

Midwest Research Institute

A New Mannich Reaction of Pyrimidines (1)

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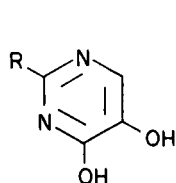
Sir:

Two types of Mannich reactions of pyrimidines have been reported in the literature (2): pyrimidines with an unsubstituted 5-position and two or three electron-releasing groups undergo Mannich reactions at the 5-position (3). Some *C*-methylpyrimidines, on the other hand, were reported to react with formaldehyde and amines to yield the corresponding (substituted-amino)ethylpyrimidines (4).

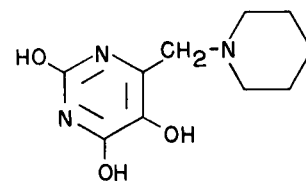
We wish to report a new Mannich reaction of pyrimidines involving the reaction of formaldehyde and primary or secondary amines with 4,5-dihydropyrimidines. In this case, the 6-position of the pyrimidine ring undergoes the Mannich reaction.

When a secondary amine was used in this reaction, the regular Mannich product was obtained. Thus, when a mixture of 6.4 g. of 35% (0.075 mole) aqueous formaldehyde, 4.4 g. (0.050 mole) of piperidine and 6.4 g. (0.050 mole) of 5-hydroxyuracil (5) (Ib) in 500 ml. of water was stirred at 0-5°, the reactants gradually went into solution, after which 6.4 g. (57% yield) of 5-hydroxy-6-(piperidinomethyl)uracil (II) precipitated as a white solid, m.p. 186-187° dec. Recrystallization from methanol gave m.p. 210-211° dec., λ max (pH 1), 283 m μ (ϵ , 6,100); λ max (pH 11), 241 (ϵ , 6,100), 310 m μ (ϵ , 5,600). *Anal.* Calcd. for C₁₀H₁₅N₃O₃: C, 53.3; H, 6.72; N, 18.7. Found: C, 53.1; H, 7.08; N, 18.8.

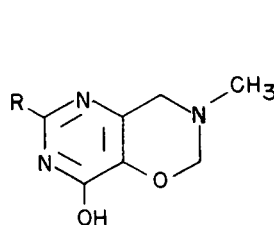
Refluxing a solution of 3.15 g. (0.025 mole) of 2-methyl-4,5-dihydroxypyrimidine (6b) (Ia), 4.3 g. (0.050 mole) of 35% aqueous formaldehyde, and 3.85 g. (0.025 mole) of 20% aqueous methylamine in 125 ml. of 50% aqueous methanol for 2 hours gave, after purification from a mixture of ethyl acetate and methanol, 1.63 g. (36% yield) of white solid, m.p. 200-202°, λ max (pH 1) 270 m μ (ϵ , 13,400); λ max (pH 11), 270 (ϵ , 13,200), 294 m μ (ϵ , 13,400). Elementary analysis (Calcd. for C₈H₁₁N₃O₂: C, 53.0; H, 6.14; N, 23.2. Found: C, 52.7; H, 6.00; N, 22.9) suggested the product as either IIIa or IVa. Nuclear magnetic resonance spectrum (7) (chemical shifts (8) for protons of CH₃-N=, 2.18 ppm; of CH₃-C=, 2.47 ppm; of =N-CH₂-C=, 3.59 ppm; and of =N-CH₂-O-, 4.63 ppm, *d*-DMSO was used as solvent) ruled out structure IVa and hence the product obtained is 3,6-dimethyl-3,4-dihydro-2*H*-pyrimido[4,5-*e*]-1,3-oxazine-8-ol (IVa). This structure assignment was further substantiated by the report that reaction of *p*-substituted phenols with formaldehyde and primary amines in a molar ratio of 1:2:1, respectively, yielded 3,4-dihydro-2*H*-benzo-1,3-oxazines (9).

I a, R = CH₃

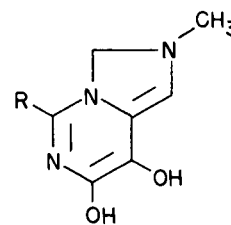
b, R = OH



II

III a, R = CH₃

b, R = OH

IV a, R = CH₃

b, R = OH

Similar reaction of 5-hydroxyuracil (5) (Ib), formaldehyde and methylamine gave, after recrystallization from water, 46% yield of white solid, m.p. 218-219° dec., λ max (pH 1), 276 m μ (ϵ , 14,300); λ max (pH 11), 240 (ϵ , 8,700), 301 m μ (ϵ , 11,500). N.m.r. spectrum (7) (chemical shifts (8) for protons of CH₃-N=, 2.37 ppm; of =N-CH₂-C=, 3.80 ppm and of =N-CH₂-O-, 4.42 ppm. *d*-DMSO was used as solvent), again, ruled out IVb as the possible structure and the product obtained is therefore 3-methyl-3,4-dihydro-2*H*-pyrimido[4,5-*e*]-1,3-oxazine-6,8-diol (IIIb). *Anal.* Calcd. for C₇H₉N₃O₃: C, 45.9; H, 4.95; N, 22.9. Found: C, 45.7; H, 5.00; N, 22.8.

Two examples of electrophilic substitution - nitrosation and coupling with diazonium salts - at the 6-position of 4,5-dihydroxypyrimidines have been reported (6,10). Attempted bromination at this position only caused extensive decomposition (6b). The Mannich reaction serves as another successful example of electrophilic attack at the 6-position of the pyrimidine ring system.

This new Mannich reaction of pyrimidines appears to be a general method for the synthesis of compounds containing the new 3,4-dihydro-2*H*-pyrimido[4,5-*e*]-1,3-oxazine ring system. Work in this field is currently being continued in our laboratory.

REFERENCES

- (1) This investigation is supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract PH-43-65-94.
- (2) The so-called 1-(morpholinomethyl)uracil, as reported by C. C. Bombardieri and A. Taurins, *Can. J. Chem.*, **33**, 923 (1955), was proved to be 5-(morpholinomethyl)uracil. See Ref. 3c.
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- (7) The nuclear magnetic resonance spectra were run on a Varian HA-100 n.m.r. spectrometer operating in the frequency sweep mode. TMS, sealed in a glass needle, was used as the lock signal. The authors are indebted to Dr. James J. Downs for the n.m.r. interpretations and discussions.
- (8) The chemical shifts are referenced to d_5 DMSO ($\delta = 2.51$ ppm) as an internal secondary standard.
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