# Synthesis and Crystal Structure of a Covalently Hydrated 8-Thia-1,4-diazacycl[3.3.2]azine (1)

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Condensation of ethyl 4-chloroacetoacetate with 4-amino-6-hydroxy-2-pyrimidinethiol produced ethyl 3-hydroxy-5-amino-7-oxothiazolino[3,2-*a*]pyrimidin-3-acetate (**7a**) on crystallization. Subsequent ring closure of **7a** produced the tricyclic 6a-hydroxy-5,6,6a,7-tetrahydro-8-thia-1,4-diazacycl[3.3.2]azin-2,5-dione (**8**). The structure of **8** was confirmed by crystal x-ray diffraction analysis.

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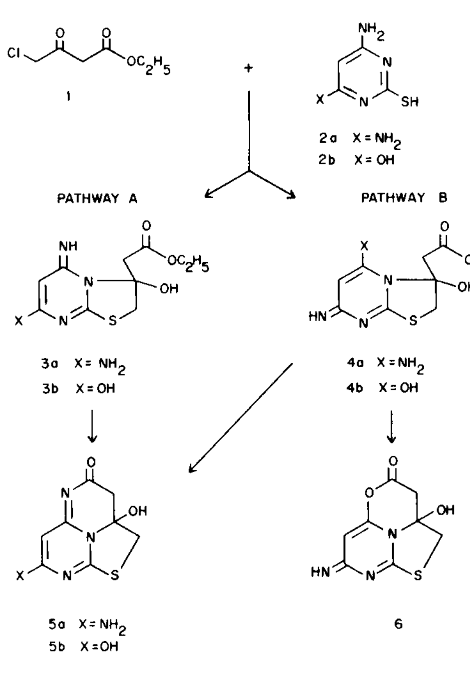
## Introduction

Recently, there has been considerable interest in the synthesis and behavior of cyclazines with heteroatoms substituted on the periphery (3-12), cyclazines being defined as tricyclic systems containing a completely conjugated perimeter of atoms held planar by a central nitrogen atom (13). Boekelheide prepared the first cyclazine with a complete carbocyclic perimeter in 1958 (13) and similar compounds with nitrogen, sulfur, and selenium incorporated on the perimeter have been synthesized since then (3-12).

In a recent publication (11), we described the synthesis of a novel 8-thia-1,4-diazacycl[3.3.2]azine by reacting ethyl 4-chloroacetoacetate (**1**) with 4,6-diamino-2-pyrimidinethiol (**2a**). No intermediate thiazolinopyrimidines (**3a** or **4a**) were isolated. Instead, a second ring closure occurred directly to yield a covalently hydrated tricyclic ring system, represented by the tautomeric structure **5a** (Scheme 1). The thiol group displaced the 4-chloro substituent of **1** while the available ring nitrogen attacked the ketone carbonyl and the primary amino moiety reacted with the ester functionality of **1**. Ring closure at *N*-1 or *N*-3 with symmetrical 4,6-diamino-2-pyrimidinethiol (**2a**) was unequivocal since either ring nitrogen condensing with the ketone carbonyl of **1** would give identical products.

Scheme I



In continuing our studies pertaining to the cyclization of ester **1** with compounds containing a thiocarbamide unit (11,14), we investigated the reaction of ester **1** with unsymmetrical 4-amino-6-hydroxy-2-pyrimidinethiol (**2b**), shown in Scheme 1. Here, depending upon the mode of cyclization, either one or both of two thiazolinopyrimidines, intermediates (**3b** or **4b**), could be generated: ring closure at *N*-3 (pathway A) giving **3b** or at *N*-1 (pathway B) yielding isomer **4b**. Additional cyclizations of **3b** and **4b** would give rise to the covalently hydrated cyclazines **5b** and **6**, respectively (Scheme 1).

Unlike the cyclization of ester **1** with pyrimidinethiol **2a** (Scheme 1) (11), a thiazolinopyrimidine intermediate, ethyl 3-hydroxy-5-amino-7-oxothiazolino[3,2-*a*]pyrimidin-3-acetate (**7a**) was isolated after condensing ester **1** with thiopyrimidine **2b** (Scheme 2). A subsequent ring closure of bicyclic intermediate **7a** produced the tricyclic 6a-hydroxy-5,6,6a,7-tetrahydro-8-thia-1,4-diazacycl[3.3.2]-

Scheme 2

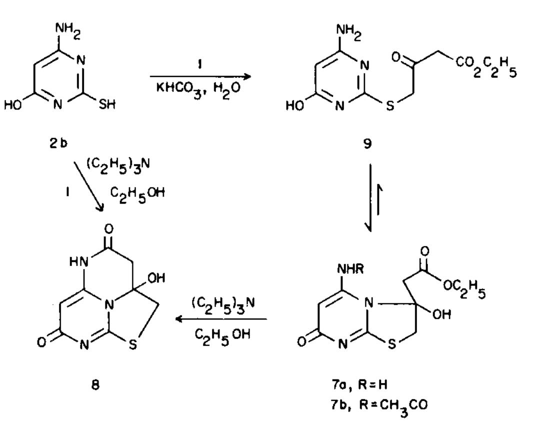


Table 1

Condensation of Ethyl 4-Chloroacetoacetate (**1**) with 4-Amino-6-hydroxy-2-pyrimidinethiol (**2b**) in Various Reaction Media

| Solvent | Base | Temperature | Time (Hours) | **7a** % Yield | **8** % Yield |
|---|---|---|---|---|---|
| Ethanol | Sodium bicarbonate | Reflux | 14 | 30 | |
| Ethanol | Triethylamine | Reflux | 7 | 15 | 35 |
| Ethanol | Triethylamine | Reflux | 30 | | 71 |
| Acetone | Potassiumm carbonate | Reflux | 12 | 30 | |
| Acetone | Potassium carbonate | RT | 12 | 68 | |
| Water | Potassium bicarbonate | RT | 20 | 93 | |

Table 2

Ring Closure of **7a** to **8** in Various Reaction Media

| Solvent | Base | Temperature | Time | **8** % Yield |
|---|---|---|---|---|
| Ethanol | Triethylamine | Reflux | 30 hours | 74 |
| Ethanol | Sodium hydroxide | Reflux | 25 hours | 20 |
| Conc. HCl | | RT | 3 days | 41 |

azin-2,5-dione (**8**, Scheme 2) rather than compound **6** (Scheme 1). Due to uncertainty in the assignment from the pmr and infrared data, the structure of **8** was elucidated by a single crystal x-ray diffraction analysis (*vide infra*).

## Discussion

Results of the condensation of ester **1** and 4-amino-6-hydroxy-2-pyrimidinethiol (6-amino-2-thiouracil) **2b**, in various reaction media are shown in Table 1. Pyrimidine **2b** could be obtained commercially or prepared directly from thiourea and ethyl cyanoacetate in ethanol with sodium ethoxide (15). Optimum yields of thiazolinopyrimidine **7a** were achieved in a potassium bicarbonate-water system at room temperature, although acetone and ethanol solvents gave the desired product (Table 1). Formation of the open chain ester, ethyl 4-amino-6-hydroxypyrimidine-2-thioacetoacetate (**9**) was initially inferred from analytical and mass spectral data; however other spectral data indicated the existence of the ring closed product **7a**.

Only one sharp carbonyl absorption occurred in the ir (potassium bromide) at 1735 $cm^{-1}$ and it was assigned to the ester carbonyl of **7a**. With the acyclic intermediate **9**, two singlets corresponding to the acetoacetate methylenes should be observed in the pmr; however with bicyclic **7a**, second order splitting would arise due to nonequivalent methylene protons being adjacent to an asymmetric center (16). In hexadeuteriodimethylsulfoxide, a complex multiplet appeared between $\delta$ 2.70 and $\delta$ 4.00 on a 60 MHz instrument. With higher resolution (220 MHz), the ethoxy methylene quartet $\delta$ 3.85 and 2 AB quartets ($-SCH_2-$, $\delta$ 3.35,J = 12 Hz; $-CH_2CO-$, $\delta$ 3.28, J = 8 Hz) were resolvable, along with several minute absorptions assigned to **9**, present in low concentration. The amino protons of **7a** resonated at $\delta$ 6.55 while the broad singlet at $\delta$ 7.15 resulted from the hydroxyl proton.

Heating the equilibrium mixture (**7a** and **9**) with excess acetyl chloride in acetonitrile-pyridine yielded the monoacetamide, ethyl 3-hydroxy-5-acetamido-7-oxothiazolino-[3,2-*a*]pyrimidin-3-acetate (**7b**), whose nmr spectrum was consistent with the bicyclic structure of **7a**.

Ring closure of **7a** to the covalently hydrated cyclazine **8** was accomplished under both acidic and basic conditions, as illustrated in Table 2. Although **8** hydrochloride was obtained from concentrated hydrochloric acid, optimum yields of **8** were achieved in triethylamine/ethanol. In fact, heating pyrimidinethiol **2b** with ester **1** in triethylamine/ethanol gave **8** directly (Table 1).

The wide band appearing at 3200-2600 $cm^{-1}$ in the infrared (potassium bromide) indicated that **8** was strongly hydrogen bonded in the solid state, and the stretch at 1725-1700 $cm^{-1}$ (actually a doublet) was assigned to the lactam carbonyls absorbing at higher frequency than usual due to strain from ring fusion. Generally, fusion of a lactam ring to another ring increases the frequency of absorption considerably (16). In hexadeuteriodimethylsulfoxide, the amide hydrogen peaked at $\delta$ 11.00 and the hydroxyl proton came at $\delta$ 7.50 while two distinct AB quartets appearing at $\delta$ 3.65 ($-SCH_2-$, J = 12 Hz) and $\delta$ 3.25 ($-CH_2CO-$, J = 16 Hz) were assigned to the pairs of methylene protons adjacent to the asymmetric center of **8**.

Since **8** was amphoteric, it formed a hydrochloride salt and was also soluble in dilute bases. The hydrochloride was obtained by stirring **8** in concentrated hydrochloric acid at room temperature. Salt stretching (3200-2500 $cm^{-1}$) and a ring strained lactam carbonyl (1715-1700 $cm^{-1}$) absorption were observed in the infrared, for the precipitate so formed. Two methylene quartets were observed in pmr (hexadeuteriodimethylsulfoxide) at $\delta$ 3.30 ($-SCH_2-$, J = 12 Hz) and $\delta$ 3.35 ($-CH_2CO-$, J = 16 Hz); the amide hydrogen resonated at $\delta$ 12.20 and the $NH^+$ and

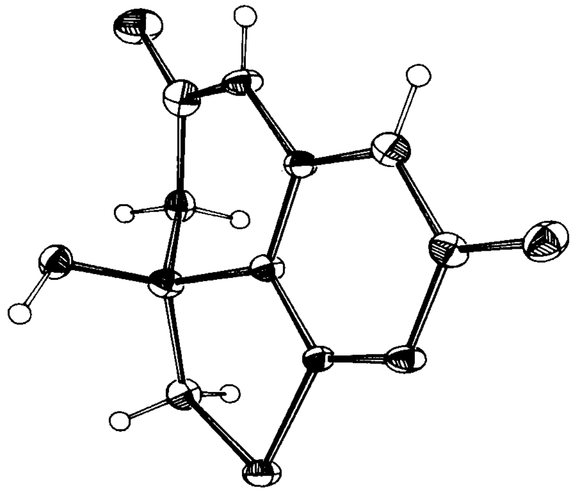


Figure 1. ORTEP drawing of **8**. All thermal ellipsoids are shown at the 50% probability level except hydrogens, which have been given an isotropic value of 0.5 for artistic purposes.

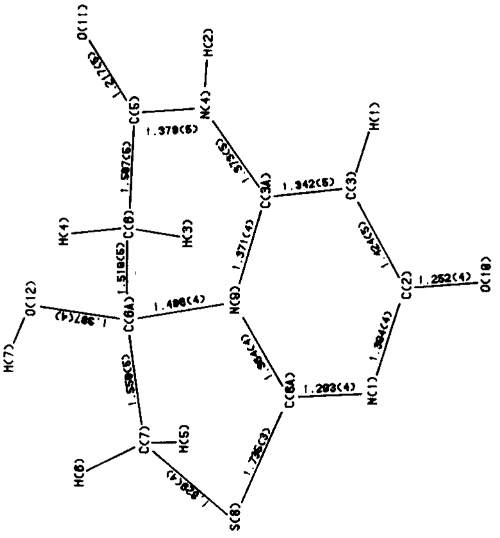


Figure 2. Numbering scheme and bonded non-hydrogen distances for **8**. The hydrogen distances are N-H = 0.85(4) Å, O-H = 0.92(5) Å and C-H(aug) = 0.92(5) Å.

hydroxyl protons at δ 8.60-9.20. Actually, the singlet at δ 12.20, being extremely downfield, may result from the hydroxy-imine proton of tautomer **5b** (Scheme 1), being present in solution as opposed to the tautomer **8** (Scheme 2).

The single crystal structure analysis of **8** confirmed the structure, as shown in Figure 1. Non-hydrogen bond distances and the numbering scheme are shown in Figure 2, and important angles are given in Table 3. More exten-

Table 3

Angles in Degrees:

| A | B | C | Angle |
|---|---|---|---|
| C(7) | S(8) | C(8A) | 92.7(2) |
| C(2) | N(1) | C(8A) | 117.6(3) |
| C(3A) | N(4) | C(5) | 125.3(3) |
| C(3A) | N(9) | C(6A) | 121.4(3) |
| C(3A) | N(9) | C(8A) | 119.5(3) |
| C(6A) | N(9) | C(8A) | 117.9(3) |
| O(10) | C(2) | N(1) | 119.6(3) |
| O(10) | C(2) | C(3) | 121.1(3) |
| N(1) | C(2) | C(3) | 119.3(3) |
| C(2) | C(3) | C(3A) | 120.0(3) |
| N(4) | C(3A) | N(9) | 116.1(3) |
| N(4) | C(3A) | C(3) | 125.0(3) |
| N(9) | C(3A) | C(3) | 118.9(3) |
| O(11) | C(5) | N(4) | 120.2(4) |
| O(11) | C(5) | C(6) | 124.8(4) |
| N(4) | C(5) | C(6) | 115.0(3) |
| C(5) | C(6) | C(6A) | 110.0(3) |
| O(12) | C(6A) | N(9) | 110.1(3) |
| O(12) | C(6A) | C(6) | 107.1(3) |
| O(12) | C(6A) | C(7) | 115.2(3) |
| N(9) | C(6A) | C(6) | 105.9(3) |
| N(9) | C(6A) | C(7) | 103.5(3) |
| C(6) | C(6A) | C(7) | 114.5(3) |
| S(8) | C(7) | C(6A) | 107.0(2) |
| S(8) | C(8A) | N(1) | 124.2(3) |
| S(8) | C(8A) | N(9) | 111.2(2) |
| N(1) | C(8A) | N(9) | 124.6(3) |

Table 4

Fractional Coordinates of Atoms

| Atom | $10^4x$ | $10^4y$ | $10^4z$ | $B_{iso}$ |
|---|---|---|---|---|
| C(1) | -2036(3) | 328(4) | 2528(2) | 11 |
| C(2) | -3234(3) | 820(5) | 2893(3) | 12 |
| C(3) | -3789(3) | 2545(6) | 2483(3) | 15 |
| C(3A) | -3168(3) | 3661(6) | 1736(3) | 11 |
| N(4) | -3624(3) | 5320(5) | 1259(3) | 13 |
| C(5) | -2922(4) | 6673(5) | 686(3) | 15 |
| C(6) | -1544(3) | 6247(5) | 624(3) | 12 |
| C(6A) | -1337(3) | 4112(5) | 440(3) | 12 |
| C(7) | 37(3) | 3453(5) | 571(3) | 13 |
| S(8) | 6(1) | 1107(1) | 1274(1) | 13 |
| C(8A) | -1482(3) | 1477(5) | 1819(3) | 10 |
| N(9) | -1986(3) | 3139(4) | 1408(2) | 10 |
| O(10) | -3805(2) | -259(4) | 3575(2) | 16 |
| O(11) | -3420(3) | 8090(4) | 282(3) | 21 |
| O(12) | -1900(2) | 3633(4) | -594(2) | 13 |
| H(1) | -4564(33) | 2883(57) | 2724(30) | 1(6) |
| H(2) | -4409(41) | 5491(69) | 1294(32) | 8(8) |
| H(3) | -1170(46) | 6600(75) | 1253(42) | 18(9) |
| H(4) | -1153(51) | 6920(93) | 37(52) | 31(12) |
| H(5) | 577(33) | 4436(64) | 1063(32) | 4(7) |
| H(6) | 357(34) | 3298(57) | -91(33) | 3(7) |
| H(7) | -1727(38) | 2469(70) | -924(37) | 10(8) |

sive crystallographic tables are available (17). The hydrogen atom positions were well determined, as is the usual case for low temperature data.

The bond distances show a high degree of conjugation in the molecule (Figure 2). Hydrogen bonding is present in the crystal, with H(7) being bonded to O(10) (distance 1.743(5) Å, symmetry operation -1/2x; -y; -1/2 + z). All other contacts in the molecule appear reasonable.

## EXPERIMENTAL

Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137-B infrared spectrometer using potassium bromide pellets unless stated otherwise. With hexadeuteriodimethyl sulfoxide as the solvent, nuclear magnetic resonance spectra were determined on a Varian Associates Model EM-360 spectrometer; the high resolution experiment was performed on a Varian HR 220 MHz High Resolution spectrometer. At 70 eV a Varian Mat CH-7 spectrometer recorded the mass spectra. Elemental analysis were performed at Midwest Micro Labs Inc., Indianapolis, Indiana. Usually based on the first crystallization, the percent yields are not considered optimum.

### Ethyl 3-Hydroxy-5-amino-7-oxothiazolino[3,2-*a*]pyrimidin-3-acetate (**7a**).

To 12.0 g. (74.4 mmoles) of 6-amino-2-thiouracil monohydrate, **2b** (Aldrich Chemicals) and 8.5 g. of potassium bicarbonate in 300 ml. of water, 14.0 g. (85.1 mmoles) of ethyl 4-chloroacetoacetate (**1**) was added all at once at room temperature. After stirring 20 hours (room temperature), the original white suspension gradually turned dark. This mixture was chilled and the insoluble white product (**7a**) was filtered from the black solution, washed thoroughly with water, then ethanol, and dried (19.0 g., 93%). Crystallized from water, yellow tinted crystals (identical m.p. and ir as the initial white precipitate) of **7a** were obtained, which melted at 172-175°; ir (potassium bromide): 3400-2700 (NH, OH, hydrogen bonded), 1735 (> C=O, 1640, 1560, 1525 (-NC=O and > C=N-) cm$^{-1}$; pmr (hexadeuteriodimethyl sulfoxide): δ 1.10 (t, 3H, -$CH_3$), 3.28 (q, 2H, J = 8 Hz, -$CH_2CO$-), 3.35 (q, 2H, J = 12 Hz, -$SCH_2$-). 3.85 (q, 2H, -$OCH_2$-), 4.60 (s, 1H, pyrimidine vinylic proton), 6.55 (broad s, 2H, -$NH_2$), 7.15 (broad s, 1H, -OH, hydrogen bonded).

Compound **7a** was insoluble in 6*N* hydrochloric acid, slightly soluble in 10% sodium bicarbonate and readily soluble in 0.25*N* sodium hydroxide. With ethanol or acetone as solvents for the above reaction, the percent yields of **7a** were somewhat less; experimental conditions and percent yields are given in Table 1.

*Anal.* Calcd. for $C_{10}H_{14}N_3O_4S$: C, 44.26; H, 4.84; N, 15.49; S, 11.80; m.w. 271. Found: C, 44.44; H, 4.83; N, 15.44; S, 11.65; $M^+$ 271.

### 6a-Hydroxy-5,6,6a,7-tetrahydro-8-thia-1,4-diazacycl[3.3.2]azin-2,5-dione (**8**).

A suspension of the thiazolinopyrimidine **7a** (3.0 g., 12.0 mmoles) in 80 ml. of ethanol and 6 ml. of triethylamine was refluxed for 40 hours with constant stirring; a clear solution was never formed. Upon cooling, 2.0 g. (74%) of **8** was filtered from the black solution, washed thoroughly with ethanol, and dried. After crystallizing from hot water, colorless **8** browned 15° prior to melting between 286 and 292° dec.; ir (potassium bromide): 3200-2500 (-NH, -OH, hydrogen bonded), 1725-1700 (-NC=O), 1650, 1600-1450 (-NC=O, > C=N-) cm$^{-1}$; pmr (hexadeuteriodimethyl sulfoxide): δ 3.25 (q, 2H, J = 16 Hz, -$CH_2CO$-), 3.65 (q, 2H, J = 12 Hz, -$SCH_2$-), 5.20 (s, 1H, C-3 vinylic proton), 7.50 (broad s, 1H, -OH, hydrogen bonded), 11.00 (broad s, 1H, amide hydrogen).

The thiazolinopyrimidine **7a** was also cyclized to **8** in ethanol/sodium hydroxide and concentrated hydrochloric acid media; yields and experimental conditions are given in Table 2. In concentrated hydrochloric acid, the precipitated salt was simply washed with water to give the free base **8**.

Tricyclic **8** was also prepared directly by heating under reflux **2b** (8.0 g., 50.0 mmoles) and **1** (9.0 g., 54.7 mmoles) in 200 ml. of ethanol and 20 ml. of triethylamine with constant stirring for 40 hours. Cooling the resulting dark suspension to room temperature, and following the work-up described above, 8.0 g. (71%) of **8** was obtained.

Compound **8** was insoluble in 6*N* hydrochloric acid, slightly soluble in 10% sodium bicarbonate and readily soluble in 0.25*N* sodium hydroxide.

*Anal.* Calcd. for $C_8H_7N_3O_3S$: C, 42.65; H, 3.14; N, 18.66; S, 14.22; m.w. 225. Found: C, 42.72; H, 3.10; N, 18.68; S, 14.12; $M^+$ 225.

### 6a-Hydroxy-5,6,6a,7-tetrahydro-8-thia-1,4-diazacycl[3.3.2]azin-2,5-dione Hydrochloride (**8**•HCl).

Compound **8** (1.5 g., 6.6 mmoles) was stirred in 10 ml. of concentrated hydrochloric acid for 1 hour at room temperature. Complete solvent evaporation on a crystallizing dish quantitatively yielded the hydrochloride which was recrystallized from methanol; m.p. > 300°; ir (potassium bromide): 3200-2500 ($NH^+$, -OH), 1715-1700 (-NC=O), 1650, 1550, 1500 (-NC=O, > C=N-) cm$^{-1}$; pmr (hexadeuteriodimethylsulfoxide): δ 3.30 (q, 2H, -$CH_2CO$-, J = 12 Hz), 3.35 (q, 2H, -$SCH_2$-, J = 16 Hz), 5.90 (s, 1H, C-3 vinylic proton), 8.60-9.20 (broad s, 2H, -NH, -OH), 12.20 (s, 1H, amide hydrogen).

*Anal.* Calcd. for $C_8H_8ClN_3O_3S$: C, 36.71; H, 3.09; Cl, 13.55; N, 16.06; S, 12.24. Found: C, 36.96; H, 3.14; Cl, 13.53; N, 15.87; S, 11.79.

### Ethyl 3-Hydroxy-5-acetamido-7-oxothiazolino[3,2-*a*]pyrimidin-3-acetate (**7b**).

At room temperature, 1.7 g. (21.6 mmoles) of acetyl chloride, diluted with 25 ml. of acetonitrile, was added dropwise to a stirred suspension of **7a** (2.5 g., 9.20 mmoles) in 80 ml. of acetonitrile and 2 ml. of pyridine, a clear solution evolving eventually. After heating under reflux 12 hours, the resulting orange solution was concentrated under reduced pressure to one fourth the original volume and transferred to a separatory funnel with ethanol (25 ml.), chloroform (100 ml.), and water (150 ml.). After shaking, the presence of some insoluble material in the separatory funnel was ignored and the organic layer was separated. Several chloroform extractions (60 ml., 3 X) were performed. Combined, the organic extracts were washed with water 150 ml., 2 X), dried (magnesium sulfate), filtered, and concentrated to 25 ml. under reduced pressure. Slow addition of a 1:1 mixture of isopropanol and ethyl ether gradually precipitated 0.8 g., (28%) of light yellow acetamide (**7b**). Low yields were attributed to the poor solubility of **7b** in chloroform, m.p. 190-192°, dec. (ethanol, ethyl ether); ir (potassium bromide): 3500-2800 (-NH, -OH), 1725-1690 (> C=O, -NC=O), 1540, 1510 (-NC=O, > C=N) cm$^{-1}$; pmr (hexadeuteriodimethyl sulfoxide): δ 1.15 (t, 3H, -$CH_3$), 2.05 (s, 3H, $CH_3CO$-), 2.90-4.30 (m, 4H, -$CH_2CO$-, -$SCH_2$-), 4.00 (q, 2H, -$OCH_2$-), 6.60 (s, 1H, pyrimidine vinylic proton), 7.55 (broad s, 1H, -OH, hydrogen bonded), 10.45 (broad s, 1H, -NH).

*Anal.* Calcd. for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.79; N, 13.42; S, 10.22; m.w. 313. Found: C, 45.76; H, 4.60; N, 13.22; S, 10.12; $M^+$ 313.

### Single-Crystal X-Ray Structure of **8**.

All crystallographic data for **8** were obtained at -140 ± 5° using a locally designed gaesous nitrogen cooling system (18). The diffractometer used was locally constructed using a Picker goniostat and generator, and a Texas Instruments 980B minicomputer for control (19). The goniostat was equipped with a highly oriented graphite monochromater and molybdenum source.

A well-formed crystal of dimensions 0.33 x 0.25 mm was used for intensity data and characterization. The crystal was mounted on a glass fiber using silicone grease and cooled on the diffractometer. A systemic search of a limited hemisphere of reciprocal space yielded reflections which could be indexed as orthorhombic, space group $P2_12_12_1$. Cell dimensions of a = 10.707 (3), b = 6.972 (2) and c = 11.626 (4), were determined by a least squares fit of angular data (21 reflections) centered in both positive and negative regions of 2θ. Centering was performed under computer control using a top/bottom-left/right slit assembly, which was also the basis of the diffractometer alignment. Based on Z = 4, the calculated density is 1.724 g./cc.

The data were corrected for Lorentz and polarization terms in the usual manner (20) and reduced to 1177 unique structure amplitudes. The ignorance factor in the calculation of the intensity errors was chosed to be 0.07, based on previous experience. Due to the nearly equidimensional size of the crystal, no absorption correction was deemed necessary ($\mu$, Mo$K\overline{\alpha}$ = 3.45 cm$^{-1}$).

Three reflections chosen as standards were monitored after every 100 measurements and showed only statistical fluctuations.

All non-hydrogen atoms were located by direct method phasing (21), and the hydrogen atoms were located by standard Fourier techniques. The structure was refined by full-matrix least squares techniques with isotropic thermal parameters for the hydrogen atoms, and the anisotropic thermal parameters for all other atoms. In addition to thermal and positional parameters, an overall scale factor and isotropic extinction parameter were refined. Complete crystallographic data are available, including observed and calculated structure amplitudes (17). The structure of **8** is shown in Figure 1, and the numbering and non-hydrogen distances in Figure 2. The angles between atoms are shown in Table 3, and the fractional coordinates in Table 4.

## REFERENCES AND NOTES

(1) Contribution No. 3281. This work was partially supported by Grant GM-10366, U. S. Public Health Service, to Indiana University.

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