SYNTHESIS AND REACTION OF 6-CYANOURACILS

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5-Bromo-1,3-dimethyluracil reacted with an equimolar sodium cyanide in N,N-dimethylformamide (DMF) to give 6-cyano-1,3-dimethyluracil, which was also obtained from 6-chloro-1,3-dimethyluracil by the same treatment as above. The 6-cyano compound was readily converted to 5-cyano-1,3-dimethyluracil when heated with a catalytic amount of sodium cyanide in DMF. The mechanism for these cine-substitutions was shown by deuterium-exchange experiments to involve an addition-elimination process. Furthermore, the reaction of a variety of 1-substituted 5-bromo-3-methyl(or H)uracils with sodium cyanide in DMF gave the corresponding 6-cyano derivatives. While, similar treatment of 1-substituted 5-bromo-3-methyluracils in 50% aq. ethanol afforded the 6-carbamoyl compounds.

Reaction of 6-cyano-1,3-dimethyluracil with some nucleophilic reagents such as sodium hydroxide, sodium methoxide, alcohols, butylamine, and hydrazines gave 5-cyano-1,3-dimethyluracil (cine-substitution product), 6-methoxy-, 6-butylamino-, 6-hydrazino-1,3-dimethyluracils (substitution products), and imidates of 6-cyano-1,3-dimethyluracil. Reaction of 5-bromo-6-cyano-1,3-dimethyluracil with hydrazine hydrate gave 6-amino-1,3-dimethyluracil, which was also obtained by reaction of 5-bromo-6-chloro-1,3-dimethyluracil with hydrazine hydrate.

Treatment of 1-sec-alkyl-6-carbamoyl-3-methyluracils in refluxing 48% hydrobromic acid causes dealkylation and hydrolysis to give 3-methylorotic acid. Similarly, the hydrolysis of 1-sec-alkyl-6-cyano-3-methyluracils in 98% H₂SO₄ at 90° gives 1-dealkylated 6-carbamoyl-3-methyluracil. On the other hand, when 1-substituents are normal alkyl groups, the hydrolysis of 1-alkyl-6-carbamoyl-3-methyluracils in refluxing 48% hydrobromic acid proceeds without dealkylation to give 1,3-disubstituted orotic acids. The most possible mechanism of the dealkylation is proposed.

In order to further investigate the reactivity of a cyano group on the uracil nucleus, 5,6-dicyano-1,3-dimethyluracil was synthesized as follow: treatment of 6-chloro-5-formyl-1,3-dimethyluracil with hydroxylamine gave the corresponding oxime, which reacted with phosphorus oxychloride to yield the 6-chloro-5-cyanoacrylic acid. This compound was treated with sodium cyanide in DMF to give the 5,6-dicyano-1,3-dimethyluracil.