β-(Isopropylideneaminooxy)ethyl Sulfide.—To a solution of sodium ethoxide (0.092 g. of sodium) in ethanol (50 ml.) was added β-(isopropylideneaminooxy)ethyl bromide (7.2 g.) and β-(isopropylideneaminooxy)ethyl mercaptan (5.32 g.). The mixture was refluxed for 2 hr. in an atmosphere of N_2, then filtered, and distilled. The product (2.5 g., 27%) boiled at 104–105° (2 mm.).

Anal. Calcd. for $C_{10}H_{20}N_2O_2S$: C, 51.70; H, 8.67; N, 12.05. Found: C, 51.74; H, 8.80; N, 11.56.

Ethyl S-(β-Isopropylideneaminooxy)ethyl Xanthate.—A solution of β-(isopropylideneaminooxy)ethyl bromide (22.5 g.) and ethyl potassium xanthate (20 g.) in ethanol (250 ml.) was boiled for 3 hr. Salts were filtered off and the filtrate was distilled to give a pale yellow liquid, 13 g. (47%), b.p. 120–121° (0.5 mm.).

Anal. Calcd. for $C_8H_{15}NO_2S_2$: C, 43.43; H, 6.83; N, 6.32. Found: C, 43.86; H, 6.94; N, 6.60.

This xanthate (2 g.) was dissolved in sodium hydroxide (5 g. in 10 ml. of water and 10 ml. of ethanol) solution at 100° for 1.5 hr. (N_2 atmosphere). The cold solution was extracted with chloroform and distillation of the extract gave the mercaptan (1.0 g.) identified by its boiling point and infrared and n.m.r. spectra.

3,3-Dimethyl-1-oxa-2-aza-4-thiacyclohexane Hydrochloride (XIV).—When β-(aminooxy)ethyl mercaptan hydrochloride (VIII) was crystallized from acetone, the salt, m.p. 145–146°, was obtained which was crystallized from ethanol.

Anal. Calcd. for $C_5H_{12}ClNOS$: C, 35.39; H, 7.12; N, 8.25. Found: C, 35.15; H, 6.92; N, 8.11.

The same product was obtained when a stream of hydrogen chloride gas was led through a dry ether solution of XI.

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Configurational Relationships among Sulfinyl Amino Acids

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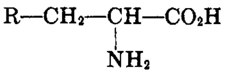
Numerous naturally occurring sulfoxides have been isolated in recent years.[2] Among these are isothiocyanate sulfoxides and sulfinyl amino acids. The sulfur atom is an asymmetric center in these compounds and consequently they exist in isomeric forms which vary in biological activity. This Note reports the results of an optical rotatory dispersion (O.R.D.) study of some sulfinyl amino acids and the significance of these results with regard to the relative and absolute configurations of these molecules.

The O.R.D. and ultraviolet parameters for several sulfinyl amino acids are listed in Table I. The alkyl sulfinyl amino acids show a low wave-length ultraviolet absorption, appearing as a shoulder, centered at 208–212 mμ which is in good agreement with the absorption maximum of saturated sulfoxides, reported[3] to be near 210 mμ in aqueous solution. This absorption band is presumably due to an n → π^* transition.[3] The O.R.D. data for the alkyl sulfinyl amino acids show a positive Cotton effect for the dextrorotatory isomers while the levorotatory isomers show a negative Cotton effect centered at slightly higher wave lengths. These Cotton effects are apparently associated with the powerfully rotating sulfoxide chromophore present in these amino acids. The O.R.D. and ultraviolet data for the isomeric 3-(n-propylsulfinyl)alanines are presented in Figure 1.

TABLE I

SOME PROPERTIES[a] OF OPTICALLY ACTIVE



$$R\text{—}CH_2\text{—}\underset{\displaystyle NH_2}{CH}\text{—}CO_2H$$

R	Absorption λ_{max}, mμ	Cotton effect: Amplitude[b] $[\phi] \times 10^{-4}$	Cotton effect: Estimated midpoint, mμ
$(+)\text{-}CH_3\text{-}\overset{O}{S}\text{-}$	210 (sh)[c]	+2.85	209
$(-)\text{-}CH_3\text{-}\overset{O}{S}\text{-}$	210 (sh)	−1.76	216
$(+)\text{-}CH_3CH_2CH_2\text{-}\overset{O}{S}\text{-}$	212 (sh)	+2.77	212
$(-)\text{-}CH_3CH_2CH_2\text{-}\overset{O}{S}\text{-}$	212 (sh)	−2.34	218
$(+)\text{-}CH_3\text{-}\overset{O}{S}\text{-}CH_2\text{-}$	208 (sh)	+1.01	207
$(-)\text{-}CH_3\text{-}\overset{O}{S}\text{-}CH_2\text{-}$	208 (sh)	−0.78	213

[a] All samples were run in distilled water. [b] Since optical purities are unknown, these are minimum values. [c] sh = shoulder.

The molecular amplitudes of the Cotton effects for the isomeric 3-(n-propylsulfinyl)alanines and the 3-(methylsulfinyl)alanines are quite similar, that of the dextrorotatory isomer being greater in both cases. The amplitudes of the isomeric 4-(methylsulfinyl)-α-amino-n-butyric acids are much smaller, apparently owing to insertion of another methylene group between the amino acid and sulfoxide chromophores. However, the positive isomer again has a larger amplitude than the negative one. That each series of alkyl sulfinyl amino acids has a more highly rotating positive isomer can be explained as being due to the presence of an L-amino acid residue. The amino acids reported in this study were originally derived from either L-cysteine or L-methionine. It has been shown[4] that L-amino acids give rise to a positive Cotton effect in the 190–215-mμ region. The amplitudes of the Cotton effects for aliphatic amino acids are not large[5] in comparison with the amplitudes of the sulfinyl amino acids. The Cotton effects observed in this study are probably a combination of both the sulfoxide and amino acid chromophores with the sulfoxide group determining the sign of the Cotton effect and the sign of rotation at the sodium line. Interaction of the two chromophores is suggested by the lower amplitude Cotton effects observed

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[3] H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962.

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[5] The amplitudes $[\phi]$ of the low wave-length Cotton effects for α-amino-n-butyric acid and norleucine are 3800 and 4600, respectively, measured in aqueous solution. These Cotton effects are centered near 200–203 mμ.

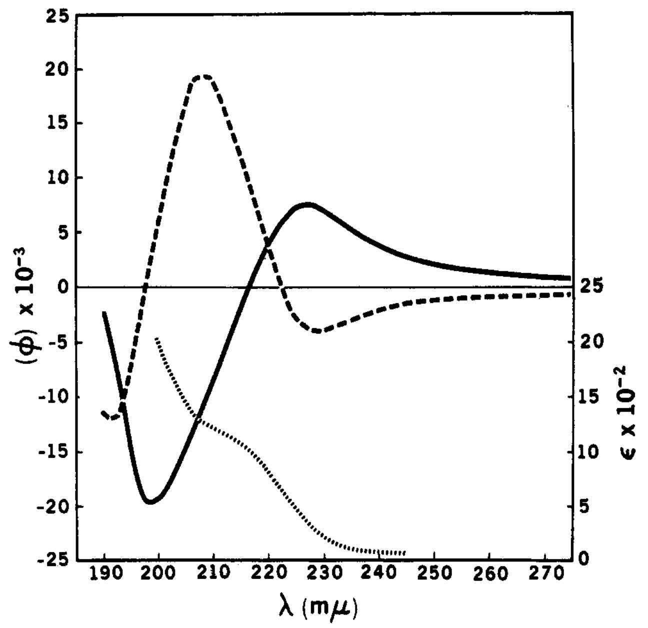

Figure 1.—Optical rotatory dispersion of (+)-3-(*n*-propylsulfinyl)alanine (———) and (−)-3-(*n*-propylsulfinyl)alanine (– – – –); ultraviolet spectrum (⋯⋯).

with the 4-(methylsulfinyl)-α-amino-*n*-butyric acids. Another possible explanation is that the levorotatory isomers might be showing Cotton effects due to both chromophores, the sulfoxide group giving rise (see Figure 1) to the negative Cotton effect centered at 218 mμ and the amino acid chromophore being centered about the descending limb of the curve at 200 mμ. However, none of the levorotatory isomers gave a shoulder on the ascending limb of the negative Cotton effect to add support to this proposal. Such shoulders have been observed[6] in certain polypeptides and proteins when two opposed Cotton effects occur in close proximity. The difference in absolute amplitudes for the isomeric 3-(methylsulfinyl)alanines (see Table I) is about 11,000. Using α-amino-*n*-butyric acid as a model compound without the sulfoxide group, one obtains a difference of (2 × 3800[5])7600. That the combination of sulfoxide and amino acid chromophores is possibly an additive feature is suggested by this example but further confirmatory evidence is desirable.

The absolute configuration about sulfur has been established by Hine[7] for (+)-3-(methylsulfinyl)alanine by X-ray analysis. Klyne, Day, and Kjaer[8] have recorded O.R.D. curves for a series of derivatives of some naturally occurring isothiocyanate sulfoxides. Negative plain curves which were very similar and nearly superimposable were obtained in the wave-length region of 300–600 mμ. These results indicate that the sulfoxides studied are of similar configuration. Variation in the number of methylene groups between the sulfoxide chromophore and the functional group on the terminal carbon atom did not effect either the sign or the shape of the O.R.D. curve.

The results obtained in the present study also indicate that the asymmetric α-carbon atom and its attached functional groups have little influence on the asymmetrically perturbed sulfoxide chromophore. Therefore, since Hine assigned[7] (+)-3-(methylsulfinyl)-alanine the (*S*)-configuration, the dextrorotatory alkyl sulfinyl amino acids described in Table I may be assigned the (*S*)-configuration about sulfur and the levorotatory isomers the (*R*)-configuration.

These conclusions may be extended to similar alkyl sulfinyl amino acids and possibly to the isothiocyanate sulfoxides.[8] The domination of the rotatory dispersion curve by the sulfoxide chromophore should permit determination of absolute configuration of dialkyl sulfoxides by observing the sign of rotation at the sodium line.

Andersen[9] recently proposed a method for assigning relative and absolute configurations to asymmetric sulfoxides. He noted[9] that Herbrandson and Cusano's[10] assignment of the (*S*)-configuration about sulfur in (−)-menthyl (−)-*p*-iodobenzenesulfinate is consistent with Hine's[7] assignment to (+)-3-(methylsulfinyl-alanine. More recently, Fleischer, Axelrod, Green, and Mislow[11] have unequivocally established the absolute configurations of (−)-menthyl (−)-*p*-iodobenzenesulfinate and of (−)-menthyl (−)-*p*-toluenesulfinate using X-ray and chemical methods. The absolute configuration about the sulfur atom is (*S*) in both cases,[11] as had been suggested previously.[10,12] The results obtained in this important paper[11] are mutually compatible with configurational assignments made by Andersen[12] and by Montanari, *et al.*,[13] to some aryl alkyl sulfoxides and also with the assignments made in this paper concerning alkyl sulfinyl amino acids.

However, there is need for further work in establishing absolute configurations of asymmetric sulfoxides. The application of O.R.D. in relating these substances will very likely prove as fruitful as it has with other chromophores.

Experimental

Materials.—The alkyl sulfinyl amino acids were obtained as described by Carson and Wong.[14] O.R.D. measurements were carried out on a Cary[15] Model 60 spectropolarimeter and ultraviolet spectra were determined on a Cary[15] 14 spectrophotometer.

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[15] Reference to a product or company name does not imply endorsement by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

Chlorination of Aromatic N-Sulfinylamines

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The chlorination of aromatic N-sulfinylamines has received little attention in the past. It is presently accepted that the chlorination proceeds under rupture of the N=SO bond to the corresponding amine hydro-