NEW SYNTHESES OF FERVENULIN 4-OXIDES

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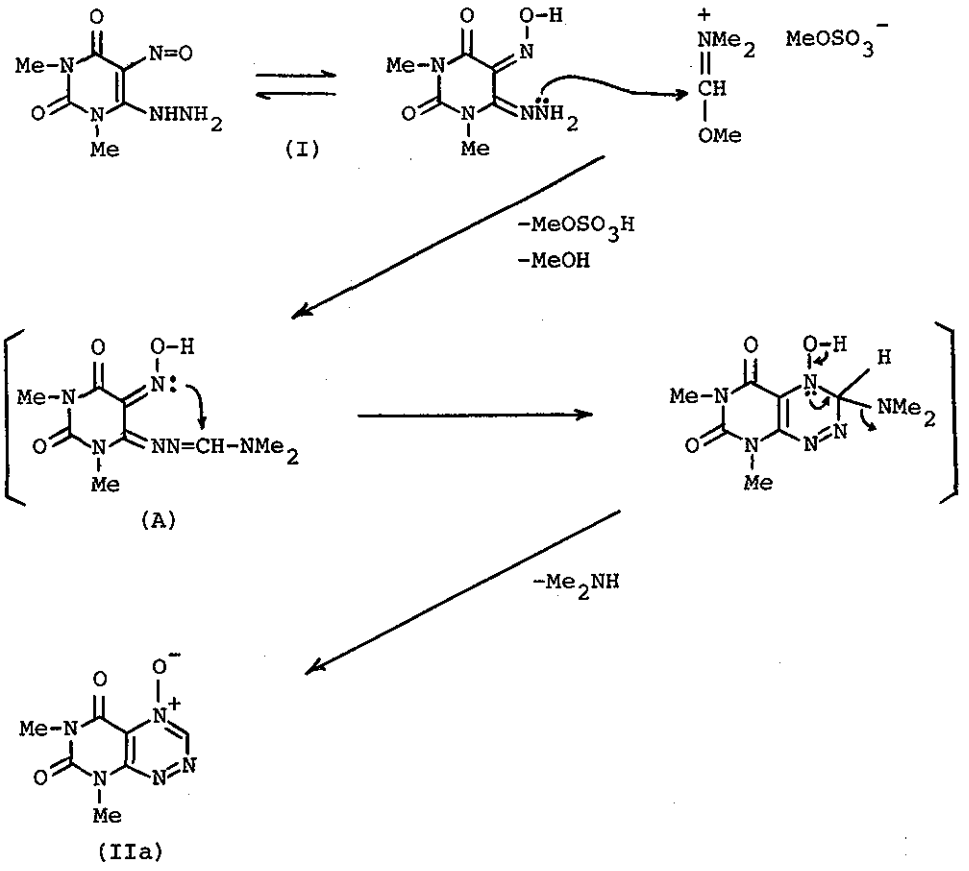
Treatment of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (I) with dimethylformamide-dimethyl sulfate, formic acid, or triethyl orthoformate afforded fervenulin 4-oxide (IIa), respectively. 3-Substituted fervenulin 4-oxides (IIb-c) were also prepared by the reaction of (I) with respective ortho esters.

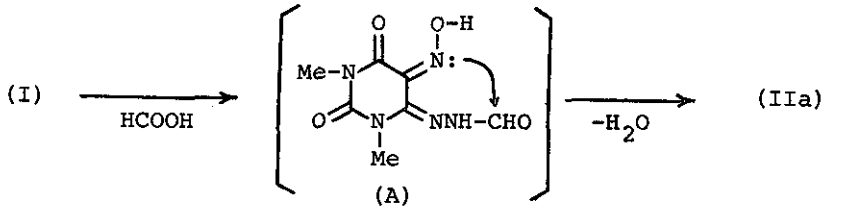
In connection with considerable current interest in the chemistry and biology of pyrimido[5,4-*e*]-*as*-triazines,[1] we have recently reported[2] that the reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (I)[3] with Vilsmeier reagent (dimethylformamide-phosphorus oxychloride) offers a facile route to readily inaccessible fervenulin 4-oxide (IIa).[4] We report here further three new synthetic approaches to (IIa) including its 3-substituted derivatives by treatment of (I) with appropriate one-carbon reagents, namely dimethylformamide-dimethyl sulfate (DMF-DMS),[5] formic acid, and ortho esters.

Method A Stirring of a mixture of (I)(0.001 mol) and DMF-DMS (0.003 mol) at room temperature for 2 hr, followed by dilution with ethanol caused the separation of (IIa)(43%). This reaction is presumably initiated by the formation of 6-dimethylaminomethyl-enehydrazino intermediate (A), followed by intramolecular cyclization[6] and subsequent aromatization by loss of dimethylamine (Scheme I).



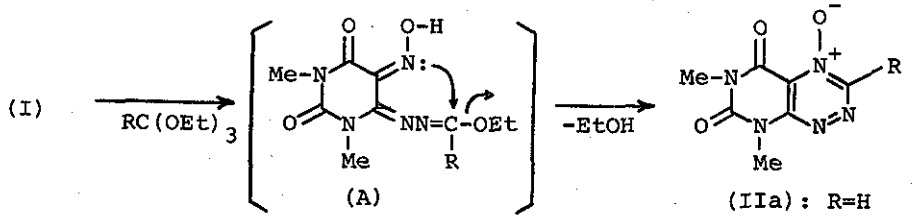
Scheme I

Method B Refluxing of (I)(0.001 mol) in formic acid (3 ml) for 30 min and evaporation of the reaction mixture afforded (IIa)(54%). This reaction probably involves the intermediacy of a 6-formylhydrazino derivative (A), which undergoes dehydrative cyclization facilitated by the nucleophilicity of an oxime group[6] to give (IIa) (Scheme II).



Scheme II

Method C Heating of (I)(0.001 mol) with triethyl orthoformate (3 ml) at 90° for 30 min caused the separation of (IIa)(71%). Similarly, the reaction of (I) with triethyl orthoacetate and triethyl orthopropionate gave 3-methyl- (IIb)[7](76%, m.p. 137-138°, ethanol) and 3-ethylfervenulin 4-oxide (IIc)(85%, m.p. 145.5-147°, ethyl acetate), respectively. A reasonable intermediate of this condensation is 6-α-ethoxyalkylidenehydrazino derivative (A), which suffers cyclization by the nucleophilic attack of the oxime[6] to give the corresponding (II)(Scheme III).



Scheme III

The structures of (IIa-c) were established by elemental analyses, satisfactory spectral data, and the formation of the corresponding fervenulins by their reduction using sodium dithionite in water.

Among three methods described above, the Method C appears to be the most useful synthetic route to fervenulin 4-oxides, thus the reaction proceeds in high yield under mild and neutral conditions. Moreover, the method seems to be quite general since the selection of appropiate ortho esters allows one to introduce practically any group into the 3-position of (IIa) as in the case of (IIb-c).

REFERENCES AND FOOTNOTES

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2 M. Ichiba, K. Senga, S. Nishigaki, and F. Yoneda, J. Heterocyclic Chem., in press.

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

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6 Participation of an oxime as a nucleophile has been reported in many cases. For example, E.C. Taylor, "Topics in Heterocyclic Chemistry," Ed., R.N. Castle, John Wiley, New York, 1969, p.1.

7 Lit. m.p. 138°: F. Yoneda, T. Nagamatsu, and K. Shinomura, J. Chem. Soc., Perkin Trans. I, 1976, 713.

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