was discarded and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a solid. The solid was triturated with ether to yield 0.12 g (70%) of **12** as a brownish yellow solid of mp 228–231 °C dec: ^1H NMR (270 MHz, Me_2SO-d_6 + CD_3OD) δ 4.46 (H_{10}, d), 4.85 (H_{11}, d), 6.21 (H_9, dd), 7.66–8.32 (8 H, m), 8.93 (H_1, d), 9.77 (H_{14}, s), $J_{1,2}$ = 7.2, $J_{8,9}$ = 10, $J_{9,10}$ = 2.6, $J_{10,11}$ = 11.2; mass spectrum, m/z 313 (M^+), 295 (base peak, $M^+ - H_2O$); UV (EtOH–THF) λ_{max} (ϵ) 224 (35600, sh) 288 (53000), 350 (5200), 367 (6600), 388 (7000); fluorescence emission spectrum (EtOH–THF) λ_{ex} (λ_{em}) 280 (405,416).

(±)-10α,11β-Dihydroxy-8α,9α-epoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (3). A mixture of dihydrodiol **12** (60 mg) and purified *m*-chloroperoxybenzoic acid (450 mg) in anhydrous THF (20 mL) was stirred at room temperature under Ar for 1 h. The mixture was diluted with ether (30 mL), extracted with ice-cooled 2% NaOH (2 × 50 ml) and water (2 × 25 ml), dried (Na_2SO_4), and concentrated to give a solid that was triturated with ice-cooled anhydrous ether (3 × 5 mL) to give **3** as a colorless crystalline solid (30 mg, 48%) of mp 215–217 °C dec: ^1H NMR (360 MHz, Me_2SO-d_6 + CD_3OD) δ 3.86 (H_9, d), 3.91 (H_{10}, d), 4.57 (H_{11}, d), 5.58 (H_8, d), 7.65–8.35 (7 H, m), 9.01 (H_1, d), 9.93 (H_{14}, s), $J_{1,2}$ = 8.4, $J_{8,9}$ = 6.3, $J_{9,10}$ = 0, $J_{10,11}$ = 8.4; high resolution mass (AEI-MS-902) spectrum, obsd 329.1034, calcd mass 329.1052; fluorescence emission spectrum (EtOH–THF) λ_{ex} (λ_{em}) 280 (397, 408).

(±)-10α,11β-Dihydroxy-8β,9β-epoxy-8,9,10,11-tetrahydrodibenz(*a*,*h*)acridine (4). To a stirred solution of dihydrodiol **12** (90 mg) in THF (14 mL) at 0 °C under Ar was added H_2O (4 mL), *N*-bromoacetamide (NBA, 42 mg), and 1 drop of concentrated HCl. The solution was stirred at 0–5 °C for 30 min. EtOAc (30 mL) was added. The organic phase was washed with ice-cooled H_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a solid. The solid was chromatographed over dry column grade silica gel with CH_2Cl_2 as developing solvent to give initially nonpolar impurities. Further elution with acetone gave desired bromo triol (80 mg, 68%) as yellow crystalline solid of mp 169–171 °C dec: ^1H NMR (360 MHz, Me_2SO-d_6 + CD_3OD) δ 4.20 (H_{10}, dd), 4.67 (H_9, m), 6.11 (H_8, d), 7.70–8.27 (7 H, m), 9.01 (H_1, d), 9.89 (H_{14}, s), $J_{1,2}$ = 7.9, $J_{8,9}$ = 4.3, $J_{9,10}$ = 3.0, $J_{10,11}$ = 7.1.

To a stirred solution of the above bromo triol (46 mg) in dry THF (10 mL) was added amberlite-400 (4 g) that had been converted to the hydroxide form. The mixture was stirred at room temperature under Ar, for 5 h, and was quickly filtered, and the filtrate was concentrated under reduced pressure. The trituration of the solid with petroleum gave diol epoxide **4** (19 mg, 49%) as colorless solid of mp 254–257 °C dec: NMR (360 MHz, Me_2SO-d_6 + CD_3OD) δ 3.93 (H_9, m), 4.22 (H_{10}, dd), 4.69 (H_{11}, dd), 5.38 (H_8, d), 7.69–8.29 (7 H, m), 8.98 (H_1, d), 9.85 (H_{14}, s), $J_{1,2}$ = 7.4, $J_{8,9}$ = 4.0, $J_{9,10}$ = 2.2, $J_{9,11}$ = 1.2, $J_{10,11}$ = 4.0; fluorescent emission spectrum (EtOH–THF) λ_{ex} (λ_{em}) 280 (395, 404).

Acknowledgment. This investigation was supported, in part, by Grant No. ES03346-01 awarded by the National Institute of Environmental Health Sciences, DHHS.

Registry No. **1**, 226-36-8; (±)-**3**, 97135-11-0; (±)-**4**, 97169-68-1; **5**, 97135-12-1; (±)-**6**, 97135-13-2; (±)-**7**, 97135-14-3; **8**, 97135-15-4; (±)-**9**, 97135-16-5; (±)-10, 97135-17-6; **10** (8-bromo deriv), 97135-20-1; (±)-11, 97149-85-4; (±)-**12**, 97135-18-7; (±)-12 (8,9-dihydro), 97135-19-8; **12** (bromotriol), 97149-86-5.

Chemistry of Pyrimidine. 2. Synthesis of Pyrimidine *N*-Oxides and 4-Pyrimidinones by Reaction of 5-Substituted Pyrimidines with Peracids. Evidence for Covalent Hydrates as Reaction Intermediates

Thomas J. Kress

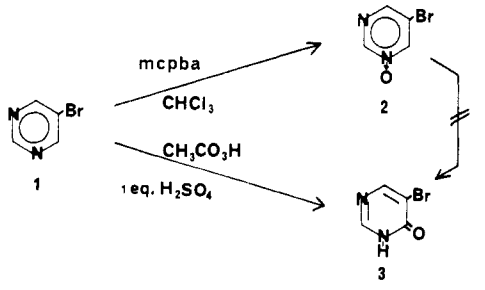
The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

Received February 5, 1985

The reaction of 5-substituted pyrimidines with peracids has been found to take divergent pathways depending on the presence or absence of a strong acid. Reaction of 5-bromo- (**1**) or 5-methoxypyrimidine (**6**) with *m*-chloroperbenzoic acid afforded the corresponding *N*-oxides in 29% and 70% yields, respectively. The formation of an *N*-oxide was not observed when either **1** or **6** was treated with 40% peracetic acid in the presence of 1 equiv of sulfuric acid. In the case of **1**, the product was 5-bromo-4(3*H*)-pyrimidinone (**3**), formed in 70% yield. From **6**, two products, 5-methoxy-4(3*H*)-pyrimidinone (**8**) and 4(5)-carbomethoxyimidazole (**9**), were formed in a combined yield of 70% (3:2 ratio of **8** to **9**). The *N*-oxides were demonstrated to be stable to the above reaction conditions and are therefore not intermediates in the formation of **3**, **8**, or **9**. Evidence for the existence of covalent hydrates makes it reasonable to suggest their formation as reaction intermediates.

Heterocyclic *N*-oxides are valuable intermediates in promoting further functionality within a ring system.[1] Our interest in developing synthetic methodology for the elaboration of pyrimidine and 5-substituted pyrimidines led us to consider the preparation of their *N*-oxides. In general, simple substituted pyrimidines afford poor yields of *N*-oxide and are either largely destroyed or do not react during attempted N-oxidation.[2,3] The yield of *N*-oxide is substantially improved when the 2,4- and/or 4,6-positions are occupied by electron-releasing substituents. In

Scheme I

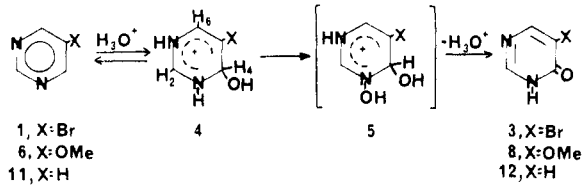


numerous instances under N-oxidation conditions, the pyrimidine ring appears to be more susceptible to other reactions such as hydrolysis, ring opening, and decomposition.[4] The variability in the outcome of these reactions

(1) Katritzky, A. R.; Lagowski, J. M. "Chemistry of Heterocyclic *N*-Oxides"; Academic Press: London, 1971.
(2) Brown, D. J. "The Pyrimidines"; Wiley Interscience: New York, 1970; Supplement I, pp 294–295.
(3) Brown, D. J. "The Pyrimidines"; Wiley Interscience: New York, 1962; pp 19, 116, 382.

0022-3263/85/1950-3073$01.50/0

Scheme II



prompted us to examine in detail the reaction of 5-substituted pyrimidines with peroxygenated reagents.

Results and Discussion

We have found that the reaction of pyrimidine (**11**) and 5-bromo- (**1**) and 5-methoxypyrimidine (**6**) with peroxygenated reagents takes divergent pathways depending on the presence or absence of aqueous strong acid. In the presence of aqueous acid the controlling factor in the outcome of the chemistry of these pyrimidines appears to involve a covalent hydrate as a reaction intermediate. The reactions of each of these compounds will be considered separately.

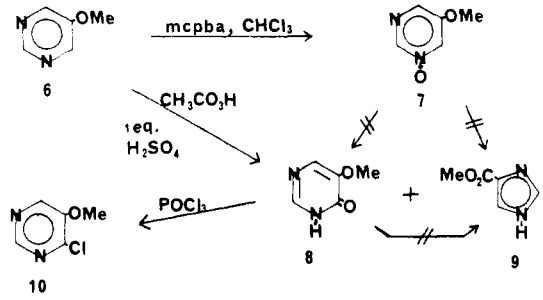
Reaction of 5-Bromopyrimidine (1) with Peracid. *m*-Chloroperbenzoic Acid (MCPBA). Treatment of **1** with 1 equiv of MCPBA in refluxing chloroform for 7 h afforded a 29% yield (54% based on recovered **1**) of 5-bromopyrimidine *N*-oxide (**2**, see Scheme I).[5] Fortunately, the *N*-oxide **2** was virtually insoluble in ether and could be separated readily from **1** by filtration. Attempts to force the reaction to completion by using longer reaction times, excess oxidant, or higher temperature led only to lower yields of **2**.

Peracetic Acid–Sulfuric Acid. Reaction of **1** with either 1 or 2 equiv of 40% peracetic acid[6] at room temperature in acetone for 24 h afforded a small amount of a white crystalline precipitate, leaving the majority of the starting material unchanged. In contrast, in the presence of 1 equiv of sulfuric acid, an exothermic reaction gave within minutes the same white crystalline precipitate in 70% yield.[7] This white solid was determined to be the hydrogen sulfate salt of 5-bromo-4(3*H*)-pyrimidinone (**3**), identical with an authentic sample prepared by another route.[8]

Initially, we considered that **3** was formed via the *N*-oxide **2**, since 4-acetoxypyrimidine is known to be the sole product on treatment of pyrimidine *N*-oxide with acetic anhydride.[9] However, reaction of **2** with 1 equiv of sulfuric acid and 40% peracetic acid in acetone gave no trace of **3** (see Scheme I).

The formation of **3** from **1** was found to occur with water as solvent, and thus it was possible to follow this reaction in a stepwise manner by ^{1}H NMR. The spectrum of **1** in D_2O containing a molar equivalent of sulfuric acid displayed singlets at 9.25 (H-2) and 9.13 ppm (H-4,6) corresponding to the ring protons of **1** and three upfield peaks at 8.32, 5.88, and 7.07 ppm (Scheme II, H-2, H-4, and H-6, respectively, of **4**, X = Br) belonging to the protons of the covalent hydrate **4** (X = Br).[10] The equilibrium in this medium between **1** and **4** (X = Br) based on integration was 70% **1** to 30% **4**. A proton NMR spectrum taken immediately after the addition of 40% peracetic acid to this mixture displayed the same peaks for **1** (X = Br) and **4** (X = Br) and two new doublets at 9.08 and 8.50 ppm. After 30 min, this sample showed neither **1** (X = Br) or **4** (X = Br) present and only the two doublets at 9.08 and 8.50 ppm ($J_{2,6} \simeq 1.0$ Hz, across nitrogen coupling) which correspond precisely to the spectrum of **3** (X = Br) in this medium. On the basis of these data, we feel that a plausible explanation for our results is the sequence described in Scheme II. That is, initial formation of the covalent hydrate **4**, followed by irreversible oxidation to **5**,[11] and subsequent loss of water affords **3**.

Scheme III



Reaction of 5-Methoxypyrimidine (6) with Peracid. MCPBA. A 70% isolated yield of 5-methoxypyrimidine *N*-oxide (**7**) was obtained on reaction of **6** with 1 equiv of MCPBA in chloroform at 25 °C for 3 days (see Scheme III). The electron-releasing effect of the methoxy group sharply increases the yield of *N*-oxide as compared with **1**.

Peracetic Acid–Sulfuric Acid. Treatment of **6** with 1 equiv of 40% peracetic acid in water for 1 h at 25 °C produced virtually no reaction.[12] In contrast to **1**, no covalent hydrate was detected by ^{1}H NMR after the addition of 1 equiv of sulfuric acid. However, after 4 h **6** was converted to a mixture of 5-methoxy-4(3*H*)-pyrimidinone (**8**, 42%) and 4(5)-carbomethoxyimidazole (**9**, 28%). The structure of **8** was assigned on the basis of spectral data and by conversion to a known compound, 4-chloro-5-methoxypyrimidine (**10**, see Scheme III). The structure of the ring contracted product **9** was determined by single-crystal X-ray analysis.

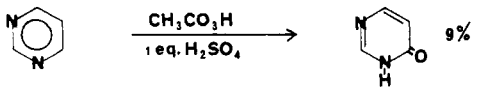
The origin of **8** and **9** was of further interest. Separate exposure of **7** and **8** to the peracetic–sulfuric acid reaction conditions resulted in no reaction. Thus **7** was not a precursor to **8** or **9** and **8** was not an intermediate in the formation of **9** (see Scheme III).

The formation of **8** probably occurs in a similar manner to that of **3** and involves the initial formation of a small amount of covalent hydrate **4** (X = OCH_3, not measurable by ^{1}H NMR) followed by oxidation and dehydration as depicted in Scheme II (X = OCH_3). The precise mecha-

(4) Javanovic, M. V. *Can. J. Chem.* **1984**, *62*, 1176.
(5) Varying parameters of time, temperature, stoichiometry, mode of addition, and solvent all gave lower yields of **2**.
(6) Peracetic acid is an "equilibrium peracid" prepared commercially by mixing aqueous hydrogen peroxide with acetic acid, using sulfuric acid as a catalyst. A commercial sample of 40% peracetic acid typically contains: 15% water, 1% sulfuric acid, 40% peracetic acid, 39% acetic acid, and 5% hydrogen peroxide.
(7) The reaction of **1**, **6**, and **11** in the presence of 1 equiv of sulfuric acid also occurs with 30% hydrogen peroxide and MCPBA as the oxidant and affords 4(3*H*)-pyrimidinones. In this paper, we have described only the reaction with 40% peracetic acid since the yields were superior.
(8) Chesterfield, J.; McOmie, J.; Sayer, E. *J. Chem. Soc.* **1955**, 3478.
(9) Bredereck, H.; Gompper, R.; Herlinger, H. *Chem. Ber.* **1958**, *91*, 2832.
(10) The previous paper in this series describes in detail the covalent hydration of 5-substituted pyrimidines. Kress, T. J. *J. Heterocycl. Chem.* **1985**, *22*, 437.
(11) For simplicity we have depicted the oxidation as occurring at N-3. The oxidation could have occurred equally as well at N-1. The loss of water from either intermediate affords the same net result.
(12) This reaction could not be performed in acetone because the sulfate salt of **6** immediately precipitated from the solution as a tacky gum.
(13) Chesterfield, J. H.; McOmie, J. F. W.; Tute, M. S. *J. Chem. Soc.* **1960**, 4590.

nism for the formation of **9** remains undefined.

Reaction of Pyrimidine (11) with Peracetic Acid–Sulfuric Acid. Treatment of **11** with peracetic acid–sulfuric acid gave no trace of pyrimidine *N*-oxide and the only isolable product in poor yield was 4(3*H*)-pyrimidinone (**12**), identical with an authentic sample. The majority of



11 12

12 was destroyed under these conditions and was converted to water soluble nonisolable products. The ^{1}H NMR spectrum of **11** in aqueous acid has been reported to display no measurable quantity of covalent hydrate **4**.[10] However, on the basis of the reaction of **1** and **6**, the formation of **12** affords additional evidence that it may be formed by the steps described in Scheme II. These results also intimate that **4** (X = H) is much less stable than **4** (X = OCH_3 or Br) and undergoes ring opening and fragmentation.

Conclusion

The vulnerability of the pyrimidine ring to undergo covalent hydration in acidic media makes it reasonable to postulate the formation of intermediate covalent hydrates in reactions with peracetic–sulfuric acid leading to a convenient synthesis of 4-pyrimidones. Treatment of pyrimidines with peracid under anhydrous conditions results in normal *N*-oxide formation.

Experimental Section

^{1}H NMR spectra were determined on a JEOL FX90Q Fourier transform spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The mass spectra were determined on a Model 21-110 Consolidated Electrodyne Corp. spectrometer. Elemental analyses were carried out at Eli Lilly and Company.

Starting Materials. 5-Bromopyrimidine (**1**), 5-methoxypyrimidine (**6**), and pyrimidine (**11**) were prepared by known literature procedures.[9] A fresh bottle (less than 2 months old) of peracetic acid was used in all experiments. Older peracetic acid gave varying results.

5-Bromopyrimidine *N*-Oxide (2). A mixture of **1** (7.95 g, 50 mmol) and MCPBA (12.4 g, 57.5 mmol) in 150 mL of chloroform was heated under reflux for 7 h, cooled to room temperature, filtered, and evaporated to dryness. The residue was dissolved in an excess of saturated aqueous sodium carbonate solution, and extracted with methylene chloride (3 × 100 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness in vacuo, affording a white solid, which by TLC (acetone/silica gel) was a mixture of **1** and **2**. This solid was slurried in 30 mL of diethyl ether and filtered and the collected solid washed with 10 mL of additional diethyl ether, affording after drying 2.53 g (29%) of **2** as white fine needles: mp 164–166 °C (lit.[14] mp 166–167 °C); mass spectrum, *m/e* (%), 174–176 (100); NMR ($CDCl_3$) δ 8.83 (H-2, d, 1 H, $J_{2,6}$ = 2 Hz), 8.23 (H-4, d, 1 H, $J_{4,6}$ = 2 Hz), 8.48 (H-6, dd, 1 H, $J_{2,6}$ = $J_{4,6}$ = 2 Hz).

Anal. Calcd for $C_4H_3BrN_2O$: C, 27.46; H, 1.73; N, 16.01. Found: C, 27.54; H, 1.72; N, 15.81.

5-Bromo-4(3*H*)-pyrimidinone (3). To a 250-mL flask equipped with a thermometer, condenser, and stirrer were added 15.8 g of **1** (0.1 mol) and 100 mL of acetone followed by a mixture of 33.3 mL (0.2 ml) of 40% peracetic acid and 5.55 mL (0.1 mol) of 18 M sulfuric acid. The mixture warmed to reflux within a few minutes, affording a white crystalline solid. This slurry was allowed to stir at ambient temperature for 1 h, cooled to 5 °C, filtered, and dried, giving 15.6 g of **3** as the hemisulfate salt, mp 163–164 °C.

Anal. Calcd for $C_4H_3N_2BrO\cdot{}^1/_2H_2SO_4$: C, 21.44; H, 1.80; N, 12.50. Found: C, 21.13; H, 2.20; N, 12.10.

This salt was slurried with water (60 mL) and the pH adjusted to 7 with aqueous 5 N sodium hydroxide, and the resulting fine white needles were filtered, washed with water, and dried, affording 10.2 g: mp 198–200 °C (a mixed melting point of **3** prepared by the method described in ref 8 was not depressed); mass spectrum, *m/e* (%), 174–176 (100; NMR (2 N DCl–D_2O) δ 9.30 (H-2, d, 1 H, $J_{2,6}$ = 1.4 Hz), 8.56 (H-6, d, 1 H, $J_{2,6}$ = 1.4 Hz); NMR (Me_2SO-d_6) δ 8.33 and 8.24 (H-2 and H-6, 2 s); UV (MeOH) λ_{max} (log ε) 231 (3.75), 282 nm (3.72).

Anal. Calcd for $C_4H_3N_2OBr$: C, 27.46; H, 1.73; N, 16.01. Found: C, 27.41; H, 1.80; N, 15.95.

An additional 2.1 g of **3** was obtained from the reaction mixture filtrate by neutralization to pH 7 with 50% aqueous sodium hydroxide and continuous extraction with chloroform bringing the total isolated **3** to 12.3 g (70%).

5-Methoxypyrimidine *N*-Oxide (7). A mixture of **6**, 2.2 g (20 mmol), and 4.96 g of *m*-chloroperbenzoic acid (23 mmol, based on 80% activity) in 50 mL of chloroform was stirred at ambient temperature for 3 days, and the resulting solid (MCPBA and *m*-chlorobenzoic acid) was removed by filtration. The filtrate was evaporated to a slurry (in vacuo), and 100 mL of a saturated aqueous sodium bicarbonate solution was added. This aqueous phase was continuously extracted with chloroform overnight. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness, giving a white powder. Crystallization from a minimum amount of ethyl acetate gave white cottony needles, 1.76 g (70%), mp 159–160 °C. An additional crystallization from ethyl acetate afforded **7** with mp 160–161 °C (lit.[14] mp 161.5–162.5 °C): mass spectrum, *m/e* (%), 126 (100), 110 (M – oxygen, 23), 99 (M – HCN, 8), 83 (20); IR ($CHCl_3$) 1215 cm^{-1} (N–O); UV (CH_3OH) λ_{max} (log ε) 316 (3.68), 266 (3.88), 217 nm (4.12); NMR (Me_2SO-d_6) δ 8.66 (H-2, d, 1 H, $J_{2,4}$ = 2 Hz), 8.06 (H-4, d, 1 H, $J_{4,6}$ = 2.5 Hz), 8.45 (H-6, dd, 1 H), 3.88 (CH_3O, s, 3 H).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.78; H, 4.70; N, 21.94.

Reaction of 5-Methoxypyrimidine (6) with Peracetic Acid–Sulfuric Acid. To a stirred solution of 2.2 g (20 mmol) of **6** in 75 mL of water was added a mixture of 6.6 mL (40 mmol) of 40% peracetic acid and 1.1 mL (20 mmol) of 18 M sulfuric acid. The reaction mixture was stirred for 1 h at ambient temperature, and the pH was adjusted to 9 with 50% aqueous sodium hydroxide. To this solution was added solid sodium bisulfite until a negative test for peroxide (starch–iodine paper) was obtained. The reaction mixture was continuously extracted with chloroform for 48 h and the organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness in vacuo, affording 1.76 g of a white solid, TLC (silica gel/acetone) showed two distinct spots at R_f 0.2 (compound a) and R_f 0.4 (compound b). Chromatographic separation was achieved with a Waters Preparative 500 HPLC (silica gel/acetone), affording pure samples as described below.

5-Methoxy-4(3*H*)-pyrimidinone (8): mp 210–211 °C (from ethanol) (lit.[13] mp 210–211 °C); 42% yield; IR (KBr) 2901, 1718, 1665, 1606 cm^{-1}; UV (MeOH) λ_{max} (log ε) 236 (3.84), 268 nm (3.72); mass spectrum, *m/e* (%) 126 (M^+, 100), 97 (94); NMR (Me_2SO-d_6) δ 7.80 (H-2, s, 1 H), 7.53 (H-6, s, 1 H), 12.5 (NH, BrS, 1 H, exchangeable by D_2O), 3.76 (CH_3, s, 3 H); NMR (5% D_2SO_4–D_2O) δ 8.95 (H-2, d, 1 H, $J_{2,6}$ = 1.0 Hz), 7.73 (H-6, d, 1 H, $J_{2,6}$ = 1.0 Hz), 3.93 (CH_3, s, 3 H).

4(5)-Carbomethoxyimidazole (9): mp 153–154 °C (white cubes from ethylacetate) (lit.[15] mp 154–156 °C); [compound **9** was identical (IR, UV, MS, NMR, mixed mp) with an authentic sample prepared by the method of Jones[16]]; IR (KBr) 2843, 1717, 1518, 1446 cm^{-1}; UV (MeOH) λ_{max} (log ε) 232 nm (4.00); mass spectrum, *m/e* (%) 126 (88), 95 (100), 67 (53), 40 (100); NMR (Me_2SO-d_6) δ 7.73 (ring H's, s, 2 H), 3.60 (CH_3, s, 3 H); NMR (D_2O) δ 7.73 (ring H's, s, 2 H), 3.83 (CH_3, s, 3 H); NMR (5% D_2SO_4–D_2O) δ 8.81 (H-2, d, 1 H, $J_{2,6}$ = 1.0 Hz), 8.06 (H-5, d, 1 H, $J_{2,6}$ = 1.0 Hz), 4.0 (CH_3, s, 3 H).

X-ray Data of 9. The compound crystallizes as colorless cubes from ethylacetate: space group $P2_1/C$, four molecules in a unit

(14) Krueger, S. A.; Paudler, W. W. *J. Org. Chem.* **1972**, *37*, 4188.

(15) Onishchuk, A. E. *Zh. Obsch. Khim.* **1955**, *25*, 984; *Chem. Abstr.* **1956**, *50*, 3413a.

(16) Jones, R. *J. Am. Chem. Soc.* **1949**, *71*, 644.

cell, a = 3.8421 ± 0.001 Å, b = 15.542 ± 0.003 Å, c = 9.662 ± 0.002 Å, β = 95.32 ± 0.01°, calculated density for $C_5H_6N_2O_2$, M, 126.1, is 1.46 g cm^{-3}. The intensities of 871 reflections were measured on a four-angle diffractometer using monochromatic copper radiation. The structure was solved by direct methods (SHELXTL) and refined by the least-squares method to R = 0.047. See supplementary material for ORTEP drawing of the molecule (Figure 1), atomic coordinates, bond distances, and angles (Tables I–V).

4-Chloro-5-methoxypyrimidine (10). Compound **8** (120 mg, 0.95 mmol) was treated with phosphorus oxychloride according to the method of Chesterfield, McOmie, and Tute,[13] giving 100 mg (73%) of a crystalline solid (mp 60–61 °C). The crude solid was sublimed [80 °C (10 mm)], affording **10** as fine white needles: mp 60–62 °C (lit.[13] mp 63–64 °C); IR ($CHCl_3$) 3000, 1562, 1547, 1461, 1449, 1430, 1400 cm^{-1}; UV (ethanol) λ_{max} (log ϵ) 275 (3.69), 221 nm (3.81); mass spectrum, m/e (%) 144–146 (80), 109 (100); NMR ($CDCl_3$) δ 8.62 (H-2, s, 1 H), 8.33 (H-6, s, 1 H), 4.03 (CH_3, s, 3 H).

Anal. Calcd for $C_5H_5N_2ClO$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.74; H, 3.49; N, 19.25.

4(3*H*)-Pyrimidinone (12). Pyrimidine (**11**) (8.0 g, 0.1 mol) was treated according to the procedure described for the preparation of **3**. Continuous extraction of the aqueous phase (24 h) with chloroform afforded after drying and filtration of the organic phase 470 mg (4.7%) of **12** as a white powder. Repetition of this experiment using acetone as the solvent gave 900 mg (9.3%) of **12**. Crystallization from ethanol yielded fine needles, mp 163–164 °C (lit.[15] mp 163–164 °C). This material was identical in all respects with an authentic sample prepared from 2-thiouracil by using the method of Brown:[17] IR ($CHCl_3$) 1704, 1675 cm^{-1}; UV (ethanol) λ_{max} (log ϵ) 221 (3.91), 268 mn (3.56); mass spectrum, m/e (%) 96 (100), 68 (40); NMR (Me_2SO-d_6) δ 8.19 (H-2, s, 1 H), 7.91 (H-6, d, 1 H, $J_{5,6}$ = 6.7 Hz), 6.33 (H-5, dd, 1 H, $J_{2,5}$ = 0.6 Hz, $J_{5,6}$ = 6.7 Hz).

(17) Brown, D. J. *J. Chem. Soc. Ind.* **1950**, *69*, 356.

Treatment of 2 with Peracetic Acid–Sulfuric Acid. To a solution of **2** (300 mg, 1.7 mmol) in 15 mL of water at 25 °C was added a mixture of 0.74 mL (3.4 mmol) of 35% peracetic acid and 0.09 mL (1.7 mmol) of 18 M sulfuric acid. This mixture was stirred at ambient temperature for 1.5 h and treated as described in the preparation of **8** and **9**. TLC on the isolated product (205 mg, 68% recovery) showed only **2** and no trace of compound **3**.

Treatment of 7 with Peracetic Acid–Sulfuric Acid. A solution of **7** (315 mg, 2.5 mmol) in 10 mL of water, 1.0 mL (6.0 mmol) of 40% peracetic acid, and 0.14 mL (2.5 mmol) of 18 M sulfuric acid was allowed to stir at ambient temperature for 4 days. The solution was treated as described in the preparation of **8** and **9**, affording a white solid (180 mg, 90% recovery), which by TLC showed only **7** and no trace of **8** or **9**.

Treatment of 8 with Peracetic Acid–Sulfuric Acid. A solution of **8** (70 mg, 0.55 mmol), 1.0 mL of D_2O, 0.03 mL (0.55 mmol) of sulfuric acid, and 0.22 mL (1.32 mmol) of 40% peracetic acid was placed in an NMR tube at 25 °C. The original spectrum of **8** (see experimental above) remained unchanged after 24 h. Another NMR sample of **8** prepared as described above showed no change after standing for 5 h at 48 °C.

Acknowledgment. I am indebted to Dr. Noel Jones and John Swartzendruber of Eli Lilly and Co. for determining the X-ray crystal structure of compound **9** and to Dr. R. D. G. Cooper for an authentic sample of this substance. I thank Dr. D. W. Balogh for reading the manuscript and Professor E. C. Taylor for many stimulating conversations.

Registry No. **1**, 4595-59-9; **2**, 36529-69-8; **3**, 19808-30-1; **3**·$^1/_2H_2SO_4$, 97234-97-4; **6**, 31458-33-0; **7**, 36529-70-1; **8**, 695-87-4; **9**, 17325-26-7; **10**, 695-85-2; **11**, 289-95-2; **12**, 4562-27-0.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, and bond angles and structure for **9** (6 pages). Ordering information is given on any current masthead page.

Preparation of Oxazoline *N*-Oxides and Imidate *N*-Oxides by Amide Acetal Condensation and Their [3 + 2] Cycloaddition Reactions

Stephen P. Ashburn and Robert M. Coates*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received January 21, 1985

2,4,4-Trimethyloxazoline *N*-oxide (**3a**), 4,4-dimethyl-2-phenyloxazoline *N*-oxide (**3b**), and ethyl *N*-methylbenzimidate *N*-oxide (**4**) have been prepared by condensation of 2-(hydroxyamino)-2-methyl-1-propanol hydrochloride (**1**) with acetamide or benzamide acetals (**2a** or **2b**). ^{13}C NMR and UV spectral data are reported for **3a,b**, as well as the related pyrroline *N*-oxides (**5a,b**) and oxazolines (**6a,b**). [3 + 2] Cycloaddition reactions of **3a**, **3b**, **4**, and **5b** with phenyl isocyanate, dimethyl acetylenedicarboxylate, and methyl phenylpropiolate were carried out. Similar reactions of **3b** with the acetylenic dipolarophiles in the presence of dimethylamine hydrochloride afforded isoxazoles **11a,b**. A mechanism involving protonation of a zwitterionic intermediate, electrocyclic ring closure, and fragmentative elimination of isobutylene oxide is proposed to explain the formation of the isoxazoles. Rate constants for the cycloaddition reactions of nitrones **3b** and **5b** with phenyl isocyanate and dimethyl acetylenedicarboxylate were determined by NMR. These data indicate that the nitrone **3b** is approximately 76 000 times more reactive than **5b** toward phenyl isocyanate and 70 times more reactive than **5b** toward dimethyl acetylenedicarboxylate.

Oxazoline *N*-oxides **3** are endocyclic nitrones at the carboxylic oxidation state. These heterocyclic compounds have been generated in solution by rearrangement of oxaziridines,[1] by thermal dissociation of a dimer,[1b] and by cyclocondensation of hydroxylamino alcohol **1** with ortho esters.[2] The ready availability and high reactivity of amide acetals[3] suggested that these activated carboxyl derivatives might also be suitable substrates for preparation of oxa-

(1) (a) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1976**, *41*, 3237–3241. (b) Hendrickson, J. B.; Pearson, D. A. *Tetrahedron Lett.* **1983**, *24*, 4657–4660.

(2) Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1984**, *49*, 3127–3133.

(3) (a) Feugeas, C.; Olschwang, D. *Bull. Soc. Chim. Fr.* **1968**, 4985–4990. (b) Feugeas, C.; Olschwang, D.; Chatzopoulos, M. *C. R. Acad. Seances, Ser. C.* **1967**, *265*, 113–116. (c) Salomon, R. G.; Raychaudhuri, S. R. *J. Org. Chem.* **1984**, *49*, 3659–3660. (d) Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1–39. (e) DeWolfe, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970; pp 420–506.

0022-3263/85/1950-3076$01.50/0