Thermolysis of *cis*- and *trans*-Aziridines 16 and 17 in Xylene in the Presence of *N*-Phenylmaleimide: Table I Results. Pyrrolidines 24, 25, and 26. The aziridine 17 (0.05 g, 0.387 mmol) was dissolved in acetonitrile (4 mL), and *N*-phenylmaleimide (0.074 g, 0.426 mmol) was added. The mixture was refluxed for 8 h at 140 °C. Removal of the solvent and silica gel chromatography (5:2 hexane–EtOAc) left the product pyrrolidines **24** (0.029 g, 0.096 mmol, 25%), **25** (0.007 g, 0.023 mmol, 6%), and **26** (0.064 g, 0.212 mmol, 55%). Performing the above reaction in 40 mL of xylene ([0.01]) led to pyrrolidines **24** (0.056 g, 0.185 mmol, 48%), **25** (0.019 g, 0.062 mmol, 16%), and **26** (0.013 g, 0.042 mmol, 11%). Carrying out the reaction with *cis*-aziridine **16** led to pyrrolidines **24** (82%) and **25** (17%).

Thermolysis of *cis*-Aziridine 6 and *trans*-Aziridine 7 in the Presence of *N*-Phenylmaleimide: Table II Results. Pyrrolidines 27 and 28. The aziridine (0.050 g, 0.210 mmol) was dissolved in 2 mL of benzene, and *N*-phenylmaleimide (0.019 g, 0.21 mmol) was added. The reaction was heated for 2 h, the solvent was removed, and the crude reaction mixture was analyzed by NMR to obtain the pyrrolidine **27**:**28** ratios. These compounds are identical with those prepared from the reduction of 2,5-diphenyl-3-methyloxazolium salt in the presence of *N*-phenylmaleimide.[1] The reactions were performed under various reaction conditions including changes in solvent, temperature, and number of equivalents of *N*-phenylmaleimide (see Table II for specifics). The use of either aziridine **6** or **7** led to the same product ratio.

Acknowledgment. This work was supported by the National Institutes of Health (CA 17918; also, RRO 2388-01 for the AM500 spectrometer).

Registry No. **6**, 6476-40-0; **7**, 7570-81-2; **8**, 102537-09-7; **9**, 113405-17-7; **10** (isomer 1), 113405-16-6; **10** (isomer 2), 113405-27-9; **11**, 102537-10-0; **14**, 55829-81-7; **15**, 113405-18-8; **16**, 113472-72-3; **17**, 34856-91-2; **18**, 113405-19-9; **19**, 113405-20-2; **21**, 113405-21-3; **22**, 113405-22-4; **23**, 113405-23-5; **24**, 113405-24-6; **25**, 113472-73-4; **26**, 113472-74-5; **27**, 113405-25-7; **28**, 113472-75-6; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; 2-methyl-5-methoxyoxazole, 53878-74-3; *N*-phenylmaleimide, 941-69-5; 2,3-dihydro-3-methyl-2,5-diphenyloxazole, 113405-26-8.

Oxidative Transformations of Minor Components of Nucleic Acids. An Anomalous Reaction Course of Oxidation of N^6,N^6-Dialkyladenosines and Related Compounds with *m*-Chloroperoxybenzoic Acid[1]

Takeshi Endo and Jiri Zemlicka*

Department of Chemistry, Michigan Cancer Foundation and Department of Internal Medicine, Wayne State University School of Medicine, Detroit, Michigan 48201

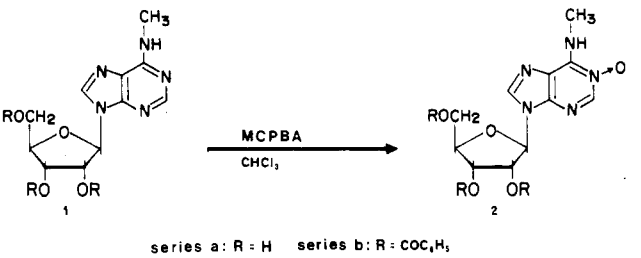
Received August 4, 1987

Oxidation of N^6-methyladenosine (**1a**) or the corresponding tribenzoate **1b** with *m*-chloroperoxybenzoic acid gave N^1-oxides **2a** and **2b** whereas N^6,N^6-dimethyladenosine tribenzoate (**3a**) afforded 2′,3′,5′-tri-*O*-benzoylinosine (**4a**) and N^6-methyl-N^6-formyl derivative **5**. The N^6,N^6-diethyladenosine **3b** and piperidine derivative **3c** yielded only **4a**, but N^6,N^6-dibenzyl compound **3d** was not oxidized. *N*,*N*-Dimethyl-2,4-dinitroaniline (**6a**) was oxidized with *m*-chloroperoxybenzoic acid to give *N*-methyl-*N*-formyl derivative **7a**, *N*-methyl-2,4-dinitroaniline (**8a**), *N*-oxide **10a**, and only traces of 2,4-dinitrophenol (**9a**). By contrast, 2-(dimethylamino)-5-nitropyridine (**6b**) afforded 5-nitro-2-pyridone (**9b**) and N-demethylated N^1-oxide **11**. 2-(Dimethylamino)pyridine (**6c**) and 2-(methylamino)-5-nitropyridine (**8b**) gave the respective N^2- and N^1-oxides **10c** and **11**. The reaction of 6-chloropurine nucleosides **15a** and **15b** with *N*,*N*-dimethylhydroxylamine gave inosine **4a** or **4b** accompanied by a smaller amount of **3a** or **3e**. 2,4-Dinitrofluorobenzene (**16**) afforded *O*-(2,4-dinitrophenyl)-*N*,*N*-dimethylhydroxylamine (**17**). Mass spectra of compounds **10a**, **10c**, and **17** provided evidence for Meisenheimer rearrangement and subsequent cyclic transformation. The *N*-oxide **10a** and hydroxylamino derivative **17** gave 2,4-dinitrophenol (**9a**), and N^2-oxide **10c** afforded fragments belonging to 2-pyridone (**9c**). Compound **17** is thermally stable whereas *N*-oxide **10a** yielded at 100 °C a mixture of **8a**, **8b**, **9a**, and **17**.

Introduction

Oxidation of nucleic acids and their components with organic peracids has been the subject of many studies.[2-4] It was established that pyrimidine and purine units such as cytosine, adenine, and guanine are transformed to the corresponding N^3- and N^1-oxides at both monomeric and polymeric levels. Little attention has been paid to similar reactions with minor components of nucleic acids, particularly *N*-methyl nucleosides. Previously, we have investigated oxidation with ruthenium tetraoxide[5] and bromine in phosphate buffer[6] of N^6,N^6-dimethyladenosine,

Scheme I



which occurs as a part of 16S and 18S ribosomal RNA and whose heterocyclic moiety is also found in the antibiotic puromycin. Both reactions led to a selective N-monodemethylation of N^6,N^6-dimethyladenine residue. By contrast, oxidation of protected N^6,N^6-dialkyladenosines with $KMnO_4$ was less selective and led to a significant

(1) The initial phase of this work was reported at the American Chemical Society/Chemical Society of Japan Chemical Congress, Honolulu, HI, April 1–9, 1979; Abstract MEDI 054.
(2) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic: New York, 1971; p 71.
(3) Kochetkov, N. K.; Budovskii, E. I. *Organic Chemistry of Nucleic Acids*; Plenum: New York, 1972; Part B, p 334.
(4) Harnden, M. R.; Brown, A. G.; Hodge, R. A. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 333.
(5) Endo, T.; Zemlicka, J. *J. Org. Chem.* **1979**, *44*, 3652.
(6) Kato, T.; Endo, T.; Zemlicka, J. *Nucleosides Nucleotides* **1982**, *1*, 81.

0022-3263/88/1953-1887$01.50/0

Scheme II

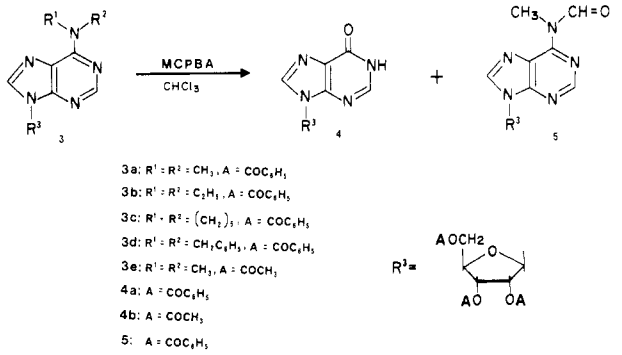


Table I. Reaction of N^6,N^6-Dialkyl-2′,3′,5′-tri-*O*-benzoyladenosines 3a–d with MCPBA

starting material (% recovered)	rctn products (% yield)	
	4a[a]	N^6-amide
3a (trace)	45	23[b]
3b (51)	49	–
3c (7)	57	–
3d (81)	–	–

[a] 2′,3′,5′-Tri-*O*-benzoylinosine. [b] Compound **5**.

attack at both alkyl groups.[7] In view of these facts we have undertaken a study of reactivity of N^6,N^6-dialkyladenosines as well as some model aromatic and heterocyclic *N,N*-dimethylamines toward another oxidizing reagent: *m*-chloroperoxybenzoic acid (MCPBA). These results and related investigations are the subject of the present paper.

Results and Discussion

A. Oxidation with MCPBA. Oxidation of adenosine with organic peracids gave the corresponding N^1-oxide.[3] Similarly, in our hands, oxidation of N^6-methyladenosine (**1a**) and the corresponding tribenzoate **1b** with MCPBA afforded exclusively N^1-oxides **2a** and **2b** in 60% yields (Scheme I).[8] The structures of **2a** and **2b** were confirmed by UV and ^{1}H NMR spectra. Thus, the UV spectrum of **2a** corresponded to that of adenosine N^1-oxide[9] with an expected bathochromic shift of both major maxima (ca. 8 nm) due to N-methylation. The ^{1}H NMR spectrum showed the presence of an *N*-methyl signal as a doublet which collapsed after addition of D_2O (**2b**) or irradiation of the NH signal (**2a**) thus eliminating the possibility of oxidation at the exocyclic (N^6) nitrogen atom.

Surprisingly, reaction of N^6,N^6-dimethyl-2′,3′,5′-tri-*O*-benzoyladenosine[5] (**3a**) with MCPBA took an entirely different course. The major product was identified as 2′,3′,5′-tri-*O*-benzoylinosine (**4a**, Scheme II, Table I) whereas *N*-methyl-*N*-formyl derivative **5**, which corresponded to a compound obtained by oxidation of **3a** with ruthenium tetraoxide,[5] was a minor component. Although chemical[10] and enzymic deamination[11] (hydrolysis) of adenosine are amply documented, a direct single-step

Scheme III

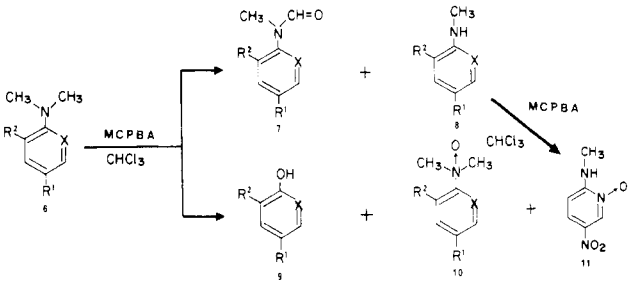


Table II. Oxidation of Some Aromatic and Heteroaromatic *N,N*-Dimethylamines with MCPBA

starting material (% recovered)	products (% yield)				
6a (18)	**7a** (15)	**8a** (17)	**9a** (4)	**10a** (10)	
6b (33)	–	–	**9b** (24)	–	**11** (7)
6c (0)	–	–	–	**10c** (90)[a]	–

[a] This product was obtained previously by oxidation of **6c** with peroxybenzoic acid[14] or acetic acid[26]–H_2O_2 in unspecified yields.

conversion of N^6,N^6-dialkyladenosine into inosine is without precedent in nucleic acid chemistry.[12]

Simple conversion of an N^6,N^6-dialkyladenosine into inosine under very mild conditions can be of considerable practical significance for the synthesis of oligonucleotides and sensitive nucleoside derivatives. Thus, the N^6,N^6-dialkylamino group can be regarded as a protecting function of heterocyclic CONH grouping. Compound **3a** does not appear to be suitable as a precursor of inosine derivative **4a** because of a significant dichotomy in the reaction course (Table I). We have therefore studied the reaction of three additional N^6,N^6-dialkyladenosines **3b–d** with MCPBA. We have found that N^6,N^6-diethyl-2′,3′,5′-tri-*O*-benzoyladenosine (**3b**) gave only inosine **4a** in 50% yield, but almost the same amount of starting material was recovered. The best substrate, to date, appears to be the *N*-piperidino derivative **3c**, which gave an almost 60% yield of inosine tribenzoate **4a** with a little (7%) of the starting material recovered. By contrast, N^6,N^6-dibenzyl-2′,3′,5′-tri-*O*-benzoyladenosine (**3d**) did not afford any product.

Comparison of the reaction course of compounds **3a–d** with MCPBA and the previously reported[5] oxidation with RuO_4 is also of interest. Whereas a lack of reactivity of N^6,N^6-dibenzyl derivative **3d** is common in both series, significant differences have clearly emerged. Thus, N^6-amide derivatives, which are the major (if not the sole[5]) products of oxidation of compounds **3a–c** with RuO_4, are, with the exception of derivative **5**, totally absent in the reaction mixture.

B. Reaction Path. Failure to isolate any *N*-oxide derivatives from oxidation of compounds **3a–c** indicated that the anticipated products might form initially but are of limited stability and undergo further transformations. Other factors that were considered included the following: (i) steric factors causing the change from initial N^1-oxidation in N^6-methyladenosine (**1a**) to (putative) N^6-oxidation in N^6,N^6-dialkyladenosines as indicated by an

(7) Kato, T.; Ogawa, S.; Ito, I. *Tetrahedron Lett.* **1981**, *22*, 3205.
(8) Compound **2a** inhibited the growth of murine leukemia L 1210 cells to the extent of 35% and it caused an approximately 50% increase in cell size at 6.5×10^{-5} M. We thank Dr. D. Kessel, Departments of Internal Medicine and Pharmacology, Wayne State University School of Medicine, for kindly communicating this result to us.
(9) Sigel, H.; Brintzinger, H. *Helv. Chim. Acta* **1965**, *48*, 433.
(10) Reference 3, p 362.
(11) Agarwal, R. P.; Cha, S.; Crabtree, G. W.; Parks, R. E., Jr. *Chemistry and Biology of Nucleosides and Nucleotides*; Harmon, R. E., Robins, R. K., Townsend, L. B., Eds.; Academic: New York, 1978; p 159.
(12) Similar biological oxidation is apparently a part of metabolism of antibiotic puromycin as shown by a tentative identification of 3′-amino-3′-deoxyinosine as one of the metabolites.[13]

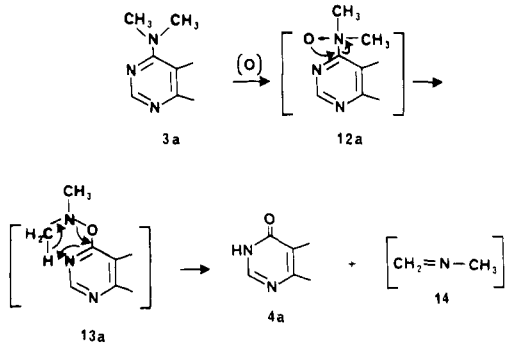
analogy with structurally similar 2-(methylamino)- and 2-(dimethylamino)pyridines;[14] (ii) the strong electronegativity of the pyrimidine portion[15] of the purine ring; and (iii) the presence of an endocyclic (N^1) nitrogen atom favorably (ortho) oriented relative to the N^6-substituent(s).

In order to assess the relative importance of these factors, we have investigated oxidation of a series of simple analogues where the strongly electron attracting endocyclic nitrogen atoms are replaced with exocyclic nitro groups of similar character.[16] Quite surprisingly, oxidation of 2,4-dinitro-*N*,*N*-dimethylaniline[17] (**6a**) with MCPBA gave a complex mixture of four products **7a**–**10a** in addition to the unchanged starting material (Scheme III, Table II). In sharp contrast, oxidation of *N*,*N*-dimethylaniline[18] and *p*-nitro-*N*,*N*-dimethylaniline[19] gave only the respective *N*-oxides. Thus, introduction of a second (ortho) nitro group abruptly changes the reaction course.

Whereas N-demethylation (see compound **8a**) is a common occurrence in many transformations of aromatic *N*-oxides,[17,20,21] the formation of 2,4-dinitrophenol (**9a**) and, particularly, *N*-formyl-*N*-methyl derivative **7a** was surprising. Nevertheless, similar compounds **4a** and **5** were obtained as products of oxidation of N^6,N^6-dimethyladenosine derivative **3a** with MCPBA. Identification of compound **9a** followed from comparison with an authentic sample of 2,4-dinitrophenol. Compound **7a** was then readily ammonolyzed to the known[17] *N*-methyl-2,4-dinitroaniline (**8a**). Mass and NMR spectra were instrumental in additional characterization of product **7a** as the *N*-formyl-*N*-methyl derivative. As expected, the electron-impact mass spectrum showed an M and M + 1 ion (*m*/*e* 225 and 226) accompanied by a fragment at *m*/*e* 197 resulting from decarbonylation of M. The ^{1}H NMR spectrum of compound **7a** revealed a significant secondary splitting, which is typical for rotationally restricted amides.[22,23]

The most polar product isolated from the reaction mixture after oxidation of amine **6a** with MCPBA was *N*-oxide **10a** (yield 10%). This product was readily deoxygenated by triphenylphosphine[24] in $CHCl_3$–methanol (1:2) to give compound **6a**. For preparative purposes it is more convenient to isolate *N*-oxide **10a** directly from the reaction mixture without any chromatography after acidification with HCl as the corresponding hydrochloride in the same yield. In addition to ^{1}H NMR spectra that were in agreement with structure **10a**, mass spectra showed the molecular ion (M) at *m*/*e* 227 as well as the expected fragments resulting from deoxygenation[25] (*m*/*e* 211) and demethylation (*m*/*e* 212) of M. During paper electrophoresis at pH 7, *N*-oxide **10a** moves toward the cathode, probably as a protonated species. This behavior is different from that of any other oxidation product, and paper electrophoresis is thus a valuable method for a rapid identification of compound **10a** in complex reaction mixtures after oxidation of **6a** with MCPBA.

Scheme IV



As already mentioned, formation of compounds **7a** and **9a** parallels the formation of derivatives **5** and **4a** observed in the nucleoside series **3a**–**c**. More striking is the very small amount of phenol derivative **9a** isolated after oxidation of **6a**. This result is in contrast to that obtained from the reaction of nucleosides **3a**–**c** where an analogous compound **4a** was the main or sole product.

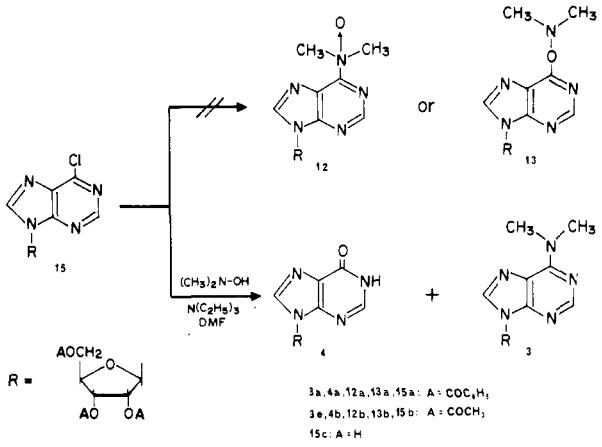
A large difference in yields between 2,4-dinitrophenol (**9a**) and the corresponding inosine derivative **4a** suggests a specific role of the endocyclic nitrogen atom situated in an ortho position to the *N*,*N*-dialkylamine moiety. We have therefore chosen an additional model compound, 2-(dimethylamino)-5-nitropyridine (**6b**), (i) containing a nitrogen atom located ortho to the dimethylamino function and (ii) of sufficient electronegativity to be compared with either nucleoside derivative **3a** or aromatic model **6a**. Oxidation of **6b** with MCPBA led to 5-nitro-2-pyridone (**9b**) and 2-(methylamino)-5-nitropyridine N^1-oxide (**11**, Table II). The latter was identical (^{1}H NMR, TLC) with an authentic sample of **11** prepared by oxidation of 2-(methylamino)-5-nitropyridine (**8b**) with MCPBA (Scheme III). The structure of **11** was further confirmed by the ^{1}H NMR spectrum, which exhibited the *N*-methyl signal as a doublet at δ 8.44 which collapsed to a singlet after addition of D_2O.

It is likely then that compound **11** resulted from intermediate **8b** (not isolated), which reacted with MCPBA to give the expected[14] endocyclic N^1-oxide. Isolation of pyridone **9b** lends further support to a hypothesis that an endocyclic ortho nitrogen atom plays an important roll in determination of product composition after oxidation with MCPBA. Thus, oxidation of both compounds that contain such a structural unit (**3a** and **6a**) gave the cyclic imides (inosine derivative **4a** and pyridone **9b**) as the major reaction products. Finally, oxidation of 2-(dimethylamino)pyridine (**6c**) with MCPBA afforded the corresponding exocyclic N^2-oxide **10c** in 90% yield (Table II). These experiments provided another striking example of dependence of the reaction course of oxidation on the presence of a second electron-attracting group (see compound **6a**).

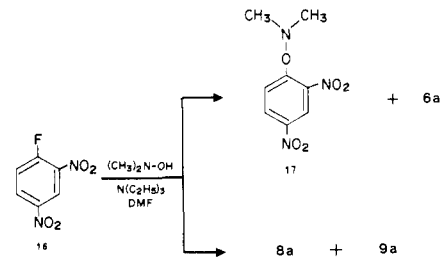
The results obtained to date have allowed us to formulate a possible working hypothesis (Scheme IV) for oxidation of nucleoside derivatives **3a**–**c**. Thus, an N^6,N^6-dialkyladenosine derivative (e.g., **3a**) is first converted to the corresponding exocyclic N^6-oxide **12a**. The latter then undergoes a Meisenheimer rearrangement[27] to give the

(13) Nagasawa, H. T.; Shirota, F. N.; Alexander, C. S. *J. Med. Chem.* **1972**, *15*, 177.
(14) Pentimalli, L. *Gazz. Chim. Ital.* **1964**, *94*, 458.
(15) Albert, A. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Wiley-Interscience: New York, 1973; Vol. 2, p 26.
(16) For a corresponding bioisosteric analogy, see: Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563 and ref 5a cited therein.
(17) Hodgson, H. H.; Nicholson, D. E. *J. Chem. Soc.* **1941**, 470.
(18) Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721.
(19) Yoshimura, T.; Asada, K.; Oae, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3000.
(20) Bickel, M. H. *Pharmacol. Rev.* **1969**, *21*, 325.
(21) Powell, M. F.; Pai, E. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 3277.
(22) Wahl, H.; Le Bris, M.-T.; Berkovitch, D. *Bull. Soc. Chim. Fr.* **1973**, 1285.
(23) Rysman de Lockerente, S.; Nagy, O. B.; Bruylands, A. *Org. Magn. Reson.* **1970**, *2*, 179.
(24) Reference 2, p 196.
(25) Bild, N.; Hesse, M. *Helv. Chim. Acta* **1967**, *50*, 1885.
(26) Wieczorek, J. S.; Plazek, E. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 249.

Scheme V



Scheme VI



N,N-dimethylhydroxylamino purine **13a**. Similar transpositions appear to be facilitated by electron-attracting groups such as α,β-unsaturated ester[28] or phosphate function.[29] The latter case[29] is particularly instructive because the rearrangement occured in situ during oxidation with MCPBA. An analogous transformation of unstable N-oxides, such as **12a**, formed during oxidation of nucleoside derivatives **3a–c** seems very plausible. The role of a strongly electron attracting function is provided by the purine moiety.[15] It should also be recognized that formation of exocyclic N^6-oxide **12a** is fully compatible with the mechanism in Scheme IV whereas involvement of the isomeric endocyclic N^1-oxide is not. Intermediate **13a** is transformed in the third step (Scheme IV) to inosine **4a** and unstable[30] formaldehyde N-methylimine (**14**). We have not been able to find an analogy for the latter process in solution chemistry, but a similar transformation takes place under the conditions of electron-impact mass spectrometry (see section D).

C. Reactions with N,N-Dimethylhydroxylamine. Further confirmation of the hypothesis shown in Scheme IV was obtained from the reaction of 6-chloro-9-(2,3,5-tri-*O*-benzoylribofuranosyl)purine (**15a**) with N,N-dimethylhydroxylamine in dimethylformamide, which gave 2′,3′,5′-tri-*O*-benzoylinosine (**4a**,80%) and derivative **3a** (20%, Scheme V). Again, as in the reaction of **3a** with MCPBA, the N-oxide derivative **12a** and the corresponding N,N-dimethylhydroxylamino derivative **13a** were conspicuously absent. The N^6,N^6-dimethylamino compound **3a** could, for example, arise by deoxygenation of intermediary N-oxide **12a** with N,N-dimethylhydroxylamine-.[31,32]

Similar results were obtained with triacetate **15b** in CH_2Cl_2. In this case the course of the reaction was followed by UV spectroscopy and TLC, which failed to show the presence of material(s) other than chloro derivative **15b** or major product **4b** (a minor amount of compound **3e** was not detected by UV). The composition of the reaction product, as determined by TLC after 22 h at room temperature, was 81% of **4b** and 18% of **3e**. Apparently, the reaction is rather insensitive toward a dramatic change in solvent polarity. Formation of inosine derivative **4b** is consistent with our hypothesis that N,N-dimethylhydroxylamino purine **13a** and hence N^6-oxide **12a** are likely intermediates in the oxidation of nucleosides **3a–c** with MCPBA. It is important to note that the reaction of chloro nucleoside **15c** with hydroxylamine or N-methylhydroxylamine gave only the corresponding N^6-hydroxyadenosines.[33,34] Again, the parallel with the oxidation of N^6-methyl and N^6,N^6-dimethyl nucleosides **1b** and **3a** is striking.

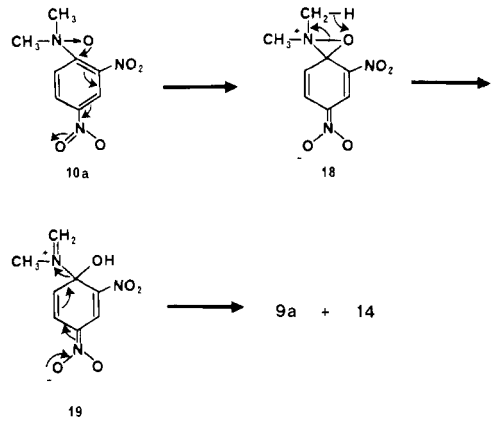
Following the strategy employed for investigation of the reaction course of oxidation of N^6,N^6-dialkyladenosine derivatives **3a–c**, we have substituted chloropurine **15a** for 2,4-dinitrofluorobenzene (**16**) in the reaction with N,N-dimethylhydroxylamine (Scheme VI). Again, the aromatic portion of **16** is strongly electronegative, but unlike **15a**, it lacks an endocyclic ortho nitrogen atom. A major product isolated in 80% yield was N,N-dimethyl-2,4-dinitrophenoxyamine[35] (**17**) accompanied by trace amounts of dimethyl- and methylamino derivatives **6a** and **8a** (obtained as a 34:66 mixture according to ^{1}H NMR) and 2,4-dinitrophenol (**9a**). Thus, as in the case of oxidation of **3a** and **6a** with MCPBA, a dramatic difference in the reaction course was observed. It should be noted that oxidation of **3a** with MCPBA and reaction of 6-chloropurine **15a** or **15b** with N,N-dimethylhydroxylamine did not afford any N-oxide **12a**, **12b** or N,N-dimethylhydroxylamino purine **13a**, **13b**. The corresponding transformations of 2,4-dinitrophenyl derivatives **6a** effected by MCPBA and **16** with N,N-dimethylhydroxylamine readily gave N-oxide **10a** and compound **17**.

The structure of **17** was confirmed by spectral studies. Thus, the UV spectrum of **17** is virtually identical with that of 2,4-dinitrophenoxyamine.[36] The ^{1}H NMR and TLC mobility are substantially different from those of N-oxide **10a** (compound **17** is much less polar than N-oxide **10a**).

D. Evidence for Meisenheimer Rearrangement and Cyclic Fragmentation Pathway under the Conditions of Electron Impact. Mass spectrometric data provided valuable supportive evidence for the structures of some of the reaction products which were discussed in section B. More importantly, mass spectra of compounds **10a**, **10c**, and **17** indicated the possibility of a fragmentation pathway similar to that described in Scheme IV. Thus, the mass spectrum of N,N-dimethylhydroxylamino derivative **17** exhibited two ions at m/e 184 [2,4-dinitrophenol (**9a**)] and 43 [formaldehyde N-methylimine (**14**)] in addition to a molecular peak at m/e 227. This observation is com-

(27) Johnstone, R. A. W. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience-Wiley: New York, 1969; Vol. 2, p 249.
(28) Winterfeldt, E.; Krohn, W. *Chem. Ber.* **1969**, *102*, 2336.
(29) Holden, I.; Segall, Y.; Kimmel, E. C.; Casida, J. E. *Tetrahedron Lett.* **1982**, *23*, 5107.
(30) For the corresponding cyclotrimerization product of **14**, see: Graymore, J. *J. Chem. Soc.* **1924**, *125*, 2283.
(31) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.
(32) Barbry, D.; Hasiak, B. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2410.
(33) Giner-Sorolla, A.; Medrek, L.; Bendich, A. *J. Med. Chem.* **1966**, *9*, 143.
(34) Giner-Sorolla, A.; O'Bryant, S. A.; Nanos, C.; Dollinger, M. R.; Bendich, A.; Burchenal, J. H. *J. Med. Chem.* **1968**, *11*, 521.
(35) Compound **17** was described without any characterization in the patent literature by reaction of sodium 2,4-dinitrophenoxide with N-chloro-N,N-dimethylamine: Bortovoi, I. M.; Pogaleeva, A. M. U.S.S.R. Patent No. 270714, May 12, 1970; *Chem. Abstr.* **1970**, *73*, P 98596*d*.
(36) Sheradsky, T. J. *Heterocycl. Chem.* **1967**, *4*, 413.

Scheme VII



patible with the cleavage mechanism which is similar to that proposed in Scheme IV. Pathways more usual in the fragmentation of *N,N*-dimethylamino derivatives[37] (loss of methyl and NCH_3 groups) were absent. Apparently, the π-electron system of compound **17** is capable of accepting a proton (hydrogen) from the relevant *N*-methyl group, presumably by a cyclic mechanism even in the absence of an endocyclic (ortho) nitrogen atom (Scheme IV). It is noteworthy that such a transformation did not take place in solution (see section C). Moreover, compound **17** is thermally stable; it did not decompose at 110 °C during melting as shown by TLC.

The fragmentation pattern of *N*-oxide **10a**, which is isomeric with **17**, exhibited some similar features. Thus, in addition to the expected ions M − 16 (deoxygenation) and M − 15 (demethylation), a minor but significant fragment of *m/e* 184 (**9a**) was also present. Its occurrence is readily explained by invoking Meisenheimer rearrangement[27,38] (see Scheme IV) followed by a cyclic fragmentation pathway from Scheme VII. To the best of our knowledge, an *N*-oxide → hydroxylamino rearrangement under the conditions of electron impact has not yet been described.

Whereas *N,N*-dimethylhydroxylamino derivative **17** exhibited reasonable thermal stability, *N*-oxide **10a** was less thermally stable. It decomposed during melting (90–95 °C) to give 2,4-dinitrophenol (**9a**) as a major component accompanied by lesser amounts of compound **17** (product of Meisenheimer rearrangement), **6a** and **8a**. It is of significant interest that **9a** and **6a** were also found in the electron-impact mass spectrum of *N*-oxide **10a**. Stability of **17** under similar conditions has ruled out the possibility that this product is an intermediate in the thermal transformation of *N*-oxide **10a** to **9a** via, e.g., the cyclic fragmentation pathway described in Scheme IV. Instead, a *direct* conversion of **10a** to **9a**, possibly through intermediates **18** and **19** (Scheme VII), appears more likely.

In view of our results (see section A), it is of considerable interest that 2-(dimethylamino)pyridine N^2-oxide (**10c**) gave pronounced peaks at *m/e* 95 (2-pyridone, **9c**) and the corresponding cleavage product at *m/e* 67 (**9c** − CO). This pathway, which follows closely that described in Scheme IV, appears to be significant in both electron impact and chemical ionization spectra of **10c**. Apparently, the proximity of an endocyclic nitrogen atom and a methyl group favorably influences the formation of 2-pyridone (**9c**) under conditions of chemical ionization as well as in solution (see oxidation of **6b** with MCPBA, Scheme III). Nevertheless, one important difference is worthy of note. Thus, oxidation of 2-(dimethylamino)pyridine (**6c**) with MCPBA gave N^1-oxide **10c** in high yield and no 2-pyridone (**9c**) (Table II). Only in the case of compound **9b** was there a significant formation of 5-nitro-2-pyridone (**9b**) (no *N*-oxide **10b** was obtained). Consequently, in sharp contrast to fragmentation under the conditions of electron impact, an additional strongly electron attracting group (*p*-nitro) is a necessary factor to drive the reaction along the route described in Scheme IV.

The endocyclic N^1-oxide **11** followed the "classical" fragmentation pattern,[25] giving rise to a minor *m/e* 153 (M − O) and more important *m/e* 152 (M − OH). Significantly, the extent of demethylation of **11** (*m/e* 154) was negligible.

E. Conclusions. An investigation of oxidation of N^6-alkyladenosine derivatives **1a**, **1b**, and **3a–d** as well as model compounds **6a–c** and **8b** with MCPBA has led to the following conclusions. N-Monosubstituted compounds **1a**, **1b**, and **8b** gave exclusively N^1-oxides **2a**, **2b**, and **11** whereas N^6,N^6-disubstituted adenosines **3a–c** afforded predominantly (**3a**) or exclusively (**3b** and **3c**) 2′,3′,5′-tri-*O*-benzoylinosine (**4**). Oxidation of model compounds **6a** and **6b** was more complex, giving products of simple N-demethylation (**8a**) or artifacts thereof (**11**), *N*-methyl-*N*-formyl derivative **7a**, and *N*-oxide **10a**. Significant oxidative degradation to phenol **9a** or cyclic imide **9b** was obtained only in the case of **6b**. From the point of view of protection of the reactive cyclic imide function in inosine, the 6-piperidinopurine derivative **3c** presently appears to be the most convenient. Transformations **3a–c** to **4a** and **15a** or **15b** to **4a** or **4b** are the first single-step, nonhydrolytic conversions of 6-amino- or 6-halogeno-substituted purine nucleosides into inosine. Reaction of **15a** and **15b** with *N,N*-dimethylhydroxylamine to give inosine **4a** and **4b** has a significant synthetic potential for preparation of sensitive purine derivatives. Experiments with models **6a–c** have indicated that a simultaneous presence of the N^1 (ortho) atom and a second suitably located electron-withdrawing substituent decisively influences the reaction course of oxidation with MCPBA. The same factor also affects the reaction of **15a**, **15b**, and **16** with *N,N*-dimethylhydroxylamine. Thus, unlike intermediates **12a**, **12b**, **13a**, and **13b**, *N,N*-dimethylhydroxylamino derivative **17** was readily obtained. Experiments described herein led to formulation of a possible reaction mechanism of oxidation of N^6,N^6-dialkyladenosines **3a–c** with MCPBA (Scheme IV). Mass spectra of compounds **10a**, **10c**, and **17** provided the first examples of *N*-oxide → hydroxylamine (Meisenheimer) rearrangement accompanied by a cyclic fragmentation pathway under the conditions of electron impact and chemical ionization which is related to the suggested mechanism of oxidation in Scheme IV.

Experimental Section

General Procedures. All solvents, reagents, and starting materials were of the highest available purity or they were purified as specified. Dimethylformamide (DMF) was stored over Linde molecular sieves, 4A. Thin-layer chromatography (TLC) was performed on 6 × 2 precoated sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany) or microcrystalline cellulose (Eastman Kodak, Rochester, NY). The spots were detected with UV light. The preparative TLC was performed with 20 × 20 cm silica gel GF 2-mm-thick layers (Uniplate, Analtech, Newark, DE). Kieselgel 60 (230–400 mesh ASTM, Merck) was employed for column chromatography. The following chromatographic solvent systems were used: S_1, $CHCl_3$–ethanol (95:5); S_2, $CHCl_3$–ethanol (7:1); S_3, $CHCl_3$–methanol (95:3); S_4, benzene–ethyl acetate (95:5); S_5, $CHCl_3$–methanol (37:3); S_6, $CHCl_3$–CCl_4 (1:1); S_7, benzene–

(37) Shaw, S. J.; Desiderio, D. M.; Tsuboyama, K.; McCloskey, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 2510.
(38) Khuthier, A. H.; Ahmed, T. Y.; Jallo, L. I. *J. Chem. Soc., Chem. Commun.* **1976**, 1001.

ethyl acetate (9:1); S_8, toluene–ethyl acetate (3:2); S_9, CH_2Cl_2–methanol (97:3); S_{10}, $CHCl_3$–methanol (50:3); S_{11}, $CHCl_3$–methanol (25:2); S_{12}, $CHCl_3$–methanol (7:1); S_{13}, $CHCl_3$–methanol (10:1); S_{14}, $CHCl_3$–methanol (6:1); S_{15}, 2-propanol–NH_4OH–H_2O (7:1:2), cellulose layer; S_{16}, $CHCl_3$–methanol (100:1); S_{17}, $CHCl_3$–methanol (100:3); S_{18}, benzene–ethyl acetate (20:1); S_{19}, $CHCl_3$–methanol (9:1); S_{20}, CH_2Cl_2–methanol (1:1), S_{21}, $CHCl_3$–methanol (5:1). Melting points were determined with a Thomas-Hoover apparatus or microscopic hot-stage apparatus (Reichert, Austria), and they were not corrected. UV spectra were obtained on a Beckman grating spectrophotometer Model DM-GT or Perkin-Elmer Lambda 5 spectrophotometer. The wavelengths of maxima are given in nanometers. Paper electrophoresis was performed on a flat plate (Savant, Hicksville, NY) at 40 V/cm and 15 °C for 1 h. ^1H NMR spectra were obtained with an FX 100 instrument (JEOL Ltd., Tokyo, Japan) at 100 MHz or a QE-300 instrument (General Electric) at 300 MHz. Chemical shifts are in δ units, coupling constants J in hertz. Electron-impact mass spectra (EI-MS) were run with a JMS-D-100 (JEOL) or Kratos MS80 RFA high-resolution instrument. Chemical-ionization mass spectra (CI-MS) were determined by using 2-methylpropane as an ionization gas. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL, or M-H-W Laboratories, Phoenix, AZ.

Starting Materials. Compunds **1b** and **3a–e** were obtained as described.[5] Derivatives **6a**, **6b**, **8a**, **8b** were prepared by the known procedure:[39] The appropriate halide was reacted with dimethylamine or methylamine hydrochloride and triethylamine in DMF. Compounds **8a** and **8b** were chromatographed on a silica gel column in CCl_4 and solvent S_6. All compounds were homogeneous on TLC (**6a** and **8a** in S_3, S_4; **6b** and **8b** in S_7, S_8), the melting points corresponded to the reported values,[17,40-42] and ^1H NMR spectra were in accord with assigned structures.

2-Chloro-5-nitropyridine. A procedure for preparation of 6-chloro-9-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)purine[43] (**15b**) was adapted as follows. 5-Nitro-2-pyridone (**9b**, 10 g, 71.4 mmol) was refluxed with 2 M (chloromethylene)dimethylammonium chloride (42.8 mL, 85.6 mmol) in $CHCl_3$ (100 mL) for 30 min. The cooled solution was applied on a column of silica gel, and the elution was completed with $CHCl_3$. 2-Chloro-5-nitropyridine was obtained as the first fraction: homogeneous on TLC (S_5); yield 10.64 g (98%); mp 101–103 °C after crystallization from methanol (lit.[44] mp 108–109 °C. The ^1H NMR spectrum was identical with that of an authentic sample.[45]

***N*^{6}-Methyladenosine (1a).** A mixture of 6-chloro-9-(β-D-ribofuranosyl)purine[43] (**15c**, 2.9 g, 10 mmol), methylamine hydrochloride (2 g, 30 mmol), and triethylamine (3 mL, 22 mmol) was stirred for 3 days in DMF (50 mL). The mixture was evaporated in vacuo (oil pump), the residue was dissolved in water (30 mL), the pH was adjusted to 8.5 with saturated aqueous Na_2CO_3, and the solution was evaporated again. The residue was coevaporated with $CHCl_3$ and ethanol whereupon it was chromatographed on a silica gel column (30 g) in solvent system S_1 (2 L). The major UV-absorbing fraction was evaporated to give compound **1a**, which was crystallized from ethanol–petroleum ether: 1.5 g (100%); homogeneous on TLC (S_2); mp 134–135 °C. UV and ^1H NMR spectra corresponded to those described.[5,46]

6-Chloro-9-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)purine (15a). This material was prepared according to a procedure described for the corresponding triacetate[43] **15b**, which was modified as follows. The resultant product was chromatographed on silica gel in CCl_4 and $CHCl_3$. Compound **15a** was obtained as TLC (S_5) homogeneous foam, 4.35 g (90.5%).

6-Chloro-9-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)purine (15b). This compound was obtained as described.[43] It was chromatographed on a silica gel column using CH_2Cl_2 as eluent: 51.5% yield; homogeneous on TLC (S_9).

***N*^{6}-Methyladenosine *N*^{1}-Oxide (2a).** A mixture of N^6-methyladenosine (**1a**, 0.5 g, 1.8 mmol) and MCPBA (2.38 g, 11.7 mmol) was stirred in $CHCl_3$–methanol (1:3, 40 mL) for 3 days at room temperature. The resultant solution was chromatographed on a silica gel column (28 × 2.1 cm). *m*-Chlorobenzoic acid was eluted with $CHCl_3$ (150 mL). The elution with solvent system S_{10} (250 mL) and then S_{11} (250 mL) afforded starting material **1a**, which was purified by preparative TLC in S_{12}, 0.16 g (32%). Elution with S_{13} (1500 mL) gave *N*-oxide **2a** (0.33 g, 63%): uniform on TLC (S_{14} and S_{15}); mp ca. 120 °C (transition point) after crystallization from ethanol; UV max (0.01 M Na_2HPO_4, pH 7) 300 (ε 2500), 270 (8800), 235 nm (35 300); NMR (CD_3SOCD_3, DSS[47]) δ 8.64 (s, 1, H_8), 8.57 (s, 1, H_2), 8.3 (br s, 1, NH), 5.91 (d, 1, $H_{1'}$, $J_{1',2'}$ = 5.4), 4.52 (m, 1, $H_{2'}$), 4.18 (m, 1, $H_{3'}$), 3.97 (m, 1, $H_{4'}$), 3.6 (m, 2, $H_{5'}$), 3.49 (poorly resolved d, 3, CH_3). Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot 0.5\ H_2O$: C, 43.15; H, 5.27; N, 22.87. Found: C, 42.96; H, 4.90; N, 22.59.

***N*^{6}-Methyl-2′,3′,5′-tri-*O*-benzoyladenosine *N*^{1}-Oxide (2b).** A mixture of tribenzoate **1b** (0.2 g, 0.34 mmol) and MCPBA (0.34 g, 1.7 mmol) was magnetically stirred in $CHCl_3$ (20 mL) for 3 days at room temperature. The resultant solution was chromatographed on a silica gel column (12 g). Elution with solvent system S_6 gave *m*-chlorobenzoic acid. Starting material **1b** was eluted with solvent system S_{16}, 65 mg (32.5%). The elution was continued with solvent S_{17} to give product **2b** as a TLC (S_3 and S_5, double development) homogeneous foam (0.13 g, 63%): ^1H NMR ($CDCl_3$) 8.50 (s, 1, H_8), 8.0 (s, 1, H_2, partially overlapped with C_6H_5), 7.4 (m, 16, NH + C_6H_5), 6.34 (2 d, 2, $H_{1'}$ and $H_{2'}$), 6.15 (br t, 1, $H_{3'}$), 4.8 (m, 3, $H_{4'}$ and $H_{5'}$), 3.63 (poorly resolved d, 1, NCH_3, after addition of D_2O it became a sharp singlet). Anal. Calcd for $C_{32}H_{27}N_5O_8 \cdot 0.5H_2O$: C, 62.13; H, 4.56; N, 11.32. Found: C, 62.16; H, 4.29; N, 11.07.

Reaction of *N*^{6},*N*^{6}-Dialkyladenosines 3a–d with MCPBA. General Procedure. A mixture of starting material **3a–d** (0.15–0.32 mmol) and MCPBA (5–10 molar equiv) in chloroform (10–20 mL) was stirred at room temperature for 16–36 h or 7 days (compound **3d**). The resultant solution was concentrated in vacuo, and the residue was directly applied on 4–7 silica gel TLC plates, which were developed in solvent system S_3 3–5 times. The following UV-absorbing bands were obtained in the order of decreasing mobility: product **5** or starting materials **3b–d**, *m*-chlorobenzoic acid, and inosine derivative **4a**. Each band except that of *m*-chlorobenzoic acid was rechromatographed in the same solvent on 1–3 TLC plates to give TLC-homogeneous compounds (S_3, S_5, and S_7) whose UV and NMR spectra corresponded to the authentic samples.[5] In addition, inosine derivative **4a** was ammonolyzed with NH_3 in methanol to give inosine which was indistinguishable from an authentic specimen (TLC, S_{15}; UV). Yields are listed in Table I.

Reaction of *N*,*N*-Dimethyl-2,4-dinitroaniline (6a) with MCPBA. Method A. Isolation of All Products. A mixture of *N*,*N*-dimethyl-2,4-dinitroaniline (**6a**, 0.1 g, 0.47 mmol) and MCPBA (0.48 g, ca. 2.2 mmol) was stirred in chloroform (15 mL) for 30 h at room temperature. The solution was applied on five 20 × 20 cm silica gel plates, which were developed with solvent system S_{10}. The fastest moving and poorly resolved zones A and B were rechromatographed on a short column of silica gel (1 × 12 cm) in solvent system S_6 (total volume 150 mL) to give a mixture of **6a** and **8a** (62 mg). Crystallization from $CHCl_3$ gave pure **8a**, 16 mg (17%), mp 173–174 °C (lit.[17] mp 176 °C) after recrystallization from methanol, which was identical (^1H NMR; TLC, S_7) with an authentic sample.

The mother liquors after crystallization of mixture **6a** and **8a** from $CHCl_3$ were evaporated, and the residue was chromatographed on two silica gel plates in solvent system S_{18} to give 24 mg (18%) of starting material **6a**, mp 87–88 °C (lit.[17] mp 87 °C) after crystallization from methanol, identical (^1H NMR, TLC, S_7) with an authentic sample.

(39) Zemlicka, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1965**, *30*, 1880.
(40) van Romburgh, P. *Recl. Trav. Chim. Pays-Bas* **1883**, *2*, 103.
(41) Wieczorek, J. S.; Plazek, E. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 785.
(42) Mangini, A.; Colonna, M. *Gazz. Chim. Ital.* **1943**, *73*, 313.
(43) Zemlicka, J.; Owens, J. In *Nucleic Acid Chemistry. Improved and New Synthetic Procedures, Methods, and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; Wiley-Interscience: New York, 1978; Part 2, p 611.
(44) Signor, A.; Scoffone, E.; Biondi, L.; Bezzi, S. *Gazz. Chim. Ital.* **1963**, *93*, 65.
(45) Pouchert, C. J. *The Aldrich Library of NMR Spectra Edition II*; Aldrich Chemical: Milwaukee, WI, 1983; Vol. 2, p 654.
(46) Kemal, O.; Reese, C. B. *Synthesis* **1980**, 1025.
(47) Sodium 3-(trimethylsilyl)-1-propanesulfonate as an internal reference.

The band C containing a small amount of *m*-chlorobenzoic acid and traces of **6a** and **8a** consisted primarily of 2,4-dinitrophenol (**9a**). Rechromatography in solvent system S_3 gave 3.5 mg (4%) of **9a** identical (UV; TLC, S_5) with an authentic sample.

The product from band D was rechromatographed on a silica gel column (10 g) in solvent system S_6 (elution of *m*-chlorobenzoic acid), S_3, and S_5. The latter solvent eluted crude *N*-formyl-*N*-methyl-2,4-dinitroaniline (**7a**), which was further purified by chromatography on two silica gel plates in S_3 (triple development) to give **7a** as a syrup: homogeneous on TLC (S_3); 15 mg (15%); ^{1}H NMR ($CDCl_3$) δ 8.85 (apparent m, 1, H_3), 8.55 (dt, 1, H_5), 8.29 and 8.26 (2 s, 1, CHO), 7.60 (d, 1, H_6, $J_{6,5}$ = 8.8), 3.53 and 3.30 (2 s, CH_3, 3); EI-MS (JMS-D-100), *m/e* 225 (8.1, M), 197 (19.0, M - CO), 179 (100.0, M - NO_2), 133 (27.9, M - 2 × NO_2), 105 (87.5, M - CO - 2 × NO_2), 104 (52.2, M - CO - 2 × NO_2 - H).

A portion of compound **7a** was ammonolyzed in methanolic NH_3 overnight at room temperature. TLC (S_3) showed the presence of *N*-methyl-2,4-dinitroaniline (**8a**) as the only product.

The band E near the origin was eluted with solvent system S_{19} to give *N,N*-dimethyl-2,4-dinitroaniline *N*-oxide (**10a**): 10 mg (10%); uniform on TLC (S_{20}) and paper electrophoresis (0.05 M Na_2HPO_4, pH 7, mobility 0.3 of 2,4-dinitrophenol toward the cathode); mp 95–97 °C (dec, hot stage); UV max (ethanol) 204 (ϵ 20900), sh 286 (1900) and 247 nm (7600); ^{1}H NMR (D_2O, DSS[47]) δ 8.76 (d, 1, H_3, $J_{3,5}$ = 2.4 Hz), 8.63 (dd, 1, H_5, $J_{5,3}$ = 2.4, $J_{5,6}$ = 9.3), 8.22 (d, 1, H_6, $J_{6,5}$ = 9.3), 3.96 (s, 6, CH_3); EI-MS 227 (11.1, M), 212 (0.3, M - CH_3), 211 (0.7, M - O), 184 (17.6, M - CH_2=NCH_3), 168 (2.9), 154 (9.5), 107 (12.6), 91 (14.1), 78 (100.0), 63 (33.6), 51 (32.9); CI-MS 227 (21.0, M), 212 (24.0, M - CH_3), 211 (19.7, M - O), 197 (6.6, M - NO), 184 (9.3, M - CH_2=NCH_3).

A portion of this product was dissolved in 1 M HCl, and the solution was lyophilized to give the corresponding hydrochloride, which was identical (UV; TLC, S_{14}) with an authentic sample prepared by method B.

Another portion of **10a** was treated with triphenylphosphine in $CHCl_3$–methanol (1:2) overnight at room temperature. TLC (S_3) showed the presence of *N,N*-dimethyl-2,4-dinitroaniline (**6a**) as the only product.

Method B. Isolation of *N,N*-Dimethyl-2,4-dinitroaniline *N*-Oxide Hydrochloride (10a). A mixture of *N,N*-dimethyl-2,4-dinitroaniline (**6a**, 1 g, 4.74 mmol) and MCPBA (3 g, 13.75 mmol) in benzene (50 mL) was stirred for 3 days at room temperature. The insoluble precipitate was filtered off, washed with chloroform (2 × 30 mL), and dissolved in 1 M HCl. The acid solution was extracted with chloroform (30 mL), and then it was lyophilized. The residue was dissolved in methanol and the product **10a** (hydrochloride) precipitated after addition of chloroform (6–7-fold excess): 0.13 g (10%); homogeneous on TLC (S_{14} and S_{21}); mp above 300 °C; ^{1}H NMR (D_2O, DSS[47]) δ 8.84 (d, 1, H_3, $J_{3,5}$ = 2.4), 8.69 (dd, 1, H_5, $J_{5,3}$ = 2.4, $J_{5,6}$ = 9.3), 8.31 (d, 1, H_6, $J_{6,5}$ = 9.3), 4.13 (s, 6, CH_3). Anal. Calcd for $C_8H_9N_3O_5$·HCl: C, 36.44; H, 3.82; N, 16.09. Found: C, 36.14; H, 3.92; N, 15.90.

Thermolysis of *N*-Oxide 10a. Compound **10a** (ca. 1 mg) was placed in a melting point capillary tube, which was then heated in a Thomas-Hoover apparatus to the melting point of **10a** (90–91 °C). After cooling, the capillary tube was crushed, and the contents were extracted with CH_2Cl_2–methanol (95:5) and examined by TLC (S_4) and paper electrophoresis (see the preceding experiment, method A). The following products were detected in addition to **10a**: **9a**, **8a**, **6a**, and **17** (order of increasing mobility in S_4).[48]

2-(Dimethylamino)pyridine *N*^{2}-Oxide (10c). 2-(Dimethylamino)pyridine (**6c**, 0.1 g, 0.82 mmol) and MCPBA (0.5 g, 2.5 mmol) were stirred in $CHCl_3$ (10 mL) for 2 days at room temperature. TLC (S_3) failed to detect any 2-pyridone (**9c**) in the reaction mixture. The resultant solution was put on a column of silica gel (5 g), which was eluted with $CHCl_3$ (removal of *m*-chlorobenzoic acid) followed by solvent system S_{17}. The latter afforded crystalline **10c**: 0.1 g (90%); homogeneous on TLC (S_3 and S_5); mp 125–127 °C (lit.[14] mp 59–60 °C and lit.[26] mp 126–128 °C); UV max (ethanol) 256 (ϵ 2276 (lit.[14] ϵ 2239)), sh 270 (1724) and 252 nm (2069); ^{1}H NMR ($CDCl_3$) δ 8.48 (d, 1), 8.34 (d, 1), 7.88 (dt, 1), and 7.31 (dq, 1) (aromatic protons), 4.07 (br s, H_2O of hydration, 1 mol), 3.51 (s, 6, CH_3); EI-MS 138 (19.3, M), 122 (66.3, M - O), 107 (51.9, M - O - CH_3), 95 (24.6, M - CH_2=NCH_3), 93 (52.2, M - O - NCH_3), 78 (84.5, M - O - $N(CH_3)_2$), 67 (29.0, 95 - CO), 52 (27.4); CI-MS 139 (100.0, M + H), 122 (73.0, M - O), 95 (51.2, **9c**), 67 (88.7, 95 - CO).

Reaction of 2-(Dimethylamino)-5-nitropyridine (6b) with MCPBA. A mixture of **6b** (0.13 g, 0.78 mmol) and MCPBA (0.51 g, 2.5 mmol) was magnetically stirred in $CHCl_3$ (15 mL) for 30 h at room temperature. The resultant solution was applied on five plates of silica gel, which were developed three times in solvent system S_3. The fastest band was rechromatographed on two plates in the same solvent (developed twice) to give **6b** (43 mg, 33%). The intermediate zone was chromatographed on a column of silica gel (1 × 3 cm) in solvent system S_{16} to afford 5-nitro-2-pyridone (**9b**, 26 mg, 24%), mp 180–184 °C (lit.[49] mp 184–187 °C), identical (^{1}H NMR; UV; TLC, S_5) with an authentic sample. The slowest band was rechromatographed on a single plate in solvent S_2 to give *N*-oxide **11** (9.5 mg, 7%), mp 225–226 °C, identical (^{1}H NMR; TLC, S_5) with a sample obtained by oxidation of 2-(methylamino)-5-nitropyridine (**8b**).

2-(Methylamino)-5-nitropyridine *N*^{1}-Oxide (11). A mixture of 2-(methylamino)-5-nitropyridine (**8b**, 0.5 g, 33 mmol) and MCPBA (3 g, 15 mmol) was stirred in $CHCl_3$ (40 mL) at room temperature for 3 days. The resultant solution was directly chromatographed on a silica gel column (40 g) in $CHCl_3$ (elution of *m*-chlorobenzoic acid) and then in solvent system S_3. The latter eluted *N*-oxide **11**, which was crystallized from methanol to give 186 mg, mp 224–226 °C. The mother liquors were chromatographed on two plates of silica gel in solvent system S_{13}, to give another portion of **11**: 105 mg (total yield 52%); UV max (ethanol) 371 (ϵ 9600), 339 (10350), 247 (13100), and 228 (12700), sh 274 nm (5200); ^{1}H NMR (CD_3SOCD_3, DSS[46]) δ 8.97 (d, 1, H_6, $J_{6,4}$ = 2.5 Hz), 8.44 (poorly resolved d, 1, NH), 8.07 (dd, 1, H_4, $J_{4,6}$ = 2.5, $J_{4,3}$ = 9.3), 6.87 (d, 1, H_3, $J_{3,4}$ = 9.3), 3.02 (d, 3, J_{CH_3NH} = 5.4); EI-MS 169 (M, 41.0), 153 (31.5, M - O), 152 (100.0, M - OH), 124 (16.8), 106 (35.6), 92 (38.4), 78 (40.6), 69 (28.8), 51 (41.0); abundances of *m/e* 140 and 141 [5-nitro-2-pyridone (**9b**)] were 0.3 and 0.8, respectively; CI-MS 170 (9.8, M + H), 154 (4.4, M + H - O). Anal. Calcd for $C_6H_7N_3O_3$·$^1/_{16}H_2O$: C, 42.32; H, 4.22; N, 24.68. Found: C, 42.47; H, 4.18; N, 24.37.

Reaction of 6-Chloropurine Nucleoside 15a with *N,N*-Dimethylhydroxylamine. A mixture of compound **15a** (0.3 g, 0.5 mmol), *N,N*-dimethylhydroxylamine hydrochloride (0.15 g, 1.5 mmol), triethylamine (0.2 mL, 1.4 mmol), and DMF (15 mL) was magnetically stirred for 30 h at room temperature. TLC (S_3) showed the presence of inosine tribenzoate (**4a**) and a small amount of N^6,N^6-dimethyladenosine derivative **3a** as the only products. The solution was evaporated in vacuo, and the residue was partitioned between saturated Na_2CO_3 (20 mL) and $CHCl_3$ (3 × 30 mL). The organic phase was dried ($MgSO_4$), and it was evaporated. The crude product was chromatographed on four plates of silica gel in solvent S_3. The faster moving zone was eluted with S_3, and the eluate was evaporated to give compound **3a** (40 mg, 13%), identical (TLC, S_3, S_7; ^{1}H NMR; UV) with an authentic sample.[5]

The slower moving band gave inosine tribenzoate (**4a**, 0.22 g, 76%) indistinguishable from material obtained by another route (TLC, S_3; ^{1}H NMR; UV). Ammonolysis with NH_3 in methanol gave inosine, which was identified by UV and TLC (S_{15}).

An experiment where *N,N*-dimethylhydroxylamine was replaced with water gave only traces of **4a** in addition to unreacted compound **15a**.

***N,N*-Dimethyl-*O*-(2,4-dinitrophenyl)hydroxylamine (17).** A mixture of 2,4-dinitrofluorobenzene (**16**, 0.15 g, 0.81 mmol), *N,N*-dimethylhydroxylamine hydrochloride (0.2 g, 2.1 mmol), and triethylamine (0.4 mL, 2.8 mmol) was magnetically stirred in DMF (20 mL) for 30 h at room temperature. The resultant solution was evaporated, and the residue was partitioned between water (30 mL) and chloroform (30 mL). The organic phase was dried ($MgSO_4$), it was evaporated, and the residue was chromatographed on two silica gel plates (20 × 20 cm) in chloroform. The faster moving UV-absorbing band was eluted, and the eluate was

(48) Compound **10a** is stable for many months at −15 °C. At room temperature, a slow decomposition was observed to give a pattern of products, **6a**, **8a**, **9a**, and **17**, resembling that from thermolysis.

(49) Tomasik, P.; Plazek, E. *Rocz. Chem.* **1965**, *39*, 1671.

evaporated to give *N,N*-dimethyl-*O*-(2,4-dinitrophenyl)-hydroxylamine (**17**) as orange crystals (0.15 g, 80%), mp 108–110 °C, homogeneous on TLC (S_4). Recrystallization from methanol afforded **17**, mp 111–113.5 °C. TLC (S_4) and paper electrophoresis of the material obtained after determination of the melting point showed only the presence of unchanged **17** in addition to traces of **9a**. UV max (ethanol) 211 (ε 14300), 244 (8800), 293 nm (10600); ^{1}H NMR ($CDCl_3$) δ 8.77 (d, 1, H_3, $J_{3,5}$ = 2.7 Hz), 8.39 (d of d, 1, H_5, $J_{5,3}$ = 2.7 Hz, $J_{5,6}$ = 9.3 Hz), 7.86 (d, 1, H_6, $J_{6,5}$ = 9.3 Hz), 2.90 (s, 6, $N(CH_3)_2$); EI-MS 227 (22.0, M), 184 (68.4, M − CH_2=NCH_3), 168 (6.1), 154 (30.2), 107 (36.9), 91 (46.2), 79 (37.4), 63 (100.0), 53 (68.4); in another run (JMS-D-100, mass range 40–240), fragments 42 (CH_2=N=CH_2), 43 (CH_3N=CH_2), and 44 ($(CH_3)_2N$) were detected; CI-MS 228 (66.8, M + 1), 227 (100.0, M) 185 (29.2, M + 1 − CH_3N=CH_2), 184 (26.5, M − CH_3N=CH_2), 168 (5.3), 154 (11.3), 125 (3.2), 107 (11.8). Anal. Calcd for $C_8H_9N_3O_5$: C, 42.29; H, 3.99; N, 18.50. Found: C, 42.37; H, 4.07; N, 18.60.

The slower moving minor bands gave a mixture of *N,N*-dimethyl- and *N*-methyl-2,4-dinitroaniline (**6a** and **8a**, 9 mg) in the ratio of 34:66 as determined by ^{1}H NMR[50] and a trace of 2,4-dinitrophenol (**9a**).

(50) Determined from the integration curve of CH_3 signals of **6a** and **8a**.

Acknowledgment. Thanks are due to Drs. Robin Hood, D. P. Lin, and Ole Mols from the Central Instrumentation Facility, Department of Chemistry, Wayne State University, for mass and 300-MHz NMR spectra. The 100-MHz spectra and some mass spectra were recorded by Dr. D. P. Lin and Walter Brukwinski at the Michigan Cancer Foundation. The work described herein was supported in part by U.S. Public Health Service Grant CA 21388 from the National Cancer Institute, Bethesda, MD, and in part by an institutional grant to the Michigan Cancer Foundation from the United Foundation of Greater Detroit.

Registry No. **1a**, 1867-73-8; **1b**, 71118-16-6; **2a**, 113509-54-9; **2b**, 113509-55-0; **3a**, 70230-70-5; **3b**, 71118-13-3; **3c**, 71118-15-5; **3d**, 71138-54-0; **4a**, 6741-88-4; **5**, 71118-18-8; **6a**, 1670-17-3; **6b**, 2554-75-8; **6c**, 5683-33-0; **7a**, 113509-56-1; **8a**, 2044-88-4; **8b**, 4093-89-4; **9a**, 51-28-5; **9b**, 5418-51-9; **10a**, 113509-57-2; **10a**·HCl, 113509-59-4; **10c**, 4465-60-5; **11**, 113509-58-3; **15a**, 3510-73-4; **15b**, 5987-73-5; **15c**, 5399-87-1; **16**, 70-34-8; **17**, 29746-97-2; $MeNH_2$·HCl, 593-51-1; Me_2NOH·HCl, 16645-06-0; 2-chloro-5-nitropyridine, 4548-45-2.

Trisubstituted Stannyllithium as a Double Electron Equivalent. Reaction with α,β-Enones[1]

Tadashi Sato,* Masami Watanabe, Toshiyuki Watanabe, Yasuo Onoda, and Eigoro Murayama[†]

Department of Applied Chemistry, Waseda University, Ookubo 3, Shinjuku-ku, Tokyo 160, Japan

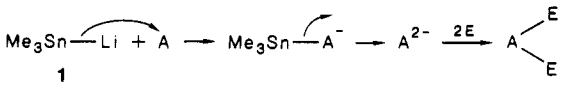
Received August 19, 1987

β-Stannyl ketones, easily available by the conjugate addition of (trimethylstannyl)lithium to α,β-enones, produced two types of ketones depending upon the substitution pattern by the treatment with titanium(IV) chloride. All the reactions proceeded through an intermediacy of cyclopropanol derivatives. The reaction involving the carbon skeleton rearrangement is promising as a synthetic method.

In our previous papers,[2] we described the versatility of the α-stannyl carbanion reagent as a synthetic tool. In these reactions, the reagent reacted with the electrophiles in two ways: first as an explicit carbanion, and second, as a latent carbanion. The net reaction is the replacement of two leaving groups in the substrate with a methylene group, so the reagent can be regarded as a methylene double anion equivalent. As another stannyl compound having an anionic center in the molecule, we chose (trimethylstannyl)lithium (**1**) which is easily available and known to react with electron acceptor A to produce stable stannyl compounds.[3] If electron-withdrawing groups still exist in the resulted stannyl compound, they can induce a heterolysis of the tin–carbon bond, leaving the bond electron on the substrate moiety as shown in Scheme I. Evidently the reagent could be regarded as a double electron equivalent, providing the electron-deficient substrate A with an ability to react with two electrophiles E. In the present study, we found that the reaction using α,β-enones as such an electron-deficient system proceeded in a unique manner and could be utilized as a synthetic method.

It has been known that stannyl compounds having a cationic center at the γ-position cyclize to cyclopropanes

Scheme I



under various conditions.[4] Recently, we reported that γ,δ-epoxy stannyl compounds could be transformed into cyclopropyl-containing derivatives by treatment with Lewis acids.[5] Evidently, the developing cationic center at the oxygen-bearing carbon induced the heterolysis of the carbon–tin bond. The stereochemistry at the reacting centers has been elaborately investigated to conclude that the reaction proceeds with inversion of configuration at both reaction centers.[6] We expected that β-stannyl ketones would behave in a similar way and produce cyclo-

[†] Present address: New Drug Research Laboratory, Chugai Pharmaceutical Co. Ltd., Japan.

(1) Preliminary report: Sato, T.; Watanabe, M.; Murayama, E. *Tetrahedron Lett.* **1986**, *27*, 1621.
(2) Sato, T.; Matsuoka, H.; Igarashi, T.; Minomura, M.; Murayama, E. *J. Org. Chem.*, in press, and references cited therein (submitted).
(3) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.
(4) Hosomi, A.; Inaba, M.; Sakurai, H. *Chem. Lett.* **1983**, 1763 and references cited therein. Kadow, J. F.; Johnson, C. R.; *Tetrahedron Lett.* **1984**, *25*, 5255.
(5) Sato, T.; Watanabe, M.; Murayama, E. *Synth. Commun.* **1987**, *17*, 781.
(6) Fleming, I.; Urch, C. J. *J. Organomet. Chem.* **1985**, *285*, 173. Davis, D. D.; Johnson, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7576.

0022-3263/88/1953-1894$01.50/0