in the sulfide V. The isomer IV is therefore defined except for the sulfoxide configuration and the conformation of the molecule. IV and cycloalliin show similar ORD curves which are characterized by a positive Cotton effect at low wavelength. When the sulfoxide in cycloalliin is reduced to the sulfide, the molecular rotation in acid becomes more negative, $[M]^{25}D$ −23.6 → −47.2 while reduction of the isomeric sulfoxide IV gives a rotation less negative $[M]^{25}D$ −145 → −112.8.

Both cycloalliin and the isomeric sulfoxide IV are believed to be configurationally pure. Repeated recrystallization under varying conditions did not change the rotation or the infrared spectrum. The (+)- and (−)- and various mixtures of the *cis*-propenylcysteine sulfoxides give similar yields of cycloalliin and of the isomer IV. This suggests that the sulfoxide probably epimerizes[9] so that the same cyclic sulfoxide is produced from either configuration and that *cis–trans* isomeriza-

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tion[9] leads to the formation of cycloalliin.[10] The possibility of the presence of other isomers in the unidentified fraction has not been eliminated. The cyclization of the naturally occurring (+)-*trans*-propenylcysteine sulfoxide, however, under the same conditions, is stereoselective in that an 88% yield of one product, cycloalliin[3] can be isolated and no other ninhydrin-reactive spots are observed.

Experimental Section[11]

The pmr spectra were obtained with Varian A-60 and HR-100 spectrophotometers. Infrared spectra were obtained with a Perkin-Elmer Model 237 instrument and ORD measurements with a Cary Model 60 spectropolarimeter.

***cis*-S-(1-propenyl)-L-cysteine (II).**—To a suspension of 15.0 g (0.0932 mole) of S-(2-propenyl)-L-cysteine (I) in 1 l. of dimethyl sulfoxide (dried with calcium hydride) there was added 15.0 g (0.134 mole) of potassium *t*-butoxide with external cooling. The pale amber solution was stirred magnetically for 18 hr at 25° (protected from moisture). The solution was then cooled in an ice bath and treated with 2 l. of ice–water and 50 ml of acetic acid. The resulting solution was passed through a column of 325 cm³ of Amberlite IR-120 (H^+). The amino acid was eluted with 2 l. of 2 *N* ammonium hydroxide. Concentration of the eluate to 125 ml yielded 6.2 g of crystalline product. Further concentration of the mother liquor to 50 ml and addition of 150 ml of ethanol yielded a second crop, 4.7 g. Recrystallization from aqueous ethanol yielded the pure compound, 9.0 g (60%), dec 179–180° (gas evol), $[\alpha]^{25}D$ +59.4° (*c* 1.27, 0.25 *N* sodium hydroxide).

Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.7; H, 6.88; S, 19.89. Found: C, 44.8; H, 6.84; S, 20.1.

Proof of the *cis* configuration of the double bond by nmr and chromatographic data have been previously reported.[4]

Cyclohexylamine Salt of N-2,4-Dinitrophenyl-*cis*-S-(1-propenyl)-L-cysteine.—This derivative, prepared by a method previously described,[12] was crystallized from acetone as orange needles, dec 174–175°, $[\alpha]^{25}D$ −60.0 (*c* 0.6, in acetic acid).

Anal. Calcd for $C_{18}H_{26}N_4O_6S$: C, 50.69; H, 6.15; S, 7.52. Found: C, 50.8; H, 6.23; S, 7.76.

(+)-*cis*-S-(1-Propenyl)-L-cysteine Sulfoxide (III).—To a suspension of 3.50 g (0.0217 mole) of *cis*-propenylcysteine (II) in 250 ml of water at 5°, there was added 2.65 ml of 32.7% hydrogen peroxide at the rate of 0.4 ml/hr with stirring in an ice bath. After 8 hr, the reaction mixture was brought to room temperature and stirred an additional 18 hr at 25°. The clear solution was concentrated *in vacuo* <25° to an oily solid which was dissolved in 7 ml of water. Absolute ethanol, 110 ml, was added slowly and the turbid solution kept at 0° for 2 days. Centrifugation yielded 2.70 g of white solid, $[\alpha]^{25}D$ +27 (water). The mother liquor, after concentration *in vacuo* to 20 ml followed by the addition of 40 ml of acetone, yielded 830 mg of solid, $[\alpha]^{25}D$ −49.9. The dextrorotatory fraction was further purified by precipitation from 94–95% ethanol five times to yield 815 mg of crystalline material with $[\alpha]^{25}D$ +84.4. Two additional recrystallizations from 3 ml of water and 15 ml of acetone yielded 580 mg of tiny colorless needles with a rotation unchanged on repeated recrystallization, dec 145–150° (hot stage), $[\alpha]^{25}D$ +118.5 (*c* 2.5, water).

Anal. Calcd for $C_6H_{11}O_3NS$: C, 40.66; H, 6.26. Found: C, 40.4; H, 6.23.

The compound moves as one spot on paper chromatography with butanol–acetic acid–water (63:10:27), rel R_f with respect to alanine 1.26. In the infrared (KBr pellet), the compound shows strong absorption at 1010 cm^{-1} (sulfoxide) and no absorption at 967 cm^{-1} where the naturally occurring *trans* isomer absorbs.

(−)-*cis*-S-(1-Propenyl)-L-cysteine Sulfoxide (III).—The levorotatory fraction (0.83 g) was combined with a similar fraction from a second oxidation (total 1.30 g, $[\alpha]D$ −49). This material was recrystallized 9 times by dissolving in one part of water followed by the addition of 40–50 parts of absolute ethanol, storage at 0° for 20–40 hr and centrifugation or filtration at 0° to yield 288 mg of white crystals, dec 128° (hot stage), $[\alpha]^{26}D$ −106.6 (*c* 2.5, water).

Anal. Calcd for $C_6H_{11}O_3NS$: C, 40.66; H, 6.26. Found: C, 40.5; H, 6.12.

On paper, with butanol–acetic acid–water (63:10:27), the compound moves as a single spot (rel R_f with respect to alanine 1.11) slightly more slowly than the (+) isomer. Mixtures of the two isomers usually travel as two overlapping spots on paper chromatography. Infrared (KBr pellet) strong absorption at 1025 cm^{-1} (sulfoxide) and no absorption near 967 cm^{-1}. The (+) and (−) isomers differ in their spectra at the sulfoxide absorption and in the regions of 1300–1450 cm^{-1} and 700–850 cm^{-1}.

Aqueous solutions of these compounds frequently deposit a precipitate of unknown composition and develop a pink or yellow color. This can be avoided by keeping the solutions cold and protected from the atmosphere. The starting material should not have a cysteine content of over 0.5%.

Cyclohexylamine Salt of N-2,4-Dinitrophenyl-(+)-*cis*-S-(1-propenyl)-L-cysteine Sulfoxide.—From 60 mg of III, $[\alpha]D$ +112, 120 mg of derivative[12] was obtained. It was recrystallized from ethanol–ether (1:3), sinters 141°, dec 142–143°, $[\alpha]^{25}D$ −94.6 (*c* 0.87, acetic acid).

Anal. Calcd for $C_{18}H_{26}N_4O_7S$: C, 48.86; H, 5.92. Found: C, 48.9; H, 5.92.

Cyclohexylamine Salt of N-2,4-Dinitrophenyl-(−)-*cis*-S-(1-propenyl)-L-cysteine Sulfoxide.—From 150 mg of (−) isomer of III, 250 mg of the crude derivative[12] was obtained. Recrystallization from ethanol yielded the pure compound as yellow needles, sinters 168°, dec 170–171. The derivative is less soluble than the corresponding derivative of the (+) isomer in ethanol or acetone, $[\alpha]^{25}D$ −166.3 (*c* 0.76, acetic acid).

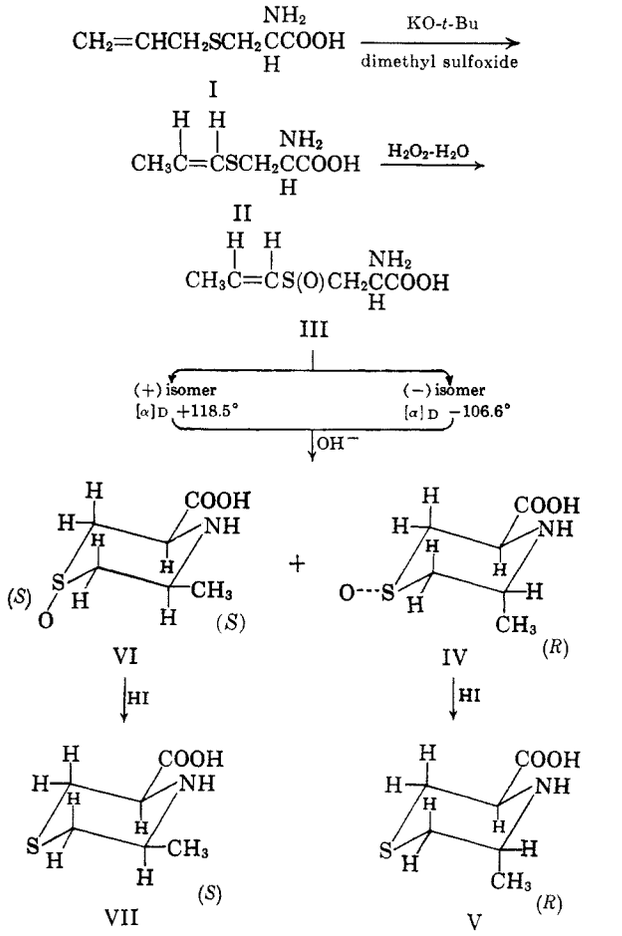

Figure 1.—Although the conformation of cycloalliin (VI) as the hydrochloride hydrate in the solid state is known, the conformations of IV and V are not known. They are drawn as shown for convenience. Inversion of the chair conformation would make the methyl group equatorial and the carboxyl group axial.

(10) That the formation of cycloalliin is not due to contamination of the *cis*-propenylcysteine sulfoxides with *trans* isomer was shown by paper chromatography (butanol–acetic acid–water).

(11) Mention of commercial products by name does not mean endorsement over products of similar quality.

(12) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **26**, 4997 (1961).

Anal. Calcd for $C_{18}H_{26}N_4O_7S$: C, 48.86; H, 5.92. Found: C, 48.7; H, 5.90.

Cyclization of *cis*-S-(1-Propenyl)-L-cysteine Sulfoxide (III) in Base.—A solution of 2.1 g of a mixture of (+) and (−) isomers of III, $[\alpha]^{26}D$ +14, in 600 ml of normal ammonium hydroxide, under nitrogen was allowed to stand for 4 days at 25°. Concentration *in vacuo* to 10 ml and dilution with 10 ml of ethanol yielded 329 mg of crystals, $[\alpha]^{26}D$ −81.3 (2.5 *N* hydrochloric acid). From the mother liquor an additional 64 mg was obtained (total yield 19%). Recrystallization from water or from aqueous ethanol gave the pure crystalline isomer IV as small prisms, dec 287–300°, $[\alpha]^{25}D$ −82.0 (*c* 2.7, 3 *N* hydrochloric acid), $[\alpha]^{25}D$ −113.0 (*c* 0.97, water).

Anal. Calcd for $C_6H_{11}O_3NS$: C, 40.66; H, 6.26. Found: C, 40.6; H, 6.22.

Optical Rotatory Dispersion of Cycloalliin (VI) and Cycloalliin Isomer (IV) in Water.—Cycloalliin had a peak at 244, a trough at 206, and a midpoint at 215 mμ (positive Cotton effect). Isomer IV showed a peak at 223, a trough at 199, and a midpoint at 211 mμ (positive Cotton effect).

In the infrared (KBr pellet) compound IV shows strong absorption in the sulfoxide region (strong 1040, med 1025 cm^{-1}). Unlike cycloalliin, the isomer does not form a stable hydrochloride. Neither cycloalliin nor its isomer forms an N-2,4-dinitrophenyl derivative. Cyclization in 0.2 *N* sodium hydroxide solution yields approximately the same results.

Isolation of Cycloalliin (VI) from the Cyclization of III.—Paper chromatography of the mother liquor, after isolation of IV, showed two ninhydrin active spots of unknown composition and a spot suggesting the presence of cycloalliin.[13] To remove primary amino compounds, the mixture was treated according to the procedure of Irreverre, *et al.*[14] The dried mother liquor was dissolved in 75 ml of water and stirred for 1 hr with 3.0 g of sodium 2,4,6-trinitrobenzenesulfonate while the pH was kept at 7–8 by the addition of 10% aqueous sodium carbonate. The solution was acidified and refrigerated for several hours. The yellow precipitate was removed by filtration and the aqueous filtrate passed through a column of 300 cm^3 of Dowex 50 (H^+). The resin was washed with water and the amino acids eluted with 2 l. of 1.5 *N* ammonium hydroxide. The elute on concentration to 4 ml followed by addition of 10 ml of acetone yielded 40 mg of IV. The filtrate on concentration yielded 300 mg of resinous crystals. Recrystallization from aqueous ethanol gave 163 mg (7.7%) of pure cycloalliin. The mother liquor, after acidification with hydrochloric acid, yielded 91 mg of cycloalliin hydrochloride hydrate to give a total yield of 11%. The compound was identified by infrared of the free amino acid, infrared of the hydrochloride hydrate, and optical rotation, $[M]^{25}D$ −23.4 (2.5 *N* hydrochloric acid). Authentic cycloalliin had $[M]^{25}D$ −23.6.

Reaction of 275 mg of (+) III, $[\alpha]D$ +118.5, with 200 ml of normal ammonium hydroxide under nitrogen at 25° for 5 days yielded 60 mg (21.8%) of cycloalliin isomer IV and 57.6 mg (16%) of cycloalliin hydrochloride hydrate. Reaction of 102 mg of (−) III, $[\alpha]D$ −106.6, under similar conditions gave 14.7 mg (14.3%) of IV and 20.3 mg (15.3%) of cycloalliin hydrochloride hydrate. Mixtures of these two compounds are readily separated by virtue of the low solubility of the isomer IV in neutral solutions and the low solubility of cycloalliin in 2 *N* hydrochloric acid.

Raney Nickel Desulfurization of IV.—A mixture of Raney nickel suspension in ethanol (10 ml) and 394 mg of IV in 150 ml of 70% ethanol was refluxed for 6 hr, filtered through Filter Aid, and the filter cake washed with 250 ml of normal ammonium hydroxide. The filtrate was concentrated to 100 ml, the nickel removed with hydrogen sulfide, and the solution then passed through a column of 75 cm^3 of Dowex 50 (H^+). The column was eluted with 600 ml of 2 *N* ammonium hydroxide and the eluate concentrated *in vacuo* to a dry crystalline solid. Recrystallization from aqueous acetone yielded 154 mg (53%) of N-isopropylalanine identified by paper chromatography and by comparison of the infrared with that of an authentic sample of N-isopropyl-L-alanine. A similar desulfurization of cycloalliin yielded the same compound.

Reduction of Cycloalliin Isomer (IV).—A solution of 660 mg of IV in 15 ml of 47% hydriodic acid was allowed to stand at room temperature for 48 hr when it was concentrated *in vacuo* to a cream colored solid. The solid was dissolved in 50 ml of water and extracted with an equal volume of carbon tetrachloride to remove iodine. Hydriodic acid was removed by treatment with a weak acid exchanger [Duolite A-4 (NH_2)] and the resulting aqueous solution (pH 4.0) was taken to dryness. Crystallization from 30 ml acetone–water (1:1) yielded 550 mg (91%) of V. Recrystallization in the same manner yielded 424 mg of small rectangular prisms, dec 287–288°, $[\alpha]^{25}D$ −70.0 (3 *N* hydrochloric acid).

Anal. Calcd for $C_6H_{11}NSO_2$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.7; H, 6.87; N, 8.68.

In the infrared, the compound showed no absorption in the sulfoxide region 1010–1050 cm^{-1}. Nmr measurements in water neutralized with trifluoroacetic acid with sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standard confirmed the structure. Integration showed the presence of nine protons attached to carbon.

Reduction of Cycloalliin (VI).—Cycloalliin hydrochloride hydrate was reduced with 47% hydriodic acid and acid and free iodine removed as in the previous reduction. The crude product was converted to the hydrochloride which was crystallized in 70% yield as needles from acetone–water (10:1), mp 244°, $[\alpha]^{25}D$ −23.9 (*c* 1.36, 2 *N* hydrochloric acid).

Anal. Calcd for $C_6H_{12}NSO_2Cl$: C, 36.45; H, 6.12; N, 7.09. Found: C, 36.5; H, 6.05; N, 7.08.

In the infrared, sulfoxide absorption (1010–1050 cm^{-1}) was absent.

Acknowledgment.—The authors are indebted to William Gaffield for ORD measurements, to Robert Lundin and Nancy Henderson for nmr spectra, and to L. M. White and Geraldine Secor for analyses.

(13) Cycloalliin does not respond to the usual ninhydrin reagents, but it can be easily detected by the copper-containing ninhydrin reagent of E. D. Moffat and R. I. Lytle, *Anal. Chem.*, **31**, 926 (1959). The cycloalliin isomer (IV) is insensitive to these reagents.

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