acid was added followed by a small amount of absolute ether. This compound, m.p. 138°, is relatively stable.

2-Phenoxyacetyl-4-propylcarbaminooxazoline (XIX).—Attempts to prepare the oxazoline by the usual method in methanol with potassium acetate or sodium methylate were unsuccessful, possibly because boiling temperature was necessary to dissolve the starting material. However, by changing the solvent from methanol to dimethylformamide, free oxazoline was prepared. To a solution of 4.34 g (0.01 mole) of XVII in 10 ml. of DMF was added 10 ml. of 1 *N* sodium methylate. After standing at room temperature for 10 min. water was added and the product was removed by extraction with ether. Evaporation of the ether left a low melting solid in practically quantitative yield, m.p. 52° after two recrystallizations from ether–petroleum ether.

Addition of the calculated amount of tosic acid to the oxazoline in acetone and subsequent recrystallization of the salt from acetone and ethyl acetate gave the hydrolysis product identical with XVIII. Free oxazoline is unaffected by 1 *N* KOH in aqueous methanol at room temperature.

N-Carbobenzoxydehydroalanine *n*-Propylamide (XXIII).—Reaction of XXII with an equivalent amount of dilute sodium methylate gave very gummy solids in 70% yield. A crystalline solid, m.p. 68°, was obtained after several recrystallizations from ether-petroleum ether. The compound took up 0.8 equiv. of bromine.

Analyses of oxazolines and dehydroalanines are listed in Table IV.

Bromination.—The possible formation of an unsaturated compound was tested by uptake of bromine. The method we used is a modification of standard methods. Less than 40 μmoles of compound was dissolved in 1.0 ml. of glacial acetic acid and 1 ml. of 0.1 *N* $KBrO_3$ (standard) and 0.1 ml. of 4 *N* HCl were added. After 5 min. 200 mg. of KI was added and the iodine was titrated with 0.1 *N* $Na_2S_2O_3$ with starch as an indicator.

TABLE IV

	Analyses, %							
	Carbon		Hydrogen		Nitrogen		Sulfur	
Compd.	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IV	54.54	54.47	4.58	4.74	10.60	10.99		
V	54.54	54.68	4.58	4.75	10.60	10.46		
VI	50.85	50.55	3.41	3.42	11.86	11.52		
X	56.31	55.91	5.45	5.46	15.16	15.27		
XII	57.28	57.27	5.07	5.17	3.70	3.87	8.50	8.79
XIX	64.10	62.90	6.92	7.02	10.68	10.76		

Bromination helped in the identification of the compounds. N-Carbobenzoxydehydroalanine benzyl ester took up 0.85 equiv. of bromine, and compound V 0.97 equiv. Compound XXIII took up 0.80 equiv. Oxazolines and other compounds did not take up more than 0.05 equiv. All phenoxyacetyl derivatives used up 1.0 equiv. of bromine due to substitution in the ring.

Oxazolines were further identified by the formation of tosic acid salts and/or their hydrolytic products, O-acylserine ester or amide tosic acid salts, as indicated above.

Acknowledgment.—The authors are pleased to express their indebtedness to Miss Roberta Rio for assistance in this work.

COMMUNICATIONS TO THE EDITOR

A New Purine Synthesis[1]

Sir:

The condensation of a 4-amino-5-nitroso-pyrimidine with an active methylene compound has become a classical synthetic route to pteridines in those cases where the intermediate anil is capable of intramolecular cyclization by addition of the *o*-amino group to an appropriately situated electrophilic center. Thus, condensation of a 4-amino-5-nitroso-pyrimidine with barbituric acid,[2] cyanoacetic acid,[3] or phenylacetonitrile[4] gives pyrimidopteridines, 7-aminopteridine-6-carboxylic acids, or 6-phenyl-7-aminopteridines, respectively. This reaction has recently been reviewed.[5] It appeared to us that this condensation was potentially capable of giving purines rather than pteridines provided that the *ortho*-situated amino group could be induced to add intramolecularly to the anil grouping itself rather than to an electrophilic center attached to the anil carbon. Aromatization to the final purine would then result from elimination or oxidation.

An attractive candidate for the active methylene component appeared to be a quaternized Mannich base, since the requisite intramolecular addition–cyclization reaction would be facilitated by the positively charged anil nitrogen. Furthermore, the terminal aromatization reaction would involve loss of trimethylamine and thus parallel the Hofmann elimination reaction, which proceeds with great facility when leading to an aromatic system.

We wish to describe a new purine synthesis based upon this principle. Thus, condensation of 1,3-dimethyl-4-amino-5-nitrosouracil (**1**) with benzyltrimethylammonium iodide in refluxing dimethylformamide solution resulted in the evolution of trimethylamine and the separation in 31% yield of 8-phenyltheophylline (**2**, R = C_6H_5).

This reaction appears to be equally applicable to other quaternized Mannich bases.[6]

The only nonquaternized Mannich base which was successfully employed in this condensation reaction was gramine. Condensation of this latter compound with **1** in refluxing dimethylformamide solution resulted in evolution of dimethylamine and the separation of the novel 8-(3′-indolyl)theophylline (**2**, R = 3′-indolyl). An attractive mechanism for this facile condensation involves initial elimination of dimethylamine from gramine, perhaps catalyzed by the nitrosopyrimidine, to 3-methyleneindolenine, followed by nucleophilic

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

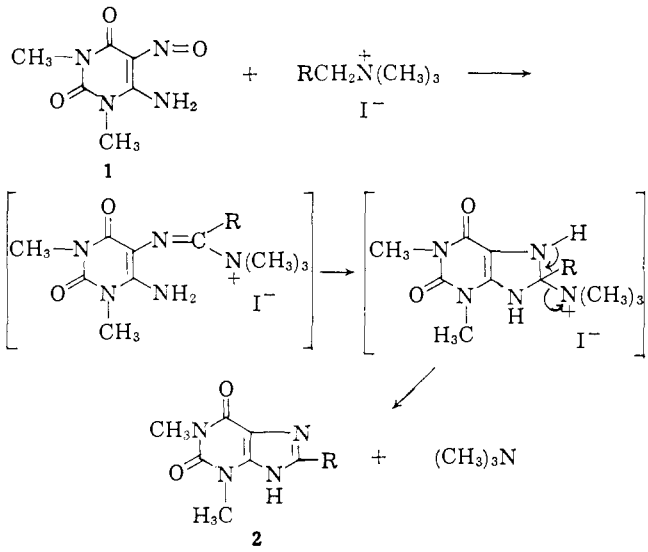
(2) G. M. Timmis, *Nature*, **164**, 139 (1949); G. M. Timmis, U. S. Patent 2,581,889 (Jan. 8, 1952); *Chem. Abstr.*, **46**, 7594 (1954).

(3) T. S. Osdene and G. M. Timmis, *Chem. Ind.* (London), 405 (1954).

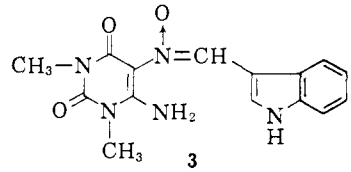
(4) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

(5) T. S. Osdene in "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., Pergamon Press, London, 1964, pp. 65–73.

(6) Additional compounds prepared by this method were **2**, R = 3′-methyl-1′-indolyl, R = 3′,5′-dimethyl-4′-hydroxyphenyl, and R = 3′-methyl-2′-hydroxyphenyl. Satisfactory analytical data were obtained for all compounds reported.



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 τ 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).