An Investigation on the Thermolytic Conversions of 5-Diazouracils into 1,2,3-Triazoles

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Received March 16, 1977

The thermolysis of 5-diazo-6-methoxy-1-methyl-1,6-dihydrouracil (**1**) has afforded methyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**2**), *bis*-(1-methyl-1,2,3-triazol-4-oyl)amine (**3**) and dimethylcarbimate (**4**). The reaction was shown to proceed with the initial formation of **2** followed by a subsequent disproportionation of **2** to give **3** and **4**. A similar thermolysis of 5-diazo-6-ethoxy-1-methyl-1,6-dihydrouracil (**9**) gave ethyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**10**) as the sole product. Double labeling experiments have indicated that a major pathway for these reactions involves an intermolecular transfer of the C-6 substituent to the C-2 position.

J. Heterocyclic Chem., 14, 647 (1977).

In connection with our studies on 5-diazouracils, (1-5) we now wish to report an unusual reaction of two of these compounds. We have found that heating 5-diazo-6-methoxy-1-methyl-1,6-dihydrouracil (**1**) at 150°, as a melt or in acetonitrile solution, afforded methyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**2**). This reaction appeared similar to the reaction of **1** with water and methanol (3,5) in that a ring interconversion of a pyrimidine to a 1,2,3-triazole was effected in both cases. However, in the thermal reaction, there was no apparent nucleophile present in the reaction medium to cause ring opening. This prompted us to initiate a study of this reaction which was designed to afford some insight into the nature of the ring interconversion.

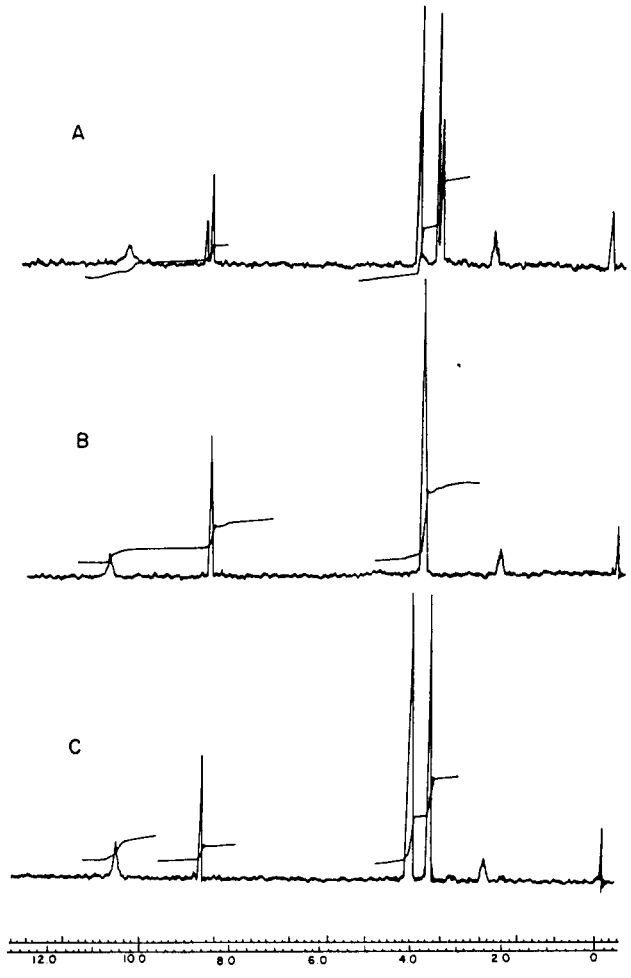
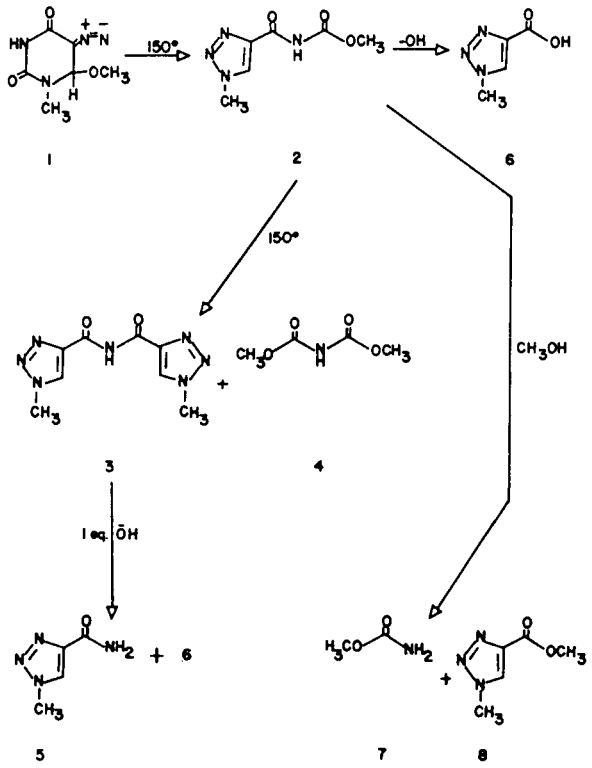


Figure 1

Compound **1** was powdered and heated as a melt (150°) until resolidification of the melt occurred. During this period of heating, a white solid formed at the top of the reaction flask. This solid was identified as dimethylcarbamate (**4**) on the basis of its spectral properties and elemental analyses. A pmr spectrum of the crude reaction mixture (Figure 1a) revealed the presence of two aromatic protons (δ 8.90 and δ 8.80) which were not in an equimolar ratio and suggested that two compounds were present.

Extraction of the mixture with hot methanol furnished an insoluble white solid which was characterized as *bis*-(1-methyl-1,2,3-triazol-4-oyl)amine (**3**) on the basis of the following data: elemental analyses and a molecular ion at m/e 235 in the mass spectrum were consistent with the empirical formula $C_8H_9N_7O_2$. The ultraviolet spectrum showed two absorption maxima (243 nm and 248 nm) and the infrared spectrum showed absorptions which were characteristic (6) of an imide group (3070 cm^{-1}, NH; 1740 cm^{-1}, C=O). The pmr spectrum (Figure 1b) revealed the presence of a six proton singlet (δ 4.20), a two proton singlet (δ 8.90) in the aromatic region of the spectrum and a broad exchangeable singlet (δ 11.10) which was consistent with the presence of an imide group.

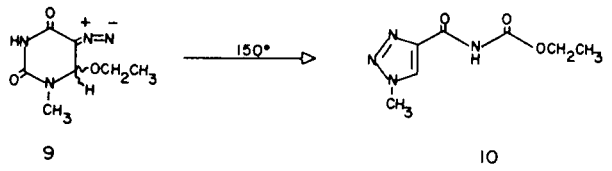
These data, especially the pmr data, were consistent with a symmetrically disubstituted imide with the substituents being *N*-methylated, five-membered heterocyclic rings containing three nitrogens (triazole). Treatment of **3** with one equivalent of sodium hydroxide gave 1-methyl-1,2,3-triazole-4-carboxamide (5) (**5**) and 4-carboxy-1-methyl-1,2,3-triazole (5) (**6**) in an equimolar ratio which confirmed the symmetrical structure of **3**.



The white solid which separated from the methanol filtrate after standing at room temperature for 18 hours was assigned the structure methyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**2**) on the basis of the following data: elemental analyses and a molecular ion at m/e 184 in the mass spectrum were consistent with the empirical formula $C_6H_8N_4O_3$. The pmr spectra (Figure 1c) revealed the presence of two methyl groups (δ 3.72 and δ 4.13), an aromatic proton (δ 8.80) and a broad exchangeable singlet (δ 10.10) which was suggestive of an imide-type proton. The infrared spectrum showed NH (3300 cm^{-1}) and C=O (1740 cm^{-1}) absorptions with an ultraviolet absorption maxima at 226 nm.

These data were consistent with an *N*-methylated, five-membered heterocyclic ring containing three nitrogens (triazole) with a methyl-*N*-formylcarbamate-exocyclic substituent. The structure of the heterocyclic ring and the positions of ring substitution were determined by heating **2** with an excess of sodium hydroxide to give **6**. A reaction of **2** with dry methanol gave methyl 1-methyl-1,2,3-triazole-4-carboxylate (5) (**8**) and methylcarbamate (**7**) in an equimolar ratio (7) which established the structure of the C-4 substituent.

It appeared that the formation of **3** and **4** in the reaction could have been the result of a disproportionation of **2**. Three additional experiments were performed to investigate the validity of this assumption. First, a disproportionation of **2** to afford **3** and **4** was observed at the melting point of **2** (181°). Second, when the thermolysis was repeated in acetonitrile solution, a single product was isolated which was identical in all respects with **2** obtained from the reaction of **1** as a melt. Third, the replacement of the C-6 methoxyl group of **1** by an ethoxy group (compound **9**) demonstrated a steric inhibition of the disproportionation reaction by giving ethyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**10**) as the sole product of thermolysis of **9** as a melt.



These studies established that **2** was the initial "stable" product of the reaction. The formation of **2** could occur by a migration of the C-6 methoxyl group to the C-2 position, followed by ring opening (N^1/C^2) and annulation between N-1 and the diazo group. We initiated double labeling experiments to establish whether the methoxyl group migration was predominantly inter- or intramolecular. These experiments were based on the fact that in an intermolecular rearrangement, the carbonyl group and methoxyl group in the ester moiety of **2** must originate from separate antecedents while in an intramolecular rearrangement these groups must have a common antecedent. Accordingly, it was a matter of employing ^{18}O for ^{16}O in **1** and mixing this labeled compound with another batch of **1** which had been labeled with deuterium on the methoxyl group. We had previously (5) prepared ***1** ($2\text{-}^{18}O$) and the preparation of the deuterium labeled compound was accomplished by recrystallization of 5-diazo-6-hydroxy-1-methyluracil (3) from methanol-d_4.

The choice for determination of the isotopic distribution in the products of the thermal reactions was made on the basis of the ion fragment m/e 59 occurring as the base

Table I

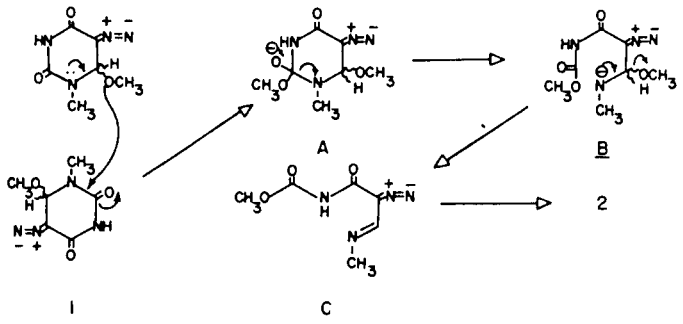
Label Present in **1**		Label found (b) in **4**, m/e			
^{18}O	d_3	59	61	62	64
-	-	100.0	0.0		
+	-	94.71	5.29		
-	+			100.0	0.0
+	+			94.71	5.29
Mixture (c) A (melt)				97.86	2.14
Mixture (c) B (acetonitrile)				97.43	2.57

(a) The abundances of the ion fragments were determined by using the Hewlett-Packard Multiple Ion Ratio computer program and the values listed are the averages of at least ten scans of the spectrum. (b) The values listed are the percentages for the isotopic composition for each sample after subtracting the natural abundance of the isotopes. (c) The lines headed "Mixture A" and "Mixture B" are mixtures of the oxygen-18 and deuterium labeled derivatives of **1** which were used for the double labeling experiments.

peak in the mass spectrum of **4**. The other peaks in the mass spectra of either **2** or **4** which would correspond to an ion fragment in which the ester moiety was still intact occurred with a relative abundance which was too low to allow computer assisted determination of the isotopic distribution.

An equimolar mixture of *1 and **1**-d_4 was thermolyzed as a melt and also in acetonitrile solution. Compound **4** was isolated directly from the neat reaction and also from the acetonitrile reaction by disproportionation of the product at 181°. An examination of the isotopic distributions in both of these reactions (Table I) demonstrated that approximately one-half of the oxygen-18 isotope was associated with the deuterium label. This suggested that a major path for the reaction probably involved an intermolecular migration of the methoxyl group.

The amount of oxygen-18 isotopic enrichment used in the double labeling studies was low and did not allow a calculation of the fraction of the reaction which must occur by an intermolecular process by a theoretical variation of the abundance of the mass spectral peaks. From the inherent experimental errors in the abundance figures, it would seem that our ability to detect an intramolecular pathway sets a minimum at about 20% for this reaction (8). Since a comparison of the data indicated that the rearrangement was mainly intermolecular, we feel that the mechanistic outline of Scheme I is the most likely course of this reaction.



I C A B 2

According to Scheme I, the reaction is initiated by an electrophilic displacement of the ether bond of **1** by the C-2 carbon of a different molecule of **1**. The intermediate which would be formed after the methoxyl group transfer could then ring open in a manner similar to the reaction of **1** with methanol (5). However, in this case the electron shift which would result in ring opening would also serve as a propagation step in the reaction by either placing a negative charge at N-1 or by expelling methoxide ion into the reaction medium at the time of ring opening. In either case, the loss of the C-6 methoxyl group would lead to the diazo intermediate *C* which is well suited for annulation (9) to afford **2**.

Acknowledgment.

The authors wish to thank Mr. L. H. Wojcik for the determination of mass spectra. This investigation was supported by Public Health Service Research Grant No. CA 11147 from the National Cancer Institute.

EXPERIMENTAL

Ultraviolet spectra were recorded on a Beckman Acta CIII recording spectrophotometer. Infrared spectra were determined on a Beckman IR8 spectrophotometer in compressed potassium bromide discs and pmr spectra (DMSO-d_6 and DMSO-d_6-deuterium oxide) on a Varian A56/60 instrument using 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard and chemical shifts are expressed in δ, parts per million from DSS. Electron impact mass spectra were recorded on a Hewlett-Packard 5930A Dodecopole instrument; ion source and direct inlet temperatures of 190°, ionizing energy 70 eV. Chemical ionization mass spectra were recorded on a Varian CH 7 instrument, modified for high pressure operation (10), using methane reagent gas; ion source and direct inlet temperatures of 190°, reagent gas pressure in the ion source 0.5 Tr. All samples for mass spectra were introduced by direct probe. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Anhydrous acetonitrile was obtained by distillation from phosphorous pentoxide and anhydrous methanol was obtained by distillation from calcium hydride. These solvents were stored over activated "Linde" type 3A 4-8 mesh molecular sieves. Concentrations *in vacuo* were performed at or below 40° unless otherwise indicated. Samples for elemental analyses were dried at 0.5 Tr in an Abderhalden apparatus using phosphorous pentoxide as the dessicant and the solvent as indicated.

Thermolysis of 5-Diazo-6-methoxy-1-methyl-1,6-dihydrouracil (**1**) to Afford Methyl *N*-(1-Methyl-1,2,3-triazol-4-oyl)carbamate (**2**), *bis*-(1-Methyl-1,2,3-triazol-4-oyl)amine (**3**) and Dimethylcarbimate (**4**).

5-Diazo-6-methoxy-1-methyl-1,6-dihydrouracil (**2**) (**1**, 2.48 g.) was placed in a 10 ml. round bottom flask which was equipped with a 6 cm (length) glass column. The flask was immersed in a Woods metal bath which had been preheated to 90° and the temperature of the bath was increased to 150° over a period of 15 minutes and then maintained at 150° for an additional 3 minutes. Dimethylcarbimate (**4**) condensed in the glass column during this period, m.p. 127-129°; ir: 3100 cm^{-1} (NH), 1752 cm^{-1} (C=O); pmr: δ 3.72 (s, 6, 2-CH_3), δ 10.5 (bs, 1, exchanged in deuterium oxide, N*H*); ms: 133/2.5 (M), 103/60 (M-CH_2O), 102/54 (M-CH_3O), 75/19 (CH_3OCONH_2), 59/100 (CH_3OOC).

Anal. Calcd. for $C_4H_7NO_4$: C, 36.10; H, 5.30; N, 10.53. Found: C, 35.89; H, 5.49; N, 10.58.

The flask was allowed to cool to room temperature and the flask was then extracted with hot methanol (2 x 30 ml.), the insoluble material was collected by filtration and then recrystallized from hot water (40 ml.) to give **3** (739 mg., 47%), m.p. 264-266°. A small sample was recrystallized from water for analysis and dried for 2 hours at the reflux temperature of *N,N*-dimethylformamide, m.p. unchanged; uv λ max (water): 243 nm (ε, 27,000) and 248 nm (ε, 26,500).

Anal. Calcd. for $C_8H_9N_7O_2$: C, 39.13; H, 4.38; N, 30.42. Found: C, 39.45; H, 4.35; N, 30.60.

The methanol filtrates were combined, concentrated *in vacuo* to 20 ml. and then allowed to stand at 5° for 3 days to give **2**

(852 mg., 34%), m.p. 178-181°. A small sample was recrystallized from methanol for analysis and dried for 4 hours at the reflux temperature of toluene, m.p. 181-183°.

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.42. Found: C, 39.45; H, 4.35; N, 30.60.

5-Diazo-6-ethoxy-1-methyl-1,6-dihydrouracil (**9**).

5-Diazo-6-hydroxy-1-methyl-1,6-dihydrouracil (2) (**5**, 1.98 g.) was added to ethanol (40 ml.), the mixture was heated at reflux temperature for 5 minutes and then concentrated to 20 ml. at reflux temperature. The light yellow crystals, which separated after standing at 5° for 6 hours were collected by filtration and dried for 4 hours at the reflux temperature of methanol to give **9** (2.16 g., 94%), m.p. 118-120°; uv, λ max (methanol): 264 nm (ε, 13,200); ir: 2100 cm^{-1} (diazo); pmr: δ 1.17 (t, pk wd 14 Hz, 3, CH_3), δ 3.12 (s, 3, CH_3), δ 3.45 (q, pk wd 22 Hz, 2, CH_2), δ 6.10 (s, 1, C*H*), δ 10.0 (bs, 1, exchanged in deuterium oxide, N*H*).

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.46; H, 4.09; N, 28.30. Found: C, 42.59; H, 4.07; N, 28.42.

Thermolysis of 5-Diazo-6-ethoxy-1-methyl-1,5-dihydrouracil (**9**) to Afford Ethyl (1-Methyl-1,2,3-triazol-4-oyl)carbamate (**10**).

5-Diazo-6-ethoxy-1-methyl-1,6-dihydrouracil (**9**, 965 mg.) was placed in a 5 ml. pear shaped flask and the flask was immersed in a Woods metal bath which had been preheated to 90°. The temperature of the bath was increased to 150° over a period of 11 minutes and then maintained at 150° for an additional 2 minutes. The flask was allowed to cool to room temperature and the solid which remained in the flask was recrystallized from hot ethanol (70 ml.) and dried for 3 hours at the reflux temperature of toluene to give **10** (829 mg., 86%), m.p. 128-129°; uv λ max (water): 227 nm (ε, 14,000); pmr: δ 1.27 (t, pk wd 14 Hz, CH_3), δ 4.17 (s, 3, CH_3), δ 4.22 (q, pk wd 22 Hz, 2, CH_2), δ 8.79 (s, 1, C*H*), δ 10.5 (bs, 1, exchanged in deuterium oxide, N*H*).

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.61; H, 5.24; N, 28.06.

Hydrolysis of Methyl *N*-(1-Methyl-1,2,3-triazol-4-oyl)carbamate (**2**) to Afford 4-Carboxy-1-methyl-1,2,3-triazole (**6**).

Methyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**2**, 157 mg.) was combined with 0.99 *N* sodium hydroxide (1.81 ml.) and water (5 ml.) and the mixture was heated at reflux temperature for 2 days. The solution was then allowed to cool to room temperature and acidified by the addition of 1.02 *N* hydrochloric acid (1.76 ml.). A white solid separated from solution after standing at 5° for 18 hours and was collected by filtration and dried for 4 hours at the reflux temperature of toluene to give **6** (67 mg., 61%), m.p. 240-242°; uv λ max (water): 211 nm (ε, 8,700); Lit. (5) m.p. 240-242°; uv λ max (water): 211 nm (ε, 8,600).

Methanolysis of Methyl *N*-(1-Methyl-1,2,3-triazol-4-oyl)carbamate (**2**) to Afford Methyl 1-Methyl-1,2,3-triazole-4-carboxylate (**8**), Methylcarbamate (**7**) and 1-Methyl-1,2,3-triazole-4-carboxamide (**6**).

Methyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**2**, 74 mg.) was dissolved in dry methanol (7 ml.) and the solution sealed in a stainless steel reaction vessel. The reaction vessel was heated in an oil bath maintained at 135° for 18 hours and then allowed to cool to room temperature. The solution was concentrated to dryness *in vacuo* to give a white solid. This solid was triturated with methanol (2 x 1 ml.) and the small amount of insoluble material was removed by filtration and recrystallized from hot methanol (1 ml.) to give **5** (1.9 mg., 4%), m.p. 246-251°; ir spectrum identical with an authentic sample (4).

The methanol filtrate was concentrated *in vacuo* to dryness and the flask was equipped with a cold water condensor. The flask was evacuated to 16 Tr and then immersed in an oil bath maintained at 90° and heated for a period of about 15 minutes. Methylcarbamate (**7**, 24 mg., 80%), m.p. 55-56°; Lit. (5) m.p. 54-55°, formed in the condensor during this period. The residue in the flask was recrystallized from hot methanol (1 ml.) to give **8** (37.9 mg., 67%), m.p. 159-161°; lit. (5), m.p. 159-161°; ir spectrum identical with an authentic sample (5).

Hydrolysis of *bis*-(1-Methyl-1,2,3-triazol-4-oyl)amine (**3**) to Afford 1-Methyl-1,2,3-triazole-4-carboxamide (**5**) and 4-Carboxy-1-methyl-1,2,3-triazole (**6**).

bis-(1-Methyl-1,2,3-triazol-4-oyl)amine (**3**, 300 mg.) was added to 0.99 *N* sodium hydroxide (1.30 ml.), the solution was heated on a steam bath for 18 hours and then allowed to cool to room temperature. The white solid which had separated from solution was collected by filtration and recrystallized from hot water (3 ml.) to give **5** (131 mg., 82%), m.p. 261-263°; uv: λ max 211 nm (ε, 12,200). The filtrate was acidified by the addition of 0.96 *N* hydrochloric acid (1.35 ml.) and then allowed to stand at 5° for 18 hours to give **6** (156 mg., 96%), m.p. 232-233°; uv λ max (water): 210 nm (ε, 8,600).

Thermal Disproportionation of Methyl *N*-(1-Methyl-1,2,3-triazol-4-oyl)carbamate (**2**) to Afford Dimethylcarbimate (**4**) and *bis*-(1-Methyl-1,2,3-triazol-4-oyl)amine (**3**).

Methyl *N*-(1-methyl-1,2,3-triazol-4-oyl)carbamate (**2**, 318 mg.) was placed in a 5 ml. round bottom flask which was equipped with a 15 cm glass condensor. The flask was placed in a metal bath which had been preheated to 94°, the temperature of the bath was increased to 190° over a period of 14 minutes and then maintained at 190° for an additional 13 minutes. During this time **2** became a melt at a bath temperature of about 183° and **4** (29.4 mg., 26%, m.p. 123-126°) was formed in the condensor; ir: 3100 cm^{-1} (NH), 1750 cm^{-1} (C=O); pmr: δ 3.78 (s, 6, 2-CH_3), δ 10.5 (s, 1, exchanged deuterium oxide, N*H*); ms: 133/2.5 (M), 103/60 (M-CH_2O), 102/54 (M-CH_3O), 57/19 (CH_3OCONH_2), 59/100 (CH_3OOC).

The flask was allowed to cool to room temperature and the material which remained in the flask was recrystallized from hot water (10 ml.) to give **3** (138 mg., 68%), m.p. 264-266°; uv λ max (water): 243 nm (ε, 17,400) and 248 nm (ε, 17,200); pmr: δ 4.22 (s, 6, 2-CH_3), δ 8.91 (s, 2, 2-C*H*), δ 11.1 (bs, 1, exchanged in deuterium oxide, N*H*).

Thermolysis of 5-Diazo-6-methoxy-1-methyl-1,6-dihydrouracil (**1**) in Acetonitrile to Afford Methyl (1-Methyl-1,2,3-triazol-4-oyl)-carbamate (**2**).

5-Diazo-6-methoxy-1-methyl-1,6-dihydrouracil (**1**, 620 mg.) was dissolved in dry acetonitrile (15 ml.) and the solution was sealed in a stainless steel reaction vessel. The reaction vessel was heated for 2 hours in an oil bath maintained at 150° and then allowed to cool to room temperature. The solution was concentrated *in vacuo* to dryness, the solid which remained was recrystallized from hot methanol (18 ml.) and dried for 4.5 hours at the reflux temperature of methanol to give **2** (558 mg., 90%), m.p. 179-181°; uv λ max (water): 226 nm (ε, 14,900); ir: 3300 cm^{-1} (NH), 1740 cm^{-1} (C=O); pmr: δ 3.70 (s, 3, CH_3), δ 4.10 (s, 3, CH_3), δ 8.80 (s, 1, C*H*), δ 10.4 (bs, 1, exchanged deuterium oxide, N*H*); ms: 184/1.91 ms.

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.42. Found: C, 39.29; H, 4.31; N, 30.09.

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