Δ^2-Cyclohexenol.—This material was prepared as described for the preparation of Δ^2-cyclopentenol. The ester was obtained in 84% yield. The rotation of the cyclohexenol was $[\alpha]^{24}D$ −10.1° (*c* 5.54, $CHCl_3$). The phenylurethan had m.p. 107–108° (lit.[13] m.p. 107°), $[\alpha]^{26}D$ −13.4° (*c* 8.9, $CHCl_3$). The 3,5-dinitrobenzoate was prepared, m.p. 123–124°, $[\alpha]^{25}D$ −13.7° (*c* 5.24, $CHCl_3$).

Δ^2-Cyclooctenol.—A similar procedure was used except that the temperature was maintained at 65°. Under these conditions one week was required to complete the reaction. The ester was obtained in 36% yield. The alcohol had $[\alpha]^{26}D$ +5.85° (*c* 5.3, $CHCl_3$). The phenylurethan had m.p. 91–92° (lit.[14] m.p. 92.5–93°), $[\alpha]^{26}D$ +13.5° (*c* 3.02, $CHCl_3$).

Bicyclo[3.2.1]octen-2-ol-4.—Reaction of bicyclo[3.2.1]octene-2[15] according to the standard procedure afforded 90% of the ester. The *p*-nitrobenzoate of the alcohol had, m.p. 83–85° (lit.[16] m.p. 84–85°) $[\alpha]^{25}D$ −5.21° (*c* 11.8, $CHCl_3$). In another experiment the alcohol was oxidized with manganese dioxide to bicyclo[3.2.1]octen-2-one-4, b.p. 85° (35 mm.), $[\alpha]^{29}D$ −8.54° (*c* 9.6, $CHCl_3$). The 2,4-dinitrophenylhydrazone had m.p. 139–140° (lit.[17] m.p. 140.5–141.5°).

Δ^2-Cyclohexenol.—A solution of cupric di-O-acetyltartarate half-methyl ester, 24.0 g. (0.043 mole) in 700 ml. of warm benzene was heated to 50° and 150 ml. of cyclohexene was added, followed by the dropwise addition of 12.0 g. (0.133 mole) of *t*-butyl hydroperoxide in 75 ml. of benzene. The mixture was allowed to react at 50° for 16 hr. and then extracted with two 100-ml. portions of 5% sodium bicarbonate solution and two 100-ml. portions of water. The solution was dried over magnesium sulfate and concentrated to give 19.9 g. (61%) of crude ester. The ester was dissolved in 75 ml. of ether and added dropwise to a stirred suspension of 9.1 g. (0.23 mole) of lithium aluminum hydride in 250 ml. of ether. After stirring for 12 hr. the excess lithium aluminum hydride was decomposed with water, the mixture was filtered, and the ether was dried over sodium sulfate and evaporated. The residue was distilled to give 4.12 g. (72%) of Δ^2-cyclohexenol, b.p. 79–80° (28 mm.), $[\alpha]^{24}D$ +10.1° (*c* 7.26, $CHCl_3$). A portion of the alcohol was converted to the phenylurethan, m.p. 108–109°, $[\alpha]^{26}D$ +15.9° (*c* 2.69, $CHCl_3$).

(13) R. Willstatter and E. Sonnenfeld, *Ber.*, **46**, 2957 (1913).
(14) A. C. Cope, M. R. Kinter, and R. T. Keller, *J. Am. Chem. Soc.*, **76**, 2757 (1954).
(15) K. Alder, *Ber.*, **88**, 144 (1955).
(16) H. Goering and V. Mayer, *J. Am. Chem. Soc.*, **86**, 3754 (1964).
(17) H. Goering, R. Greiner, and M. Sloan, *ibid.*, **83**, 1391 (1961).

A New Synthesis of 5-Nitropyrimidines[1]

EDWARD C. TAYLOR AND ALEXANDER MCKILLOP

Department of Chemistry, Princeton University, Princeton, New Jersey

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A general procedure for the oxidation of 5-nitroso- to 5-nitropyrimidines with 30% hydrogen peroxide in trifluoroacetic acid is described.

To date more than 125 publications have dealt with the synthesis and use, as intermediates, of 5-nitropyrimidines.[2] The nitro group in the 5-position of a pyrimidine ring activates a 6-substituent toward nucleophilic displacement reactions, aldol-type condensations, or oxidation, and, upon reduction, conversion occurs to a 5-aminopyrimidine, a versatile intermediate for the synthesis of purines, pteridines, and other condensed pyrimidine heterocycles.[3] Furthermore, deoxygenation by the use of triethyl phosphite of 5-nitropyrimidines has afforded pyrrolopyrimidines by the generation of nitrene intermediates which insert into appropriate *ortho* substituents.[4] Novel condensed pyrimidines are also available through direct intramolecular interaction of the 5-nitro group with an adjacent guanidino substituent.[5]

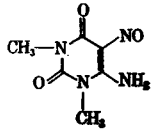
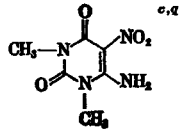
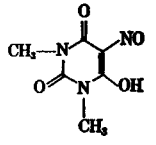
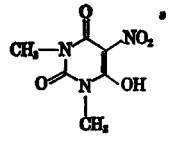
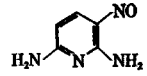
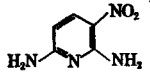
These 5-nitropyrimidine intermediates have invariably been prepared either by nitration of a 5-unsubstituted pyrimidine[2] or by direct synthesis utilizing a nitro-substituted alicyclic moiety, such as nitroacetonitrile.[6] The former procedure is the more versatile of the two, but employs, of necessity, such vigorous acidic and oxidative conditions that sensitive groupings are often altered, either by oxidation or by hydrolysis. Typical examples are the hydrolytic desulfurization observed with nitric acid and 2-mercaptopyrimidines,[7] and the oxidation of aliphatic side chains to carboxylic acids.[8] Furthermore, aryl substituents can also undergo nitration,[8] and the procedure is thus inapplicable to systems where there is more than one possible site for nitration. The direct synthesis of 5-nitropyrimidines by ring-closure reactions is severely limited in scope because of the inaccessibility of a sufficient variety of nitro-containing acyclic precursors.

Among the most readily accessible of all 5-substituted pyrimidines are the 5-nitroso derivatives, of which a remarkable variety has been described.[2,9] We wish to report in this paper a facile, generally applicable method for the oxidation of 5-nitrosopyrimidines to 5-nitropyrimidines which mitigates or eliminates most of the disadvantages accompanying the previously employed procedures for the preparation of 5-nitropyrimidines.

We have found that a wide variety of 5-nitrosopyrimidines are oxidized directly and in high yield to 5-nitropyrimidines by treatment of a trifluoroacetic acid solution of the nitrosopyrimidine with 30% hydrogen peroxide at room temperature. The initial intensely colored solution rapidly fades to yellow, at which time the reaction is judged complete. The 5-nitropyrimidine is isolated either by filtration or by dilution of the pertrifluoroacetic acid solution with water. Typical conversions, reaction times required, and yields are summarized in Table I.

(1) This work was supported by a grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Pa.
(2) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962.
(3) For discussions and references, see (a) "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., Pergamon Press Ltd., Oxford, 1964; (b) "The Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., J. and A. Churchill Ltd., London, 1957; (c) "The Chemistry and Biology of Pteridines," G. E. W. Wolstenholme and M. P. Cameron, Ed., J. and A. Churchill Ltd., London, 1954.
(4) E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, **30**, 655 (1965).
(5) J. A. Carbon, *ibid.*, **26**, 455 (1961).
(6) (a) See ref. 2, p. 139 ff; (b) G. Simchen, *Angew. Chem.*, **76**, 860 (1964).
(7) See ref. 2, p. 281.
(8) See ref. 2, p. 141.
(9) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

TABLE I

No.	Starting material			Product			Yield, %[a]	M.p., °C.	Physical form	Formula	Calcd., %			Found, %		
	R	R_1	R_2	R	R_1	R_2					C	H	N	C	H	N
1[b]	Ph	NH_2	NH_2	Ph	NH_2	NH_2[c]	87	269–270	Pale yellow powder	$C_{10}H_9N_5O_2$	51.94	3.92	30.29	51.82	3.96	30.29
2[b]	CH_3	NH_2	NH_2	CH_3	NH_2	NH_2[d]	85	>360	Colorless powder	$C_5H_7N_5O_2$						
3[e]	OH	OH	NH_2	OH	OH	NH_2[f]	97	>360	Pale yellow needles	$C_4H_4N_4O_4$						
4[g]	NH_2	NH_2	OH	NH_2	NH_2	OH[g]	91	>360	Colorless needles	$C_4H_5N_5O_3$	28.07	2.95	40.93	27.36[h]	3.05	41.20
5[b]	OH	NH_2	NH_2	OH	NH_2	NH_2[c]	85	>360	Pale yellow powder	$C_4H_5N_5O_3$	28.07	2.95	40.93	28.07	3.05	41.02
6[i]	CH_3	OH	NH_2	CH_3	OH	NH_2[j]	82	>360	Colorless powder	$C_5H_6N_4O_3$	35.30	3.55	32.93	35.06	3.58	32.67
7[k]	NH_2	NHC_2H_5	OH	NH_2	NHC_2H_5	OH[c]	96	342–344 dec.	Colorless needles	$C_6H_9N_5O_3$	36.18	4.55	35.17	36.22	4.69	35.12
8[l]	$NHCH_3$	NH_2	OH	$NHCH_3$	NH_2	OH[c]	91	350–352 dec.	Pale yellow powder	$C_5H_7N_5O_3 \cdot 0.25H_2O$	31.66	3.70	36.94	31.70	3.85	36.99
9[m]	$N(CH_3)_2$	NH_2	OH	$N(CH_3)_2$	NH_2	OH[e]	81	305–306 dec.	Pale yellow needles	$C_6H_9N_5O_3$	36.18	4.55	35.19	36.40	4.84	34.99
10[n]	SH	NH_2	NH_2	OH	NH_2	NH_2[c]	92	>360								
11[o]	SH	OH	NH_2	OH	OH	NH_2[f]	66	>360								
12[b]	SCH_3	NH_2	NH_2	OH	NH_2	NH_2[c]	84	>360								
13[b]	H	NH_2	NH_2	OH	NH_2	NH_2[c]	60	>360								
14[p]				 [c,q]			92	232–235	Colorless needles	$C_6H_8N_4O_4 \cdot H_2O$	33.03	4.62	25.68	33.39	4.49	25.78
15[r]				 [s]			97	145–147	Pale yellow needles	$C_6H_7N_3O_5$						
16[t]				 [u]			96	234–236	Yellow needles	$C_5H_6N_4O_2$	38.96	3.92	36.25	38.77	4.15	36.09

[a] Although yields in almost all instances reported were highly satisfactory, no effort was made to determine optimum conditions. [b] Ref. 9. [c] New compound. [d] Identified by comparison (infrared) with an authentic sample prepared from 2-methyl-4,6-dihydroxy-5-nitropyrimidine by chlorination to 2-methyl-4,6-dichloro-5-nitropyrimidine, followed by amination with ammonia in methanol: J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944). [e] W. Traube, *Chem. Ber.*, **33**, 1371 (1900). [f] Identified by comparison (infrared) with an authentic sample prepared by direct nitration of 6-aminouracil: P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951). [g] P. D. Landauer and H. N. Rydon, *J. Chem. Soc.*, 3721 (1953). [h] A satisfactory carbon analysis could not be obtained. Microanalytical difficulties of this kind are often encountered with very high-melting nitrogen-containing heterocycles. [i] W. Traube, F. Schottländer, C. Goslich, R. Peter, F. A. Meyer, H. Schlüter, W. Steinbach, and K. Bredow, *Ann.*, **432**, 266 (1923). [j] R. S. Karlinskaya, N. V. Khromov-Borisov, and V. A. Ivanova, *Zh. Obshch. Khim.*, **34**, 3734 (1964). [k] H. S. Forrest, R. Hull, H. J. Rodda, and A. R. Todd, *J. Chem. Soc.*, 3 (1951). [l] S. Yamada, I. Chibata, and D. Kiguchi, *Tanabe Seiyaku Kenkyu Nempo*, **2**, 13 (1957); *Chem. Abstr.*, **52**, 1177*c* (1958). [m] B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2866 (1951). [n] A. Bendich, J. F. Tinker, and G. B. Brown, *ibid.*, **70**, 3109 (1948). [o] Y. Mizuno, T. Ueda, M. Kobayashi, Y. Shimizu, and T. Murakami, *Yakugaku Zasshi*, **77**, 686 (1957); *Chem. Abstr.*, **51**, 16494*b* (1957). [p] F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2798 (1954). [q] Prepared independently in 60–80% yield by nitration of 1,3-dimethyl-6-aminouracil. This nitration has not previously been reported (see Experimental). [r] F. F. Blicke and R. L. Schaaf, *J. Am. Chem. Soc.*, **78**, 5857 (1956). [s] Identified by comparison (infrared) with an authentic sample prepared by hydrolysis of 1,3-dimethyl-5-nitro-6-chloropyrimidine: T. K. Liao and C. C. Cheng, *J. Heterocyclic Chem.*, **1**, 212 (1964). [t] Ref. 19; these authors also report the oxidation of 2,6-diamino-3-nitrosopyridine with hydrogen peroxide in ammonium hydroxide to 2,6-diamino-3-nitropyridine in unspecified yield. [u] This compound has been reported previously [German Patent 628,605 (April 7, 1936); *Chem. Abstr.*, **30**, 6137 (1936)]; however, its method of preparation was not indicated and no physical properties were reported; see also footnote *t*. [v] Ref. 5.

It will be noted that the 2-mercapto-5-nitrosopyrimidines **10** and **11**, and the 2-methylmercapto-5-nitrosopyrimidine **12** (see Table I) were converted to the corresponding 2-hydroxypyrimidines under these conditions. Such oxidative hydrolytic desulfurization has been encountered previously[7,10] in the reactions of 2-mercaptopyrimidines with hydrogen peroxide and alkali and, in the present instance, can serve as a distinct synthetic advantage, since the 2-mercaptopyrimidines are more readily accessible intermediates than the corresponding 2-hydroxypyrimidines. Furthermore, it will be noted that the action of pertrifluoroacetic acid on 4,6-diamino-5-nitrosopyrimidine (**13**) yielded the corresponding 2-hydroxy derivative by direct hydroxylation. This reaction is reminiscent of the conversion of pteridine to 4-hydroxypteridine by peracetic acid[11]; C-hydroxylation of nitrogen-containing heterocycles by peracids is not uncommon.[12]

An almost quantitative conversion of 2,6-diamino-3-nitrosopyridine (**16**) to 2,6-diamino-3-nitropyridine was also realized; these conditions would appear to be effective in general for the oxidation of aromatic nitroso to nitro compounds.[13]

The only previously recorded oxidations[14] of 5-nitroso- to 5-nitropyrimidines are the conversion of 1,3-dimethyl-6-cyanato-5-nitrosopyrimidine with a mixture of sulfuric and nitric acids to 1,3-dimethyl-6-carboxy-5-nitropyrimidine,[15] and a remarkable (and unconfirmed) conversion of 1,3-dimethyl-5-nitrosobarbituric acid to 1,3-dimethyl-5-nitrobarbituric acid with concentrated hydrochloric acid.[16] A claim by Biltz and Sedlatscheck[17] that 5-nitrosopyrimidines can be oxidized to 5-nitropyrimidines with concentrated nitric acid could not be confirmed in our hands; in fact, although oxidation does take place, the products are definitely not those claimed. We will report independently on the nature of this unusual oxidation reaction.

(10) E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2262 (1962).

(11) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(12) T. Sasaki and K. Minamoto, *Chem. Pharm. Bull.* (Tokyo), **12**, 1329 (1964).

(13) In a few instances aromatic nitroso compounds have been converted to nitro compounds by the use of a mixture of glacial acetic acid, 30% hydrogen peroxide, and sulfuric acid under rather vigorous conditions [R. R. Holmes and R. P. Bayer, *J. Am. Chem. Soc.*, **82**, 3454 (1960)]. The use of peroxy acids for the oxidation of aromatic amines to aromatic nitro compounds is well documented (for leading references, see Holmes and Bayer[13]).

(14) In the discussion of a paper presented at the CIBA Foundation Symposium on the Chemistry and Biology of Purines [G. E. W. Wolstenholme and C. M. O'Connor, Ed., J. and A. Churchill, Ltd., London, 1956, p. 140], Dr. G. M. Timmis mentioned the oxidation of a 5-nitrosopyrimidine with peracetic acid in 40% yield. This work has never been published. We have found that the oxidation of 5-nitroso- to 5-nitropyrimidines can indeed be effected with peracetic acid, but the reaction is both much slower than with pertrifluoroacetic acid, and the solubility of the 5-nitrosopyrimidine in glacial acetic acid is much less, thus leading to problems attendant upon a heterogeneous oxidation.

(15) R. Baythien, *Ann.*, **389**, 214 (1912).

(16) W. Techow, *Chem. Ber.*, **27**, 3082 (1894).

(17) H. Biltz and K. Sedlatscheck, *ibid.*, **57**, 339 (1924).

Experimental[18]

General Oxidation Procedure.—Aqueous 30% hydrogen peroxide (6 ml.) was added dropwise over a period of 1.5 hr. to a stirred solution of 3.0 g. of the 5-nitrosopyrimidine in 30 ml. of trifluoroacetic acid. The temperature of the reaction mixture was maintained below 35°. The initial, intensely colored solutions underwent a series of color changes and, after stirring at room temperature for 6–11 hr., became pale yellow. The reaction mixture was diluted with 75 ml. of cold water, stirring was continued for an additional 30 min., and the precipitated product was filtered off, washed with cold water and ethanol, and dried.

Purification of the 5-Nitropyrimidines.—Compounds **1**, **9**, **14**, and **15** were best purified by crystallization from methanol, aqueous dimethylformamide, water, and ethanol, respectively. Compound **2** was purified by heating in 6 *N* hydrochloric acid, treating with charcoal, and adjusting the pH of the filtrate to 9 with aqueous ammonium hydroxide. Compounds **3–5**, **8** and **10–13** were best purified by heating in 2 *N* sodium hydroxide, treating with charcoal, and acidifying the filtrate with glacial acetic acid. Compound **6** was purified by slow sublimation at 170° (0.1 mm.).

2,6-Diamino-3-nitropyridine.—Oxidation of 2,6-diamino-3-nitrosopyridine (**16**) was carried out as described above. Dilution of the reaction mixture with water resulted in the separation of the trifluoroacetate salt of 2,6-diamino-3-nitropyridine as bright yellow needles. Attempted crystallization from water led to partial decomposition. An aqueous solution of the salt was adjusted to pH 10 with 2 *N* sodium hydroxide solution and the yellow precipitate of 2,6-diamino-3-nitropyridine was collected by filtration and dried. Recrystallization from aqueous ethanol gave long orange needles, m.p. 234–236° (lit.[19] m.p. 230° dec.).

Nitration of 1,3-Dimethyl-6-aminouracil.—To a stirred suspension of 10.0 g. of 1,3-dimethyl-6-aminouracil in 10 g. of concentrated sulfuric acid was added 10.0 g. of nitric acid. A vigorous exothermic reaction ensued, with the color changing from bright violet to pale yellow over a period of 5 min. The pale yellow solution was stirred at room temperature for 30 min. and then poured over 50 g. of ice. The precipitated 1,3-dimethyl-5-nitro-6-aminouracil was collected by filtration (yield 8.6 g., 67%) and crystallized from water or from aqueous ethanol.

(18) Melting points were determined on a Thomas–Hoover silicon-bath apparatus and are uncorrected. Microanalyses were performed by the Robertson Microanalytical Laboratory, Florham Park, N. J. Where appropriate, identity of compounds was confirmed by comparison of infrared spectra determined by the normal Nujol mull technique on a Perkin-Elmer Model 237B Grating Infracord.

(19) A. E. Chichibabin and O. A. Zeide, *J. Russ. Phys.-Chem. Soc.*, **50**, 522 (1920); *Chem. Abstr.*, **18**, 1496 (1924).