Mechanistic Aspects of the Oxidation of 1,3-Disubstituted 6-Amino-5-nitrosouracils with Lead Tetraacetate: The Formation of Pyrimido[5,4-*g*]pteridinetetrone 10-Oxides

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Received March 18, 1991

Lead tetraacetate oxidation of 1,3-disubstituted 6-amino-5-nitrosouracils **1** in glacial acetic acid results in the formation of 1,3,6,8-tetrasubstituted pyrimido[5,4-*g*]pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxides **2**. ESR studies and a number of chemical observations suggest a novel reaction sequence involving oxidative dimerization of **1** followed by intramolecular cyclization, oxidation, and homolytic elimination of nitrous oxide.

In 1972, two of the present authors (Y.M. and E.C.T.), together with McKillop, reported that 6-amino-1,3-dialkyl(methyl and *n*-butyl)-5-nitrosouracils (**1a,b**) undergo smooth oxidation with lead tetraacetate (LTA) in acetic acid to give the corresponding 1,3,6,8-tetrasubstituted pyrimido[5,4-*g*]pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxides **2a,b**, along with minor amounts of 4,6-dialkyl-(methyl and *n*-butyl)furazano[3,4-*d*]pyrimidine-5,7-(4*H*,6*H*)-diones (**3a,b**).[1] The structure of **2a** was assigned on the basis of degradation studies[1] and was confirmed both by independent synthesis[2] (thermal condensation of **1a** with 6-chloro-1,3-dimethyl-5-nitrosouracil) and by X-ray crystallography.[3]

The 10-oxides **2** exhibit a number of remarkable photochemical properties, many of which appear to be unique for heterocyclic *N*-oxides. For example, **2b** functions efficiently under photochemical conditions as an electron acceptor, as an agent for oxygen atom transfer, and as a dehydrogenation reagent, depending upon the nature of the substrate.[4] In addition, many of these 10-oxides **2** exhibit cytotoxic, antileukemic, antibacterial, and antimycoplasma activities. These diverse properties are probably the consequence of an exceptionally weak N–O bond in the 10-oxide due to its two flanking carbonyl groups and its attachment to the strongly electron-deficient pyrazine ring, itself annulated to two electron-deficient uracil rings.

The present paper addresses itself to the mechanism of formation of **2** from **1**, which has remained obscure since our original discovery of the formation of **2** from **1** upon LTA oxidation. We propose a reasonable reaction pathway involving oxidative dimerization of **1**, followed by an intriguing intramolecular rearrangement accompanied by homolytic elimination of nitrous oxide. Our results also delineate the limitations of this overall transformation; formation of the 10-oxides **2** is limited to 1,3-disubstituted 6-amino-5-nitrosouracils, whereas N-1 and/or N-3 unsubstituted 6-amino-5-nitrosouracils or -pyrimidines (e.g., **1d–f**, **4**,[5] and **6**[6]) are oxidized by LTA exclusively to furazano[3,4-*d*]pyrimidines.

Results

Under the reaction conditions previously utilized for the conversion of **1a,b** to **2a,b**, 6-amino-1,3-diphenyl-5-nitrosouracil (**1c**) was oxidized with LTA in glacial acetic acid to give the 10-oxide **2c** in 80% yield, together with a small amount of 4,6-diphenylfurazano[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**3c**). Reaction of the 1,3-unsubstituted or 1- or 3-monosubstituted uracils **1d**,[7] **1e**,[8] and **1f**,[9] respectively, with LTA under the same conditions gave only the furazano[3,4-*d*]pyrimidines **3d**, **3e**, and **3f**, respectively; 10-oxides corresponding to **2** were not obtained. Similarly, the pyrimidines **4** and **6** were converted exclusively to the corresponding furazano[3,4-*d*]pyrimidines **5** and **7**, and again no oxidative dimerization was observed (Scheme I).[10] It thus seems clear that a requisite structural feature for oxidative dimerization of 6-amino-5-nitrosouracils **1** to **2** is the presence of substituents on both N-1 and N-3.[11]

An investigation of the stoichiometry of the conversion of **1a** to **2a** was also informative. One full equivalent of LTA is required for this conversion. A gas that evolves during the reaction was shown by GC analysis to be nitrous oxide rather than nitrogen, as was originally suggested.[1] The oxidative dimerization of **1a** with LTA to **2a** thus corresponds to the following equation:

$$2C_6H_8N_4O_3 + 2Pb(OAc)_4 \downarrow$$
$$C_{12}H_{12}N_6O_5 + N_2O + 2Pb(OAc)_2 + 4\ AcOH$$

Treatment of 6-amino-1,3-di(*n*-butyl)uracil (**8**) with nitrosonium tetrafluoroborate[12] in acetonitrile containing

(1) Taylor, E. C.; Maki, Y.; McKillop, A. *J. Org. Chem.* **1972**, *37*, 1601.
(2) Maki, Y.; Sako, M.; Taylor, E. C. *Tetrahedron Lett.* **1971**, 4271.
(3) Details will be published independently.
(4) (a) Sako, M.; Shimada, K.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1985**, *26*, 6493; **1986**, *27*, 3877. (b) *Idem. J. Am. Chem. Soc.* **1986**, *108*, 6039. (c) *Idem. J. Chem. Soc., Chem. Commun.* **1986**, 1704. (d) Shimada, K.; Sako, M.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1987**, *28*, 207. (e) Maki, Y.; Sako, M.; Shimada, K.; Murase, T.; Hirota, K. *The Role of Oxygen in Chemistry and Biochemistry*; Ando, W., Morooka, Y., Eds.; Elsevier: Amsterdam, 1988; p 465. (f) Maki, Y.; Shimada, K.; Sako, M.; Kitade, Y.; Hirota, K. *Chem. Pharm. Bull.* **1988**, *36*, 1714. (g) Maki, Y.; Shimada, K.; Sako, M.; Hirota, K. *Tetrahedron* **1988**, *44*, 3187. (h) Maki, Y.; Sako, M.; Oyabu, I.; Murase, T.; Kitade, Y.; Hirota, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1780. (i) Maki, Y.; Oyabu, I.; Ohara, S.; Sako, M.; Kitade, Y.; Hirota, K. *Chem. Pharm. Bull.* **1989**, *37*, 3239. (j) Maki, Y.; Sako, M.; Murase, T.; Kitade, Y.; Hirota, K. *Heterocycles* **1990**, *30*, 279. (k) Sako, M.; Ohara, S.; Shimada, K.; Hirota, K.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 863. (l) Sako, M.; Ohara, S.; Hirota, K.; Maki, Y. *Tetrahedron* **1990**, *46*, 4171.
(5) Schneider, H.-J.; Pfleiderer, W. *Chem. Ber.* **1974**, *107*, 3377.
(6) Ritzmann, G.; Ienaga, K.; Kiriasis, L.; Pfleiderer, W. *Chem. Ber.* **1980**, *113*, 1535.
(7) Taylor, E. C.; Cain, C. K. *J. Am. Chem. Soc.* **1949**, *71*, 2282.
(8) Pfleiderer, W. *Chem. Ber.* **1957**, *90*, 2272.
(9) Ukai, T.; Yamamoto, Y.; Kanemoto, S. *J. Pharm. Soc. Jpn.* **1954**, *74*, 674.
(10) Oxidative intramolecular cyclization of 6-amino-5-nitrosopyrimidines with LTA leading to furazano[3,4-*d*]pyrimidines has been demonstrated with a series of 4,6-diamino-5-nitrosopyrimidines. Cf. Taylor, E. C.; Beardsley, G. P.; Maki, Y. *J. Org. Chem.* **1971**, *36*, 3211.
(11) Analogous results were obtained when iodosobenzene diacetate (IBDA) was employed as an oxidant in place of LTA. These IBDA oxidations, however, proceeded more slowly than in the cases using LTA.

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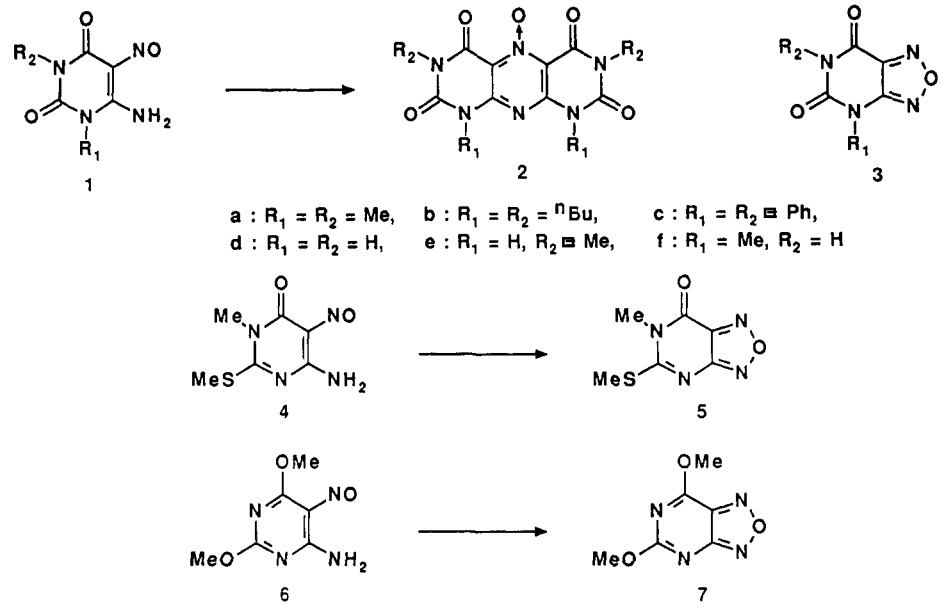
Scheme I



Scheme II

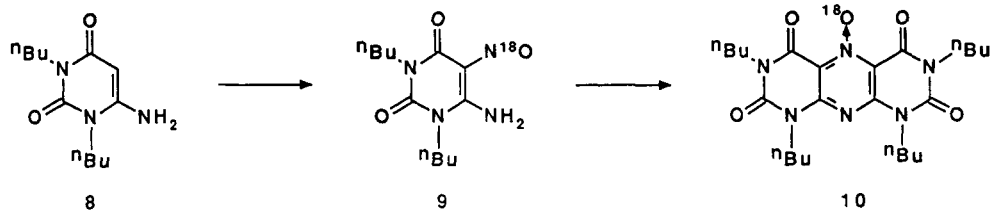
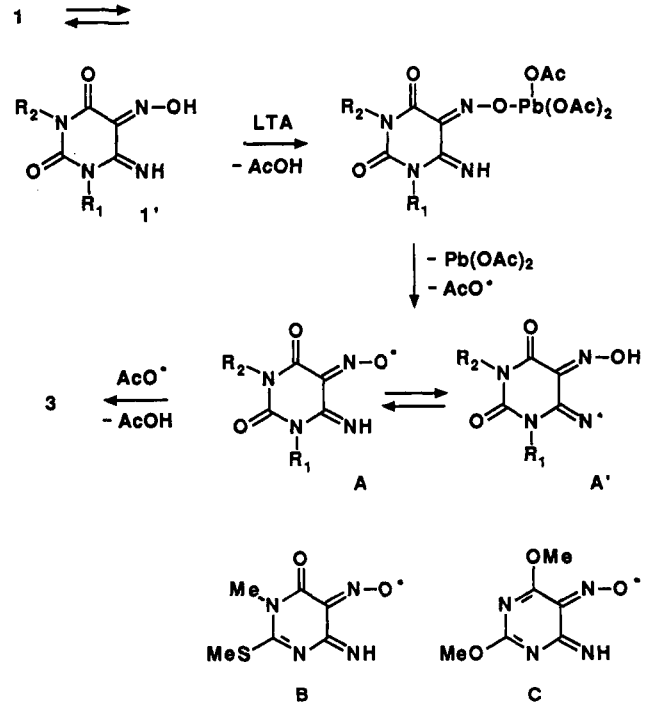


Figure 1. ESR spectrum of a radical generated during the oxidation of 6-amino-1,3-dimethyl-5-nitrosouracil (**1a**) with LTA in acetic acid. The spectrum was taken upon mixing **1a** and LTA in glacial acetic acid at ambient temperature. Conditions: microwave frequency, 9.23 GHz; microwave power, 1 mW; modulation amplitude, 0.02 G; modulation frequency, 100 KHz; magnetic field sweep rate, 25 G/min; time constant, 0.1 s.

^{18}O-labeled water (^{18}O content 97%) gave the 5-nitroso derivative **9** (^{18}O content, 29%) in almost quantitative yield. Subsequent oxidation of **9** with LTA in glacial acetic acid under the usual conditions then gave the *N*-oxide **10**, which was shown by mass spectrometry to be labeled with ^{18}O in the 10-oxide position (^{18}O content, 27%). The origin of the *N*-oxide oxygen in **2** is thus shown unequivocally to be the oxygen atom of the nitroso grouping in its precursor **1** (Scheme II).

Finally, examination of the ESR spectrum of the reaction mixture of **1a** with LTA in glacial acetic acid (Figure 1) showed the generation of a fairly stable nitrogen-containing radical that exhibited a strong signal with hyperfine structure (triple triplet, a_N = 29.8 G and $a_{N'}$ = 2.8 G). The

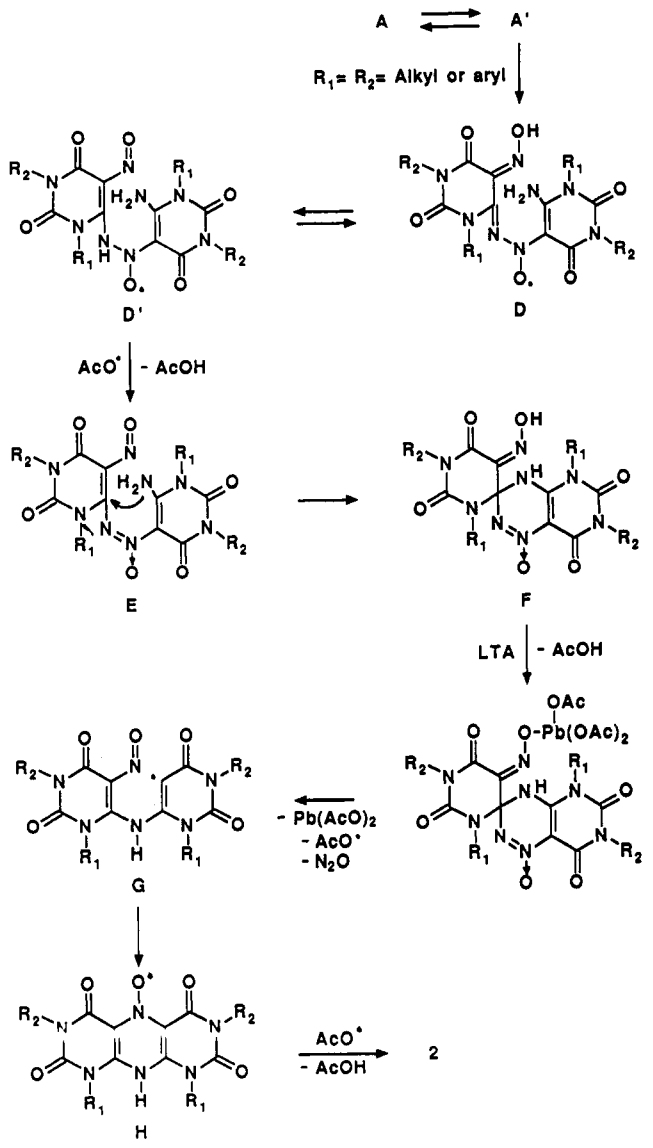
Scheme III



ESR spectrum of the reaction mixture of **4** and LTA, under high modulated conditions, revealed the presence of a weak signal with triplet character (a_N = 30.7 G, $a_{N'}$ = 3.1 G). The ESR spectrum of the reaction mixture of **6** with LTA showed a very weak, poorly resolved triplet signal (a_N = ca. 31 G). We suggest that these nitrogen-containing radicals are probably iminoxyl radicals (see Scheme III,

(12) (a) Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386. (b) Rastetter, W. H.; Gadek, T. R.; Tane, J. P.; Frost, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 2228.

Scheme IV



intermediates A, B and C), with A the most stable.[13,14]

Discussion

Although LTA oxidations of organic substrates can take place either by radical or ionic mechanisms,[15] the detection of nitrogen-containing radicals by ESR spectroscopy in the oxidation of 1 (vide supra) suggests a radical pathway. Our proposal for the mechanism of the conversion of 1 to 2 is summarized in Schemes III and IV; the critical first step is assumed to be one-electron oxidation of 1 (best rationalized in terms of the imino–oxime tautomer for 1) to an iminoxyl radical A.[13] In all probability (from the ESR data summarized above), 4 and 6 also undergo one-electron oxidation to their corresponding iminoxyl radicals B and C. However, A was observed by ESR spectroscopy to be considerably more stable than B or C (probably because of the much reduced aromaticity of the uracil ring in A[16]); the less stable iminoxyl radicals B and C therefore undergo preferential intramolecular trapping and subsequent hydrogen atom abstraction to give furazanopyrimidines 5 and 7. The much more stable A, on the other hand, can react with a molecule of starting material to initiate the cascade of reactions depicted in Scheme IV leading to the 1,3,6,8-tetrasubstituted pyrimido[5,4-*g*]pteridine-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxides 2 in preference to intramolecular trapping to give 3. An associated factor in the formation of 2 from 1 may be the tautomeric preference of 1 for the imino–oxime form, which has been trapped previously in intermolecular reactions.[17] Thus, capture of the imino radical A′ (a tautomer of A) by 1 gives a dimeric nitroxyl radical D:[18] subsequent hydrogen abstraction from D′ by an acetoxy radical gives the azoxy intermediate E, which cyclizes to a spiro intermediate F. At this point in the overall conversion the second half-equivalent of LTA is required; oxidation and loss of N_2O leads to G, which then gives the 10-oxide 2 via oxidation of the nitroxyl radical H by an acetoxy radical. However, despite extensive effort, we were not able to isolate and characterize the presumed intermediates E and F, so that the overall reaction scheme, although reasonable in view of our experimental observations, must be considered speculative.

Since it was not possible to form the 10-oxides 2 by peracid oxidation of the corresponding pyrimido[5,4-*g*]-pteridinetetrones,[1] oxidative dimerization of 1 with LTA remains the only viable method for the preparation of these intriguing and synthetically versatile N-oxides.

Experimental Section

General. Melting points were measured on a Yanagimoto micro hotstage melting point apparatus and are uncorrected. ^1H NMR (270 MHz) spectra were recorded on a JEOL JNM-GX 270 FT NMR spectrometer, and chemical shifts are reported in ppm (δ) downfield from Me_4Si as an internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, m = multiplet, and br = broad), coupling constant (in Hz), and assignment. Infrared spectra were recorded

(13) ESR studies on the oxidation of oximes with LTA have shown that the principal intermediates are the iminoxyl radicals (a_N = ~30 G), which are best represented as hybrids with nitrogen- and oxygen-centered structures. For convenience, the iminoxyl radicals discussed in this paper are formulated as the oxygen-centered structures; cf. Gilbert, B. C.; Norman, R. O. C. *J. Chem. Soc. B* **1966**, 86. Lemaire, H.; Rassat, A. *Tetrahedron Lett.* **1964**, 2245.

(14) The triple triplet nature of the ESR signal given in Figure 1 can be considered to originate primarily from coupling with two ^{14}N atoms, although the coexistence of another radical species is not ruled out on the basis of the hyperfine structure. A shoulder at lowest field and a minor peak at the highest field may be due to the coexistence of another minor radical (N_1 = 32.0 G, N_2 = 2.75 G; the *g* value shifts to high field by 600 mG), which has characteristics similar to those of the main radical species. A computer simulation was in excellent agreement with the actual spectrum given in Figure 1.

The unequal intensity of the primary lines in Figure 1 is probably due to the anisotropic effect of ^{14}N. Taking the nitrogen anisotropy into consideration (cf. Kano, K.; Mori, K.; Uno, B.; Goto, M.; Kubota, T. *J. Am. Chem. Soc.* **1990**, *112*, 8645 and references cited therein), a computer simulation for the ESR spectrum of A proved to be superimposable on the observed spectrum [ΔH(m) = 1.00 G - 0.10 G × m + 0.30 G × m^2; ΔH(m), line width of nuclear spin (m)]. We can therefore reconcile the observed ESR spectrum with the presence of A. Note that the pyrimidines that do not dimerize (4 and 5), but which lead to furazano[3,4-*d*]-pyrimidines, show analogous weak signals.

(15) Hendrickson, J. B. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 47. Butler, R. N. *Synthetic Reagents*; Pizey, J. S., Ed.; John Wiley & Sons: New York, 1977; Vol. 3, p 277.

(16) Kwiatkowski, J. S.; Pullman, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; p 256. Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. In *The Tautomerism of Heterocycles. Advances in Heterocyclic Chemistry, Supplement 1*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1976; p 129.

(17) Cf. Pfleiderer, W.; Kempter, F. E. *Angew. Chem.* **1967**, *79*, 234. Taylor, E. C.; Inbasekaran, M. *Heterocycles* **1978**, *10*, 37.

(18) Intermolecular trapping of A′ by the nitroso group is supported by a cross-over experiment utilizing equimolar amounts of 1a and 4 to give 1,3,6-trimethyl-7-(methylthio)pyrimido[5,4-*g*]pteridine-2,4,5-(1*H*,3*H*,6*H*)-trione 10-oxide (40%) [MS *m/z* 320 (M^+, 21), 320 (M^+ - O, 78), 305 (M^+ - O - CH_3, 7), 291 (M^+ - O - NMe, 19), 275 (100), 247, 231, 188, 107; ^1H NMR (DMSO-d_6) δ 2.77 (3 H, s, SMe), 3.24 (3 H, s, NMe), 3.51 (3 H, s, NMe), 3.62 (3 H, s, NMe); UV (MeOH) λ_{max} 378.4, 286 (sh), 280.0, 252.6 nm], in addition to 2a (44%), 3a (17%), and 5 (59%). Another cross-over experiment was carried out using 1a and 1b, cf. ref 1.

on a Hitachi Model 215 infrared spectrometer. Mass spectra were determined on a JEOL JMS-D 300 spectrometer operating at 70 eV, and UV-vis spectra were measured with a Shimadzu 260 spectrometer. Elemental analyses were performed by the microanalytical laboratory of Gifu Pharmaceutical University. ESR spectra were recorded on a JEOL JES-REX ESR spectrometer. Gas chromatographic analysis was carried out by using a Shimadzu GC-9APT equipped with silica gel (60–80 mesh), 3 m × 3.0 mm i.d. column. For thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Column chromatography was performed on silica gel (Wakogel C-300).

Materials. Anhydrous solvents were distilled and stored over activated 4-Å sieves before use. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Compounds **1d–f**, **4**, and **6** were prepared according to the corresponding literature procedures.[5-9]

Preparation of 6-Amino-1,3-diphenyl-5-nitrosouracil (1c). To a stirred solution of 6-chloro-1,3-diphenyluracil (598 mg, 2.0 mmol) (prepared easily by chlorination of 1,3-diphenylbarbituric acid with $POCl_3$[19]) in dry DMF (3 mL) was added sodium azide (145 mg, 2.2 mmol), and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was poured into water, and the solution was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting residue was purified by column chromatography (chloroform/acetone (40:1)) to give 6-azido-1,3-diphenyluracil (581 mg, 95%), which was recrystallized from ethanol: mp 163–164 °C dec; mass m/z (rel intensity) 305 (M^+, 12), 277 ($M^+ - N_2$, 26), 186 ($M^+ - C_6H_5NCO$, 4), 158 ($M^+ - C_6H_5NCO - N_2$, 40), 144, 130, 119 (C_6H_5NCO, 42), 103 (100); ^1H NMR ($CDCl_3$) δ 5.77 (1 H, s, C_5-H), 7.20–7.30 (4 H, m, ArH), 7.35–7.55 (6 H, m, ArH); IR (KBr) 3120, 2140, 1720, 1665, 1625, 1595 cm^{-1}; UV (MeOH) λ_{max} 286.8, 212.2 nm. Anal. Calcd for $C_{16}H_{11}N_5O_2$: C, 62.94; H, 3.63; N, 22.94. Found: C, 63.19; H, 3.67; N, 22.86.

To a stirred solution of 6-azido-1,3-diphenyluracil (610 mg, 2.0 mmol) in dry THF (10 mL) was added $LiAlH_4$ (80 mg, 2.1 mmol) in small portions at 0 °C, and then the mixture was stirred for 30 min. The solution was evaporated to dryness after quenching of excess $LiAlH_4$ by the addition of a small amount of methanol. The resulting residue was purified by column chromatography (chloroform/methanol (40:1)) to give 6-amino-1,3-diphenyluracil (513 mg, 92%), which was recrystallized from ethanol: mp 279–281 °C; mass m/z (rel intensity) 279 (M^+, 51), 160 ($M^+ - C_6H_5NCO$, 100), 144, 132, 119 (C_6H_5NCO, 22); ^1H NMR ($CDCl_3$) δ 4.68 (2 H, br s, C_6-NH_2), 5.11 (1 H, s, C_5-H), 7.15–7.60 (10 H, m, ArH); IR (KBr) 3300, 3140, 1715, 1640, 1595 cm^{-1}; UV (MeOH) λ_{max} 268.4, 206.6 nm. Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.82; H, 4.67; N, 14.93. In this reaction, a small amount of *N,N'*-diphenylurea was obtained as a byproduct.

To a stirred solution of 6-amino-1,3-diphenyluracil (419 mg, 1.5 mmol) in acetic acid (5.0 mL) containing concd HCl (0.5 mL) was added dropwise an aqueous solution of $NaNO_2$ (98% purity, 111 mg, 1.6 mmol) at 5 °C, and then the stirring was continued for 30 min. The reaction mixture was diluted with water, and the solution was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting residue was washed with ethanol and recrystallized from ethanol to give **1c** (383 mg, 83%): mp 254–257 °C; mass m/z (rel intensity) 308 (M^+, 20), 291 ($M^+ - OH$, 11) 265, 189 ($M^+ - C_6H_5NCO$, 9), 172, 161, 157, 144, 129, 119 (C_6H_5NCO, 100); IR (KBr) 3350, 1740, 1690, 1620, 1500 cm^{-1}; UV (MeOH) λ_{max} 319.6, 229.2 nm. Anal. Calcd for $C_{16}H_{12}N_4O_3 \cdot {}^1/_2C_2H_5OH$: C, 60.97; H, 4.51; N, 16.73. Found: C, 60.81; H, 4.23; N, 17.03.

Reaction of 6-Amino-1,3-diphenyl-5-nitrosouracil (1c) with LTA. To a stirred solution of **1c** (309 mg, 1.0 mmol) in glacial acetic acid (10 mL) was added LTA (90% purity, 544 mg, 1.1 mmol) at ambient temperature, and then the stirring was continued for 30 min. The residue obtained after removal of the solvent under reduced pressure was poured over water, and the suspension was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting residue was subjected to column chromatography using 10% acetone in chloroform as an eluent to give 4,6-diphenylfurazano[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**3c**; 37 mg, 12%) and 1,3,6,8-tetraphenylpyrimido[5,4-*g*]pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxide (**2c**; 227 mg, 80%). **3c**: mp 215–217 °C (from ethyl ether); mass m/z (rel intensity) 306 (M^+, 69), 276 ($M^+ - NO$, 8), 187 ($M^+ - C_6H_5NCO$, 43), 157, 129, 119 (C_6H_5NCO, 42), 77 (100); ^1H NMR ($CDCl_3$) δ 7.31 (2 H, dd, J = 7.8 and 1.5, ArH), 7.45–7.60 (8 H, m, ArH); IR (KBr) 1755, 1710, 1620, 1595, 1540 cm^{-1}; UV (MeOH) λ_{max} 275, 217.6 nm. Anal. Calcd for $C_{16}H_{10}N_4O_3$: C, 62.74; H, 3.29; N, 18.29. Found: C, 62.97; H, 3.28; N, 18.41. **2c**: mp > 300 °C (from methanol); mass m/z (rel intensity) 568 (M^+, 2), 552 ($M^+ - O$, 7), 433 ($M^+ - C_6H_5NCO - O$, 4), 286, 169, 119 (C_6H_5NCO, 11), 44 (100); ^1H NMR ($CDCl_3$) δ 6.98 (4 H, dd, J = 8.0 and 2.2, ArH), 7.12 (4 H, dd, J = 8.0 and 1.5, ArH), 7.10–7.30 (6 H, m, ArH), 7.40–7.50 (6 H, m, ArH); IR (KBr) 1735, 1690, 1575, 1540 cm^{-1}; UV (MeOH) λ_{max} 366.8, 272.6, 209.8 nm. Anal. Calcd for $C_{32}H_{20}N_6O_5$: C, 67.60; H, 3.55; N, 14.78. Found: C, 67.45; H, 3.60; N, 14.67.

Oxidation of 6-Amino-5-nitrosouracil (1d) with LTA. To a suspension of **1d** (32 mg, 0.21 mmol) in glacial acetic acid (5 mL) was added LTA (122 mg, 0.25 mmol), and then the mixture was stirred at ambient temperature for 1 day. The UV spectrum of the reaction mixture showed no absorption band at 370 nm, which is characteristic of the pyrimidopteridine ring system. After removal of the precipitate (6 mg, **1d** by TLC analysis and UV spectroscopy, 19%) and solvent, the resulting residue was subjected to column chromatography (chloroform/methanol (20:1)) to give furazano[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**3d**; 21 mg, 66% based on the employed **1d**), which was recrystallized from ethyl ether: mp 248–251 °C; mass m/z (rel intensity) 154 (M^+, 100), 122, 111 ($M^+ - HNCO$, 32), 97, 81; IR (KBr) 3230, 1760, 1725, 1700, 1640 cm^{-1}; UV (MeOH) λ_{max} 275.8, 232.8 nm. Anal. Calcd for $C_4H_2N_4O_3 \cdot {}^1/_{20}(C_2H_5)O$: C, 31.96; H, 1.60; N, 35.50. Found: C, 31.87; H, 1.74; N, 35.65.

Oxidation of 6-Amino-3-methyl-5-nitrosouracil (1e) with LTA. To a suspension of **1e** (17.1 mg, 0.10 mmol) in glacial acetic acid (5 mL) was added LTA (54.3 mg, 0.11 mmol), and then the mixture was stirred at ambient temperature for 1 day. TLC analysis (chloroform/methanol (10:1)) of the reaction mixture showed the presence of a sole product whose R_f value was higher than that of **1e**, along with unchanged **1e**. After removal of the precipitate (8.0 mg, **1e** by TLC analysis and UV spectroscopy, 47%) by filtration, the filtrate was evaporated to dryness. The resulting residue was subjected to column chromatography (chloroform/methanol (30:1)) to give 6-methylfurazano[3,4-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione (**3e**; 8.0 mg, 48% based on the employed **1e**), which was recrystallized from ethyl ether: mp 167–169 °C; mass m/z (rel intensity) 168 (M^+, 100), 138 ($M^+ - NO$, 16), 111 ($M^+ - MeNCO$, 18); ^1H NMR (DMSO-d_6) δ 3.29 (3 H, s, NMe), 12.77 (1 H, br s, NH); IR (KBr) 3200, 1745, 1710, 1640 cm^{-1}; UV (MeOH) λ_{max} 270 (sh), 243.4 nm. Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.98; H, 2.41; N, 33.49.

Oxidation of 6-Amino-1-methyl-5-nitrosouracil (1f) with LTA. To a suspension of **1f** (86.0 mg, 0.5 mmol) in glacial acetic acid (10 mL) was added LTA (299 mg, 0.61 mmol), and then the mixture was stirred at ambient temperature overnight. TLC analysis (chloroform/methanol (10:1)) of the reaction mixture showed complete consumption of **1f** and the presence of one major product and two minor products whose R_f values were higher than that of **1f**. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography (chloroform/methanol (10:1)) to give 4-methylfurazano[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**3f**; 58 mg, 68%) [mp 179–180 °C (from ethyl ether); mass m/z (rel intensity) 168 (M^+, 96), 138 ($M^+ - NO$, 23), 125 ($M^+ - HNCO$, 33), 67 (100); ^1H NMR (DMSO-d_6) δ 3.41 (3 H, s, NMe), 12.16 (1 H, br s, NH); IR (KBr) 3200, 3100, 1760, 1710, 1625, 1555 cm^{-1}; UV (MeOH) λ_{max} 282.6, 232.4, 206.6 nm. Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.40, N, 33.33. Found: C, 35.96; H, 2.43; N, 33.52], the unknown minor product (9 mg) [mass m/z 224 (46), 208 (90), 195 (29), 189 (9), 152 (7), 136 (21), 109 (18); ^1H NMR (DMSO-d_6) δ 3.41 (3 H, s, NMe), 7.82 (1 H, br, NH), 8.19 (1 H, br, NH); UV (MeOH) λ_{max} 336.8, 249.6, 236.4 nm], and 3-(carbamoylmethylamino)-4-carboxy-1,2,5-oxadiazine (13 mg, 14%) [mp 305–310 °C dec (from methanol); mass m/z (rel intensity) 186 (M^+, 26), 168 ($M^+ - H_2O$, 70), 156 ($M^+ - NO$, 15), 138 ($M^+ - H_2O - NO$, 14), 125 ($M^+ - H_2O - HNCO$, 30), 109,

(19) Goldner, H.; Dietz, G.; Carstens, E. *Liebigs Ann. Chem.* **1966**, *691*, 142.

67 (100); ^{1}H NMR (DMSO) δ 3.37 (3 H, s, NMe), 9.0 and 9.5 (each 1 H, each br, NH_2), 11.31 (1 H, br, CO_2H); IR (KBr) 3550, 3500, 3380, 3200, 1720, 1695, 1630, 1560, 1520 cm^{-1}; UV (MeOH) λ_{max} 313.4, 224.0 nm. Anal. Calcd for $C_5H_6N_4O_4 \cdot H_2O$: C, 29.41; H, 3.95; N, 27.45. Found: C, 29.36; H, 3.86; N, 27.44].

Oxidation of 6-Amino-3-methyl-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one (4) with LTA. To a solution of **4** (21 mg, 0.1 mmol) in glacial acetic acid (2 mL) was added LTA (57 mg, 0.12 mmol), and then the mixture was stirred for 30 min. TLC analysis (chloroform/acetone (10:1); chloroform/methanol (10:1)) of the reaction mixture showed complete consumption of **4** and the presence of a sole product whose R_f value was higher than that of **4**. After removal of the solvent, the residue was purified by column chromatography (chloroform) to give 6-methyl-5-(methylthio)furazano[3,4-*d*]pyrimidin-7(6*H*)-one (**5**; 20 mg, 96%), which was recrystallized from ethyl ether: mp 142–143 °C; mass *m/z* (rel intensity) 198 (M^+, 39), 183 (M^+ – Me, 10), 168 (M^+ – NO, 42), 153, 131, 125, 111, 67 (100); ^{1}H NMR ($CDCl_3$) δ 2.72 (3 H, s, SMe), 3.64 (3 H, s, NMe); IR (KBr) 1725, 1710, 1595, 1535 cm^{-1}; UV (MeOH) λ_{max} 306.4, 248.2, 204.6 nm. Anal. Calcd for $C_6H_6N_4O_2S$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.64; H, 3.13; N, 28.43.

Oxidation of 6-Amino-2,4-dimethoxy-5-nitrosopyrimidine (6) with LTA. To a solution of **6** (18.5 mg, 0.1 mmol) in glacial acetic acid (2 mL) was added LTA (57 mg, 0.12 mmol), and then the mixture was stirred at ambient temperature for 1 h. TLC analysis (chloroform/acetone (10:1)) of the reaction mixture showed the presence of a sole product whose R_f value was higher than that of **6**. After removal of the solvent under reduced pressure, the residue was purified by column chromatography using chloroform as an eluent to give 5,7-dimethoxyfurazano-[3,4-*d*]pyrimidine (**7**; 17.6 mg, 96%), which was recrystallized from ethyl ether: mp 105–106 °C; mass *m/z* (rel intensity) 182 (M^+, 37), 152 (M^+ – NO, 100), 111; ^{1}H NMR ($CDCl_3$) δ 4.17 (3 H, s, OMe), 4.31 (3 H, s, OMe); IR (KBr) 1625, 1565, 1545 cm^{-1}; UV (MeOH) λ_{max} 303.0, 247.2, 205.6 nm. Anal. Calcd for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.84; H, 3.35; N, 30.58.

Determination of the Gas Evolved during Oxidation of 6-Amino-1,3-dimethyl-5-nitrosouracil (1a) with LTA. The LTA oxidation of **1a** (3.68 g, 20.0 mmol) in glacial acetic acid (20 mL) was carried out in a sealed flask (50 mL) equipped with a balloon. The reaction was mildly exothermic and proceeded with evolution of a gas to give 1,3,6,8-tetramethylpyrimido[5,4-*g*]-pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxide (**2a**) and 4,6-dimethylfurazano[3,4-*d*]pteridine-5,7(4*H*,6*H*)-dione (**3a**) as previously reported.[1] GC analysis showed that the gas collected in the balloon was nitrous oxide whose retention time is clearly distinguishable from that of nitrogen [retention time, N_2O = 9.17 min; N_2 = 1.22 min (column temperature, 60 °C; injection temperature, 80 °C; detector temperature, 90 °C; carrier gas, He (40 μL/min); detector, TCD; current 150 μA)].

Preparation of 1,3,6,8-Tetra-*n*-butylpyrimido[5,4-*g*]pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-[^{18}*O*]Oxide (10). To a solution of 6-amino-1,3-di-*n*-butyluracil (**8**; 239 mg, 1.0 mmol) in acetonitrile (7.0 mL) containing $H_2{}^{18}O$ (25 μL; ^{18}O content, 97%) was added dropwise at 0 °C a solution of nitrosonium tetrafluoroborate[12] (140 mg, 1.2 mmol) in acetonitrile, and then the mixture was stirred for 30 min. The mixture was briefly heated to 50 °C after gas evolution had subsided. After removal of the solvent under reduced pressure, the resulting residue was poured over water and the mixture was extracted with chloroform. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give [*N*-^{18}*O*]-6-amino-1,3-di(*n*-butyl)-5-nitrosouracil (**9**; 267 mg, 99%; ^{18}O content, 29%, by MS) in an almost pure state. ^{18}O-Labeling of the nitroso group in **9** was confirmed by comparison of the fragmentation pattern of its mass spectrum with that of **1b**, and its ^{18}O content was conveniently determined by comparison of the peak intensity of $M^+ + 2$ with that of M^+ in the mass spectra of **9** and **1b**.

Oxidation of the [N-^{18}O]-6-amino-5-nitrosouracil (122 mg, 0.45 mmol) with LTA (246 mg, 0.5 mmol) followed by column chromatographic purification using chloroform as the eluent gave the ^{18}O-labeled *N*-oxide **10** (93 mg, 84%; ^{18}O content, 27%, by MS) together with the furazanopyrimidine. ^{18}O-Labeling of the *N*-oxide oxygen in **10** was confirmed by the observation of the M^+ (*m/z* 490) and $M^+ - 18$ (*m/z* 472) peaks in the mass spectrum of **10**. Its ^{18}O content was conveniently determined by comparison of the peak intensity of $M^+ + 2$ with that of M^+ in the mass spectra of **10** and **2b**.

Registry No. **1a**, 6632-68-4; **1c**, 135396-30-4; **1d**, 5442-24-0; **1e**, 61033-04-3; **1f**, 6972-78-7; **2c**, 135396-31-5; **3c**, 135396-32-6; **3d**, 135396-33-7; **3e**, 135396-34-8; **3f**, 135396-35-9; **4**, 42026-60-8; **5**, 135396-36-0; **6**, 73978-73-1; **7**, 135396-37-1; **8**, 41862-16-2; **9**, 135396-38-2; **10**, 132716-85-9; 6-chloro-1,3-diphenyluracil, 5759-74-0; 6-azido-1,3-diphenyluracil, 135396-39-3; 6-amino-1,3-diphenyluracil, 135396-40-6; 3-(carbamoylmethylamino)-4-carboxy-1,2,5-oxadiazine, 135396-41-7; lead tetraacetate, 546-67-8.

Supplementary Material Available: Computer simulations of the ESR spectra of radical A and Figure 1 (2 pages). Ordering information is given on any current masthead page.