The Absolute Configurations of the Methionine Sulphoximines

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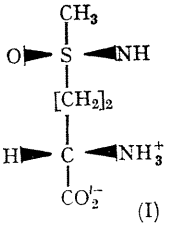
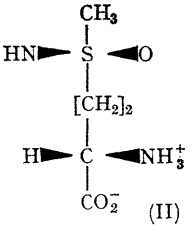
METHIONINE SULPHOXIMINE, a toxic factor from "agenized" zein and wheat flour,[1] contains, apart from the usual asymmetric C-2, a chiral, tetraco-ordinate sulphur atom. The stereochemistry of the sulphur diastereoisomers, likely to exhibit different biological activity,[1] poses an interesting problem. We report the absolute configurations of the four stereoisomeric methionine sulphoximines (I, II, and their mirror images).

A 1 : 1 mixture of 2(*S*),S(*S*)- and 2(*S*),S(*R*)-methionine sulphoxide,[2] produced by oxidation of L-methionine,[3] was converted, upon reaction with sodium azide in conc. sulphuric acid, into a mixture of 2(*S*),S(*S*)- and 2(*S*),S(*R*)-methionine sulphoximine, in a ratio close to 1 : 1 as inferred from the i.r. spectrum. Attempts to separate these by chromatography or fractional crystallization were unsuccessful.

However, combination with two molar equivalents of (+)-camphor-10-sulphonic acid,[5] in hot ethanol–ethyl acetate, 1 : 3, gave (i) a crystalline, slightly soluble salt (A) $C_5H_{12}N_2O_3S$, 2 $C_{10}H_{16}O_4S$,[6] m.p. 178°, $[\alpha]_D^{24}$ +38·5° (*c* 2, EtOH), and (ii) a more soluble, amorphous salt, (B), with the same composition.



(I)



(II)

Ion exchange of (A) (Amberlite IR-120H, elution with NH_3) gave a pure diastereoisomeride (C) of methionine

sulphoximine,† m.p. 235°, $[\alpha]_D^{22}$ + 39° (*c* 2, 1N-HCl). Similarly, (B) afforded the other pure diastereoisomeride,† (D), m.p. 239°, $[\alpha]_D^{22}$ +34° (*c* 2, 1N-HCl). (C) and (D) exhibited identical n.m.r. and mass spectra, whereas conspicuous and analytically useful differences were noted in their solid-phase (KBr) i.r. spectra.

Isomer (C) was chosen for an *X*-ray study as it gave much the better crystals. The study has shown by a comparison of the *relative* configurations at C-2 and S that the molecule possesses the absolute configuration 2(*S*),S(*R*), (I). From this follows the configuration of the other three stereoisomeric methionine sulphoximines.

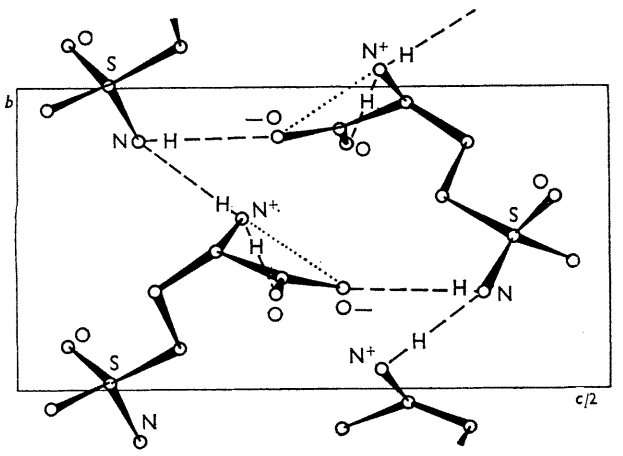


FIGURE. *The* [100] *projection of* 2(S),*S*(R)-*methionine sulphoximine, showing the absolute configurations of the molecules. Broken lines indicate intermolecular hydrogen bonds: the dotted lines indicate intramolecular zwitterion close contacts.*

Crystallographic data: $C_5H_{12}N_2O_3S$, *M* 180, orthorhombic, space group $P2_12_12_1$, $a = 5{\cdot}33$. $b = 7{\cdot}16$, $c = 21{\cdot}50$ Å, $Z = 4$. 455 *hkl* reflections were estimated from Weissenberg photographs (Cu-K_α radiation). The structure (see Figure) was solved using sulphur as heavy atom and *R* is at present 0·103. The molecule adopts a curled conformation and participates in both intra- and inter-molecular hydrogen bonding to form sheets parallel to (001) separated only by van der Waals' contacts. The *S*-methyl group is readily distinguished by its bond length (1·75 Å), and the distinction between nitrogen and oxygen is based partly on crystallographic evidence, and partly on the interpretation of the hydrogen bonding shown in the Figure. The S–O bond length (1·48 Å) agrees with values found in a variety of contexts, *e.g.*, 1·49 Å in *S*-methylcysteine sulphoxide.[6] The S–N bond is 1·56 Å, which agrees within experimental error with the only S–NH bond reported (1·53 Å for dimethyl sulphone di-imine[7]). Apart from the N–S–O angle of 118° the angles at S are all close to tetrahedral. This appears to be the first reported *X*-ray study on the geometry of a sulphoximine.

This assignment of the absolute configurations of the methionine sulphoximines may prove helpful in further studies of their biological properties, including their function as inhibitors of glutamine synthetase.[8] (Already, Dr. Meister in a private communication has reported that direct comparison of samples of (I) and (II) has shown that (II), the 2(*S*),S(*S*)-isomer, is much the more active as an inhibitor of glutamine synthetase). Chemically this assignment provides an entrance to the configurationally defined, alicyclic, chiral sulphoximines, and offers additional means of studying various stereochemical conversions, *e.g.*, sulphoxide → sulphimine → sulphoximine.[9] Studies toward these ends are in progress in the Danish laboratory.

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† Combustion analyses for C,H,N, and S were within 0·2% of theory.

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