A New Synthesis of the Pyrimido[4,5-*d*]pyrimidine Ring. Preparation of Pyrimido[4,5-*d*]pyrimidine-2,4,5,7-tetrone (1a)

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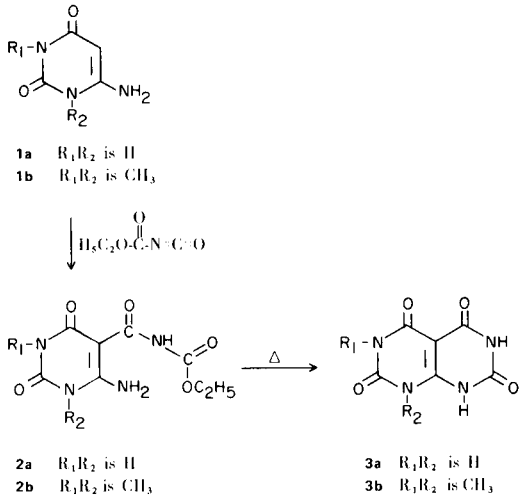
Sir:

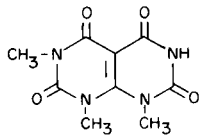
We wish to report a new and simple synthesis of derivatives of the pyrimido[4,5-*d*]pyrimidine ring. Trisubstituted pyrimido[4,5-*d*]pyrimidines have been investigated in some detail (2-6) because of the pharmacological activity observed (2,3,6,7) with certain derivatives. On the other hand tetrasubstituted pyrimido[4,5-*d*]pyrimidines with functional groups at positions 2,4,5 and 7 have been very little studied (4,8). In the present work we have devised a novel and useful synthesis of such compounds from readily available pyrimidine intermediates.

6-Aminouracil (**1a**) in dimethylformamide treated with approximately one mole of ethyl isocyanatoformate resulted in above 90% yield of 6-amino-5[*N*-(carbethoxy)-carboxamido]uracil (**2a**); λ max (*p*H 1), 248 nm, ε 1.47 x 10^4; 266 nm, ε 2.08 x 10^4; λ max (*p*H 11), 275 nm, ε 2.1 x 10^4; pmr (DMSO-d_6), δ 1.33 (3H, t, -CH_2 CH_3); δ 4.7 (2H, d-CH_2 CH_3); δ 7.57 (1H, bs, -NH-); δ 9.8 (1H, bs-NH-); δ 11.37 (2H, d-NH_2); δ 12.53 (1H, s-NH-). Heating of **2a** at 240-280° resulted in the loss of ethanol and gave a 70% yield of pure pyrimido[4,5-*d*]pyrimidine-2,4,5,7-tetrone (**3a**). Similar treatment of 6-amino-1,3-dimethyluracil (**1b**) with ethyl isocyanatoformate gave 6-amino-5-[*N*-(carbethoxy)carboxamido-1,3-dimethyluracil (**2b**); λ max (*p*H 1), 242 nm, ε 1.27 x 10^4; 268 nm, ε 1.13 x 10^4; λ max (*p*H 11), 227 nm, ε 3.85 x 10^4; [257 nm]S, ε 1.03 x 10^4; 273 nm, ε 1.7 x 10^4 in above yield. Ring closure of 2.4 g. of **2b** occurred at 260° to give 1.65 g. of pure 1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4,5,7-tetrone (**3b**); λ max (*p*H 1), 242 nm, ε 1.1 x 10^4; 268 nm, ε 0.97 x 10^4; λ max (*p*H 11), 227 nm, ε 3.36 x 10^4; 272 nm, ε 1.52 x 10^4.

That the reaction of ethyl isocyanatoformate had indeed occurred at position 5 was supported by the lack of a C_5 proton and the presence of 2 protons (NH_2) at δ 11.0-11.5 in the pmr spectra of **2a** and **2b** in DMSO-d_6. The reactivity of the 5-position toward electrophilic attack is not unexpected since various 1,3-diketones have been shown (9) to ring close with 6-aminouracil to yield pyrido-[2,3-*d*]pyrimidines. Similarly, 6-amino-1,3-dimethyluracil (**1b**) undergoes acylation at position 5 with acetic anhydride (10). The present work, however, is the first reported example of reaction of an isocyanate at position 5 of the pyrimidine ring.



The structure **3a** and **3b** are supported by elemental analysis, pmr spectra and mass spectral data. The parent peak of **3a** at 196 and the parent peak of **3b** at 224 confirmed the ring closure to the pyrimido[4,5-*d*]pyrimidine ring. This reaction sequence has also been extended to include 1,3-dimethyl-6-methylaminouracil to yield 1,3,8 trimethylpyrimido[4,5-*d*]pyrimidine-2,4,5,7-tetrone (**4**); λ max (*p*H 1), 228 nm, ε 2.21 x 10^4; 247 nm, ε 1.59 x 10^4; 277 nm, ε 1.65 x 10^4; λ max (*p*H 11), 227 nm, ε 1.85 x 10^4; [250 nm]S, ε 1.19 x 10^4; 281 nm, ε 0.81 x 10^4 in an overall yield of 66% from 1,3-dimethyl-6-methylaminouracil.



4

The simple synthesis of pyrimido[4,5-*d*]pyrimidines of the type exhibited by **3a**, **3b** and **4** would appear to be general and should provide a direct approach to numerous 2,4,5,7-tetrasubstituted derivatives *via* phosphorus oxychloride chlorination and subsequent nucleophilic substitution of the requisite chloropyrimido[4,5-*d*]pyrimidines

(2) as exemplified by known reactions already documented with this and related ring systems (11).

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