The Preparation of Pyrimido[5,4-*e*]-*as*-Triazine-5,7(6*H*,8*H*)-dione (1)

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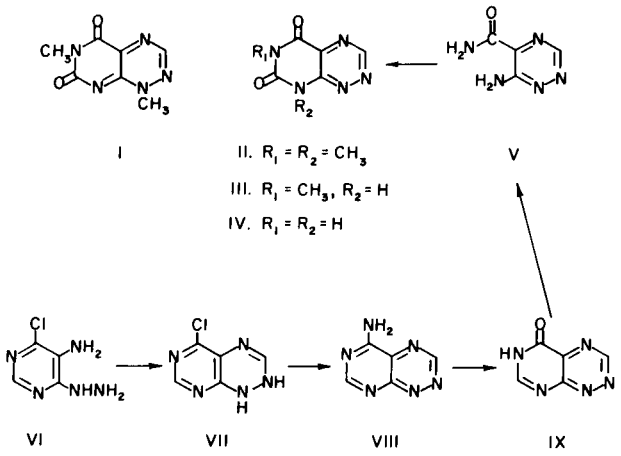
Sir:

The group of antibiotics that possess the pyrimido-[5,4-*e*]-*as*-triazine ring system has received considerable attention (2). The synthesis of I (Toxoflavin) (3), one of the toxic principles produced by *Pseudomones cocovenenans;* II (Fervenulin) (3,4), isolated from *Streptomyces fervens* n. sp. and from *Streptomyces rubrireticuli;* and the monomethyl derivative III (5) prompted the preparation of the parent ring system IV.

Although compounds I-III were prepared from pyrimidine intermediates, some difficulties were encountered in the synthesis of I and III. The preparation of I from a 4-hydrazino-5-nitropyrimidine *via* a 5-amino-4-hydrazinopyrimidine was unsuccessful because of the reductive cleavage of the hydrazino group during the reduction of the nitro group (3). In the preparation of III by the cyclization of a 5-amino-4-hydrazinopyrimidine, the latter was also cyclized to a *s*-triazolo[4,3-*c*]pyrimidine (5). These difficulties were avoided by the preparation of IV from 6-amino-*as*-triazine-5-carboxamide (V). Previously the preparation of heteroaromatic *as*-triazines similar to V from simple reactants was unsuccessful (6). The successful route involved the cyclization of 5-amino-4-chloro-6-hydrazinopyrimidine (VI) with ethyl orthoformate to give 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (VII) (7), treatment of VII with hot aqueous ethanolic sodium azide to give 5-aminopyrimido[5,4-*e*]-*as*-triazine (VIII) (8), hydrolysis of the amino group of VIII with sodium hydroxide to give 5-oxo-5,6-dihydropyrimido[5,4-*e*]-*as*-triazine (IX), and cleavage of the pyrimidine ring of IX with hot aqueous ethanolic triethylamine to give V.

Although acylation of substituted 2-aminopyrazine-3-carboxamide with ethyl chloroformate followed by cyclization of the resulting carbamate derivative with sodium ethoxide gave substituted 2,4-dioxo-1,2,3,4-tetrahydropteridines (9), the conversion of 2-aminopyrazine-3-carboxamide itself to a pteridine by a variation of this procedure was unsuccessful (10). This result and the lability of the amide group of V in sodium hydroxide prompted the use of a neutral or slightly acidic medium for the conversion of V to IV. Treatment of V with the phosgene-pyridine complex (11) in hot dioxane and recrystallization of the



crude product from glacial acetic acid, then water gave a 37% yield of IV; m.p. > 264°; λ max in mμ (ϵ x 10^{-3}): *p*H 1-232 (14.4), 265 sh, 332 (4.97); *p*H 7-236 sh, 248 (11.5), 264 sh, 350 (2.60), 385 (2.89); *p*H 13-259 (19.4), 312 (2.03), 392 (3.92); $\bar{\nu}$ max in cm^{-1}: 1715 (broad), 1570, 1555; pmr (DMSO-d_6): τ 0.32 (1) (CH), -2.13 (2) (NH). Apparently this is the first instance in which the phosgene-pyridine complex has been used as a cyclization reagent to give condensed uracil derivatives (12). Alkylation of IV with methyl iodide in DMF containing potassium carbonate gave II, m.p. 177° [lit. m.p. 175.7° (2), 178-179° (3,4)].

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