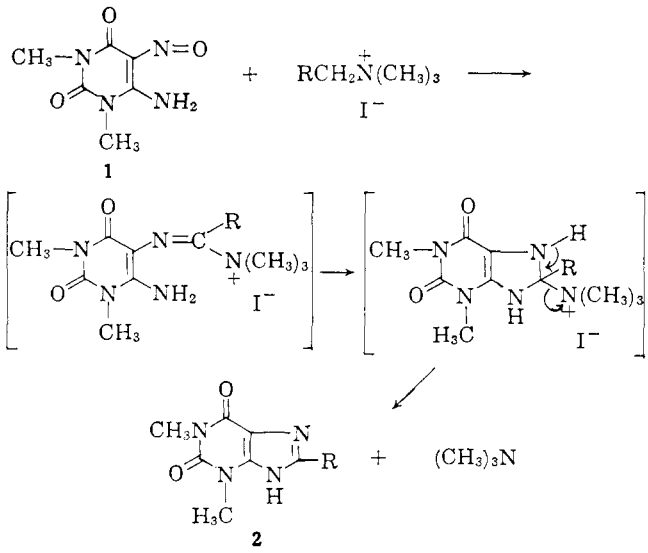
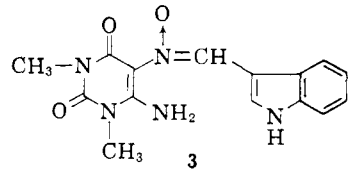


addition of the nitroso nitrogen to the methylene grouping in a manner analogous to the common Michael reaction (skatylation) observed with gramine.[7] The product of this condensation would be the nitrone (**3**),



which should undergo immediate intramolecular addition of the *ortho*-situated amino group to the polarized >C=N→O bond.[8] Dehydration of this addition product leads directly to **2** (R = 3′-indolyl).

It is interesting to note that the methylene component need not be activated provided that condensation with the 5-nitroso group is intramolecular and that sufficiently strenuous conditions are employed. Thus, it has recently been reported[9] that 4-amino-5-nitrosouracil derivatives carrying $-CH_2-$ or $-CH_3$ substituents on the 4-amino group are cyclized by thermally induced intramolecular dehydration to 8-substituted xanthines.

(7) For an exhaustive discussion of these reactions see H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, G.m.b.H., Weinheim/Berstr., 1960.

(8) The formation of a nitrone by condensation of a quaternized pyrrole Mannich base with *p*-dimethylaminonitrosobenzene has been demonstrated [A. Triebs and G. Fritz, *Angew. Chem.*, **66**, 562 (1954)], but the reaction appeared to fail with gramine itself.

(9) H. Goldner, G. Dietz, and E. Carstens, *Naturwiss.*, **51**, 137 (1964).

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## Synthesis of 8-Substituted Theophyllines. Isolation of a 7-N-Oxide Intermediate and an Unusual Leuckart Reduction with Dimethylformamide[1]

*Sir:*

We wish to describe a new synthesis of 8-substituted theophyllines in which a 7-N-oxide has been characterized as an intermediate, and an unusual Leuckart-type reduction of the latter effected by dimethylformamide.

Treatment of 1,3-dimethyl-4-amino-5-nitrosouracil (**1**) with benzaldehyde in dimethylformamide solution results in the evolution of dimethylamine and the separation of 8-phenyltheophylline (**6**).[2] Concentration of the filtrate gives a second, lower melting product which is extremely light sensitive; m.p. dec. above 169°. *Anal.* Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.25; H, 4.39; N, 20.71. Although this compound is isomeric with the simple anil **2**, its solubility in dilute sodium hydroxide solution and the observation that it gives a positive ferric chloride test identifies it as the 7-N-oxide **3**.[3] This was confirmed by methylation in dilute alkaline solution with dimethyl sulfate to give a white, light-stable crystalline O-methyl derivative **4**; n.m.r. ($DCCl_3$) sharp, unsplit singlets at $\tau$ 6.65, 6.45, and 5.92. *Anal.* Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.76; H, 4.79; N, 19.95. Catalytic reduction results in cleavage of the O-methyl group with the formation of 8-phenyltheophylline (**6**).

Heating the N-oxide **3** in dimethylformamide results in the evolution of dimethylamine and the formation of **6**; the N-oxide **3** is clearly an intermediate in the conversion of **1** to **6**. The reduction of **3** by dimethylformamide may be explained by formation of an intermediate complex (**5**), which can undergo an intramolecular oxidation–reduction sequence either by transfer of a hydride ion to the 8-position of the purine ring (path a) or by direct collapse to **6**, carbon dioxide, and dimethylamine (path b), perhaps *via* a cyclic transition state involving the 6-carbonyl group. In both cases considerable driving force would derive from the delocalization possible in the initially formed anions. To our knowledge this is the first example of the participation of dimethylformamide alone as the reducing agent in a Leuckart-type reduction.

Since a mixture of the N-oxide **3** and 8-phenyltheophylline (**6**) was formed in the above reaction of **1**, benzaldehyde, and dimethylformamide, reduction of **3** must take place slowly under these conditions, and it was reasoned that addition of a more effective reducing agent to the reaction medium should result in higher yields of **6**. In accordance with this expectation, addition of formic acid resulted in the formation of **6** in moderate yield; no N-oxide was isolated. We were able to isolate and characterize 1,3,6,8-tetramethyl-2,4,5,7-(1H,3H,6H,8H)pyrimido[5,4-*g*]pteridinetetrone (**7**)[4] and 1,3-dimethyluric acid[5] as by-products in this reaction.

The reaction of **1** with aldehydes in a mixture of dimethylformamide and formic acid appears to be a general synthesis of 8-substituted theophyllines. Indole-

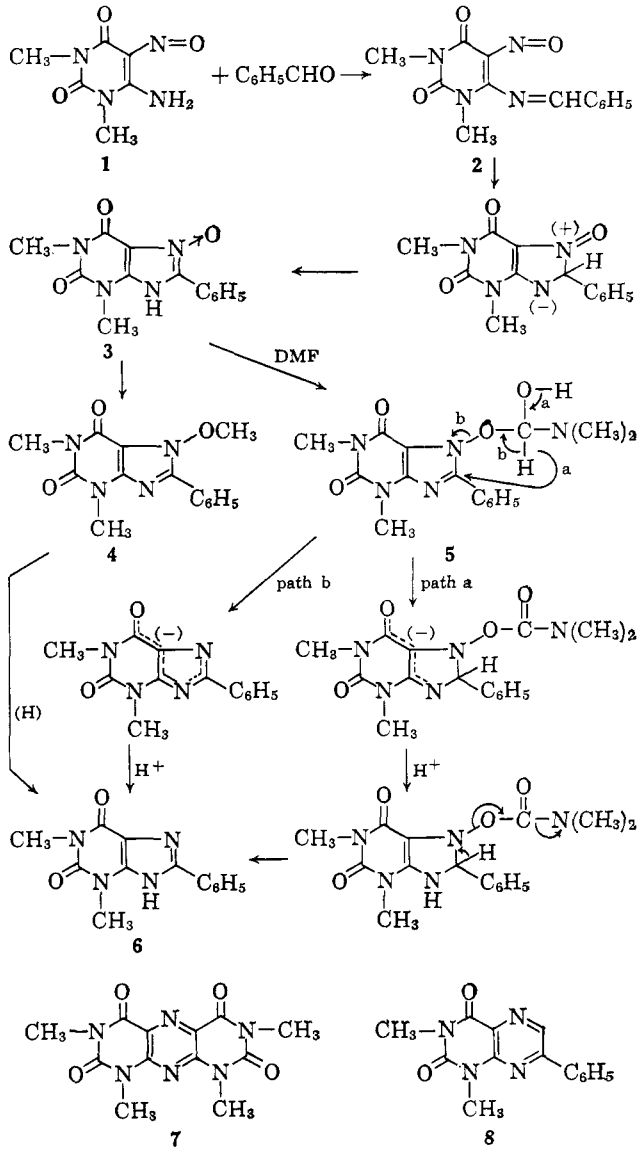
(1) This work was supported by a research grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) This compound has been described by G. P. Hager and C. Kaiser, *J. Am. Pharm. Assoc.*, **43**, 148 (1954); it was prepared by condensation of 1,3-dimethyl-4,5-diaminouracil and benzoic acid in the presence of phosphorus oxychloride.

(3) Some years ago Timmis (G. M. Timmis, I. Cooke, and R. G. W. Spickett in "The Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., J. and A. Churchill, Ltd., London, 1957, p. 134) reported some preliminary experiments in which a purine 7-N-oxide resulted from the reaction of a 4-amino-5-nitrosopyrimidine with an aldehyde anil. The reaction failed with aldehydes themselves. This work has not been reported in detail.

(4) E. C. Taylor, C. K. Cain, and H. M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954).

(5) W. Traube, *Ber.*, **33**, 3035 (1900).




3-carboxaldehyde, 1-naphthaldehyde, *p*-nitrobenzaldehyde, and anisaldehyde gave the corresponding 8-substituted theophyllines: 8-(3′-Indolyl)theophylline melted >360°. *Anal.* Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.01; H, 4.44; N, 23.86. 8-(1′-Naphthyl)theophylline melted at 328–329°. *Anal.* Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29. Found: C, 66.70; H, 4.54; N, 18.36. 8-(*p*-Nitrophenyl)theophylline melted >360°. *Anal.* Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.25. Found: C, 51.61; H, 3.69; N, 23.19. 8-(*p*-Methoxyphenyl)theophylline melted >360°. *Anal.* Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.55; H, 4.97; N, 19.74.

By analogy with the preceding results, condensation of **1** with phenylglyoxal should have given 8-benzoyltheophylline, or perhaps the secondary alcohol formed by reduction of the carbonyl group with formic acid. However, the reaction took a completely unexpected course and gave 1,3-dimethyl-7-phenyl-2,4-(1H,3H)-pteridinedione (**8**)[6] and 1,3-dimethyl-4-amino-5-benzamidouracil (**9**) (m.p. 287–289°; $\nu_{max}^{Nujol}$ 3400, 3355, and 3200 cm.$^{-1}$. *Anal.* Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.97; H, 5.09; N, 20.23) in approximately equal amounts. The former compound must arise by initial reduction of **1** with formic acid to 1,3-dimethyl-4,5-diaminouracil, followed by condensation with phenylglyoxal (thus giving the 7-phenyl isomer exclusively),[7-9] while the latter compound apparently arises by initial condensation of the 4-amino group of **1** with phenylglyoxal followed by reduction of the nitroso group to the hydroxylamino stage, cyclization, dehydration, and deformylation.

During the course of this work it was noted that **1** behaved anomalously on heating. The compound decomposes at its melting point with copious evolution of brown fumes and the loss of its characteristic lavender color, but as the temperature is raised above the melting point the melt resolidifies to an orange solid which does not melt below 360°. We have identified the latter compound as the pyrimidopteridine **7** and suggest that it arises by a reverse-nitrosation reaction (which apparently can be either thermally or acid induced) to give 1,3-dimethyl-4-aminouracil, which then condenses with unchanged **1** to give **7**.[10]

The many complex reactions undergone by the 4-amino-5-nitrosopyrimidine **1** under apparently straightforward conditions call attention to the possibility that similar complications may arise with other 4-amino-5-nitrosopyrimidines, which are ubiquitous intermediates for the synthesis of purines, pteridines, and other fused pyrimidine heterocycles.

(6) G. P. G. Dick, H. C. S. Wood, and W. R. Logan, *J. Chem. Soc.*, 2131 (1956).

(7) A. Albert, *Quart. Rev.* (London), **6**, 227 (1952).

(8) W. R. Boon, *J. Chem. Soc.*, 2146 (1957).

(9) R. B. Angier, *J. Org. Chem.*, **28**, 1398 (1963).

(10) M. Ridi, C. Pellerano, and E. Masi, *Ann. Chim.* (Rome), **53**, 1717 (1963); *Chem. Abstr.*, **60**, 10,684*b* (1964).

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## A Nuclear Magnetic Resonance Study of a Carbonium Ion Exchange Reaction

*Sir:*

We wish to report that halide exchange occurs between covalent trityl halides and trityl cations and that the n.m.r. method readily provides data on the rates and mechanism of this exchange process.

The n.m.r. spectrum[1] of a methylene chloride solution of tris(*p*-tolyl)methyl chloride (I) exhibits sharp lines at −424.5 and −139.5 c.p.s. for phenyl and methyl protons while the carbonium ion tris(*p*-tolyl)-methyl hexachloroantimonate (II) displays an $A_2B_2$ quartet centered at −457.5 c.p.s. (phenyl) and a singlet at −162 c.p.s. (methyl). The individual spectra are essentially independent of temperature and solvent, in contrast to a mixture of the two components.

Time-averaged, temperature-dependent methyl proton resonances of an equimolar mixture of I and II in methylene chloride are shown in Fig. 1. At 37° the sharp singlet is at precisely the chemical shift (−151 c.p.s.) expected for exchange averaging of the methyl protons of I and II and varies directly with the mole fraction of the constituents. As the temperature is

(1) Varian A-60 spectrometer; internal TMS.