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

Shigeo Sendag, Kosaku Hirota, and Tetsuji Asao
Gifu College of Pharmacy, Mitahora, Gifu, Japan

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% H₂SO₄ 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) 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. Similar treatment of Ib and Ic gave the same product (II) in high yields (80-100%).

\[
\begin{align*}
\text{(Ia)} & \quad R = \text{cyclohexyl} \\
\text{(Ib)} & \quad R = \text{iso-Pr} \\
\text{(Ic)} & \quad R = \text{sec-Bu}
\end{align*}
\]

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°).

\[
\begin{align*}
\text{(Id)} & \quad R = \text{Me} \\
\text{(Ie)} & \quad R = \text{Pr} \\
\text{(If)} & \quad R = \text{Bu} \\
\text{(IIId)} & \quad R = \text{Me} \\
\text{(IIle)} & \quad R = \text{Pr} \\
\text{(IIIf)} & \quad R = \text{Bu}
\end{align*}
\]
Heating Ia-c in 98% H$_2$SO$_4$ 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.

\[\text{(Ia-c)} \xrightarrow{98\% \text{H}_2\text{SO}_4} \text{(Va) } R=\text{cyclohexyl}\]
\[\text{(Vb) } R=\text{iso-Pr}\]
\[\text{(Vc) } R=\text{sec-Bu}\]

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.

\[\begin{align*}
\text{(Ia-c)} & \quad \text{or} \quad \text{(Va-c)} \\
& \quad \xrightarrow{\text{H}^+} \\
& \quad \left[\begin{array}{c}
\text{CH}_3\text{-N} \\
\text{O} \\
\text{N} \\
\text{R} \\
\text{X}
\end{array}\right] \quad \xrightarrow{\text{fission}} \\
& \quad \left[\begin{array}{c}
\text{CH}_3\text{-N} \\
\text{O} \\
\text{N} \\
\text{X} \\
\text{OH} \\
\text{R}^+
\end{array}\right] \quad \xrightarrow{\text{protonation}} \\
& \quad \text{(III)} \quad \text{or} \quad \text{(IV)}
\end{align*}\]

Therefore, 1-benzyl-6-carbamoyl-3-methyluracil (Ig; R=CH$_2$Ph), 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.

REFERENCES


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

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