A Novel Synthesis of 1,3-Dimethyl-6-azalumazines

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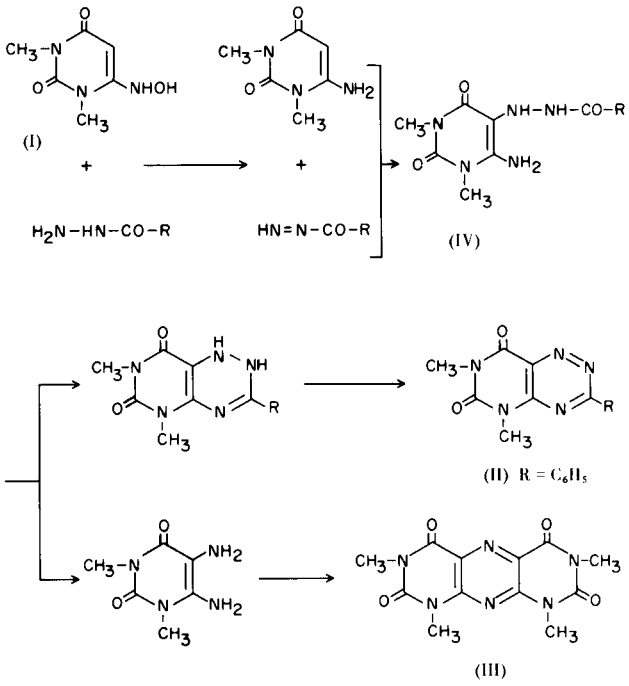
Sir:

The 6-azapteridine (pyrimido[4,5-*e*]-*as*-triazine) system has become of recent interest because of the discovery that some 1,3-dimethyl-6-azalumazine derivatives exhibit antiviral activity (1-3). We now wish to report a novel synthesis of 1,3-dimethyl-6-azalumazines (1,3-dimethyl-1*H*,3*H*-6-azapteridine-2,4-dione) consisting of treatment of 1,3-dimethyl-6-hydroxylaminouracil (I) with acid hydrazides.

Heating I with equimolar benzhydrazide under reflux in dimethylformamide for several hours followed by cooling gave 1,3,7,9-tetramethyl-(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]-pteridine-2,4,6,8-tetrone (III) (4) (14.3%). The dimethylformamide filtrate was evaporated under reduced pressure, the syrupy residue was diluted with water and after several days a precipitate of 1,3-dimethyl-7-phenyl-6-azalumazine (II) (5), identical with an authentic sample (2), was collected. Compound I with several other acid hydrazides under the same conditions yielded the corresponding 7-substituted 1,3-dimethyl-6-azalumazines (see Table) along with III (10-15%).

When compound I was refluxed alone in dimethylformamide, no products were obtained and the starting material was recovered. Therefore, the reaction presumably is initiated by an intermolecular oxidation-reduction

SCHEME I



TABLE

7-Substituted 1,3-Dimethyl-6-azalumazines

Substituent	M.p. (°C)	Recrystallization Solvent	Appearance	Yield (%)
Phenyl	137-139	Benzene	Yellow needles	15.7
p-Aminophenyl	>300	Methanol	Orange powder	32.6
o-Hydroxyphenyl	292	Methanol	Pale yellow prisms	28.6
2-Furyl	275-276	Methanol	Pale yellow powder	14.8
2-Thienyl	249-250	Methanol	Yellow powder	16.2
3-Pyridyl	245	Methanol	Pale yellow needles	18.7
4-Pyridyl	292-294	Methanol	Pale yellow needles	24.0

reaction between I and an acid hydrazide, followed by combination of the resulting 6-amino-1,3-dimethyluracil and acyldiimide giving a Michael adduct (IV). This could then by cyclized and dehydrogenated to give a 1,3-dimethyl-6-azalumazine. Reduction of IV by an acid hydrazide to 5,6-diamino-1,3-dimethyluracil followed by oxidative dimerization could also yield III.

REFERENCES

(1) E. C. Taylor and S. F. Martin, *J. Org. Chem.*, **35**, 3792 (1970) and references cited therein.

(2) F. Yoneda, K. Ogiwara, M. Kanahori, S. Nishigaki, E. C. Taylor, "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto and Y. Iwanami, Eds., International Academic Printing Co. Ltd., Tokyo, 1970, p. 145.

(3) For a recent review on 6-azapteridines, see F. Yoneda, *Kagaku no Ryoiki*, **24**, 1077 (1970).

(4) F. Yoneda and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), in press, and references cited therein.

(5) Satisfactory microanalytical and spectral data were obtained for all of the products.