A New Synthesis of Fervenulin 4-Oxide

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The reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (I) with Vilsmeier reagent (dimethylformamide-phosphorus oxychloride) afforded fervenulin 4-oxide (II) in good yield.

J. Heterocyclic Chem., **14**, 175 (1977).

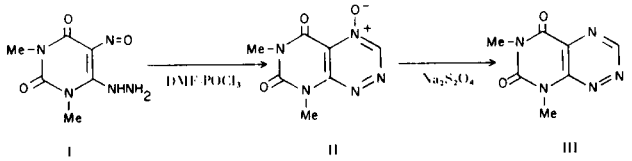
Sir:

In connection with considerable recent interest in the chemistry and biology of pyrimido[5,4-*e*]-*as*-triazines (1), we wish to report a new convenient synthesis of fervenulin 4-oxide (II), which can not be obtained by conventional peroxyacid oxidation (2), by treatment of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (I) (3) with Vilsmeier reagent (dimethylformamide-phosphorus oxychloride).

The suspension of I (10 mmoles) in dimethylformamide (3 ml.) was stirred at 0° while the Vilsmeier reagent, prepared from dimethylformamide (40 mmoles) and phosphorus oxychloride (10 mmoles), was added dropwise. After stirring for 30 minutes at room temperature, the solution was diluted with ethanol and evaporated *in vacuo*. The residue was poured onto ice-water and the precipitated solid was recrystallized from ethanol to give II (72%, m.p. 179-180°). The structure of II (4) was assigned by elemental analysis, satisfactory spectral data, especially the presence of its strong parent ion and remarkable M-16 ion in the mass spectrum, and the formation of an antibiotic fervenulin (III) (5) (78%) by its reduction using sodium dithionite in water (Scheme I).

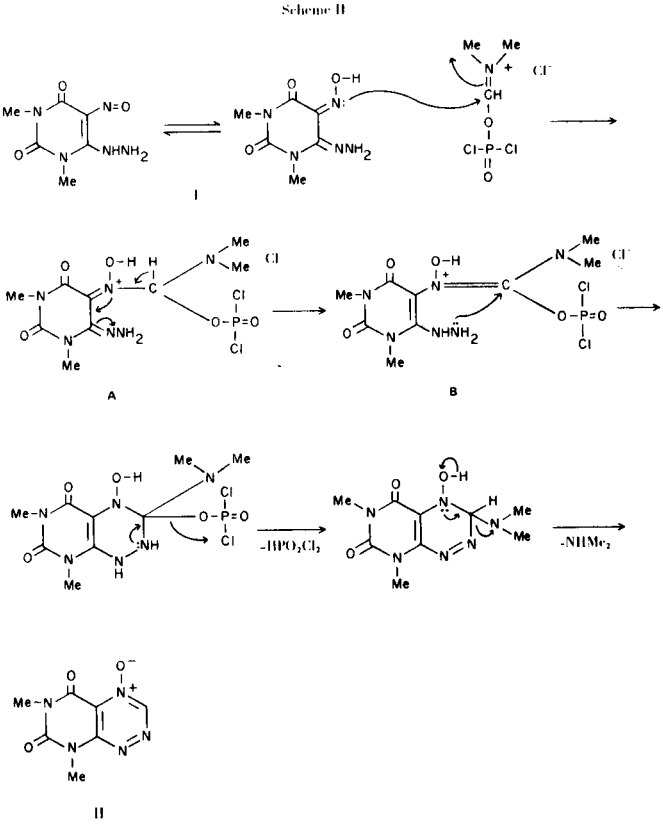
As depicted in Scheme II, the formation of II is best rationalized by assuming the initial nucleophilic attack of

Scheme I



I II III

Scheme II



the oxime of the imino oxime tautomeric form of I on the Vilsmeier reagent to give the adduct (**A**), followed by prototropic rearrangement to the protonated anil (**B**), and

subsequent intramolecular cyclization involving the loss of dichlorophosphoric acid and dimethylamine.

We consider this strikingly simple approach to 1 offering considerable potential not only to prepare less accessible pyrimido[5,4-*e*]-*as*-triazine 4-oxides (6) but also other heterocyclic *N*-oxides. To our knowledge this is the first instance in which the Vilsmeier reagent has been used for the synthesis of heterocyclic *N*-oxides.

REFERENCES AND NOTES

(1) Recent advances in the chemistry and biology of pyrimido-[5,4-*e*]-*as*-triazines have been reviewed by D. J. Brown and R. K. Lynn, "Chemistry and Biology of Pteridines," W. Pfleiderer, Ed., Walter de Gruyter, New York, 1975, p. 575.

(2) The oxidation of fervenulin with trifluoroperacetic acid has been reported to give fervenulin 1-oxide exclusively: G. Blankenhorn and W. Pfleiderer, *Chem. Ber.*, **105**, 3334 (1972).

(3) W. Pfleiderer and K.-H. Schündehütte, *Ann. Chem.*, **615**, 42 (1958).

(4) *Anal.* Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 39.92; H, 3.41; N, 33.76; λ max (ethanol): 240 nm (log ε 4.10), 304 (3.21), 323 sh (2.78); nmr (deuteriochloroform): δ 3.45 (3H, s, N-CH_3), 3.80 (3H, s, N-CH_3), 10.30 (1H, s, C^3-H).

(5) References cited in (1).

(6) The only reported procedure for the exclusive formation of pyrimido[5,4-*e*]-*as*-triazine 4-oxides is that of nitrosative cyclization of aldehyde uracil-6-yl hydrazones in the presence of diethyl azodicarboxylate: F. Yoneda, T. Nagamatsu and K. Shinomura, *J. Chem. Soc., Perkin Trans. 1*, 713 (1976).