A New Synthesis of Fervenulin (1,3-Dimethyl-7-azalumazine)

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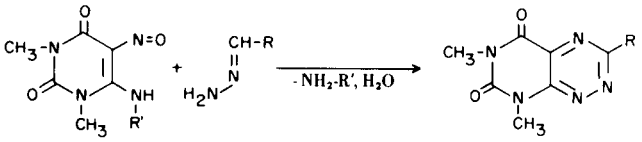
Sir:

We wish to report a new convenient synthesis of Fervenulin (Planomycin; 1,3-dimethyl-7-azalumazine) (1,2) and analogs, consisting of treatment of 6-amino-1,3-dimethyl-5-nitrosouracil (I) with aldehyde hydrazones. Stirring a suspension of I in aprotic solvents such as dimethylformamide or dimethylsulfoxide with stoichiometric amounts of 37% aqueous formaldehyde and 80% hydrazine hydrate while cooling at 0-2° for *ca.* 10 minutes followed by mild refluxing of the mixture for 3 hours resulted in the gradual discharge of the purple color of I. Concentration of the reaction mixture *in vacuo*, extraction with chloroform, evaporation of the chloroform and then treatment of the residue with 50% aqueous methanol caused Fervenulin to separate in 30-40% yield and in a good state of purity. The product was identical in all respects with an authentic sample prepared by an alternative route (1). Similarly, heating I with other aldehydes and hydrazine hydrate led to the formation of the respective 6-substituted-1,3-dimethyl-7-azalumazines (see Table).

The reaction essentially involves I and the aldehyde hydrazones, since aldehydes and hydrazine react instantly to give the hydrazones. In fact, somewhat better yields of 6-substituted-1,3-dimethyl-7-azalumazines were obtained when I was allowed to react with a preformed aldehyde hydrazone.

SCHEME I



R' = H, CH_3

Reaction of 1,3-dimethyl-6-methylamino-5-nitrosouracil with benzaldehyde hydrazone in dimethylformamide also yielded 1,3-dimethyl-6-phenyl-7-azalumazine in good yield.

REFERENCES

(1) E. C. Taylor and F. Sowinski, *J. Am. Chem. Soc.*, **90**, 1374 (1968) and references cited therein.

(2) W. Pfleiderer and G. Blankenhorn, *Tetrahedron Letters*, 4699 (1969).

TABLE

Reaction of 6-Amino-1,3-dimehtyl-5-nitrosouracil with Aldehydes and Hydrazine Hydrate in Dimethylformamide

Aldehyde	Product (a)	M.p. (°C)	Yield (%)
Formaldehyde	1,3-Dimethyl-7-azalumazine (Fervenulin) (1)	175	35
Benzladehyde	1,3-Dimethyl-6-phenyl-7-azalumazine (2)	270	49
p-Chlorobenzaldehyde	6-*p*-Chlorophenyl-1,3-dimethyl-7-azalumazine	275	52
p-Bromobenzaldehyde	6-*p*-Bromophenyl-1,3-dimethyl-7-azalumazine	303	38
p-Nitrobenzaldehyde	1,3-Dimethyl-6-*p*-nitrophenyl-7-azalumazine (2)	323	52
Salicylaldehyde	1,3-Dimethyl-6-*o*-hydroxyphenyl-7-azalumazine	282	85
Veratraldehyde	6-(3,4-Dimethoxyphenyl)-1,3-dimethyl-7-azalumazine	305	48
Piperonal	1,3-Dimethyl-6-(3,4-methylenedioxyphenyl)-7-azalumazine	203	72
Cinnamaldehyde	1,3-Dimethyl-6-styryl-7-azalumazine	263	35
Picolinaldehyde	1,3-Dimehtyl-6-(2-pyridyl)-7-azalumazine (2)	285	45
Nicotinaldehyde	1,3-Dimehtyl-6-(3-pyridyl)-7-azalumazine (2)	213	57
Isonicotinaldehyde	1,3-Dimethyl-6-(4-pyridyl)-7-azalumazine (2)	262	37
Thiophene-2-aldehyde	1,3-Dimethyl-6-(2-thienyl)-7-azalumazine	272	15

(a) Satisfactory microanalytical and spectral data were obtained for all compounds.