

Pyrimidine *N*-Oxides. Oxidation of 5-Nitroso-2,4,6-triaminopyrimidine (1).

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The peroxytrifluoroacetic acid oxidation of 5-nitroso-2,4,6-triaminopyrimidine (**1b**) led to the formation of two products: 5-nitro-2,4,6-triaminopyrimidine 1-*N*-oxide (**2**) and 5-nitro-2,4,6-triaminopyrimidine 1,3-di-*N*-oxide (**3**). On the basis of previous experience **2** was the sole expected oxidation product. However, **3** represents a rather unexpected development in that di-*N*-oxides in the pyrimidine series are uncommon. The yields are good for both products and structures are assigned on the basis of elemental analysis, mass spectral data, and chemical reactions. The reaction sequence is also discussed.

Our initial interest in the direct oxidation of pyrimidines to give *N*-oxide derivatives was based on the fact that no such compounds bearing either hydroxy or amino functions had been prepared. Recently, the oxidation of cytosine and cytidine was accomplished (3,4). Because of the continuing interest in purine *N*-oxides as oncogenic agents (5) we decided to pursue the approaches to pyrimidine *N*-oxides which could be cyclized to purine *N*-oxides. For our study we chose to start with 2,4,6-triaminopyrimidine (**1a**), since oxidation of this system would lead to only one isomer. Furthermore, on ring closure to a purine only two isomers would be possible and one of these is already known (6).

Although the oxidation of **1a** gave only degradation products (presumably through electrophilic attack at position 5) we adopted the method of Taylor (7) for the oxidation of 5-nitrosopyrimidines to 5-nitropyrimidines. Taylor reported the peroxytrifluoroacetic acid oxidation of a number of amino- and hydroxy-substituted 5-nitrosopyrimidines but not the oxidation of 5-nitroso-2,4,6-triaminopyrimidine (**1b**). O'Brien and co-workers (8) applied the same oxidizing conditions to 2,4-diamino-5-nitroso-6-(*p*-bromoanilino)-pyrimidine and reported the formation of an *N*-oxide as well as the oxidation of the nitroso group.

The action of hydrogen peroxide in trifluoroacetic acid on **1b** gave the desired 5-nitro-2,4,6-triaminopyrimidine 1-*N*-oxide (**2**) as well as 5-nitro-2,4,6-triaminopyrimidine 1,3-di-*N*-oxide (**3**).

Compound **2** was identified by means of elemental analysis, ultraviolet spectrum, positive ferric chloride test (for *N*-oxides (9)) and reduction products. Treatment of **2** with sodium dithionite gave **5**, whereas reduction with palladium on carbon in hydrogen atmosphere gave **4**. An

interesting development here is that if the catalytic reduction is carried out in 90% formic acid rather than in water compound **6** is obtained. The structure of compound **6** (5-hydroxymethylamino-2,4,6-triaminopyrimidine 1-*N*-oxide) was assigned on the basis of elemental analysis and infrared spectral data. The lack of a carbonyl absorption and the presence of hydroxy absorption coupled with the absence of reactions associated with the formyl group suggested the reduced structure. This result can be explained by considering the reduction of **2** to **4** followed by formylation of the amino group and, while still in the reducing medium, subsequent reduction of the formamido group. Formyl groups in the 5-position of pyrimidines are easily reduced under similar conditions (10).

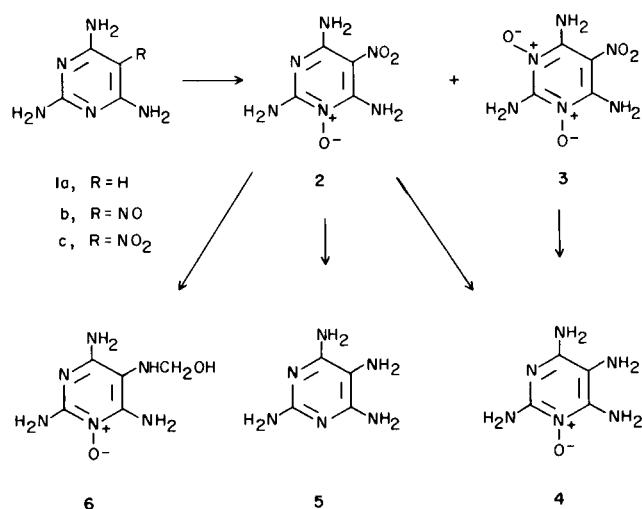


TABLE I

Compound	Ultraviolet Data		Elemental Analysis		R _f Solvent Systems	
	λ MAX ($\epsilon \times 10^{-4}$)	pH	Calcd.	Found	A	B
2	325 (1.41)	1-2	C, 25.78	25.48	0.39	0.47
	218 (1.84)		H, 3.23	3.32		
	327 (1.24)	6-7	N, 45.13	45.21		
	203 (2.45)					
	330 (1.15)	10-11				
3	334 (1.01)	1-2	C, 23.79	23.73	0.18	0.70
	224 (1.76)		H, 2.97	3.20		
	207 (1.90)		N, 41.58	41.40		
	339 (1.20)	6-7				
	259 (0.99)					
	227 (1.60)					
	207 (2.06)					
4	unstable	10-11			0.11	-
	275 (0.74)	1-2	-	-		
	283 (0.61)	6-7				
	216 (1.66)					
6-0.5 H₂SO₄	290 (0.51)	10-11			0.20	0.70
	271 (0.96)	1-2	C, 25.53	25.51		
	212 (2.11)		H, 4.68	4.80		
	273 (0.42)	6-7	N, 35.74	35.72		
	222 (2.30)					
	273 (0.45)	10-11				

The structure of compound **3** is assigned on the basis of the following observations: elemental analysis, ultraviolet spectrum, positive ferric chloride test (for *N*-oxides), reduction products and mass spectral data. Palladium on carbon in hydrogen atmosphere will also reduce **3** to **4**. The *N*-oxide function facilitates this reaction as shown by the polarographic reduction of **2**. In a comparison of the reduction of the nitro group in **1c** and **2**, it was found that only the nitro group was reduced and at a lower potential in **2** than in **1c**.

The mass spectrum of **3** shows a parent ion peak at 202 and significant peaks at 186 and 170. Each of these latter values represents a decrease of 16 molecular weight units which may be attributed to loss of oxygen. The physical data for **2,3,4**, and **6** are found in Table I.

We were rather surprised at the high yields obtained for **3** in view of the scarcity of di-*N*-oxide derivatives reported. Ochiai gives the general view regarding di-*N*-oxides: "... simultaneous formation of mono- and di-*N*-oxides has been shown to occur in pyrazine and benzopyrazine series (i.e., quinoxaline and phenazine) and only monoxide

has been obtained in other series" (11). One explanation of our results may rest in the fact that both ring nitrogens can be found between amino groups which, in oxidation reactions, are known to be very good electron donors. In such a situation each nitrogen can be treated separately and should be less susceptible to other electronic influences. Even though the first *N*-oxide formed is electron-withdrawing the rather strong oxidizing power (12) of peroxytrifluoroacetic acid is sufficient to attack the second ring nitrogen fairly easily. Comparable reaction conditions employing hydrogen peroxide in glacial acetic acid do not affect **1b** while the peroxide in 90% formic acid converts **1b** to **1c**. We are currently examining the relative strengths of these peroxyacids.

We have examined the course of the reaction using paper chromatography. By following the disappearance and appearance of the various products on paper, we find that the reaction proceeds as follows: **1b** → **1c** → **2** → **3** (13). We have confirmed this sequence by subjecting the nitro compound, **1c**, to the same conditions and obtained both **2** and **3**. However, the amount of hydrogen peroxide added is important. If only two equivalents of peroxide

are added to **1b** the reaction stops primarily at the mono-*N*-oxide stage. Excess peroxide leads to the formation of the di-*N*-oxide in good yield. The two steps take place simultaneously but, depending on conditions, a predominance of either **2** or **3** can be obtained. With a large excess of hydrogen peroxide the reaction is completed in several hours.

The observations of O'Brien and co-workers (8) of *N*-oxide formation (position unspecified) of an unsymmetrical triamino derivative and our own data prompts us to investigate further the scope of the reaction. The formation of mono- and di-*N*-oxides in such good yields offers the promise of general methods for the synthesis of purine and pteridine *N*-oxides bearing the oxide in the pyrimidine ring.

EXPERIMENTAL

Infrared spectra were obtained on a Beckmann Model IR-12 as KBr discs. Ultraviolet spectra were recorded on a Cary Model 14. Mass spectra were obtained on an AEI MS-12 low resolution mass spectrometer. Elemental Analyses were carried out by the Galbraith Laboratories, Knoxville, Tennessee. Paper Chromatography employed Whatman No. 1 paper and the following solvent systems: A, 1-butanol (4); acetic acid (1); water (1); and B, 3% ammonium chloride.

Oxidation of 5-Nitroso-2,4,6-triaminopyrimidine (**1b**).

Aqueous 30% hydrogen peroxide (24 ml.) was added dropwise over a period of two hours to a stirred, dark red solution of **1b** (12.0 g.; 0.078 mole) in 120 ml. trifluoroacetic acid while maintaining the temperature below 35°. After stirring overnight at room temperature, 2.06 g. of **2** was collected by filtration of the reaction mixture. An additional 2.00 g. was obtained after cooling the filtrate. Purification was effected by recrystallization from water. The yield was 28%.

Addition of 150 ml. water to the filtrate from above caused the precipitation of 7.59 g. of **3** (48%). This could also be purified by recrystallization from water.

Oxidation of 5-Nitro-2,4,6-triaminopyrimidine (**1c**).

The procedure is the same as above but higher yields of **3** are obtained here.

Reduction of 5-Nitro-2,4,6-triaminopyrimidine 1-*N*-oxide (**2**). Method A.

A suspension of 5.63 g. (0.030 mole) of **2** in 50 ml. water was treated with 2.5 g. of 5% palladium on carbon under hydrogen atmosphere in a Parr apparatus. After three equivalents of hydrogen were absorbed (ca. 3.5 hours) the catalyst was removed by filtration and 2*N* sulfuric acid added to yield **4** as the sulfate.

Method B.

A solution of 6.26 g. (0.033 mole) of **2** in 120 ml. of 90% formic acid was treated with 3.00 g. of 5% palladium on carbon in

the same manner as above. Removal of the catalyst and the solvent left a white solid. This was converted to the sulfate by treating with 2*N* sulfuric acid. A yield of 3.78 g. (49%) of **6** was obtained. This substance gave a purple color with ferric chloride. Compound **3** can also be converted to **6** under the same conditions.

Method C.

A solution of 0.93 g. (0.005 mole) of **2** in 40 ml. boiling water was treated with sodium hydrosulfite according to the method of O'Brien (8). The product obtained was compared to the reduction product from **1c** and assigned the structure **5** on the basis of ultraviolet spectra.

Method D.

The polarographic reduction of **2** was carried out according to the procedure of McGinn and Brown (14). 5-Nitro-2,4,6-triaminopyrimidine (**1c**) was studied in parallel. Solutions were made up in the concentration range 1.25×10^{-4} to 6.25×10^{-5} and determinations were made in the pH range 1.4-10.7. In nearly every case the reduction potential for **2** was lower than that for **1c**. The only exception was at pH 7.3 and it is not known whether this reversal is significant.

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