Synthesis of a Novel 8-Thia-1,4-diazacycl[3.3.2]azine (1)

E. Campaigne and T. P. Selby (2)

Chemistry Laboratories of Indiana University, Bloomington, Indiana 47401

Received May 22, 1978

A unique covalently hydrated cyclazine adduct, 2-imino-6a-hydroxy-4,5,6,6a-tetrahydro-7*H*-8-thia-1,4-diazacycl[3.3.2]azin-5-one hydrochloride was prepared by reacting ethyl 4-chloroacetoacetate with 4,6-diamino-2-thiopyrimidine in neutral alcohol. Neutralization gave 2-imino-5,6a-dihydroxy-6,6a-dihydro-7*H*-8-thia-1,4-diazacycl[3.3.2]azine which decomposed to 4,6-diamino-2-acetonylthiopyrimidine upon heating in water. Warming the hydrated hydrochloride in concentrated hydrochloric acid caused dehydration to yield 2-imino-5-hydroxy-6H-8-thia-1,4-diazacycl[3.3.2]azine hydrochloride. Partial isomerization (20%) to 2-imino-5-hydroxy-7*H*-8-thia-1,4-diazacycl[3.3.2]azine hydrochloride occurred during recrystallization from aqueous acidic methanol. The free base, 2-imino-5-hydroxy-7*H*-8-thia-1,4-diazacycl[3.3.2]azine was obtained after neutralizing either of the tautomeric hydrochlorides. Treating the free base with trifluoroacetic acid produced a mixture of the trifluoroacetate salts of the two tautomeric bases. Isomerization of one trifluoroacetate salt into the other in trifluoroacetic acid was observed by pmr at room temperature. Both 2-amino-5-hydroxy-7-nitroso-8-thia-1,4-diazacycl[3.3.2]azine and 2-amino-5-hydroxy-6-nitroso-8-thia-1,4-diazacycl[3.3.2]azine were isolated after nitrosation of the hydrochloride mixture.

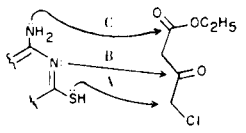
J. Heterocyclic Chem., 16, 151 (1979).

Indroduction.

Within the last twenty years, cyclazines and various thiazolo[3,2-*d*]pyrimidines have been the subject of several studies (3-6), and their biological activity has been of concern (7,8). Cyclazines have been defined as tricyclic systems containing a completely conjugated perimeter of atoms held planar by a central nitrogen atom (3). The first cyclazine to be synthesized was unsubstituted cycl[3.3.2]azine, made by Boekelheide in 1958 (3). Since then, several dozen have been prepared, the principal types having either a carbocyclic or a carbon-nitrogen periphery. Recently, Taurins has outlined the past experimentation pertaining to this field in the first review on "The Chemistry of Cyclazines" (9) and Ceder has updated the cyclazine nomenclature procedure along with proposing modifications in naming this class of compounds (10).

Two nomenclature systems for naming cyclazines are in present use: the IUPAC rules and Boekelheide's method (8). Because the Boekelheide nomenclature is simpler, more convenient, and makes the system more quickly recognizable, it is more widely used; the compounds reported here are named according to this latter method.

Although a 5-thia-1,3,6-triazacycl[3.2.3]azine system has been synthesized (11), the preparation of thiadiazacyclazines have not been reported. In continuing our studies on the reactions between ethyl 4-chloroacetoacetate (**1**) and thioamide derivatives (12), the synthesis of a novel 8-thia-1,4-diazacycl[3.3.2]azine was accomplished by cyclizing the ester **1** with 4,6-diamino-2-thiopyrimidine **2**. As opposed to the usual methods for preparing cyclazines (9), in which several reagents were typically incorporated into the experimental procedure, here only two starting materials (ester **1** and thiopyrimidine **2**) were utilized in the direct construction of the thiadiazacyclazine ring nucleus (figure 1). The thiol group initially displaced the 4-chloro substituent of **1** (A), while the available ring nitrogen attacked the ketone carbonyl (B). Finally, the primary amino moiety reacted with the ester functionality of **1** (C). While an unsymmetrical 4-amino-2-thiopyrimidine might form isomers when condensed with chloroacetoacetate, *via* ring closure at N-1 or N-3, with symmetrical 4,6-diamino-2-thiopyrimidine (**2**) the cyclization should be unequivocal since either ring nitrogen condensing with the ketone carbonyl of **1** gives identical products.



1

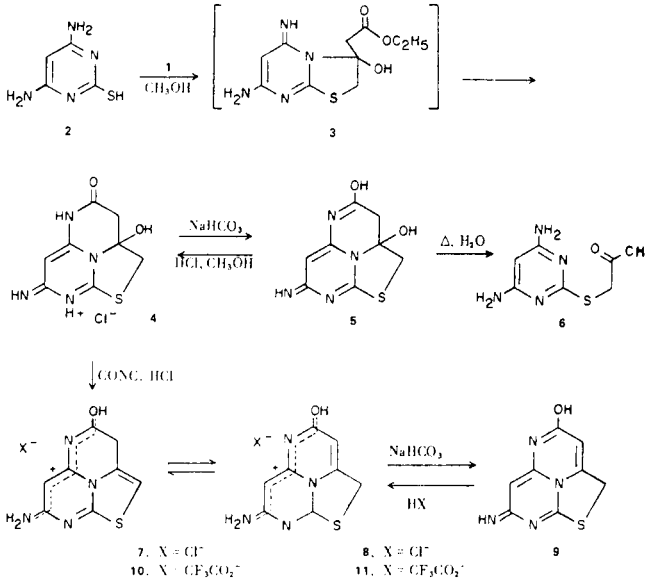
Figure 1.

Discussion.

When ester **1** was allowed to react with thiopyrimidine **2** in methanol, no intermediate thiazolinopyrimidine (**3**) (Scheme 1) was obtained. Instead, a second ring closure occurred to yield the hydrated cyclazine ring system, 2-imino-6a-hydroxy-4,5,6,6a-tetrahydro-7*H*-8-thia-1,4-diazacycl[3.3.2]azine-5-one hydrochloride (**4**). A hydrated cyclazine such as **4** has not been previously reported

0022-152X/79/010151-06$02.25

Scheme I



to our knowledge, and this aminocarbinol would not have a planar structure. The assigned structure (**4**) is based on the following spectral evidence. Being adjacent to an asymmetric center, the C-6 and C-7 methylene protons were not chemical shift equivalent and coupled with each other to give rise to second order splitting in the pmr (13). Bond formation between the ring nitrogen and the ketone carbonyl induced asymmetry as well as rigidity into the molecule. A complex multiplet (superimposed AB quartets) between δ 3.00 and 4.00 (-SCH_2-, -CH_2CO-) and a pyrimidine vinylic proton singlet at δ 6.05 appeared in the pmr (DMSO-d_6) of **4**. Protonation of the imine moiety did not take place; the broad singlet at δ 8.50 was assigned to the hydroxyl proton, the 8.75 singlet to the imine hydrogen, the δ 12.30 peak to the amide hydrogen and the broad singlet at δ 9.15 to a protonated nitrogen. At 1725-1700 cm^{-1}, an amide carbonyl stretch along with a salt stretch at 3400-2800 cm^{-1} occurred in the ir spectrum (potassium bromide).

Hydrochloride **4** was neutralized with sodium bicarbonate to form the free base, 2-imino-5,6a-dihydroxy-6,6a-dihydro-7*H*-8-thia-1,4-diazacycl[3.3.2]azine (**5**), scheme I. Between 3300 and 2700 cm^{-1}, a broad band occurred in the ir spectrum (potassium bromide), however, no significant carbonyl absorption was recorded and the hydroxyl imine tautomer (**5**) was considered as existing in the solid state. Reprotonation of **5** in acidic methanol regenerated the hydrochloride **4** (Scheme 1). Because **5** was insoluble in dimethyl sulfoxide, the free base **5** was dissolved in trifluoroacetic acid and the pmr of the salt taken, which showed a quartet (2H, -SCH_2-, J = 13 Hz) at δ 4.00 and a broad singlet (2H, -CH_2CO-) at δ 3.55.

Attempted recrystallization of **5** from water resulted in the formation of a decomposition product, 4,6-diamino-2-acetonylthiopyrimidine (**6**), which crystalized. Decomposition proceeded by hydrolysis of the amide function and ring opening of the aminocarbinol, followed by decarboxylation. As evidenced by pmr and ir (potassium bromide) data, compound **6** occurs as the open chain structure. Treating the thiopyrimidine **2** with chloroacetone in aqueous sodium bicarbonate produced an unequivocal sample of **6**.

Regiospecific elimination of water at the 6a-7 position of the covalently hydrated hydrochloride **4** to yield 2-imino-5-hydroxy-6*H*-8-thia-1,4-diazacycl[3.3.2]azine hydrochloride (**7**) was achieved by heating in concentrated hydrochloric acid (Scheme 1); it was assigned structure **7** by spectral data. Due to insolubility in neutral solvents, the pmr was taken in trifluoroacetic acid and produced the following absorptions: a methylene singlet at δ 4.40 (2H, $COCH_2$-) and two vinylic proton singlets at δ 6.65 (1H, pyrimidine vinylic proton, C-3) and δ 7.25 (1H, thiazole vinylic proton, C-7). Salt stretching at 3400-2700 cm^{-1} appeared in the ir (potassium bromide).

Recrystallizing **7** from isopropanol and aqueous hydrochloric acid consistently gave a tautomeric mixture of **7** and the analogous 6-6a double bond isomer, 2-imino-5-hydroxy-7*H*-8-thia-1,4-diazacycl[3.3.2]azine hydrochloride (**8**) in a ratio of 80:20, respectively. The relative amounts were determined by integration of the C-6 (**7**) and C-7 (**8**) methylene proton resonances in the pmr. Tautomer **8** was never isolated in pure form. In trifluoroacetic acid, peaks at δ 4.85 (singlet, 2H,-CH_2S-, δ 6.45 (singlet, 1H, C-6) and δ 6.55 (singlet, 1H, C-3) were recorded for **8** along with absorptions from **7**. It was concluded that compound **7** was kinetically favored in the dehydration but the equilibrium mixture of **7** and **8** which existed not only in solution but also in the solid state, was thermodynamically favored.

The free base, 2-imino-5-hydroxy-7*H*-8-thia-1,4-diazacycl[3.3.2]azine (**9**), assigned as the hydroxylimine tautomer, was obtained after neutralizing **7** or a mixture of **7** and **8** with sodium bicarbonate. The structure of **9** was confirmed by spectral data.

The pmr spectrum also showed 6 peaks, 2 methylene and 4 vinylic proton singlets, after dissolving free base **9** in trifluoroacetic acid, but their intensities were found to be time dependent. Analytically pure trifluoroacetate salt (presumably a mixture of **10** and **11**) was precipitated from trifluoroacetic acid solution by slow addition of isopropanol but the recrystalized off-white salt melted between 140 and 152°. After redissolving this salt in trifluoroacetic acid, the pmr still revealed the same absorptions resulting from an 80:20 mixture of the salts **10** and **11** (scheme 1); the relative amounts were de-

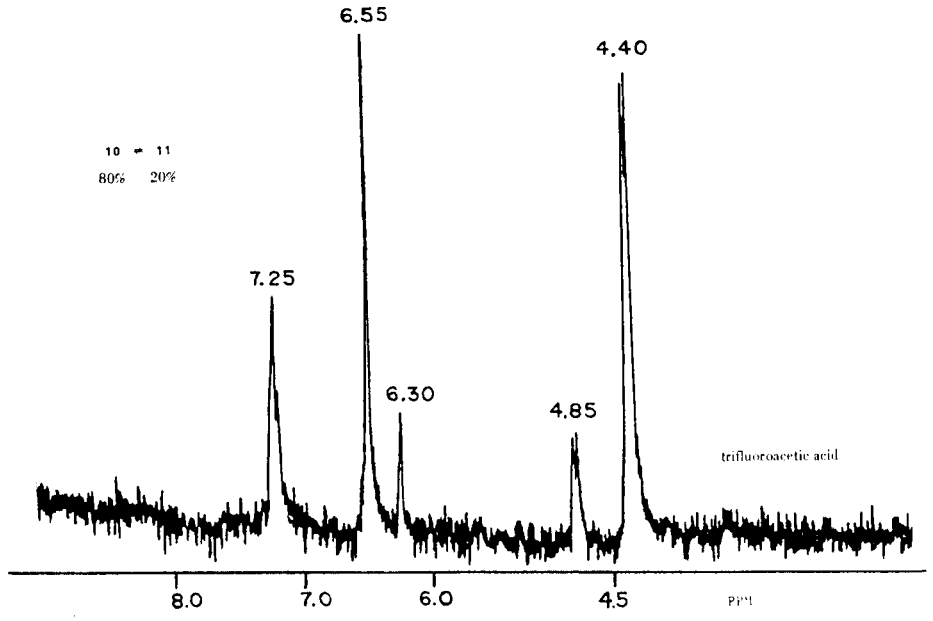


Figure 2. The pmr, in trifluoroacetic acid, of the equilibrium mixture between the trifluoroacetate salts **10** and **11**, at room temperature.

termined by intensities of the methylene proton doublets. The peaks at δ 4.85 (-SCH_2-), δ 6.30 (C-6 vinylic proton) and δ 6.55 (C-3 vinylic proton) were assigned to the salt **11** with the double bond in the 6-6a position, while trifluoroacetate **10** yielded chemical shifts at δ 4.40 (-CH_2CO-), δ 6.55 (C-3 vinylic proton) and δ 7.25 (C-7 vinylic proton). Chemical shift values for the **7**, **8**, **10**, and **11** vinylic and methylene ring protons are compared in Table 1. When the recrystalized free base **9** was dissolved in trifluoroacetic acid and the pmr taken immediately, a mixture of **10** and **11** was still observed but in the ratio 8:92. Gradually, over a 36 hour period, a final equilibrium mixture (80:20) of **10** and **11** was attained at room temperature, the final pmr spectrum is shown in Figure 2 (14).

Almost pure (98%) hydrochloride **8** was evidenced in solution by pmr after dissolving free base **9** in trifluoroacetic acid with a trace of hydrochloric acid added. The three singlet peaks of the thermodynamically unfavored hydrochloride **8** were the sole absorptions in the pmr. After precipitation from solution, by addition of isopropanol, the usual equilibrium mixture (80:20) of **7** and **8** was isolated. Eighty percent isomerization to **7** occurred upon crystalization as illustrated by a repeated pmr spectrum analysis. Thus, pure hydrochloride **8** was unstable as a solid. Reprotonating the free base in concentrated hydrochloric acid also gave the usual 80:20 mixture of **7** and **8**. In summary, the free base exists principally as the pyrimidinol **9**, but in the salt, 80% of the equilibrium favors the thiazolium structure (**7**, **10**).

Table I

Pmr (60 mHz) Proton Absorptions for the C-3, C-6, and C-7 Vinylic and Methylene Protons of the Various Cyclazine Adducts (a) in Trifluoroacetic Acid

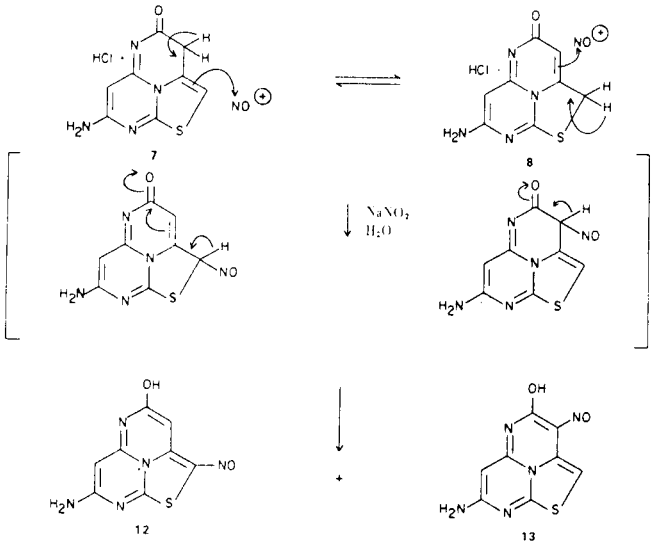
Compound	C-3	C-6	C-7
7	6.65 (1H)	4.40 (2H)	7.25 (1H)
8	6.55 (1H)	6.45 (1H)	4.85 (2H)
10	6.55 (1H)	4.40 (2H)	7.25 (1H)
11	6.55 (1H)	6.30 (1H)	4.85 (2H)
12	6.70 (1H)	8.90 (1H)	- - - -
13	6.40 (1H)	- - - -	7.05 (1H)

(a) Chemical shift values were recorded in ppm with TMS as an internal standard.

Nitrosating **7** or the tautomeric mixture of **7** and **8** in aqueous acidic media yielded a mixture of two isomers, assigned structures **12**, 2-amino-5-hydroxy-7-nitroso-8-thia-1,4-diazacycl[3.3.2]azine and **13**, 2-amino-5-hydroxy-6-nitroso-8-thia-1,4-diazacycl[3.3.2]azine (scheme 2). Whether the reaction was carried out at room temperature and the reactants, sodium nitrite and **7**, **8** added together at once or the addition of aqueous sodium nitrite to aqueous **7**, **8** was performed dropwise in an ice bath, the same approximate ratio of the two products were always isolated: 75-80% of one, tentatively assigned to **12** and 20-25% of the other, attributed to **13**. It is significant that the starting material had an 80:20 ratio of two tautomers (**7** and **8**) and the product also had close to an 80:20 ratio of the two structural isomers (**12** and **13**).

Mechanistically, the simplest way of rationalizing these

Scheme 2



results would either be: one, to assume the equilibrium between **7** and **8** was relatively slow compared to the rate of nitrosation of both species or two, **7** and **8** had comparable reactivities. As illustrated (Scheme 2) species **7** would give rise to isomer **12** while structure **8** would yield isomer **13**. Further in depth experimentation would be needed for a complete analysis of this phenomenom: nevertheless these results did support the actual existence of tautomers **7** and **8**.

Yellow colored **12** was isolated pure after several recrystalizations of the crude reaction product from aqueous dimethyl sulfoxide. The vibrational spectrum (potassium bromide) of **12** and the mixture were similar except for the presence of a broad absorption at 950 cm^{-1} in the mixture (actually due to **13**); a wide band appeared between 3300 and 2700 cm^{-1} (hydrogen bonded NH and OH groups) and absorptions appeared at 1640, 1560, and 1480 cm^{-1}.

In DMSO-d_6, four down-field proton resonances were recorded in the pmr for the mixture (**12** and **13**). The two singlets at δ 8.50 and δ 5.90 were attributed to the C-6 and C-3 protons of **12** and the singlets at δ 6.30 and δ 5.60 to the C-7 and C-3 protons of **13**. The recrystalized product (**12**) gave two peaks at δ 8.50 and δ 5.90 only.

Addition of excess acetone to the initial recrystalization filtrate yielded a second crop of crystals and several recrystalizations of these (once in acetone-dimethyl sulfoxide and once in methanol) resulted in analytically pure yellowish green **13** being isolated. Two one-proton singlets at δ 6.30 (C-7) and δ 5.60 (C-3) were the sole absorptions in the pmr (DMSO-d_6) of **13**; a broad band occurred between 3300 and 2900 cm^{-1} (hydrogen bonded NH and OH groups) while two prominent peaks appeared at 1640 and 1560 cm^{-1} in the ir (potassium bromide).

Both nitrosation adducts **12** and **13** were extremely hydroscopic and analyzed correctly as the hydrates. Unlike compound **12**, **13** did not give a mass ion peak in the mass spectrum.

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 DMSO-d_6 or trifluoroacetic acid as solvents, nuclear magnetic resonance spectra were determined on a Varian Associates Model EM-360 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 crystalization, the percent yields are not considered optimum.

2-Imino-6a-hydroxy-4,5,6,6a-tetrahydro-7*H*-8-thia-1,4-diazacycl-[3.3.2]azine-5-one Hydrochloride (**4**).

To a stirred suspension of 4,6-diamino-2-thiopyrimidine (**2**) (Aldrich Chemicals) (10.0 g., 70.0 mmoles), in 350 ml. of methanol, 25.0 g. (79.0 mmoles) of ethyl 4-chloroacetoacetate (**1**) was added all at once, at room temperature. Upon heating, the resulting black solution was refluxed for 14 hours. The off-white hydrated cyclazine hydrochloride (**4**) precipitated immediately upon cooling and addition of ethyl ether (200 ml). Hydrochloride **4** was filtered, washed with ether, and dried (14.0 g. 77%), m.p. > 300° (ethanol, methanol): ir (potassium bromide): 3400-2800 (-NH^+, -OH), 1725-1700, 1680, 1650-1625, 1575-1525 (HNC=O, C=N) cm^{-1}; pmr (DMSO-d_6): δ 3.00-4.10 (m, 4H,-SCH_2-, ClH_2CO-), 6.05 (s, 1H, C-3 vinylic proton), 8.50 (broad s, 1H,-OH, hydrogen bonded), 8.75 (broad s, 1H, imine proton), 9.15 (broad s, 1H, NH^+), 12.30 (broad s, 1H, amide or hydroxyl imine hydrogen).

Free base **5** (0.50 g., 2.20 mmole) and 1 ml. of concentrated hydrochloric acid were added to 40 ml. of methanol and the mixture refluxed several hours. After cooling, the hydrochloride **4** (0.50 g., 86%) precipitated, was filtered and dried.

Anal. Calcd. for $C_8H_9ClN_4O_2S$: C, 36.85; H, 3.49; Cl, 13.61; N, 21.49; S, 12.28; m.w. - HCL = 224. Found: C, 37.03; H, 3.60; Cl, 14.00; N, 21.29; S, 12.28; M^+ = 224 m/e.

2-Imino-5,6a-dihydroxy-6,6a-dihydro-7*H*-8-thia-1,4-diazacycl[3.3.-2]azine (**5**).

Placed in an ice bath, an aqueous suspension (30 ml.) of hydrochloride **4** (2.0 g., 7.70 mmoles), in a 250 ml. round bottom flask, was slowly neutralized with a 5% sodium bicarbonate solution and stirred for 20 minutes after reaching room temperature. During the neutralization, a dark brown solution gradually formed, after which the light brown free base **5** precipitated. A yield of 1.6 g. (93%) of **5** was obtained after filtering, washing with water and drying, m.p. > 300°. Due to decomposition during recrystalization in aqueous media, a recrystallized sample was not obtained. However, compound **5** did produce a molecular ion peak in the mass spectrum at 224 (m.w. 224) and **5** could be converted back to the hydrochloride **4** by protonation in acidic methanol; ir (potassium bromide): 3300-2700 (-NH,-OH, hydrogen bonded), 1660, 1625-1550, 1475 (C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 3.55 (s, 2H, -CH_2CO-), 4.00 (q, 2H,

-SCH_2-, J = 13 Hz), 6.25 (s, 1H, C-3 vinylic proton).

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.85; H, 3.60. Found: C, 42.90; H, 4.00.

4,6-Diamino-2-acetonylthiopyrimidine (**6**).

Free base **5** (1.6 g., 7.14 mmoles) in 60 ml. of water was heated on a steam bath for 0.5 hours, a dark brown solution slowly formed. Upon cooling to room temperature, 0.90 g. (64%) of pyrimidine **6** crystallized, and was filtered, dried and recrystallized from 2-propanol-ethanol. Light brown crystals of **6** melted at 185-187°; ir (potassium bromide): 3500, 3300 (-NH_2), 1725 (C=O). 1625, 1575, 1500 (C=N) cm^{-1}; pmr (DMSO-d_6): δ 2.25 (s, 3H, -$COCH_3$), 2.80 (s, 2H, -SCH_2-), 5.15 (s, 1H, C-5 pyrimidine ring proton), 6.05 (broad s, 4H,-NH_2,-NH_2).

Pyrimidine **6** was prepared directly by adding 1.0 g. (7.00 mmoles) of thiopyrimidine **2**, 1.5 g. of potassium bicarbonate, and excess chloroacetone (1.3 g., 14.0 mmoles) to 40 ml. of water and stirring 3 days as a milk white suspension. Excess chloroacetone was utilized due to the unfavorable solubility in the aqueous medium. Insoluble **6** (1.2 g., 87%) was filtered, washed with water, then ethanol, and dried. This product had m.p. and spectral properties identical to the decomposition product discussed above, although the color was white.

Anal. Calcd. for $C_7H_{10}N_4OS$: C, 42.40; H, 5.10; N, 28.27; S, 16.15; m.w. = 198. Found: C, 42.12; H, 5.07; N, 28.48; S. 15.97; M^+ = 198 m/e.

2-Imino-5-hydroxy-6*H*-8-thia-1,4-diazacycl[3.3.2]azine Hydrochloride (**7**) and 2-Imino-5-hydroxy-7*H*-8-thia-1,4-diazacycl[3.3.2]-azine Hydrochloride (**8**).

In 40 ml. of concentrated hydrochloric acid, 6.0 g. (23.0 mmoles) of **4** was heated for 20 hours as a yellow suspension with constant stirring. After cooling to room temperature, excess 2-propanol (150 ml.) was added and the mixture stirred for 30 minutes. The insoluble material was allowed to settle on the botton and the alcohol decanted. Methanol (100 ml.) was then added and the light brown hydrochloride (**7**) was filtered, washed with methanol, and dried (4.5 g., 81%), m.p. > 300° (crude precipitate, crystalization promoted isomerization); ir (potassium bromide): 3400-2700 (NH^+), 1680, 1640, 1550, 1520 (C=O) and C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 4.40 (s, 2H, -CH_2CO-), 6.65 (s, 1H, C-3 vinylic proton) 8.25 (s, 1H, C-7 vinylic proton).

After recrystalizing **7** from a water, 2-propanol, hydrochloric acid mixture, an 80:20 mixture of **7** and **8** was obtained after filtering and drying; m.p. > 300°; ir (potassium bromide): 1720, 1680, 1675, 1640, 1550, 1520 (C=O, C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 4.40 (s, 8/5H, -CH_2CO- of **11**, 4.85 (s, 2/5H, -SCH_2- of **12**) 6.40-6.60 (broad s, 2/5H, C-3 and C-6 vinylic protons of **8**), 6.65 (s, 4/5H, C-3 vinylic proton of **7**), 7.25 (s, 4/5, C-7 vinylic proton of **7**).

Reprotonating the free base **9** (0.5 g., 2.43 mmoles) in 15 ml. of concentrated hydrochloric acid, 0.5 hour at room temperature, with constant stirring, gave the same mixture of hydrochlorides **7** and **8**. Excess methanol (60 ml.) was added to the final suspension and the insoluble material filtered, washed with methanol, and dried to yield 0.45 g. (70%) of **7** and **8**. The spectral characteristics of this product were identical to the originally obtained mixture of **7** and **8**.

Anal. Calcd. for $C_8H_7ClN_4OS$: C, 39.58; H, 2.92; N, 23.09; S, 13.19; m.w. -HCl 206. Found: C, 39.60; H, 2.77; N, 22.81; S, 12.95; M^+ 206 m/e.

2-Imino-5-hydroxy-7*H*-8-thia-1,4-diazacycl[3.3.2]azine (**9**).

Dissolved in 25 ml. of water, 2.0 g. (8.30 mmoles) of **7** was neutralized at room temperature with constant stirring by slow addition of a 5% sodium bicarbonate solution. Light brown free base **9** precipitated immediately (1.45 g., 84%) and was filtered, washed with water, and dried. Compound **9** was recrystalized from water, m.p. > 300°; ir (potassium bromide); 3300-2800 (NH, OH), 1610-1640, 1530-1550 (C=O) cm^{-1}; pmr (trifluoroacetic acid, actually a 92:8 mixture of the protonated species **10** and **11**): δ 4.40 (d, 4/25H, J = 3 Hz -CH_2CO- of **10**), 4.85 (d, 46/25H, -SCH_2- J = 3 Hz of **11**), 6.30 (s, 23/25H, C-6 vinylic proton of **11**), 6.55 (s, 1H, C-3 vinylic protons of **10** and **11**), 7.20-7.30 (broad s, 2/25H C-7 vinylic proton of **10**).

Anal. Calcd. for $C_8H_6N_4OS$: C, 46.59; H, 2.94; N, 27.18; S, 15.53; m.w. = 206. Found: C, 46.44; H, 2.77; N, 26.90; S, 15.82; M^+ = 206 m/e.

2-Imino-5-hydroxy-7*H*-8thia-1,4-diazacycl[3.3.2]azine Trifluoroacetate (**10**) and 2-Imino-5-hydroxy-6*H*-8-thia-1,4-diazacycl[3.3.2]azine Trifluoroacetate (**11**).

Free base **9** (1.0 g., 4.90 mmoles) was dissolved in 20 ml. of trifluoroacetic acid and warmed on a steam bath; a dark colored solution resulted. Slow addition of ethanol to the stirred solution at room temperature precipitated a mixture of **10** and **11** (1.2 g., 77%), which was filtered (hood), washed with ethanol, dried and recrystalized from methanol-ethanol, m.p. 140-152°; ir (potassium bromide): 3300-2700 (NH^+), 1710, 1690 (C=O), 1600-1660, 1540, 1500 (C=N) cm^{-1}; pmr (trifluoroacetic acid, actually an 80:20 mixture of **10** and **11**): δ 4.40 (d, 8/5H, J = 3 Hz -SCH_2- of **10**), 4.85 (d, 2/5H, J = 3 Hz -CH_2CO- of **11**), 6.30 (s, 1/5H, C-6 vinylic proton of **11**), 6.55 (s, 1H, C-3 vinylic protons of **10** and **11**), 7.25 (s, 4/5H, C-7 vinylic proton of **10**).

Anal. Calcd. for $C_{10}H_7F_3N_4O_3S$: C, 37.49; H, 2.21; N, 17.50; S, 10.00. Found: C, 37.65; H, 2.40; N, 17.82; S, 10.44.

2-Amino-5-hydroxy-7-nitroso-8-thia-1,4-diazacycl[3.3.2]azine (**12**).

A 100 ml. round bottom flask containing 30 ml. of water, 1.2 g. (5.0 mmoles) of hydrochloride **7** and two drops of concentrated/-hydrochloric acid was cooled in an ice bath. With constant stirring, 0.40 g. (5.80 mmoles) of sodium nitrite dissolved in 30 ml. of water was added dropwise to the dark brown solution over a period of 45 minutes. Room temperature was gradually obtained and the resulting yellow-green suspension was stirred for 20 hours. A mixture of **12** and **13** (1.1 g., 94%) was isolated after filtering, washing with water, and drying. If the two reactants, **7** (0.50 g., 2.08 mmoles) and sodium nitrite (0.15 g., 2.17 mmoles), dissolved in 15 ml. of water, were added immediately to 25 ml. of water at room temperature and the mixture stirred 10 hours, the same mixture of **12** and **13** (0.43 g., 95%) was obtained; pmr (trifluoroacetic acid): δ 6.40 (s, 1/4H, C-3 proton of **13**), 6.70 (s, 3/4H, C-3 proton of **12**), 7.05 (s, 1/4H, C-7 proton of **13**), 8.90 (s, 3/4H, C-6 proton of **12**).

The crude mixture (1.5 g.) of **12** and **13** was dissolved in 30 ml. of dimethyl sulfixide by heating and filtered. Slow addition of about 8 ml. of water caused precipitation of a mixture enriched in component **12**. Recrystalization of this precipitate from aqueous dimethyl sulfoxide yielded pure yellow **12** (0.3 g. 24%) which was filtered, washed thoroughly with water, and dried, m.p. > 300°; ir (potassium bromide): 3300-2700 (hydrogen bonded NH and OH groups), 1640, 1560, 1480 (C=N) cm^{-1}; pmr (DMSO-d_6): δ 5.90 (s, 1H, C-3 proton) 7.60 (broad s, 2H, -NH_2) 8.50 (s, 2H, C-6 proton).

Anal. Calcd. for $C_8H_7N_5O_3S$: C, 37.93; H, 2.77; N, 27.66; S, 12.64; m.w. -H_2O = 235. Found: C, 37.86; H, 2.61; N, 27.33; S, 12.52; M^+ = m/e 235.

2-Amino-5-hydroxy-6-nitroso-8-thia-1,4-diazacycl[3.3.2]azine (**13**).

On a steam bath, 40 ml. of dimethyl sulfoxide and a crude mixture of **12** and **13** (3.50 g., 13.8 mmoles) were heated as a green colored suspension for 0.5 hours. After cooling, the mixture was reheated for another 20 minutes, and then cooled for a second time. With stirring, 10 ml. of water was added at room temperature and the mixture stirred for several minutes. The insoluble material was filtered, using a glass fritted funnel. Filter paper was not used since a considerable amount of dimethyl sulfoxide was present. Excess acetone (300 ml.) was added to the clear-brown filtrate and the resulting suspension allowed to set for 20 hours; the precipitate was filtered (0.9 g.), washed with acetone and dried. By heating on a steam bath, this material was dissolved in 20 ml. of dimethyl sulfoxide and filtered. Addition of excess acetone (150 ml.) to the cooled filtrate precipitated 0.30 g. (9%) of yellowish-green **13** which was filtered, washed with acetone, dried, and recrystalized from methanol: m.p. $> 300^\circ$; ir (potassium bromide): 3300-2900 (NH and OH, hydrogen bonded), 1640, 1560 (C=N), 950 cm^{-1}; pmr (DMSO-d_6): δ 5.60 (s, 1H, C-3 proton), 6.30 (s, 1H, C-7 proton), 7.50 (broad s, 2H,-NH_2).

Anal. Clacd. for $C_8H_5N_5O_2S\cdot 1/2H_2O$: C, 39.34; H, 2.45; N, 28.68; S, 13.11. Found: C, 39.32; H, 2.38; N, 28.74; S, 13.50.

REFERENCES AND NOTES

(1) Contribution No 3198, supported in part by U.S. Public Health Service Grant GM-10366.

(2) Taken in part from a thesis to be submitted by T. P. S. for the degree Doctor of Philosophy to Indiana University.

(3) R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *J. Am. Chem. Soc.*, 81, 1459 (1959).

(4) R. D. Brown and B. A. M. Coller, *Mol. Phys.*, 2, 158 (1958).

(5) D. Farquhar and D. Leaver, *Chem. Commun.*, 24 (1969).

(6) B. A. Hess, Fr., L. J. Schaad, and D. W. Holyoke, Jr., *Tetrahedron*, 28, 3657 (1972).

(7) R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.*, 62, 1785 (1973).

(8) V. Boekelheide and A. Miller, *J. Org. Chem.*, 26, 431 (1961).

(9) A. Taurins, "The Chemistry of Cyclazines", in "Chemistry of Heterocyclic Compounds", Vol. 30, John Wiley and Sons, Inc., New York, N. Y., 1978, pp. 245-270.

(10) O. Ceder and B. Beijer, *J. Heterocyclic Chem.*, 13, 1029 (1975).

(11) O. Ceder and B. Beijer, *Tetrahedron*, 30, 3657 (1974).

(12) E. Campaigne and T. P. Selby, *J. Heterocyclic Chem.*, 15, 401 (1978).

(13) R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1974.

(14) A kinetic study on the isomerization of **11** to **10** was performed at room temperature in trifluoroacetic acid by pmr (integration of tautomeric methylene proton peaks). The isomerization exhibited reversible kinetics. Equilibrium was attained in approximately 36 hours and the half-life was 4.5 hours.

$$\text{Ln}\ \frac{[11] - [11]_{eq}}{[11]_o - [11]_{eq}}$$

as a function of time (hours) yields a straight line plot. Therefore, at room temperature **10** and **11** were continually interconverting.