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N-NITROSOTHIALDINE. SYNTHESIS, X-RAY CRYSTALLOGRAPHY, AND N-N ROTATIONAL BARRIER

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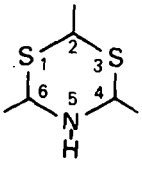
Abstract-Crystalline N-nitrosothialdine (2) has been prepared in 38% yield by treating thialdine (1) with n-butyl nitrite and acetic acid in hexane. X-Ray crystallography of 2 revealed that its three methyl groups are all cis and, rather surprisingly, all equatorial; this finding contrasts sharply with results for other nitrosamine heterocycles which have been investigated, whose bulky alpha substituents are forced into a primarily axial orientation by the large steric requirement of the N-N-O system. The equatorial methyl group both displaces the nitroso group from the C-N-C plane and twists it somewhat about the N-N bond. N-Nitrosothialdine's unusually low barrier to rotation about the N-N bond (72 kJ/mole) is attributed to this steric crowding, combined with inductive electron withdrawal by the two sulfur atoms.

Thialdine (dihydro-2,4,6-trimethyl-4H-1,3,5-dithiazine, 1) is an easily prepared heterocyclic amine which has enjoyed the frequent attention of organic chemists since it was first described by Wöhler and Liebig in 1847[1]. Recently, it has been reported as a constituent of a variety of foodstuffs[2] and flavors[3,4], as well as in the pyrolysis of certain foodstuff components[5,6]. This led us to speculate that it might form a stable N-nitroso derivative (2) in the human food chain, but exposure of thialdine to classical nitrosation conditions (nitrite and mineral acid) was found[5] not to produce 2 in detectable yield. Nevertheless, since other nitrosation mechanisms exist in nature, and since most N-nitroso compounds are capable of producing cancer in experimental animals[7], the possibility that N-nitrosothialdine might pose a carcinogenic risk for people led us to attempt its synthesis under a variety of potentially nitrosating conditions, and to isolate a quantity of 2 sufficient for proper toxicological tests. The present paper describes a convenient preparative method for crystalline 2, and summarizes its spectral and conformational properties.



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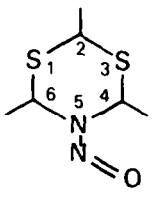


2

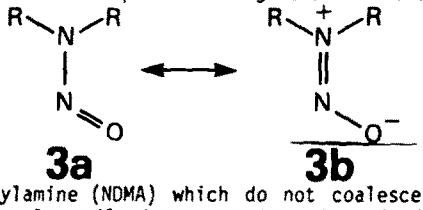
Nitrosation of thialdine

Sakaguchi, et al., have reported[5] that 2 cannot be produced by exposing 1 to aqueous nitrite. We have confirmed this observation, finding that the starting material is extensively degraded under these conditions. However, the decomposition proved not to be a simple reversion to the mixture of acetaldehyde, ammonia, and hydrogen sulfide from which 1 so easily forms[1].

In some nonaqueous N-nitrosating systems, on the other hand, we have observed production of 2 in yields of up to 50%, as detailed in the Experimental section. For preparing bulk quantities of 2, we added acetic acid to a saturated solution of 1 in hexane containing excess n-butyl nitrite, whereupon yellow crystals of 2 deposited on the vessel walls. The product, m.p. 79°C, was isolated in 38% yield.

NMR Studies

Because of the considerable double bond character of the N-N linkage in most nitrosamines, as represented in structure 3, their N-N rotational barriers are normally large enough that syn and anti substituents in otherwise symmetrical molecules can be distinguished in their NMR spectra[8-14]; for example, there are two different methyl singlets in the 100 MHz spectrum of gaseous N-nitroso-



3a 3b

dimethylamine (NDMA) which do not coalesce to one signal until the temperature is raised to 158°C[9]. N-Nitrosothialdine proved to be no exception, with the room temperature spectrum in dimethyl sulfoxide-d_6 solution at 200 MHz (Figure 1a) consisting of three one-proton methinyl quartets plus the three corresponding methyl doublets.

However, as the temperature was raised, broadening of the protons alpha and beta to the nitrosamine group was noted. Coalescence of the methyl signals was observed at 78° under these conditions (Figure 1b), corresponding to a rotational barrier of 72 kJ/mole (17.2 kcal/mole). At 141°, the alpha methyl signals had sharpened into a time-averaged (fast rotation) doublet integrating for twice the area of the corresponding peak for the methyl group at C-2 (Figure 1c).

We believe that this unusually low barrier is attributable to two major factors. One is the attachment of an electron-withdrawing sulfur substituent at each alpha carbon atom. This circumstance is expected to reduce the relative contribution of the canonical form represented by 3b to the net electronic structure of 2 by diminishing the availability of the ring nitrogen's free pair of electrons for resonance interaction with the nitroso group. While the actual magnitude of the effect might be small in 2, similar effects of heteroatom substitution have been observed previously in nitrosamine NMR spectra[10]. In agreement with this postulate, the UV spectrum of 2 shows an abnormally low ϵ_{max} (45.7) at an unusually high λ_{max} (390 nm) in ethanol, suggestive of an isolated nitroso chromophore[15].

The second barrier-lowering influence can be inferred from the X-ray crystallographic data presented in the next section, which show that the three methyl groups are cis to one another. This means that the methyl group at C-2 would generate 1,3 steric interactions with both of the other methyls if they were to take a triaxial orientation in a chair conformation. We will infer in the next section that this factor forces N-nitrosothialdine into an unexpected 4,6-diequatorial conformation in the crystal, giving rise to significant out-of-plane deformation of the nitrosamine group. The deformation presumably can be achieved only by working against a substantial potential energy gradient, since the resonance interactions represented in structure 3 should be at a maximum when the five-atom C_2N_2O system is fully coplanar. Assuming that crystal forces play no important role in establishing the conformation of crystalline 2, the all-equatorial preference and associated crowding should persist in solution, lowering the barrier to rotation about the N-N bond. That this, in fact, occurs is indicated by ^{13}C NMR (see following paragraph). It would be interesting to study the coalescence of methyl signals in all-cis-2,4,6-trimethyl-N-nitrosopiperidine, which is configurationally analogous to 2; its rotational barrier should be higher than that of 2 by roughly the magnitude of the sulfur atoms' inductive contribution to barrier lowering, providing a measure of the latter factor's magnitude.

In addition to confirming the inference which had already been made from chromatographic and melting point data that our sample of 2 was configurationally pure, i.e. consisted of only one of the three possible isomers thereof, the NMR spectra provided evidence upon which a configurational assignment could be proposed. The presence of alternating heteroatoms in the thialdine ring precludes reliance on vicinal proton coupling constants for stereochemical information. Nevertheless, two of the three possible configurational assignments can be tentatively ruled out on the basis of the observed ^1H and ^{13}C NMR spectra of 2. The isomer having trans methyl groups at C-4 and C-6 should have two stereochemically nonequivalent conformers (for a total of six different methyl signals) which interconvert by rotation about the N-N bond accompanied by a conformational inversion of the ring. The observation of just three different methyl doublets (Figure 1a) suggests that this isomer is not present, although other explanations cannot be rigorously excluded. The configurational isomer of 2 having the C-2 methyl group trans to both the C-4 and C-6 methyl groups could conceivably exist in a conformation with the C-4 and C-6 methyl groups 1,3-diaxial. However, this appears unlikely from ^{13}C NMR data (see Experimental); the syn-anti differential shielding, Δsa, of the C-4 and C-6 methyl groups is only 1.6 ppm for 2, in contrast to the Δ sa of 3.7 ppm reported[16] for the 1,3-diaxial methyls in N-nitroso-2,6-dimethyl-4-phenylpiperidine, a compound in which the configuration of both methyls is trans to the C-4 phenyl group and which exists in a conformation having both methyls axial. Since ^{13}C NMR data indicate that the C-2 methyl group of 2 is in the equatorial position due to the excellent agreement of its chemical shift (20.4 ppm) with that of an equatorial 2-methyl-1,3-dithiane (20.2 ppm)[17], in contrast to the resonance of the axial 2-methyl-1,3-dithiane isomer which appears at 25.4 ppm[17], the presence of the isomer of 2 having the C-2 methyl group trans to both the C-4 and the C-6 methyl groups can be tentatively ruled out. Thus, the configurational isomer of 2 having all three methyl groups cis to one another appears to be the only isomer compatible with both proton and carbon NMR data. Although definitive conclusions cannot be made on the basis of these data alone, this configurational assignment was confirmed using single crystal X-ray diffraction methods, as described in the next section.

Crystal structure of N-nitrosothialdine

The three methyls of 2 proved to be in the all-cis configuration, as shown in Figure 2.

This finding in turn suggests an all-cis structure for thialdine (1) itself, since the mild, nonaqueous conditions used in nitrosatively converting it to 2 seem unlikely to have provoked epimerization; indeed, the all-cis arrangement in 1 might reasonably be expected to follow from the conditions of its synthesis, in which the three acetaldehyde molecules were presumably individually free to assume a lowest-energy orientation (i.e. that which would ultimately be all-equatorial) as they assembled during the cyclization process. However, Butenko, et al.[18], have concluded on the basis of dipole moment data that the C-2 methyl group of thialdine is trans to the other two. Since the possibility that the skeleton of 1 might have isomerized during conversion to 2 (either by a ring cleavage-recyclization process or via carbanion formation[19,20] at one of the ring carbon atoms) cannot be rigorously excluded, further work is in progress to confirm the structure of thialdine as well.

While an all-equatorial conformation would be expected for all-cis 1, we had anticipated that 2 might be conformationally very different, because bulky substituents alpha to the nitrosamine function in a variety of molecules ranging from the N-nitroso derivative of cis-2,6-dimethylpiperidine[11,12] to that of 2-piperidinecarboxylic acid[13] have been shown to prefer the axial orientation or, as in the case of N-nitroso-2,2,6,6-tetramethylpiperidine[11,14,16,21], to force the ring into a non-chair conformation. In fact, a conformation was observed for 2 in which all three methyl groups were found in the equatorial position (Figure 2). Apparently, three pairwise axial-axial methyl interactions suffice to depopulate the all-axial conformation in 2, whereas one such interaction in N-nitroso-cis-2,6-dimethylpiperidine[11,12] does not.

This forcing of the methyl groups at C-4 and C-6 into a normally unfavorable position might be expected to result in crowding of the nitroso group. The X-ray studies showed that this was indeed the case, with the non-bonded separation between the oxygen atom and the syn methyl group (2.720Å) being 0.7Å less than the sum of their van der Waals radii. Non-bonded contact between the nitroso nitrogen and the anti methyl group was also significant, as the observed separation of 2.919Å was substantially less than the van der Waals distance of 3.5Å.

The consequences of this crowding on the conformation of the nitrosamine function can be analyzed in terms of two different modes of strain relief. One led to a position for the nitroso group that was outside of the $^{4}C\text{-}N\text{-}^{6}C$ plane, as represented in Figure 3. The distortion was such that the line defined by the N-N bond made an average angle of 13° with the $^{4}C\text{-}N\text{-}^{6}C$ plane, with the nitroso nitrogen being on the opposite side of the plane from the alpha methyl carbons.

The other mode of strain relief found the nitroso group twisted about the N-N bond, yielding a dihedral angle of 5.3°± 0.6° for the O-N-N-syn C system, as indicated in Figure 4. However, the N-N bond did not appear to be substantially weakened, as the bond distance (1.327Å ± 0.004Å) was the same as that of NDMA.[22] Thus the five-atom C_2N_2O system showed significant departures from coplanarity in compound 2, such that the resultant displacement of the oxygen atom from the $^{4}C\text{-}N\text{-}^{6}C$ plane was 0.75Å. By contrast, NDMA has been shown to be an "exactly planar" molecule in the crystalline phase, allowing the resonance interactions represented in structure 3 to be maximized. To our knowledge, 2 and NDMA are the only N-nitroso compounds thus far subjected to X-ray crystallographic investigation. It would be interesting to determine whether 2 is unique among dialkylnitrosamines in showing such distortions. Further studies now being planned will focus on this question.

Experimental

Warning

Most N-nitroso compounds produce cancer in experimental animals[7], and should be handled, stored, and discarded with due respect for their carcinogenic potency.

General

Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus, and are corrected. Ultraviolet data were collected on a Varian Techtron UV-Vis Spectrophotometer, Model 635, in ethanol solution. Infrared spectra were recorded on a Perkin-Elmer Model 283 Infrared Spectrophotometer in KBr pellets. Mass spectra were determined using a JEOL Model JMS-01SG-2 Mass Spectrometer after introducing the sample via the solid probe. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Gas chromatography was done using a Shimadzu GC-Mini 1 Gas Chromatograph with flame ionization detector on a 1.8m x 3mm stainless steel column of Apiezon L on 100/120 mesh Supelcoport with 20 ml/min of helium as carrier gas; injector (glasslined), column, and detector temperatures were 120°, 150°, and 120°, respectively, with higher injector temperatures inducing decomposition of both 1 and 2; retention times were 2.65 min for thialdine and 7.68 min for N-nitrosothialdine.

NMR Studies

NMR Measurements were made on a Varian XL-200 instrument operating at 200 MHz for ^{1}H NMR and at 50.3 MHz for ^{13}C NMR. The variable temperature probe was calibrated with an ethylene glycol standard. Chemical shifts in the Experimental part are in ppm downfield from internal tetramethylsilane reference, and were determined in chloroform-d solution. The variable temperature studies described in Figure 1 and in the text were performed on dimethyl sulfoxide-d_6 solutions 1M in 2; the coalescence temperature of 78° was for the methyl doublets at C-4 and C-6, which differed in chemical shift by 57Hz. The free energy of activation ($\Delta G^{\ddagger}$) was calculated from the coalescence temperature using the Eyring equation. Syn and anti assignments were supported by decoupling. Carbon resonances were assigned by selective irradiation of the corresponding proton resonances.

Reagents

Thialdine (Chemical Abstracts Service No. 638-17-5) was prepared in 96% yield by the method[1] of Wöhler and Liebig, mp 43°C; its mass, infrared, and ^{1}H NMR spectra matched those reported by Brinkman, et al[3]. ^{13}CNMR:

δ 61.1(2C,C-4/6), 44.0(1C,C-2), 22.6 (2C,C-4/6 CH_3), 21.8(1C,C-2 CH_3). Gases were supplied by Air Products, Inc. Nitric oxide was passed through a tower of potassium hydroxide pellets to remove nitrogen dioxide before use. Compressed air was filtered through a plug of glass wool. Other gases were admitted directly from cylinders.

Treatment of Thialdine with Nitrosating Agents

Dinitrogen Tetroxide. Thialdine (0.1g) was dissolved in 10 ml of ether in a reaction flask which was equipped with a septum to permit withdrawal of aliquots for gas chromatographic analysis. The system was purged with a slow stream of argon under cooling in a dry ice/acetone bath. The gas inlet tube was then switched to the cylinder of dinitrogen tetroxide, and an excess was allowed to flow through the flask for 30 min. Gas chromatography showed that no thialdine was left after this time, but no peak corresponding to 2 could be detected. Similar results were obtained when the N_2O_4 was allowed to flow for 5 min through an ice-cooled flask of thialdine in ether. The desired product, 2, was exposed to these conditions for 10 min at dry ice temperature, whereafter no peak due to N-nitrosothialdine could be found in the chromatogram. Apparently, neither 1 nor 2 is stable to treatment with N_2O_4.

Nitrosyl Chloride. The gas chromatographic peaks for 1 and 2 also disappeared when ether solutions of these compounds were treated with NOCl for 10-15 min in a dry ice bath under conditions which were otherwise identical to those for the N_2O_4 reactions described above. Thus, both compounds were unstable toward this reagent as well.

Dinitrogen Trioxide. Thialdine gave variable results when exposed as above to N_2O_3 for 10 min in ether solution. After 1 hr in a dry ice bath, yields as high as 50% were observed by gc, but no unreacted thialdine was seen. Warming of the reaction mixture sometimes led to extensive (even audible) decomposition of the product. No reaction of 1 was seen at room temperature, and 2 was stable when exposed to N_2O_3 at -78°.

Nitric Oxide. Bubbling NO through ether solutions of 1 and 2 in reaction vessels which were carefully purged with argon had no effect on the gas chromatograms. When nitric oxide was deliberately mixed with air in alternating bursts of 5 min each for 1 hr at dry ice temperature, results were the same as those described for N_2O_3, including variable yields and product decomposition.

Sodium Nitrite in Methylene Chloride. Thialdine (16 mg) was dissolved in 10 ml of methylene chloride, and 35 mg of powdered sodium nitrite was added. The slurry was stirred for eight days at 22°C, during which time no evidence for nitrosamine formation could be detected.

Nitrous Acid. Thialdine (214 mg) was dissolved in 30 ml of water containing 1.3 mmole of hydrochloric acid. A solution of 90 mg of sodium nitrite in 10 ml of water was slowly dropped into the stirring reaction mixture. The colorless solution turned cloudy and red soon after mixing, but there was little evidence of bubbling. A red oil deposited which partitioned into ether when that solvent was added to the reaction mixture. The two-phase mixture was allowed to stand for several hours, during which time the red-brown color of the ether layer lightened considerably. When the ether evaporated, a white aqueous emulsion remained which was neutral to pH paper. Basification produced no observable change, except that the vapors emitted on warming the solution turned wet litmus paper blue. Acidification with HCl turned the solution reddish again.

Butyl Nitrite. Two 10-ml ether solutions 0.1 M in thialdine were each treated with 2 mmole of n-butyl nitrite. One of the solutions was treated with 0.1 mmole of thallous ethoxide prior to butyl nitrite addition. Only traces (<2%) of 2 could be detected by gc over 7 days at room temperature. Acetic acid strongly promoted the butyl nitrite-thialdine reaction, as fully described in the next paragraph.

N-Nitrosothialdine

Nitrosation of 1 was performed by dissolving 30 g (0.18 mole) of thialdine in minimal (500 ml) hexane at 0°. To this was added 5 ml (0.087 mole) of glacial acetic acid and 50 ml (44 g, 0.43 mole) of n-butyl nitrite. After standing overnight at room temperature, the yellow precipitate was collected and washed with cold hexane. The filtrate was evaporated to produce more solid. Five crops of crystals were so collected. These were combined and recrystallized from methanol to give 13.3 g (0.07 mole, 38%) of yellow needles, m.p.79°; ^{1}H NMR: δ 5.64 (q, 1H, J=7Hz, C-4/6 CH anti to oxygen), 4.92 (q, 1H, J=7Hz, C-4/6 CH syn to oxygen), 4.80 (q, 1H, J=7Hz, 2-CH), 1.86 (d, 3H, J=7Hz, C-4/6 CH_3 anti to oxygen), 1.58 (d, 3H, J=7Hz, C-4/6 CH_3 syn to oxygen), 1.32 (d,3H, J=7Hz, 2-CH_3); ^{13}C NMR (22°): δ 61.4 (C-4/6 anti to oxygen), 55.7 (C-4/6 syn to oxygen), 42.3 (C-2), 22.9 (C-4/6 CH_3 anti to oxygen), 21.3 (C-4/6 CH_3 syn to oxygen), 20.4 (C-2 CH_3); IR:ν 1455 cm^{-1} (N=O) (no evidence of ν 3280 cm^{-1} N-H peak present in IR of 1); UV: λ max (log ε) 390(1.66), 242 (3.78); MS: m/e 192[M^+](4), 162(5), 102(12), 71(5), 70(100), 60(6), 59(8), 44(3), 42(5), 32(18); Found: C, 37.57; H, 6.48; N, 14.64; S, 33.02. $C_6H_{12}N_2OS_2$ requires: C, 37.48; H, 6.29; N, 14.57; S, 33.34.

X-Ray Crystallographic Study of N-Nitrosothialdine

Single crystal X-ray diffraction methods were employed to conclusively assign the configuration of 2. Yellow single crystals of 2, suitable for X-ray studies, were grown from methanol. Axial photographs and preliminary intensity measurements indicated monoclinic, 2/m, symmetry. The systematically absent reflections were those required by the centrosymmetric space group $P2_1/m$-C_{2h}^2 (No. 11), or by the noncentrosymmetric space group $P2_1$-C_2^2 (No.4), with a = 4.644(1)Å, b = 12.679(4)Å, c = 8.241(2)Å, β = 100.13 (2)°, and Z = 2 at 20°C. The various statistical indicators using normalized structure factors were consistent with the choice of the centrosymmetric space group $P2_1/m$, as were all of the subsequent stages of structure determination and refinement. An

irregularly shaped crystal of N-nitrosothialdine with minimum and maximum dimensions of 0.48 and 0.63 mm, respectively, was glued to the end of a thin glass fiber. The crystal was then accurately centered on a computer controlled four-circle Nicolet autodiffractometer using graphite-monochromated MoK$\bar{\alpha}$ radiation with a 4° take-off-angle and a normal-focus X-ray tube. Each 1° wide (ω) scan was divided into 19 steps and the 13 contiguous intervals which had the highest single accumulated count at their midpoint were used to calculate the net intensity. Background counts were measured at omega settings 1.0° above and below the calculated value for each reflection. A total of 1144 independent reflections were collected in two concentric 2θ shells. Data were reduced by means of Lorenz and polarization corrections. Nonhydrogen atoms were located directly using MULTAN and refined anisotropically. Two refinement cycles gave R_1=0.065 and R_2=0.082 for 499 independent data points having 2θ MoK $\bar{\alpha}$ <43° and I>3 σ (I). Positions of the hydrogen atoms were then located by difference Fourier synthesis and least squares refined isotropically. During refinement, anomalous dispersion corrections were applied to the sulfur atoms. Also, the oxygen atom was statistically disordered across the crystallographic mirror plane at y=1/4 (both positions were assigned an occupancy factor of 0.50). Final refinement gave R_1= 0.037 and R_2=0.046 for 802 independent data points having 2θ MoK $\bar{\alpha}$ <55° and I>3 σ (I). Crystal data, structure factor tables and refined coordinates and bond distances are available from the authors or from the Cambridge Crystallographic Data Centre (cf Tetrahedron 35, 448 (1979)).

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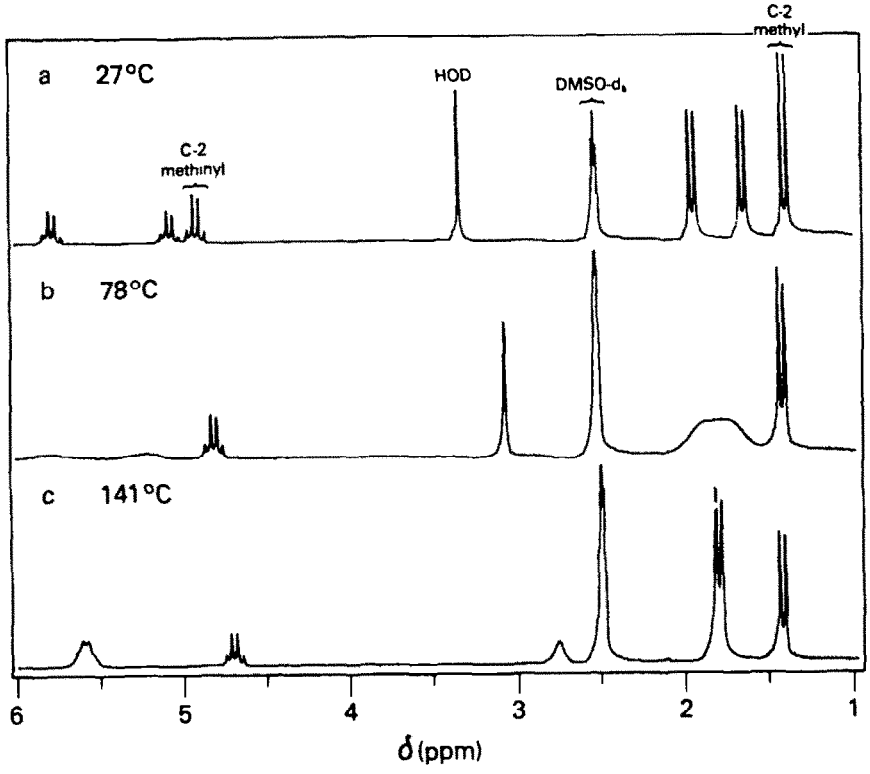

Figure 1. NMR Spectra of 2: a) at 27°C; b) at 78°C; c) at 141°C.

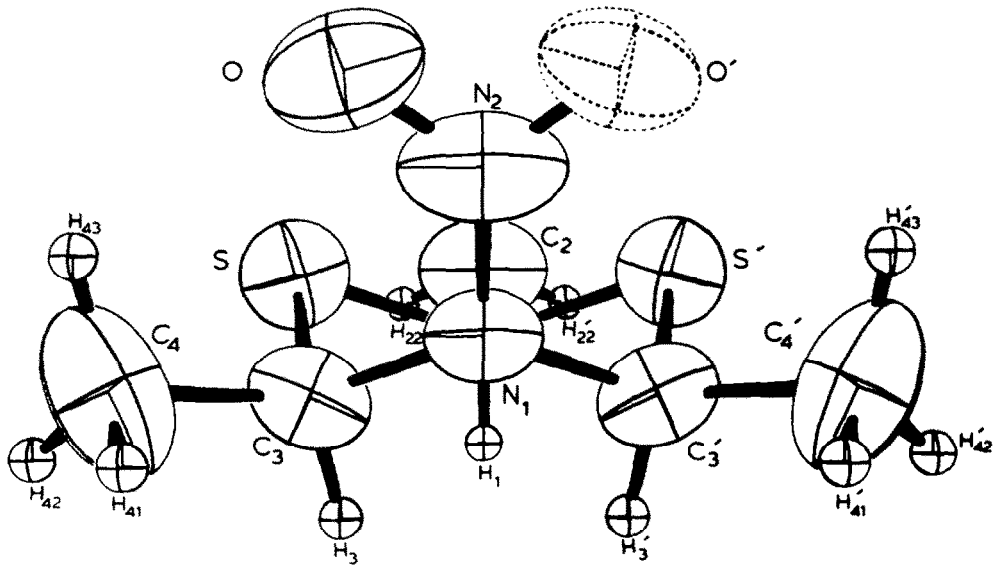

Figure 2. Solid state molecular structure of N-nitrosothialdine, 2. Nonhydrogen atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of the electron density. Hydrogen atoms are represented by arbitrarily small spheres which are in no way representative of their true thermal motion. Primed (') atoms are related to non-primed atoms by the crystallographic mirror plane at y=1/4. The oxygen atom of the nitroso group is statistically disordered across the crystallographic mirror plane at y =1/4.

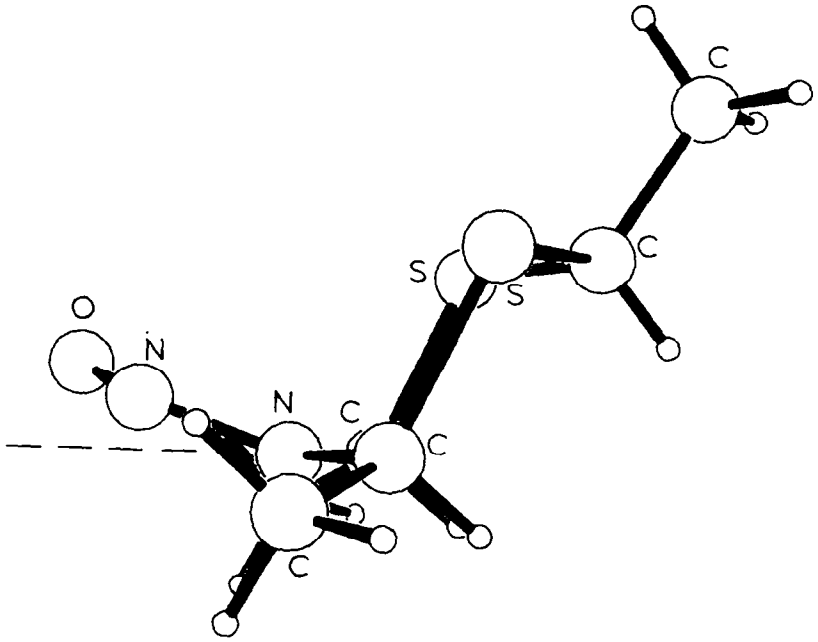

Figure 3. Perspective ORTEP drawing showing displacement of nitroso group from $^{4}C\text{-}N\text{-}^{6}C$ plane. For purpose of clarity, only one of the positions for the nitroso oxygen has been shown.

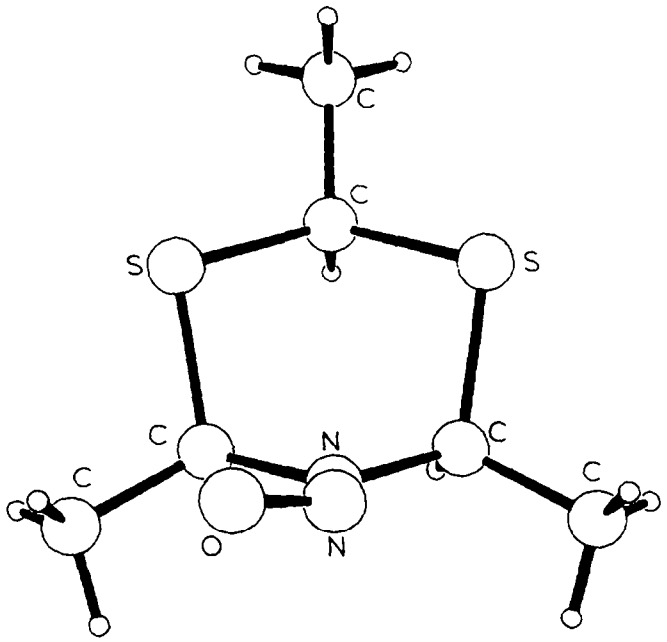

Figure 4. Perspective ORTEP drawing showing twisting of nitroso group about N-N bond. For purposes of clarity, only one of the positions for the nitroso oxygen has been shown.