[1,2,4]Triazines. 4. Regiospecific Ring Closure Reactions Involving 6-Amino-5-hydrazino[1,2,4]triazin-3(2*H*)-ones and Orthoesters

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6-Amino-5-hydrazino[1,2,4]triazin-3(2*H*)-one, **3**, was treated with a variety of orthoesters and concentrated acid forming mixtures of ring-closed and open-chain derivatives. These mixtures were converted in warm aqueous acid to the *s*-triazolo[5,1-*d*][1,2,4]triazin-3(2*H*)-ones, **11b**, **14b**, and **15b** by a regiospecific ring closure at N-4 of the [1,2,4]triazine ring and subsequent Dimroth-like rearrangement of the initially formed *s*-triazolo[4,3-*d*][1,2,4]triazin-3(2*H*)-ones (**11a**, **14a**, **15a**).

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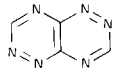
Introduction.

We have been interested in various aspects of the chemistry of the [1,2,4]triazine ring system for several years (1), owing to its suggested biological activity (2). Lately, our interest has been directed towards the synthesis of compounds represented by structures **1** and **2** and we wish to report our results concerning the regiospecificity of ring closure reactions involving 6-amino-5-hydrazino[1,2,4]triazin-3(2*H*)-one, **3**, and single carbon ring closure ragents since it was envisioned that compounds such as **1** might be prepared in this fashion.



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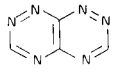

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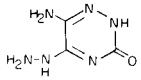
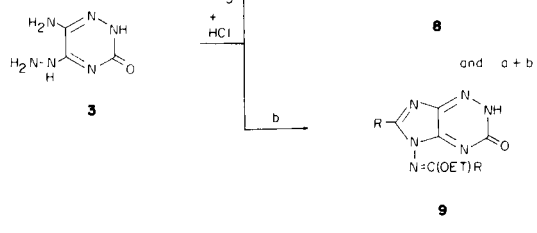


3

Compound **3** represents an extremely interesting intermediate with respect to regioselectivity when treated with single carbon ring closure reagents. For example, when 6-alkyl-5-hydrazino[1,2,4]triazin-3(2*H*)-ones were treated with formic acid, ring closure at N-4 of the [1,2,4]triazine ring was observed and the product of the reaction underwent rearrangement *via* a Dimroth-like process producing *s*-triazolo[5,1-*d*][1,2,4]triazin-3(2*H*)-ones (3). However, 5-amino-6-hydrazinopyrimidines afforded *N*-aminoimidazolopyrimidines under similar conditions (4). E. C. Taylor, *et al.*, (5) reported that formic acid and 4-alkyl-5-amino-6-hydrazinopyrimidines gave a mixture of imidazolopyrimidines and dihydropyrimidino[1,2,4]triazines. Orthoesters, concentrated hydrochloric acid and 5-amino-4-hydrazinopyrimidines closed to dihydropyrimidino-[1,2,4]triazines (4b) and imidazolopyrimidines (6). This information suggests the following modes of closure when **3** is treated with orthoesters and acid (Scheme I).

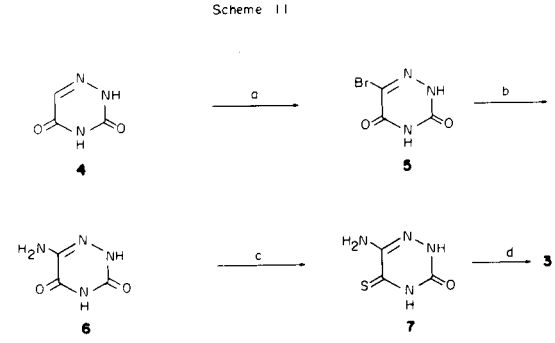
Scheme I



Discussion.

The synthesis of **3** was patterned after a method first reported by Kaja and Kawase (7). Thus, 6-azauracil, **4**, was treated with bromine water, as described by Chang (8), affording **5**. Compound **5** and aqueous ammonia gave **6** which afforded **7** upon oxygen-sulfur exchange with phosphorus pentasulfide in pyridine. Displacement of sulfur with hydrazine in ethanol produced **3** in reasonable yield (see Scheme II). Compound **3** was characterized by its infrared spectrum which contained NH stretching at 3400 and 3300 cm^{-1}, C=O stretching at 1730 and NH bending at 1630 cm^{-1}.

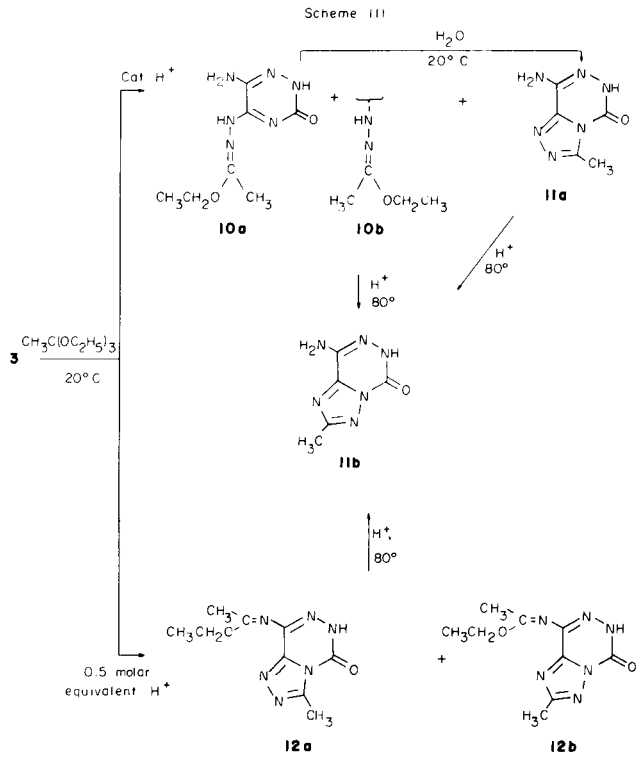
Scheme II



a, Br_2/H_2O, RT; b, NH_3/H_2O, Cu°, 120°; c, P_2S_5/C_5H_5N, reflux; d, N_2H_4 (95%), C_2H_5OH, reflux.

When **3** was treated with triethyl orthoacetate (TEOA) and a limited amount of concentrated hydrochloric acid at room temperature, the reaction followed a pathway different from either a or b, Scheme I. The proton spectrum of the crude product was consistent with that expected for

Scheme III



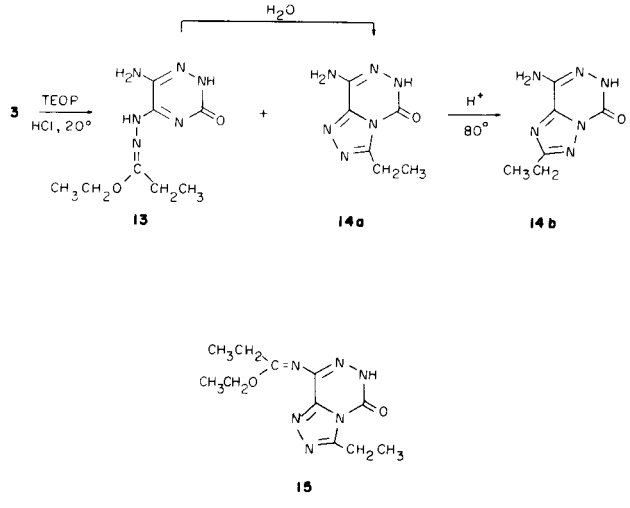
a mixture of the stereoisomers, **10a** and **10b**, Scheme III, which formed in a 2:1 ratio. The significant resonances employed in making these assignments were methyl singlets at δ 1.85 and δ 1.95. These resonances integrated in a ratio of 2:1 with the isomer possessing the more deshielded methyl predominating. Additional evidence for the structures assigned to **10a** and **10b** was found in the overlapping triplets assigned to the more highly shielded methyl (δ 1.25) and a multiplet corresponding to the methylene protons of the ethyl group (δ 4.2). We were not able to assign the resonances mentioned above to the major or minor isomer. The spectrum also contained a third resonance at δ 2.80 which we eventually were able to assign to the methyl group in **11a**. This component formed in varying amounts (by integration), but always represented a minor constituent of the reaction mixture.

When the mixture of **10a, 10b** and **11a** was warmed to 80° in dilute acid, ring closure at N-4 was the only pathway observed. The closure to give **11a** was complicated by the fact that this compound underwent a Dimroth-like rearrangement (9) affording **11b**. That, in fact, **11b** derived from **11a** in this fashion, was suggested in the literature (3) and by the following observations. When **10a** and **10b** were stirred at room temperature in water, a slow conversion into **11a** occurred. This conversion was confirmed by an examination of the proton spectrum of the product which exhibited no resonances consistent with retention of the ethyl group, but possessed a singlet at δ 2.80, a broad singlet at δ 6.5, and a second broad resonance at δ 11.6. The downfield resonances underwent deuterium-hydrogen exchange. Compound **11a** underwent rapid isomerization into **11b** when warmed in dilute acid. The stuctural assignment for **11b** rests upon spectral data, *i.e.*, its infrared spectrum which contains NH stretching at 3425 and 3300 cm^{-1} and C=O stretching at 1730 cm^{-1}. Also the position of the methyl resonance in the proton spectrum was useful in assigning these structures since Daunis, *et al.*, (3) suggest that **11b** should exhibit a more shielded methyl resonance than **11a**, δ 2.80 in **11a** *vs.* δ 2.51 in **11b**. Other spectral data were consistent with the structure proposed for **11b** (see Experimental).

When the amount of concentrated acid was increased to approximately one-half molar equivalent, the course of the reaction was altered with ring closure at N-4 predominating and conversion of the 6-amino group of **3** into an imidate ester. Once again this conclusion was supported by the proton resonance spectrum of the crude mixture which was consistent with ring closure (methyl resonances at δ 2.8 and δ 2.5) along with imidate ester formation involving the 6-amino group (triplet and quartet associated with the ethyl group and a methyl singlet at δ 2.0). High performance, medium pressure, liquid chromatography (hpmplc) permitted isolation of **12b** (Scheme III) and all spectrtal data, as well as CHN analysis, were consistent with the structure assigned. Unfortunately, compound **12a** isomerized to **12b** during the separation procedure. The mixture of **12a** and **12b** was converted into **11b** upon warming in dilute acid. Finally, when more than one molar equivalent of concentrated acid was employed in the orthoester reaction, **11b** was the only product isolated.

When compound **3** was treated with triethyl orthopropionate (TEOP) similar results were obtained. That is, **3** and TEOP in limited acid afford a 1:1 mixture of **13** and **14a** (Scheme IV). The basis for this conclusion results

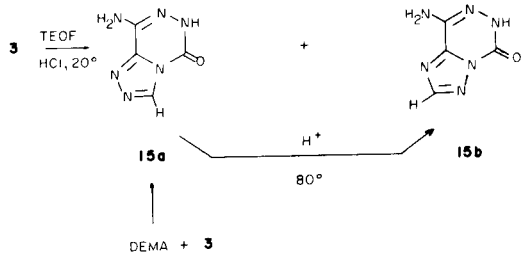
Scheme IV



from the appearance of three methylene quartets centered at δ 2.55, δ 3.50 and δ 4.50. The δ 3.50 resonance is consistent with the methylene protons of **14a**. Interestingly, no stereoisomer of **13** was observed, possibly because of steric effects associated with the more bulky ethyl group. Our assignment of the structure for **13** is arbitrary, and spectral data does not rule out the possibility of assigning a structure such as **15**. All attempts to isolate this component led to the formation of **14b**.

The mixture isolated from the TEOP and acid reaction underwent conversion into **14a** when stirred in water at 20° and **14a** was smoothly converted into **14b** when warmed in acid. All spectral data are consistent with the structures proposed (see Experimental).

Scheme V



When **3** was treated with triethyl orthoformate (TEOF) in limited or excess concentrated acid, the only products detected were **15a** and **15b** (Scheme V). The ratio of **15a** to **15b** varied depending upon acid concentration and reaction time. The structure **15a** was suggested by the highly deshielded proton resonating at δ 9.41. When this mixture was warmed in dilute acid the rearrangement into **15b** was completed in a short time as indicated by the absence of the δ 9.41 resonance and the enhancement of a resonance at δ 8.5.

Compound **15a** could be prepared in excellent yield by employing diethoxymethyl acetate (DEMA), previously employed by C. Temple, Jr., *et al.*, (4), as a single carbon ring closure reagent. The rearrangement into **15b** in dimethyl sulfoxide and trifluoroacetic acid, conveniently followed by proton spectroscopy, was complete in approximately two hours at 35°.

Unfortunately, despite repeated recrystallization and/or hpmplc purification, a satisfactory nitrogen analysis for **15b** was never obtained. However, the carbon and hydrogen analyses were within range of experimental error (see Experimental). This discrepancy occurred regardless of the method of preparation: TEOF/H^+ or DEMA.

When **3** was refluxed in orthoesters without any acid, ring closure occurred exclusively at N-4 followed by a thermally induced rearrangement. Thus **3** and TEOA afforded **11b** directly, and **3** and TEOF produced **15b**. In some cases small amounts of compounds which appeared to have undergone reaction at the 6-amino group were noted. Orthoesters did not react with **3** in the absence of acid at room temperature.

The regiospecificity of this facile ring closure deserves some comment. We have excluded the formation of compounds illustrated in a, Scheme I, based upon the absence of spin-coupled resonances in the δ 6.8-7.8 region of the proton spectrum. Such absorptions were reported when TEOF and acid were the closure reagents (6,10). While no literature information is available with regard to chemical shifts for the products of TEOA and TEOP, such spin-coupling is reasonable and not observed in the proton spectra of our product mixtures. Structures such as **9** have been excluded by our observation of the Dimroth-like rearrangement which is not generally observed in fused imidazoles. Recent experiments conducted in this laboratory have suggested a possible explanation for the regiospecific behaviour of **3** and orthoesters since the 6-amino group of **3** seems to lack nucleophilic character towards the reagents employed in this study. This lack of reactivity does have a precedent in previous studies (8), and might drive the ring closure to N-4 of the triazine ring. The formation of **12a** and **12b** must be rationalized as subsequent to the closure at N-4.

In summary, when 6-amino-5-hydrazino[1,2,4]triazin-3(2*H*)-one was treated with a variety of orthoesters and concentrated acid, mixtures of ring closed and open chain derivatives formed. These mixtures were converted in warm acid to *s*-triazolo[5,1-*d*][1,2,4]triazin-3(2*H*)-ones by a regiospecific ring closure at N-4 of the [1,2,4]triazine ring and subsequent Dimroth-like rearrangement of the initially formed *s*-triazolo[4,3-*d*][1,2,4]triazin-3(2*H*)-ones. No evidence for any other closure pathway was observed for this system.

EXPERIMENTAL

General.

All solvents were dried and purified prior to use by standard methods. All reagents were employed as received except when otherwise noted. Infrared spectra were recorded on a Beckman Acculab 2 as potassium bromide discs. Ultraviolet spectra were measured on a Perkin-Elmer Hatachi 200 employing water as a solvent unless otherwise noted. Proton spectra were measured on a Perkin-Elmer R24B spectrometer and chemical shifts are reported on the δ scale relative to TMS as an internal standard. Mass spectra were recorded on a Hitachi RMU-6 spectrometer. Melting points are uncorrected and were obtained on a Mel-Temp device. Hpmplc was accomplished on Silica Woelm 32-63 (Universal Scientific, Inc.) employing a Michael-Miller system (Ace Glass). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, or Atlantic Microlab, Inc., Atlanta, Georgia.

6-Amino[1,2,4]triazin-3(2*H*)-one-5(4*H*)-thione (7).

Compound **6** (1.0 g, 8 mmoles) was dissolved in hot pyridine (50 ml) and phosphorus pentasulfide (0.90 g, 4 mmoles) was cautiously added to the hot solution and the solution was refluxed for 2 hours. After cooling to room temperature, the pyridine was removed under reduced pressure

and the oily residue was dissolved in aqueous potassium hydroxide (50 ml, 1 *M*). The orange solution was treated with charcoal, filtered and acidified with hydrochloric acid (12 *M*). The yellow precipitate was collected (0.45 g, 40%); ir: 3400 cm^{-1}, 3300, 1700, 1620, 1310; uv: λ max (log ε), 342 (3.59), 301 (3.63), 237 (3.65), 205 (4.05).

6-Amino-5-hydrazino[1,2,4]triazin-3(2*H*)-one (**3**).

Compound **7** (1.0 g, 7 mmoles) was suspended in ethanol (50 ml) and hydrazine (95%, 20 ml) was added. The mixture was refluxed for 24 hours and the crude residue collected. Concentration of the ethanol solution afforded additional material, combined weight (0.89 g, 90%). Recrystallization from water afforded white plates; ir: 3400 cm^{-1}, 3300, 1735, 1675, 1635, 1400, 1050; uv: λ max (log ε), 285 (3.83), 237 (3.87); ms: 142 (M^+, 100).

Anal. Calcd. for $C_3H_6N_6O$: C, 25.35; H, 4.26; N, 59.15. Found: C, 25.59; H, 4.50; N, 58.85.

Compound **3** with TEOA and Catalytic Concentrated Hydrochloric Acid.

Compound **3** (0.4 g, 3 mmoles) was suspended in TEOA (5 ml) and concentrated hydrochloric acid (0.05 ml, 12 *M*) was added. The mixture was stirred at room temperature overnight. Excess TEOA was removed under reduced pressure at room temperature and the oily yellow precipitate was washed with cyclohexane. Nmr (DMSO-d_6) revealed the following resonances: δ 1.25, overlapping triplets, J = 8 Hz for each, O-CH_2-CH_3; 1.85, singlet, H_3C-C=N; 1.95, singlet, H_3C-C=N; 2.80, singlet, CH_3; 4.2, multiplet, O-CH_2-CH_3.

8-Amino-5-methyl-*s*-triazolo[4,3-*d*][1,2,4]triazin-3(2*H*)-one (**11a**).

The residue (0.12 g) obtained by treating **3** with concentrated hydrochloric acid was stirred in water (10 ml) overnight and the resulting precipitate was collected and dried at room temperature (0.8 g); nmr (DMSO-d_6): δ 2.78, s, 3; 6.5, broad s, deuterium oxide exchangeable, 2; 11.6, broad s, deuterium oxide exchangeable, 1; ir: 3380 cm^{-1}, 3310, 3200, 1725, 1645, 1560, 1450, 1370. All attempts to purify this compound lead to rearrangement.

8-Amino-6-methyl-*s*-triazolo[5,1-*d*][1,2,4]triazin-3(2*H*)-one (**11b**).

The precipitate (0.2 g) obtained by treating **3** with concentrated hydrochloric acid was warmed in dilute hydrochloric acid (10 ml, 1 *M*) for three hours and the acid was removed under reduced pressure. The yellow solid (0.1 g) was purified by hpmplc (ethyl acetate, 5 ml/minute), affording after removal of the solvent, 0.08 g of colorless plates, mp 246-248°; ir: 3420 cm^{-1}, 3300, 1730, 1635, 1550, 1415, 1370, 1300; nmr (DMSO-d_6): δ 2.5, s, 3, CH_3; 6.4, broad s, 2, NH_2; 11.8, broad s, 1, NH; uv: λ max (log ε); 292 (3.52), 245 (3.68), 222 (4.2); ms: 167 (M + 1, 22), 166 (M^+, 100), 110 (M^+ − 56, 25), 109 (M^+ − 57, 40).

Anal. Calcd. for $C_5H_6N_6O \cdot 1/8H_2O$: C, 35.66; H, 3.60; N, 49.91. Found: C, 35.98; H, 3.77;N, 50.10.

Compound **3** with TEOA and 0.5 Molar Equivalents of Concentrated Hydrochloric Acid.

Compound **3** (0.4 g, 3 mmoles) was suspended in TEOA (5 ml) and concentrated hydrochloric acid (0.1 ml, 12 *M*) was added. The mixture was stirred at room temperature overnight. Removal of the TEOA under reduced pressure at room temperature afforded 0.48 g of crude material. The nmr (DMSO-d_6) disclosed the following information about the crude mixture: a triplet at δ 1.3, J = 6 Hz, CH_2CH_3; a singlet at 2.0, CH_3-C=N-; singlets at 2.5 and 2.8, CH_3; and a quartet at 4.4, J = 6 Hz, -OCH_2CH_3.

Ethyl *N*-(6-Methyl-3(2*H*)oxo-*s*-triazolo[5,1-*b*][1,2,4]triazine-8-yl)acetimidate (**12b**).

The crude residue obtained above was dissolved in 2-propanol (2.5 ml) and subjected to hpmplc (ethyl acetate, 7 ml/minute). The initial fraction, colorless needles, 0.23 g, mp 174-176°; was identified as **12b**. Ir: 3210 cm^{-1}, 3120, 2930, 1735, 1665, 1280, 1215, nmr (Unisolve): δ 1.36, t, J = 6 Hz, 3, CH_2-CH_3; 2.06, s, 3, CH_3-C=N; 2.56, s, 3, CH_3; 4.36, q, J = 6 Hz, 2, O-CH_2CH_3; 12.8, broad s, 1, NH; ms: 236 (M^+, 49).

Anal. Calcd. for $C_9H_{12}N_6O_2$: C, 45.74; H, 5.13; N, 35.58. Found: C, 45.67; H, 5.33; N, 35.25.

8-Amino-5-ethyl-*s*-triazolo[4,3-*d*][1,2,4]triazin-3(2*H*)-one (**14a**).

Compound **3** (0.5 g, 3.5 mmoles) and TEOP (5 ml) had concentrated hydrochloric acid (0.1 ml, 12 *M*) added. The mixture was stirred at room temperature overnight. The solid that remained was collected and air dried (0.3 g). The nmr of the crude revealed a complex multiplet at δ 1.3, a quartet at 2.35, a quartet at 3.35, a quartet at 4.35 and a broad singlet at 10. The precipitate was suspended in water and stirred at room temperature for 15 hours. The residue was collected and afforded 0.15 g of material idenified as **14a** from the following spectral data; ir: 3400 cm^{-1}, 3280, 2930, 1745, 1645, 1370, 1335; nmr (DMSO-d_6): δ 1.3, t, J = 7 Hz, 3, CH_3; 3.06 q, J = 7 Hz, 2, CH_2; 6.32, broad s, 2, NH_2; 11.3, broad s, 1, NH. All attempts to purify **14a** lead to rearrangement.

8-Amino-6-ethyl *s*-triazolo[5,1-*d*][1,2,4]triazin-3(2*H*)-one (**14b**).

Compound **3** (0.3 g, 2.1 mmoles) in TEOP (7 ml) had concentrated hydrochloric acid (0.1 ml, 12 *M*) added and the mixture was stirred at room temperature overnight. The precipitate was collected and suspended in dilute hydrochloric acid (10 ml, 1 *M*) then kept at 90° for 2 hours. Removal of the solvent under reduced pressure afforded 0.13 g of crude product. Fional purification by hpmplc (ethyl actate, 7 ml/minute) affording **14b** as colorless plates, mp 213-214°; ir: 3380 cm^{-1}, 3300, 3200, 2930, 1720, 1630, 1560; nmr (DMSO-d_6): δ 1.3, t, J = 8 Hz, 3, CH_3; 2.84, q, J = 8 Hz, 2, CH_2; 12.4 broad s, 1, NH; uv: λ max (log ε); 291 (3.66), 247 (3.73), 222 (4.26); ms: 181 (M^+ + 1, 47), 180 (M^+, 100), 124 (M^+ − 56, 30), 123 (M^+ − 57, 80).

Anal. Calcd. for $C_6H_8N_6O$: C, 39.99; H, 4.48; N, 46.66. Found: C, 40.12; H, 4.65; N, 46.21.

8-Amino-*s*-triazolo[5,1-*d*][1,2,4]triazin-3(2*H*)-one (**15b**).

Compound **3** (0.2 g, 1.4 mmoles) in TEOF (2 ml) had concentrated hydrochloric acid (0.1 ml, 12 *M*) added. The resulting mixture was stirred at room temperature overnight. The yellow precipitate (0.18 g) was collected and dried. The nmr spectrum of this material revealed singlets at δ 9.4 and 8.6. This mixture was suspended in dilute hydrochloric acid (10 ml, 1 *M*) and warmed at 80° for 3 hours. Removal of the solvent under reduced pressure afforded 0.12 g of yellow material. Final purification by hpmplc (ethyl acetate, 10 ml/minute) affording 0.1 g of white irregular prisms, mp stable with slight decomposition to 300°; ir: 3300 cm^{-1}, 3170, 2920, 1730, 1630, 1565, 1380, 1350, 1150; nmr (DMSO-d_6): δ 6.4, broad s, 2, NH_2; 8.5, s, 1, CH and 12.0, broad s, 1, NH; uv: λ max (log ε) 290 (3.32), 248 (3.53), 219 (3.94); ms: 153 (M^- + 1, 12), 152 (M^+, 100), 96 (M^+ − 56, 37), 95 (M^+ − 57, 32).

Anal. Calcd. for $C_4H_4N_6O$: C, 31.58; H, 2.65. Found: C, 31.98; H, 3.01. (Note: no acceptable N analysis for this compound was ever obtained.)

Compound **3** and DEMA.

Compound **3** (0.3 g, 2.1 mmoles) in DEMA (15 ml) was stirred at room temperature overnight. The yellow solid (0.26 g, 81%) that resulted was refluxed in dilute hydrochloric acid affording 0.2 g of a compound which was identical in all respects with **15b**.

Acknowledgements.

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