# Stereochemistry of Thialdine

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Thialdine (dihydro-2,4,6-trimethyl-4H-1,3,5-dithiazine), **1**, was shown on the basis of X-ray diffraction data to have the all-*cis* configuration, I.

Thialdine (dihydro-2,4,6-trimethyl-4H-1,3,5-dithiazine), **1**, is a heterocyclic base first synthesized by Wöhler and Liebig (2) over a century ago and recently recognized as a constituent of certain foodstuffs (3,4). We have been interested in learning the stereochemical relationship among the molecule's three methyl groups, but have found apparently conflicting evidence concerning this point in the literature. On the one hand, Butenko, *et al.* (5) have concluded on the basis of dipole moment data that the 2-methyl group is *trans* to the other two, as shown in structure II; this interpretation has been used in assigning
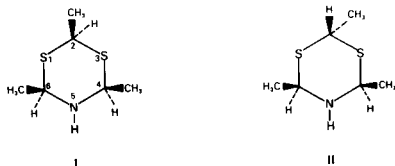


the configurations of several thialdine homologs isolated from a foodstuff odor concentrate (4). On the other hand, the *N*-nitroso derivative **2** has recently been shown by X-ray crystallography (3) to have the all-*cis* configuration, III; while epimerization at C-2 (or double epimerization at
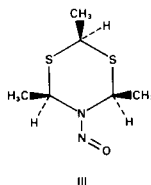


C-4 and C-6) *via* carbanion formation (6) is certainly conceivable in a molecule such as *N*-nitrosothialdine, we consider this unlikely to have occurred during the synthesis and isolation of **2** in view of the mild conditions (anhydrous, non-basic medium, room temperature) used in its preparation (3) from thialdine, and tentatively concluded that thialdine must itself have the all-*cis* configuration, as shown in I.

In this paper, we report cmr and X-ray crystallographic data for **1** which resolve the ambiguity in the literature concerning its stereochemistry and confirm that thialdine

indeed has the all-*cis* configuration, I.

## Results and Discussion.

Stereochemical assignments can often be made on the basis of cmr chemical shifts. In thialdine, the finding of only one $^{13}C$ signal for the 4- and 6-methyl groups (see Experimental) suggests that they are *cis* to each other, since they would be stereochemically (and probably also magnetically) nonequivalent if they were *trans*. Also, since the methyl group of 2-methyl-1,3-dithiane has a chemical shift of 20.2 ppm when in the equatorial position, and 25.4 ppm when axial (7), the 2-methyl chemical shift in thialdine of 21.8 ppm tends to support an equatorial assignment. Assuming that the most stable conformation of thialdine

Table I

Atomic Coordinates for Nonhydrogen Atoms in Crystalline Thialdine (a)

| Atom Type (b) | Fractional Coordinates | | |
|---|---|---|---|
| | x | y | z |
| Molecule 1 | | | |
| $S_1$ | 0.2472 (1) | −0.03289 (6) | 0.19342 (6) |
| $S_3$ | 0.2610 (1) | −0.03959 (6) | −0.02056 (6) |
| $N_5$ | 0.1793 (3) | 0.1070 (2) | 0.0692 (2) |
| $C_2$ | 0.3556 (4) | −0.0703 (2) | 0.1040 (2) |
| $C_3$ | 0.3676 (5) | −0.1674 (2) | 0.1089 (3) |
| $C_4$ | 0.2636 (4) | 0.0773 (2) | −0.0037 (2) |
| $C_5$ | 0.1945 (4) | 0.1182 (2) | −0.1018 (2) |
| $C_6$ | 0.2450 (4) | 0.0826 (2) | 0.1695 (2) |
| $C_7$ | 0.1505 (5) | 0.1240 )3) | 0.2374 (3) |
| Molecule 2 | | | |
| $S_1$ | −0.0534 (1) | 0.61431 (7) | 0.07503 (7) |
| $S_3$ | −0.4145 (1) | 0.63391 (6) | 0.02403 (7) |
| $N_5$ | −0.2172 (3) | 0.6852 (2) | −0.0999 (2) |
| $C_2$ | −0.2454 (5) | 0.5650 (2) | 0.0741 (3) |
| $C_3$ | −0.2525 (6) | 0.5395 (3) | 0.1778 (3) |
| $C_4$ | −0.3730 (4) | 0.6515 (2) | −0.0990 (2) |
| $C_5$ | −0.5044 (4) | 0.7092 (3) | −0.1545 (3) |
| $C_6$ | −0.0799 (4) | 0.6339 (2) | −0.0577 (2) |
| $C_7$ | 0.0730 (4) | 0.6750 (3) | −0.0741 (3) |

(a) The numbers in parentheses are the estimated standard deviations in the last significant digit. (b) Atoms are labelled in agreement with Figure 1a and 1b.

would contain at least two equatorial methyl groups, cmr therefore suggests that the configuration of thialdine is as shown in I.

An X-ray crystallographic analysis of thialdine (1) confirmed these spectroscopically-based structural assignments and established the configuration as I. Final atomic coordinates for nonhydrogen atoms of thialdine which resulted from the X-ray structural study are given with estimated standard deviations in Table I. Bond lengths and angles involving nonhydrogen atoms in 1 are presented in Tables II and III, respectively. Additional information regarding hydrogen atoms is also available (8).

Table II

Bond Lengths Involving Nonhydrogen Atoms in Crystalline Thialdine (a)

| Type (b) | Length, Å | |
| --- | --- | --- |
| | Molecule 1 | Molecule 2 |
| $S_1-C_2$ | 1.806 (3) | 1.803 (4) |
| $S_3-C_2$ | 1.815 (3) | 1.811 (4) |
| $S_1-C_6$ | 1.838 (3) | 1.845 (4) |
| $S_3-C_4$ | 1.845 (3) | 1.850 (4) |
| $N_5-C_4$ | 1.444 (4) | 1.428 (4) |
| $N_5-C_6$ | 1.442 (4) | 1.433 (4) |
| $C_2-C_3$ | 1.523 (5) | 1.518 (6) |
| $C_4-C_5$ | 1.510 (4) | 1.511 (5) |
| $C_6-C_7$ | 1.516 (5) | 1.512 (5) |

(a) The numbers in parentheses are the estimated standard deviations in the last significant digit. (b) Atoms are labelled in agreement with Figure 1a and 1b.

Table III

Bond Angles Involving Nonhydrogen Atoms in Crystalline Thialdine (a)

| Type (b) | Angle, degrees | |
| --- | --- | --- |
| | Molecule 1 | Molecule 2 |
| $C_2S_1C_6$ | 100.4 (2) | 98.8 (2) |
| $C_2S_3C_4$ | 98.6 (2) | 98.7 (2) |
| $C_4N_5C_6$ | 117.0 (3) | 117.5 (3) |
| $S_1C_2S_3$ | 113.1 (2) | 112.8 (2) |
| $S_1C_2C_3$ | 109.4 (3) | 109.3 (3) |
| $S_3C_2C_3$ | 108.6 (3) | 109.4 (3) |
| $S_3C_4N_5$ | 114.5 (2) | 115.4 (2) |
| $S_3C_4C_5$ | 108.3 (2) | 107.3 (3) |
| $N_5C_4C_5$ | 110.5 (3) | 110.9 (3) |
| $S_1C_6N_5$ | 115.1 (2) | 114.6 (2) |
| $S_1C_6C_7$ | 107.0 (2) | 107.6 (3) |
| $N_5C_6C_7$ | 110.5 (3) | 110.4 (3) |

(a) The numbers in parentheses are the estimated standard deviations in the last significant digit. (b) Atoms are labelled in agreement with Figure 1a and 1b.

The structural analysis shows that crystals of thialdine are composed of discrete $S_2NC_6H_{13}$ molecules. The asymmetric unit contains two crystallographically-independent molecules. Perspective drawings of both molecules which illustrate the naming scheme are shown in Figure 1 (molecule 1 in Figure 1a and molecule 2 in Figure 1b). These drawings represent the contents of the asymmetric unit specified by the atomic coordinates of all atoms and the anisotropic thermal parameters (8).
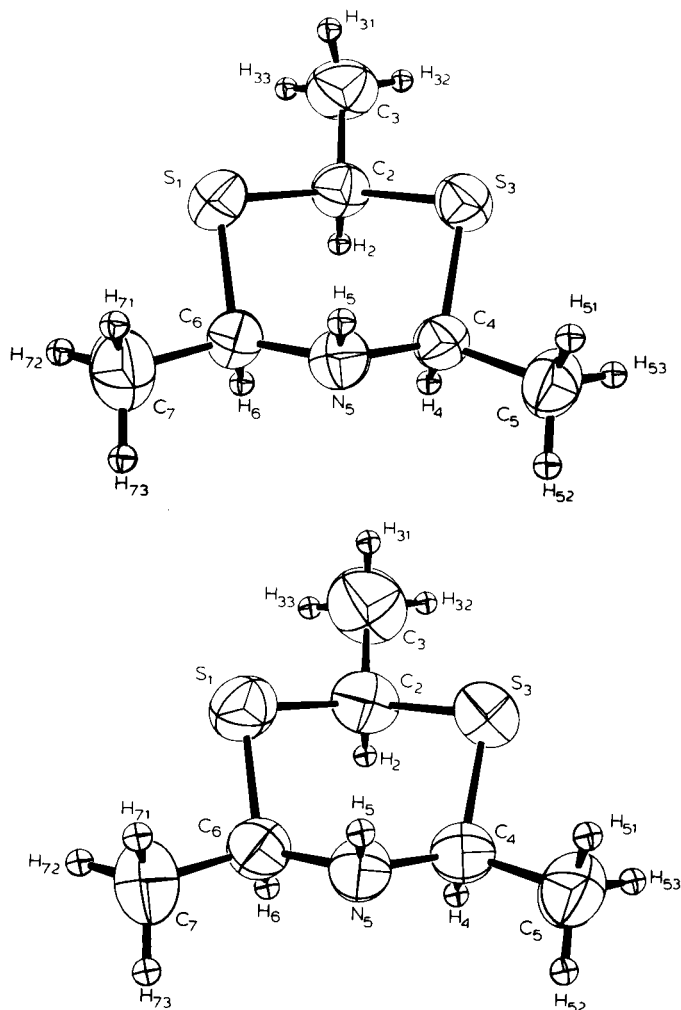


Figure 1a and 1b. ORTEP (17) drawing for the solid-state structure of thialdine (1) with the two crystallographically independent molecules shown in 1a and 1b (8). All nonhydrogen atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of the electron density. Hydrogen atoms are represented by arbitrary small spheres.

Both independent molecules of thialdine exist in configuration I, with the six-membered ring adopting a chair conformation and all methyl groups occupying equatorial positions. The nearly isostructural nature of the two solid state conformations of thialdine can be readily seen from Figure 1 and the metrical parameters of Tables II and III. Although neither molecule is required to possess any rigorous crystallographic symmetry, both are approximately

symmetrical with $N_5$, $H_5$, $C_2$, $H_2$, and $C_3$ determining a pseudo-mirror plane. These five atoms are coplanar (Table IV) to within 0.005 Å in each molecule of thialdine.

Comparison of the analogous compounds **1** and **2** with respect to certain structural features provides additional support for conclusions made earlier (3) concerning intra-molecular steric crowding in **2**. In the solid state, the N-nitroso derivative **2** possesses crystallographic symmetry with the nitroso oxygen atom (statistically) disordered between the two sites across the mirror plane defined by $N_5$, $N$, $C_2$, $C_3$, $H_2$, and $H_{31}$ (Figure 2). Thus when making
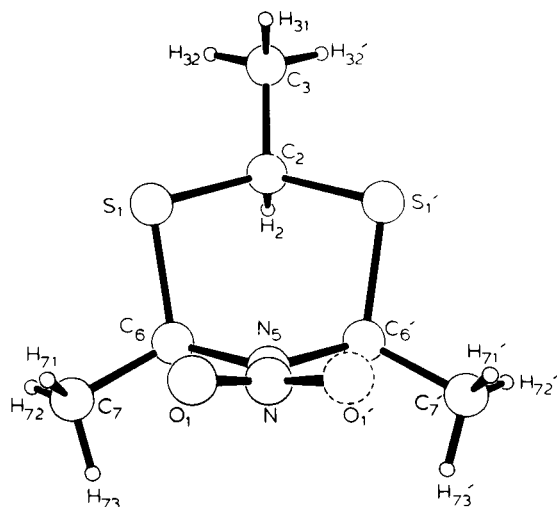


Figure 2. Perspective drawing of the N-nitrosothialdine molecule (**2**). Primed atoms are related to non-primed atoms by the crystallographic mirror plane at $y = \frac{1}{4}$.

structural comparisons between **1** and **2**, the parameters for the two molecules of thialdine should be averaged over chemically-equivalent groupings in both molecules according to (pseudo) symmetry. The average lengths of 1.809(4,4,6,4) Å (see note 9 for definitions of numbers in parentheses), 1.845(4,3,7,4) Å, and 1.437(4,6,9,4) Å for the $S_1$-$C_2$, $S_1$-$C_6$ and $N_5$-$C_6$ bonds in **1** are nearly identical to those of 1.806(2) Å, 1.824(2) Å, and 1.460(3) Å observed for corresponding bonds in **2**. The average ring C-to-methyl C bond lengths are also quite comparable (1.515(5,4,8,6) Å in **1** and 1.519(5,4,4,2) Å in **2**). The average C-H and N-H bond lengths of 0.97(4,3,6,24) Å and 0.82(3,3,3,2) Å in **1** are typical X-ray values for these parameters and are in excellent agreement with values determined for similar bonds in other high-precision studies (10). The following bond angles in **1** and **2** are also comparable, with average values of 99.1(2,6,13,4)°, 117.3(3,3,3,2)° and 113.0(2,2,2,2)° for $C_2$-$S_1$-$C_6$, $C_6$-$N_5$-$C_4$, and $S_1$-$C_2$-$S_3$ in **1** and corresponding values of 98.4(1)°, 116.4(2)°, and 112.5(2)° in **2**. The only ring bond angle having substantially different values in **1** and **2** is

the $S_1$-$C_6$-$N_5$ angle, with values of 114.9(2,4,5,4)° in **1** and 110.1(2)° in **2**. This difference presumably results from the replacement of the amine hydrogen atom in **1** by the NO group in **2** and is probably sterically induced, even though nitrogen atom $N_5$ is formally $sp^3$-hybridized in **1** and $sp^2$-hybridized in **2**. The 2.720(6) Å nonbonded O···C contact between the nitroso oxygen and the $C_7$ methyl carbon is 0.68 Å less than the sum of the van der Waals radii for oxygen and a methyl group, and 0.38 Å less than the van der Waals sum for oxygen and carbon. (Values for the van der Waals radii used here were obtained from reference 11.) With the nonbonded $H_{71}$····$O_1$ contact in **2** being 0.38 Å less than the van der Waals value, the $C_7$ methyl group in **2** is clearly oriented in such a way as to minimize its nonbonded contacts with the nitroso oxygen atom. The methyl groups of **2** exert a reciprocal effect on the nitroso group, displacing it from coplanarity with the $C_6$-$N_5$-$C_6'$ system (3). The effect of this steric crowding between adjacent nitroso and methyl groups is to open the $N_5$-$C_6$-$C_7$ angle from 110.6(3,2,3,4)° in **1** to 115.9(3)° in **2**. With this portion of the molecule in **2** essentially locked sterically into position, the intraring angle at $C_6$ decreases in **2** relative to **1**. The $S_1$-$C_6$-$C_7$ bond angle has values of 107.6(3,4,7,4)° in **1** and 109.7(2)° in **2**. The data in Table IV are totally consistent with this analysis since the dihedral angle between the $S_1$,$S_3$,$C_4$,$C_6$ least-squares mean

Table IV

Comparison of Selected Least-Squares Mean Planes in **1** and **2**

| Plane | Atoms Defining the Plane (a) | Equation of Mean Plane (b,c) |
|---|---|---|
| I | $N_5$,$H_5$,$C_2$,$H_2$,$C_3$ | $0.270X - 0.030Y - 0.962Z = -0.60$ |
| | | $-0.968X + 0.113Y - 0.224Z = 3.01$ |
| | $N_5$,$N$,$C_2$,$C_3$,$H_2$,$H_{31}$ | $0.000X - 1.000Y - 0.000Z = -3.17$ |
| II | $S_1$,$S_3$,$C_4$,$C_6$ | $-0.964X - 0.000Y - 0.265Z = -2.14$ |
| | | $-0.065X - 0.981Y - 0.181Z = -9.57$ |
| | $S_1$,$S_1'$,$C_6$,$C_6'$ (d) | $-0.850X + 0.000Y - 0.527Z = -1.36$ |
| III | $N_5$,$C_4$,$C_6$ | $-0.547X - 0.827Y - 0.130Z = -2.23$ |
| | | $0.162X - 0.428Y - 0.889Z = -3.63$ |
| | $N_5$,$C_6$,$C_6'$ (d) | $0.838X + 0.000Y - 0.546Z = -0.33$ |
| IV | $S_1$,$S_3$,$C_2$ | $-0.525X - 0.844Y - 0.108Z = -0.64$ |
| | | $0.180X - 0.364Y - 0.914Z = -4.56$ |
| | $S_1$,$S_1'$,$C_2$ (d) | $0.872X - 0.000Y - 0.490Z = 1.36$ |

(a) Atoms are labelled in agreement with Figure 1a and 1b for **1** and with Figure 2 for **2**. (b) X, Y, and Z are orthogonal coordinates measured in Å along a, b, and the normal to (001), respectively. Equations and displacements are given in the order: molecule 1 of **1**, molecule 2 of **1**, and **2**, respectively. (c) Angles in degrees between the normals to selected pairs of planes are: I-II, 90.3°, 90.4° and 90.0° (for molecule 1 of **1**, molecule 2 of **1**, and **2**, respectively); corresponding values for I-III are, respectively, 89.9°, 90.3°, and 90.0°; for II-III, 55.8°, 55.2°, 64.8° for II-IV, 57.7°, 59.3°, 61.1°; and for III-IV, 2.0°, 4.1°, 3.7°. (d) Primed (') atoms are related to non-primed atoms in **2** by the crystallographic mirror plane at $y = \frac{1}{4}$, as shown in Figure 2.

plane and that for $C_4$, $N_5$ and $C_6$ is 9.3° larger in **2** than in **1**. Furthermore, this is the only substantial difference in

dihedral angle between planar groupings of **1** and **2**. There are no intramolecular contacts in **1** which are substantially less than the appropriate van der Waals values, indicating freedom from steric crowding in this molecule.

## EXPERIMENTAL

The nmr spectra were obtained in deuteriochloroform on a Varian XL-200 instrument operating at 200 megahertz for $^1$H and 50.3 megahertz for $^{13}$C: $\delta = 1.47$ (d, J = 7, 4 + 6 -CH$_3$, 6H), 1.51 (d, J = 7, 2 -CH$_3$, 3H), 4.11 (q, J = 7, 4 + 6 -CH, 2H), 4.25 (q, J = 7, 2 -CH, 1H); $^{13}$C: $\delta = 21.8$ (1C, 2 -CH$_3$), 22.6 (2C, 4 + 6 -CH$_3$), 44.0 (1C, 2 -CH), 61.1 (2C, 4 + 6 -CH). All shifts were referenced to internal tetramethylsilane and assignments are fully supported by homo-and heteronuclear decoupling. The proton spectrum was nearly identical to that reported by Brinkman, et al. (12).

X-Ray Crystallographic Study of Thialdine (**1**).

Single crystals of thialdine (S$_2$NC$_6$H$_{13}$), obtained by slow evaporation of a concentrated methanol solution after synthesis according to the method of Wöhler and Liebig (2), were suitable for X-ray studies when sealed in thin-walled glass capillaries. They were monoclinic, space group P2$_1$/n (a special setting of P2$_1$/c-C$_{2h}^5$, No. 14), (13), with $a = 8.499(1)$Å, $b = 15.656(3)$Å, $c = 13.975(2)$Å, $\beta = 102.63(1)°$, and Z = 8 at 20 ± 1°C ($\mu_o$(MoKα) = 0.49 mm$^{-1}$; d$_{calcd.}$ = 1.20 g cm$^{-3}$) (14a).

Intensity measurements were made on a Nicolet P1 autodiffractometer using 1.0°-wide $\omega$ scans and graphite-monochromated MoKα radiation for an irregularly-shaped crystal with minimum and maximum dimensions of 0.63 and 0.75 mm, respectively. A total of 4152 independent reflections having $2\theta < 55°$ (the equivalent of the limiting CuKα sphere) were measured in two concentric shells of increasing $2\theta$. A scanning rate of 6.0°/minute was employed for the scan between $\omega$ settings 0.50°, respectively, above and below the calculated Kα doublet value ($\lambda$Kα = 0.71073) for those reflections having $0° < 2\theta \le 43°$; a scanning rate of 4.0°/minute was employed for the remaining reflections. Each of these 1.0° scans was divided into 19 equal (time) intervals and those 13 contiguous intervals which had the highest single accumulated count at their midpoint were used to calculate the net intensity from scanning. Background counts, each lasting for one-fourth the total time for the net scan (13/19 of the total scan time), were measured at $\omega$ settings 1.0° above and below the calculated Kα doublet value for each reflection.

The structure was solved by direct methods with the 18 nonhydrogen atoms of two nonequivalent thialdine molecules located in an E-map calculated from a trial set of phases. Isotropic unit-weighted full-matrix least-squares refinement for the 18 nonhydrogen atoms gave (15) $R_1$ (unweighted, based on F) = 0.090 and $R_2$ (weighted) = 0.097; anisotropic refinement converged to $R_1 = 0.067$ and $R_2 = 0.079$ for 1436 reflections having $2\theta_{MoKα} < 43°$ and $I > 3\sigma(I)$. These and all subsequent structure factor calculations employed recent tabulations of atomic form factors (14b) and an anomalous dispersion correction (14c) to the scattering factor of the sulfur atoms.

A difference Fourier synthesis based on the fully refined anisotropic model contained peaks which corresponded to chemically anticipated positions of the 26 hydrogen atoms. The final cycles of empirically-weighted (16) full-matrix least-squares refinement which employed isotropic thermal parameters for hydrogen atoms and anisotropic thermal parameters for all others converged to $R_1 = 0.037$ and $R_2 = 0.039$ for 1999 independent reflections having $2\theta_{MoKα} < 55°$ and $I > 3\sigma(I)$ (see note 8).

All calculations were performed on a Data General Eclipse S-200 computer with 64K of 16-bit words, a floating-point processor for 32- and 64-bit arithmetic, and modified versions of the Nicolet E-XTL interactive crystallographic software package.

## REFERENCES AND NOTES

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(8) A complete crystal structure analysis report for compound **1**, tables of atomic coordinates for hydrogen atoms, anisotropic thermal parameters for nonhydrogen atoms, bond lengths and angles involving hydrogen atoms, and observed and calculated structure factors from the final cycle of least-squares refinement are avaliable from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England. Any request should include the full literature citation for this paper.

(9) The first number in parentheses following an averaged value of a bond length or bond angle is the root-mean-square estimated standard deviation of an individual datum. The second and third numbers, when given, are the average and maximum deviations from the averaged value, respectively. The fourth number represents the number of individual measurements which are included in the average value.

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(15) The R values are defined as

$$R_1 = \Sigma \ \|F_o| - |F_c\| / \Sigma |F_o|$$

and

$$R_2 = \{\Sigma \ w(|F_o| - |F_c|)^2 / \Sigma w |F_o|^2\}^{1/2}$$

where w is the weight given each reflection. The function minimized is $\Sigma w(|F_o| - K|F_c|)^2$, where K is the scale factor.

(16) Empirical weights were calculated from the equation

$$\sigma = \Sigma_0^3 \ a_n |F_o|^n =$$

$0.892 - 2.68 \times 10^{-2}|F_o| + 5.73 \times 10^{-4}|F_o|^2 - 1.71 \times 10^{-6}|F_o|^3,$

where $F_o$ values were calculated from the fully-refined model using unit-weighting and an $I > 3\sigma(I)$ rejection criterion.

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