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DEALKYLATION OF 1-sec-ALKYL-6-CARBAMOYL(OR CYANO)-3-METHYLURACILS UNDER ACIDIC CONDITIONS

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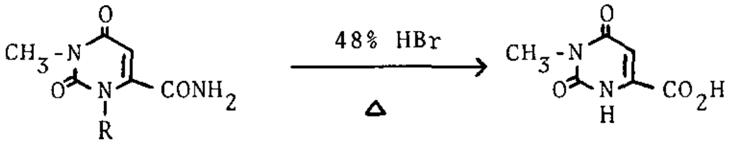
Hydrolysis of 1-sec-alkyl-6-carbamoyl-3-methyluracils in refluxing 48% hydrobromic acid causes dealkylation at the 1-position to give 3-methylorotic acid. Treatment of 1-sec-alkyl-6-carbamoyl(or cyano)-3-methyluracils in 98% H_2SO_4 afford 1-dealkylated 6-carbamoyl-1-methyluracils.

It is well known that pyrimidine and purine nucleosides are hydrolyzed under acidic conditions at N-glycosyl bond to yield the corresponding pyrimidines or purines, and sugars.[1] Some mechanisms for the hydrolysis have been discussed by many investigators.[2]

In the course of our investigation for new synthesis of 1,3-disubstituted orotic acids, we found that hydrolysis of 1-sec-alkyl 6-carbamoyl(or cyano)-3-methyluracils in strong acids caused dealkylation at the N-1 position. Our dealkylation reaction would give a significant suggestion for the hydrolysis mechanism of nucleosides.

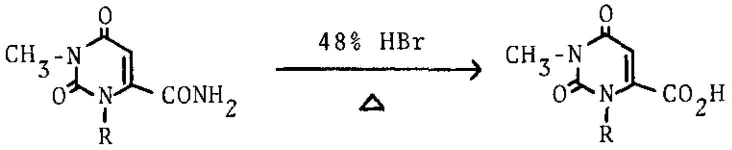
Thus, refluxing 1-cyclohexyl-6-carbamoyl-3-methyluracil (Ia)[3] in 48% hydrobromic acid for 2 hr afforded 3-methylorotic acid (II) quantitatively, mp >300°, identical with an authentic sample prepared by the selective methylation of orotic acid.[4] Similar treatment of Ib and Ic gave the same product (II) in high yields (80-100%).



(Ia) R=cyclohexyl
(Ib) R=*iso*-Pr
(Ic) R=*sec*-Bu

(II)

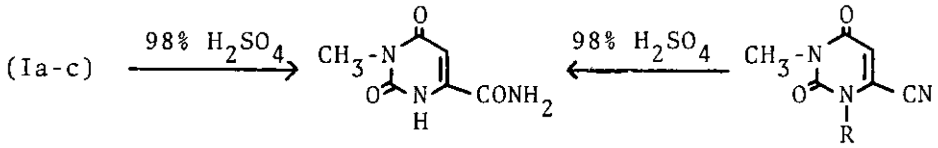
When the N(1)-substituents were normal alkyls, however, the hydrolysis of Id-f under the above conditions proceeded without dealkylation and afforded 1,3-disubstituted orotic acids(IIId, 87%, mp 145-148°; IIIe, 66%, mp 164-168°; IIIf, 93%, mp 172-174°).



(Id) R=Me
(Ie) R=Pr
(If) R=Bu

(IIId) R=Me
(IIIe) R=Pr
(IIIf) R=Bu

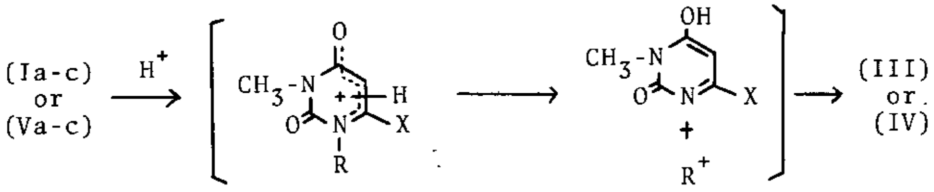
Heating Ia-c in 98% H_2SO_4 at 90° caused only the dealkylation to yield 6-carbamoyl-3-methyluracil(IV)(mp >300°) in good yields. And 1-*sec*-alkyl-6-cyano-3-methyluracils(Va-c) gave the dealkylated and hydrolyzed compound(IV)(45-70%) under the same conditions.



(IV)

(Va) R=cyclohexyl
(Vb) R=*iso*-Pr
(Vc) R=*sec*-Bu

From the above results, the reaction mechanism is believed to be as follows. Namely the dealkylation of Ia-c and Va-c occurred as a result of the initial protonation of the uracil ring followed by fission of the N-C bond at the 1-position, because the secondary alkyl residue dissociated thereby is stabilized as a carbonium ion which is more stable than that of normal alkyls.



Therefore, 1-benzyl-6-carbamoyl-3-methyluracil(Ig; $R=CH_2Ph$), having a benzyl group which is generally stable as a benzyl ion after fission of the N-C bond, was refluxed in 48% hydrobromic acid to give the expected compound (II) and benzyl bromide[5] in quantitative yield. This fact well supports the above mechanism.

On the other hand, the dealkylation reaction of 6-H(or methyl)-1-sec-alkyl-3-methyluracils did not proceed, recovering the starting material. Therefore it is considered that electron attracting groups such as a carbamoyl and a cyano group at the 6-position have a great influence on the dealkylation reaction.

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5 Benzyl bromide was identified with an authentic sample by ir spectroscopy.

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