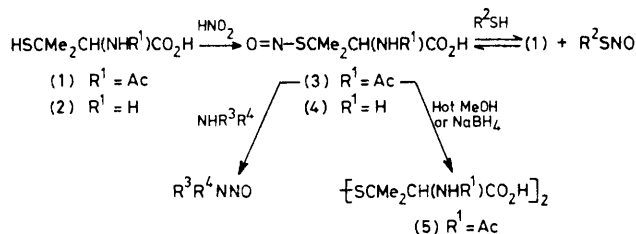


An Unusually Stable Thionitrite from *N*-Acetyl-D,L-penicillamine; X-Ray Crystal and Molecular Structure of 2-(Acetylamino)-2-carboxy-1,1-dimethylethyl Thionitrite†

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Summary *N*-Acetyl-D,L-penicillamine (**1**) was converted by HNO_2 into a thionitrite (**3**) which was stable as a solid and atypically so even in solution; X-ray structural parameters are given for (**3**), and both homolytic and heterolytic reactions are described.

THIONITRITES recently reported had half lives at -2°C in CCl_4 of 2 s to 350 min.¹ Trityl thionitrite, Ph_3CSNO , the only relatively stable thionitrite known heretofore, is a stable solid but decomposes in 10 min in boiling CHCl_3 .² We now report the thionitrite (**3**), which is apparently the most stable so far found. Widespread interest in (**1**) and/or (**2**) for synthesis of antibiotics, studies of chelation, and biomedical applications enhance the interest in (**3**).



The thionitrite (**3**) was prepared by adding NaNO_2 (20 mmol) in 20 ml of water to (**1**) (10 mmol) dissolved in $\text{MeOH}-1\text{N HCl}$ (20 ml each) with 2 ml of conc. H_2SO_4 , during 20 min with vigorous stirring at *ca.* 25°C . After 15 min more, (**3**) was separated off, washed well with water, and air-dried (63%), to give deep green crystals with red reflections, m.p. $152-154^\circ\text{C}$ (decomp.).[‡] X-Ray crystallography confirmed the structure and provided the first parameters reported for a SNO group (Figure).[§] When the same procedure was used with D-(**2**), pure (**4**) could not be isolated; however, solutions of (**4**) (green by transmitted light, reddish by reflected light) follow Beer's Law, and concentrations can be determined at 595 nm ($\pm 0.0\%$ at 20 mM; $\pm 20\%$ at 5 mM); fluorescence spectra are too weak for practicable determinations.

Solid (**3**) is unchanged so far (9.5 months; t.l.c., n.m.r., m.p.). In refluxing MeOH (0.111 M) after 2 h, the colour disappeared, and (**3**) gave the disulphide (**5**)[‡] (100%), m.p.

† Abstracted from a forthcoming doctoral dissertation of R.R.

‡ The spectral and analytical properties of this compound were in accord with its structure.

§ Compound (**3**) crystallizes in the monoclinic space group $P2_1/c$ with $Z = 4$, $a = 7.001(2)$, $b = 12.724(3)$, $c = 12.378(2)$ Å and $\beta = 107.82(2)^\circ$; 1710 reflections out to $48^\circ 2\theta$ were collected with Nb-filtered Mo radiation on a four-circle diffractometer. Two theta scans consisting of five peak steps and two background measurements (repeated for weak reflections) were used. A 1% decrease in the intensity of three monitor reflections after 50 h of X-ray exposure suggests minimum radiation damage or other decomposition. Full matrix least-squares refinement with anisotropic thermal parameters (isotropic for hydrogen) gave $R = 4.6\%$, and a final difference synthesis showed no difference density outside $\pm 0.25 \text{ e}/\text{Å}^3$. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

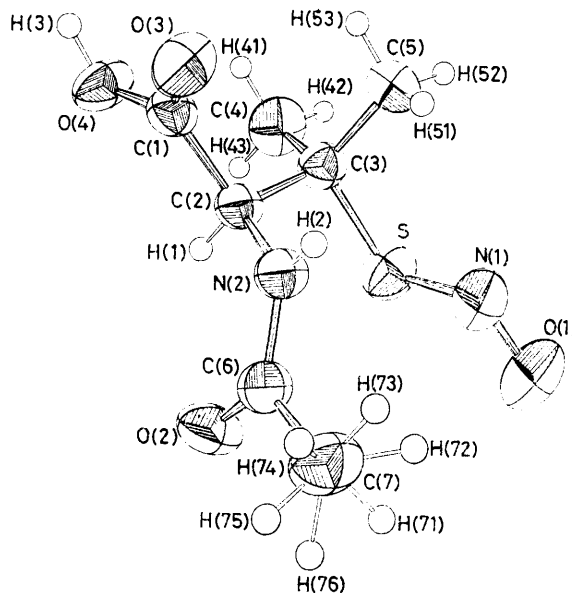


FIGURE. ORTEP drawing of (**3**) showing 50% probability ellipsoids. Bond distances: C(3)—S, 1.841(3); S—N(1), 1.771(3), and N(1)—O(1), 1.214(4) Å. Bond angles: S—N(1)—O(1), $113.2(2)^\circ$ and C(3)—S—N(1), $100.4(1)^\circ$. Intermolecular hydrogen bonds were found between H(3)—O(2) and H(2)—O(3). The methyl group, C(7), showed rotational disorder, which was approximated by six evenly spaced 'half-hydrogen' atoms H(71)—H(76).

$128-131^\circ\text{C}$ (decomp.). Under comparable conditions, Ph_3CSNO was decolourised in 15 min to give $(\text{Ph}_3\text{CS})_2$ (93%); our solid Ph_3CSNO began to decompose after 2 months. In dimethylformamide (DMF), (**3**) is decomposed by heat or light but otherwise is relatively stable; after 50 h at *ca.* 27°C , 95% survived in the dark and 67% in ambient light.

The ready homolysis of (**3**) was indicated by thermally or photochemically induced polymerization of methyl methacrylate. Thus in the dark at 90°C , 45 mM solutions of (**3**) benzoyl peroxide gave hard polymers with methyl

methacrylate in 2 and 0.3 h, respectively; 33 and 29 h were required with u.v. irradiation at *ca.* 27 °C (100 W, quartz); controls of monomer seemed unchanged in all instances.

Reactions presumed to be heterolytic also took place readily. Thus NaBH₄ reduces (3) readily in EtOH to (5) (56%, 10 min). Thionitrites (RSNO) typically thioalkylate thiols (R'SH) to give disulphides (RSSR').^{1,3} In contrast, with (3) and a thiol, equilibration of NO between the two seems to predominate. Thus n.m.r. experiments in CD₃OD suggested that in 24 h a 1:1 molar mixture of (3) and PhCH₂SH gave an equilibrium mixture containing mostly (1). With PhCH₂SH in DMF, PhCH₂SNO was isolated after 24 h in 64% yield as red oil, which then gave (PhCH₂S)₂ in 100% yield; with Ph₃CSH, Ph₃CSNO was isolated in 73% yield. Amines were nitrosated (*cf.* ref. 1). With *N*-

methylaniline and (3), *N*-methyl-*N*-nitroso-aniline was isolated in 40% yield; with aniline hydrochloride (1.0 equiv.) and HCl (2.5 equiv.), the production of benzenediazonium chloride was shown by isolation of the β-naphthol coupling product [overall from (3), 25%].

We confirm that penicillamine (2) with HNO₂ for 5 h gives 2,2-dimethylthiirancarboxylic acid.⁴ Our finding that a strong green colour develops immediately and persists for *ca.* 25 min suggests that the thionitrite is a precursor to the diazonium intermediate invoked [*cf.* (9) of ref. 4].

We thank the Merck Sharp and Dohme Research Laboratories, the Vanderbilt Research Council, and the Vivian Allen Fund (G.E.C.) for support of this work.

(Received, 1st December 1977; Com. 1228.)

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