connaissance, ait été déterminée. Pour le composé étudié, les valeurs des longueurs de liaison sont plus courtes, celles des angles plus grandes que les valeurs correspondantes du produit cité. Ceci peut sans doute s'expliquer par la présence des cycles naphtyles. Cependant les longueurs des liaisons et les angles montrent que la conjugaison entre les deux phényles reste faible.

$C(1^i)$–$O(2^i)$	1,436 (7) Å	$C(1^i)$–$O(2^i)$–$C(2^i)$	112,3 (8)°
$C(2^i)$–$O(2^i)$	1,369 (6) Å	$O(2^i)$–$C(1^i)$–$C(11^{ii})$	112,1 (8)°
$C(1^i)$–$C(11^{ii})$	1,512 (7) Å.		

Code de symétrie: (i) x, y, z; (ii) $y, x, -z$.

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Absolute Configuration of Natural Methionine Sulfoximine

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Abstract. (2*S*,*SS*)-2-Amino-4-(*S*-methylsulfonimidoyl)-butanoic acid, $C_5H_{12}N_2O_3S$, $M_r = 180{\cdot}2$, orthorhombic, $P2_12_12_1$, $a = 5{\cdot}3472\ (4)$, $b = 9{\cdot}3990\ (8)$, $c = 16{\cdot}155\ (1)$ Å, $U = 811{\cdot}9\ (2)$ Å^3, $Z = 4$, $D_x = 1{\cdot}47$ g cm^{-3}, D_m not measured, $\lambda = 1{\cdot}5418$ Å, μ(Cu $K\alpha$) $= 32{\cdot}3$ cm^{-1}, $F(000) = 384$, $R = 0{\cdot}028$ and $wR = 0{\cdot}037$ for 1494 observed data. The absolute structure reveals the (2*S*,*SS*) configuration. In the crystal lattice, the packing is maintained by hydrogen bonds. Redissolved crystals exhibit toxicity towards mice and *Bacillus subtilis*.

Introduction. Methionine sulfoximine was found for the first time in 'agenised' flour (Mellanby, 1946; Bentley, McDermott, Moran, Pace & Whitehead, 1950). It was shown to be formed by the action of nitrogen trichloride (an improving agent for flour) on wheat proteins. It induces convulsions in several mammalian species and also inhibits the growth of various living organisms. In addition it was found to be a potent inhibitor of glutamine synthetases from different organisms (Meister, 1974; Jeannoda, Rakoto-Ranoromalala, Valisolalao, Creppy & Dirheimer, 1985). We recently identified the neurotoxic compound cnestine (formerly called glabrin) (Jeannoda, Creppy & Dirheimer, 1984) from the Madagascan plants of the Connaraceae family *Cnestis glabra*, *C. polyphylla* and *Rourea orientalis* as *S*-(3-amino-3-carboxypropyl)-*S*-methyl sulfoximine (Jeannoda, Valisolalao, Creppy & Dirheimer, 1985). The present paper describes the crystallographic structure of this natural methionine sulfoximine.

Experimental. Methionine sulfoximine was isolated from root barks of *C. glabra*, *C. polyphylla* and *R.*

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orientalis (Connaraceae) as previously described (Jeannoda, Creppy & Dirheimer, 1984).

Colourless crystals of methionine sulfoximine extracted from *C. glabra* were grown from an ethanol–water (70%) mixture. Enraf–Nonius CAD-4 diffractometer, graphite-monochromatized Cu $K\alpha$ radiation. 25 reflections ($25 < \theta < 30°$) for measuring lattice constants for data collection, crystal $0{\cdot}15 \times 0{\cdot}18 \times 0{\cdot}38$ mm, $3 < \theta < 63°$ (hkl and Friedel pair $hk\bar{l}$), ω–2θ scans, scan width $(0{\cdot}70 + 0{\cdot}14\tan\theta)°$. Intensities of three reflections monitored every 2 h of exposure time showed no significant variation. Lp corrections and empirical absorption correction using ψ-scan data (reflections 400 and 301) with transmission factors varying between 0·92 and 0·99 (North, Phillips & Mathews, 1968). 1545 unique reflections, 1494 (96·7%) with $I > 3\sigma(I)$, where $I = S(C-RB)$ and $\sigma(I) = [S^2(C + R^2B) + (pI^2)]^{1/2}$, where C represents total counts recorded during scan, R the ratio of scan time to background counting time, S the scan rate, B the total background count and p (= 0·04) is a factor introduced to reflect instrumental stability. Structure solved using Patterson and Fourier techniques. All computations performed with the Enraf–Nonius *SDP* (Frenz, 1978). Refinement on F by full-matrix least-squares methods. H atoms from difference syntheses included and refined isotropically. Non-H atoms refined anisotropically. Absolute configuration was obtained through anomalous atomic dispersion (Cromer & Waber, 1974). The discrepancy between the R factors for the two possible absolute configurations is very significant (0·028 as compared to 0·038 for the other enantiomer). The (2*S*,*SS*) configuration was confirmed; this assignment was checked by use of Hamilton's method in which the significance of the discrepancy between the R factors for the two absolute configurations is estimated (Hamilton, 1965). Final $R = 0{\cdot}028$, $wR = 0{\cdot}037$ for 1494 observed data, $R = 0{\cdot}030$ for all data, $w = 1/\sigma^2(F)$. The final cycle of least-squares refinement contains 148 variables and the final largest parameter shift is less than $0{\cdot}06\sigma$. The final difference map was essentially featureless showing the highest peak at 0·26 e Å^{-3}.

Final fractional coordinates are listed in Table 1. Table 2* contains molecular dimensions. The illustrations were prepared with *ORTEP* (Johnson, 1970).

Discussion. The crystal structure is composed of discrete methionine sulfoximine molecules located on general positions. Fig. 1 displays the absolute stereochemistry together with the atomic numbering scheme used. This structure can be compared with that of the (2*S*,*SR*) isomer described elsewhere (Neidle & Rogers, 1970). The tetrahedral geometry of the sulfur atom is in good agreement with that reported for the (2*S*,*SR*) isomer. The S—O(3) bond length of 1·453 (1) Å and the S—N(2) bond length of 1·529 (1) Å appear to be characteristic of double bonds. The S—C(5) bond length of 1·751 (2) Å and the S—C(4) bond length of 1·788 (1) Å are quite normal for single-bond character. A large deviation from a tetrahedral angle at sulfur is also observed for the O(3)—S—N(2) angle [120·25 (9)°]. The bond lengths C(2)—C(3) [1·533 (2) Å] and C(2)—N(1) [1·480 (2) Å] are in good agreement with those generally found in amino acids in contrast to the anomalous reverse values reported in the (2*S*,*SR*) isomer [1·48 (3) and 1·59 (2) Å]. Therefore the influence of the slight positive charge on the N atom

Table 1. *Atomic coordinates in the asymmetric unit cell*

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as: $B_{eq} = \frac{4}{3}[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

	x	y	z	B_{eq}/B_{iso}*(Å^2)
S	0·69172 (8)	0·98375 (4)	0·99729 (2)	2·056 (7)
O(3)	0·4409 (2)	1·0412 (2)	1·00593 (8)	3·44 (3)
N(2)	0·7315 (4)	0·8363 (2)	0·95948 (8)	2·92 (3)
C(5)	0·8695 (5)	1·0980 (2)	0·9350 (1)	3·00 (4)
C(4)	0·8365 (4)	0·9927 (2)	1·09691 (9)	2·23 (3)
C(3)	0·7671 (4)	1·1261 (2)	1·14544 (9)	1·92 (3)
C(2)	0·8423 (3)	1·1121 (2)	1·23662 (9)	1·58 (3)
N(1)	0·7185 (3)	1·2265 (1)	1·28432 (8)	1·82 (3)
C(1)	1·1268 (3)	1·1232 (2)	1·24844 (9)	1·84 (3)
O(1)	1·2517 (3)	1·0125 (1)	1·2470 (1)	3·79 (3)
O(2)	1·2142 (2)	1·2463 (1)	1·25559 (8)	2·84 (3)
H(N2)	0·660 (5)	0·780 (3)	0·988 (2)	5·1 (6)
H1(C5)	1·031 (5)	1·048 (3)	0·933 (2)	6·3 (7)
H2(C5)	0·882 (5)	1·183 (2)	0·962 (1)	3·8 (5)
H3(C5)	0·806 (4)	1·096 (2)	0·888 (1)	3·0 (4)
H1(C4)	1·027 (4)	0·985 (2)	1·082 (1)	4·6 (6)
H2(C4)	0·788 (4)	0·902 (2)	1·120 (1)	2·3 (4)
H1(C3)	0·846 (3)	1·212 (2)	1·1218 (9)	1·1 (3)
H2(C3)	0·598 (4)	1·141 (2)	1·143 (1)	3·6 (5)
H(C2)	0·784 (4)	1·017 (2)	1·2581 (9)	1·6 (3)
H1(N1)	0·776 (3)	1·299 (2)	1·2700 (9)	0·9 (3)
H2(N1)	0·725 (4)	1·215 (2)	1·343 (1)	3·8 (5)
H3(N1)	0·533 (5)	1·228 (2)	1·276 (1)	4·6 (6)

* Hydrogen atoms were refined isotropically.

Table 2. *Bond lengths* (Å) *and angles* (°)

S—O(3)	1·453 (1)	C(1)—O(2)	1·252 (2)
S—N(2)	1·529 (1)	C(2)—N(1)	1·480 (2)
S—C(5)	1·751 (2)	C(2)—C(1)	1·537 (2)
S—C(4)	1·788 (1)	C(3)—C(2)	1·533 (2)
C(1)—O(1)	1·237 (2)	C(4)—C(3)	1·524 (2)
O(3)—S—N(2)	120·25 (9)	C(2)—C(1)—O(2)	116·3 (1)
O(3)—S—C(5)	109·2 (1)	O(1)—C(1)—O(2)	125·3 (2)
O(3)—S—C(4)	107·20 (7)	N(1)—C(2)—C(1)	109·2 (1)
N(2)—S—C(5)	104·51 (9)	C(3)—C(2)—N(1)	108·7 (1)
N(2)—S—C(4)	110·01 (8)	C(3)—C(2)—C(1)	111·9 (1)
C(5)—S—C(4)	104·65 (9)	C(4)—C(3)—C(2)	111·1 (1)
C(2)—C(1)—O(1)	118·3 (2)	S—C(4)—C(3)	113·4 (1)

* Lists of anisotropic thermal parameters of non-H atoms, molecular dimensions including H atoms, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43024 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

cannot account for the discrepancy observed in that structure, since in both structures the electronic distribution is quite similar.

The dimensions of the carboxy group show no differences from those of other amino acids. The amino N(1) atom lies −0·0754 (1) Å out of the mean plane defined by C(2), C(1), O(1) and O(2). A planar configuration is observed in almost all other amino acids except for DL-methionine (Mathieson, 1952) and L-arginine (Karle & Karle, 1964) with −0·7 and −0·28 Å deviations, respectively. A deviation of −0·5 Å from planarity is reported for the (2*S*,*SR*)-methionine sulfoximine. In the present structure, the deviation is comparatively small and can be ascribed to the mode of packing involving hydrogen bonds in the crystal lattice (Table 3). A stereoscopic view of the packing is shown in Fig. 2.

The methionine sulfoximine crystals, which were obtained from an ethanol–water mixture (used in this study), were dissolved in distilled water to test their toxicity. These solutions inhibited growth, and DNA, RNA and protein syntheses in *Bacillus subtilis* and were also toxic to mice as they inhibited their glutamine synthetase in brain and liver.

Four isomers of methionine sulfoximine may exist. The (2*R*) isomers were found to be inactive (Bentley, McDermott, Moran, Pace & Whitehead, 1950). Neidle & Rogers (1970), failing to get satisfactory crystals of the (2*S*,*SS*) diastereoisomer, carried out a crystallographic study of the (2*S*,*SR*) isomer of the synthetic

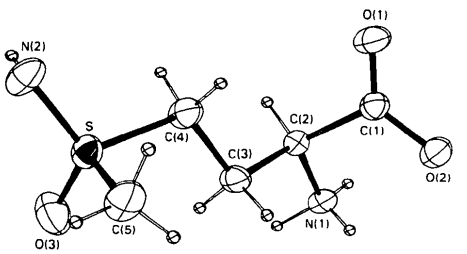

Fig. 1. (2*S*,*SS*)-Methionine sulfoximine.

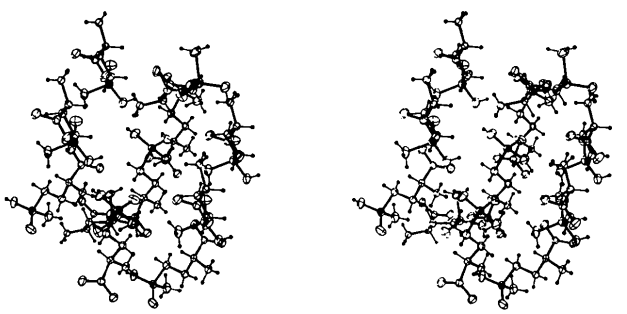

Fig. 2. Stereoscopic view of the molecular packing.

Table 3. *Intermolecular hydrogen bonds*

Atoms *a b c*	*N/uvw**	Distances (Å) *a–b*	*b–c*	*a–c*	Angles (°) *a–b–c*
N(1)–H1(N1)···O(1)	4/202	0·78 (2)	2·03 (2)	2·740 (2)	150·66 (1·7)
N(1)–H2(N1)···N(2)	2/120	0·96 (2)	1·96 (2)	2·903 (2)	170·39 (1·9)
N(1)–H3(N1)···O(2)	1/$\bar{1}$00	1·00 (3)	1·74 (3)	2·743 (2)	174·50 (2·1)
O(1)···H1N(1)–N(1)	4/2$\bar{1}$2	2·03 (2)	0·78 (2)	2·740 (2)	150·66 (1·7)
O(2)···H3N(1)–N(1)	1/100	1·74 (3)	1·00 (3)	2·743 (2)	174·50 (2·1)

* Atoms not in the crystal-chemical unit (*i.e.* not listed in Table 1) are specified by the subscript *N/uvw* which denotes the manner in which the atomic parameters can be derived from the corresponding atom in the crystal unit. *N* refers to one of the following symmetry operations: (1) *x*, *y*, *z*; (2) $-x+\frac{1}{2}, -y, z+\frac{1}{2}$; (3) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; (4) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$. The *u*,*v*,*w* digits code a lattice translation as $ua + vb + wc$.

compound. Further biological testing of both (2*S*) diastereoisomers showed that only the (2*S*,*SS*) form inhibited glutamine synthetase and induced convulsions in animals (Manning, Moore, Rowe & Meister, 1969; Rowe & Meister, 1970). Our results confirm this finding since the cnestine crystals used for the crystallographic study exhibited high toxicity towards mice (convulsive dose in mice: 30 mg kg^{-1}) and *B. subtilis* strains (efficient dose: 0·2 μg ml^{-1} of minimal medium). Therefore, cnestine, the convulsant principle of *C. glabra*, *C. polyphylla* and *R. orientalis* (Connaraceae), is methionine sulfoximine in the (2*S*,*SS*) form.

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