

Figure 3

aromatic proton at positive five with a down field shift for the amino hydrogens between the chlorine and the *N*-oxide relative to the monochloro derivative.

In view of the rather unusual chlorination reaction which accompanied the oxidation in acetic acid, it was felt that a closer investigation of the reactions in both media was required. The starting material, **1**, was oxidized as before in both acetic and trifluoroacetic acids, the respective peracids being formed *in situ* by the addition of 90% hydrogen peroxide to the pure aliphatic acids. The reaction mixtures were then followed by paper chromatography over a period of several days.

The oxidation in trifluoroacetic acid was not particularly informative. After twenty-four hours all starting material had reacted leaving three uv absorbing products, two of which could be identified as the monochloro *N*-oxide (**2**) and the dichloro *N*-oxide (**3**). The third spot, which could not be identified, was presumed to be a secondary oxidation product of **2**.

In the weaker oxidizing media of the peroxyacetic acid, there was no complicating secondary oxidation product with which to contend. In addition, the reactions which did occur were slow enough to be followed by the technique used. Compound **2** showed a maximum at 3 days and steady decrease to 14 days, similarly for **6**. Compound **3** appeared on the third day, and steadily increased thereafter while **1** could no longer be detected on the fourth day. Apparently, **1** is being oxidized to **2**, then either **1** or **2** or both are being attacked to give an active chlorine (9). This active chlorine preferentially chlorinates **1** to give **6**, since the appearance of **3** from the chlorination of **2** does not occur for three days. The three competing reactions of oxidation, chlorination, and ring opening (10) consume **1** after two days. The 5-chloro compound, so produced during three days, is then slowly oxidized to **3** over the remaining period. The remaining monochloro *N*-oxide **2**, produced from **1**, is slowly chlorinated to give **3** by the active chlorine generated from ring

opened **1** or by attack of the peroxyacid on **2**. After 14 days, the only detectable product is the dichloro *N*-oxide (**3**).

That the two compounds **2** and **6** could produce **3** under the reaction conditions examined was verified by a series of reactions shown in Figure 3. Thus, **6** was oxidized by peroxytrifluoroacetic and peroxyacetic acids to the corresponding **3**, while **2** was found to give **3** in the presence of chlorine, peroxytrifluoroacetic or peroxyacetic acids. The starting material **1** was also shown to give **6** in the presence of chlorine (11).

Finally, it was noted that if **2** is allowed to react with either peroxyacetic or peroxytrifluoroacetic acids, some of it will decompose liberating an active chlorine which chlorinates **2** to form **3**. During the decomposition the only uv absorbing substances present are **2** and **3** and a symmetrical triazine (10). Once **2** is converted to **3**, however, it appears to be stable in either media even at temperature as high as 40-50°. The most probable explanation of this is that ring opening is initiated by an electrophilic attack by the peroxyacid at the open five position, which, in the dichloro compound, is blocked by the chlorine atom. Other examples of this are known such as the oxidation of 5-nitro-2,4,6-triaminopyrimidine which gives little or no ring opened products, while 2,4,6-triaminopyrimidine gives only a rearranged product (10).

EXPERIMENTAL.

Infrared spectra were obtained on a Perkin Elmer Model 700 as potassium bromide discs. Ultraviolet spectra were recorded on a Cary Model 14. Mass spectra were obtained on an AEI MS-12 low resolution mass spectrometer. The nmr spectra were obtained using a Varian T-60 nuclear magnetic resonance spectrometer, with TMS as the internal standard. Elemental analyses were carried out by the Galbraith Laboratories, Knoxville, Tennessee. Paper chromatography employed Whatman No. 1 paper and the following solvent systems: A, 3% aqueous ammonium chloride; and B, 1-butanol (4): acetic acid (1): water (1). The chromatograms were developed using the ascending technique.

6-Chloro-2,4-diaminopyrimidine 3-*N*-Oxide (**2**).

A solution of hydrogen peroxide (90%, 2 g.) in trifluoroacetic acid (100 ml.) was added dropwise through the top of a condenser to a stirred solution of **1** (10 g.) in trifluoroacetic acid (50 ml.) at 0°.

After the reaction mixture was allowed to warm to room temperature and kept for several days, 10 ml. of water was added and the reaction mixture evaporated in a shallow dish to 20% its original volume. The white trifluoroacetic acid salt of **2** precipitated from the solution, was filtered and neutralized as a slurry in 50 ml. of water. The white solid remaining was filtered, washed with 20 ml. of cold water and dried at 85° *in vacuo* overnight (7.2 g., 65% yield). An analytical sample was prepared by three recrystallizations from ethyl alcohol; m.p. 190° dec. R_f values are 0.63 (solvent A) and 0.73 (solvent B). Nmr (DMSO- d_6): 365 Hz (1, CH); 451 Hz (4, NH₂); uv in λ max (ϵ): pH 1 = 293 (12,000),

228 (8,600); $\text{pH } 7 = 290$ (5,800), 218 (31,000); $\text{pH } 11 = 292$ (5,700), 228 (32,000).

Anal. Calcd. for $\text{C}_4\text{H}_5\text{ClN}_4\text{O}$: C, 29.93; H, 3.11; N, 34.90. Found: C, 29.92; H, 3.17; N, 34.67.

2,4-Diamino-5,6-dichloropyrimidine 3-*N*-Oxide (**3**).

(a) To a solution of 3 g. of **1** dissolved in 50 ml. of glacial acetic acid was added 2.5 g. of 90% hydrogen peroxide. The reaction was allowed to stir for 14 days, during which time a large quantity of solid (1.3 g.) precipitated. The reaction mixture was stirred another day with Pd/C (in order to destroy excess peroxides), filtered and the filtrate allowed to evaporate to dryness. Neutralization of the filtrate residue as an aqueous slurry gave 0.8 g. (40% yield based on half of **1** being used as the source of chlorine) of **3**. An analytical sample was prepared by one recrystallization from water and three recrystallizations from ethyl alcohol; m.p. 185° dec. R_f values are 0.54 (solvent A) and 0.80 (solvent B). Nmr (DMSO- d_6): 458 Hz (2, NH_2); 474 Hz, (2, NH_2); uv in λ max (ϵ): $\text{pH } 1 = 310$ (10,000), 237 (9,500) $\text{pH } 7 = 303$ (6,100), 231 (28,000); $\text{pH } 11 = 303$ (5,900), 231 (28,000).

Anal. Calcd. for $\text{C}_4\text{H}_4\text{Cl}_2\text{N}_4\text{O}$: C, 24.64; H, 2.06; N, 28.74. Found: C, 24.73; H, 2.02; N, 28.89.

(b) Using a method similar to that for the preparation of **6**, 6-chloro-2,4-diaminopyrimidine 3-*N*-oxide (500 mg.) was dissolved in 9 ml. of dilute hydrochloric acid and treated with a rapid stream of chlorine for several minutes. The solution was then neutralized, filtered, and the precipitate recrystallized from ethyl alcohol (42% yield).

(c) A solution of 2,4-diamino-5,6-dichloropyrimidine (**6**) (1 g.) (11) in trifluoroacetic acid (25 ml.) was kept at 0° , and 90% hydrogen peroxide (0.5 g.) was added. After stirring overnight, the reaction mixture was worked up in a manner similar to that for the preparation of **2** in (a). The product was obtained in 80% yield after one recrystallization from ethanol.

Compounds from (a) to (c) had identical ir and R_f values (Solvents A and B). Chromatographic evidence was also obtained for a similar oxidation of **6** to its aromatic *N*-oxide using acetic acid over a period of several days.

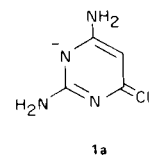
Chromatographic Conditions for Analysis of Oxidation Reactions.

About 200 mg. of **1**, recrystallized from water and dried, was placed in each of two small test tubes, one containing 5 ml. of trifluoroacetic acid and the other enough acetic acid for solution. After the compound had dissolved, two drops of 90% hydrogen peroxide was added to each. The solutions were mixed by shaking and an aliquot from each spotted on duplicate sheets of Whatman No. 1 filter paper. Over a period of several days similar

aliquots were spotted and the time noted. At the end of fourteen days the four papers, two for each reaction condition, were eluted in the Solvent A and B.

REFERENCES

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- (2) Taken from the thesis of D. L. V. submitted to the Department of Chemistry in partial fulfillment of the M. S. degree.
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- (5) In order to distinguish between structures **2** and **4**, we had to rely on results in other series and nmr data. Scheinfeld *et al.* (6) state that in the purine ring amino and methyl groups appear to provide strong activation for *N*-oxidation at the adjacent position. Chloro and methoxy groups, on the other hand, tend to deactivate the adjacent nitrogen by inductive electron withdrawal but provide activation elsewhere in the ring by resonance. In our system resonance formula, **1a** would be the chief contributor to this result.



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- (10) See T. J. Delia and D. L. Venton, *J. Heterocyclic Chem.*, **7**, 1183 (1970) for a discussion of ring opening and rearrangements occurring during the course of this reaction.
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