SYNTHESIS OF 3-METHYLXANTHOSINE

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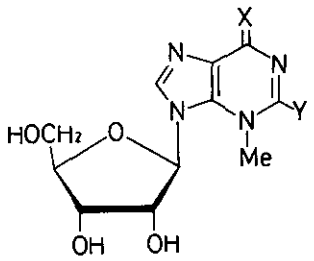
Abstract —— Treatment of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-(methylamino)imidazole-4-carboxamide (VIb) with EtOCOCl followed by cyclization with 1 *N* NaOH gave 3-methylxanthosine (Va). The glycosidic bond of Va underwent acid hydrolysis at a rate more than 1000 times greater than that of xanthosine.

Although the cleavage of the glycosidic bonds of nucleosides is of prime importance, the mechanisms and factors which affect the rate are not fully elucidated.[1] Recent syntheses and rate studies on the hydrolysis of 3-methyladenosine (I),[2] 3-methylguanosine (II),[3,4,5] and 3-methylinosine (III)[6] have revealed the extreme lability of the glycosidic bonds of these nucleosides under acidic conditions. 3-β-D-Ribofuranosylwye (IV), whose structure is closely related to II, also has been shown to be unusually susceptible to acidic hydrolysis.[3,5] The rate studies on the hydrolysis of the glycosidic bonds of these nucleosides over the wide range of pH should be helpful for an understanding of the mechanisms. However, none of the base moieties of these nucleosides (I—IV) are stable under alkaline conditions.[2,4,5,6] We considered that 3-methylxanthosine (Va) must be a better substrate for constructing the full rate—pH profile, because it was expected to undergo glycosidic bond cleavage moderately fast[7] and because the base moiety should be stable under the required reaction conditions.[4] Although Adler and Gutman reported evidence for the formation of small amounts of Va by the reaction of xanthosine with CH_2N_2, they failed isolating Va.[7] This communication presents the first practical synthesis of Va.

We already reported the synthesis of 3,9-dimethylxanthine (Vc) as a model for the synthesis of Va, from 1-methyl-5-(methylamino)imidazole-4-carboxamide (VIc) through 5-[(ethoxycarbonyl)methylamino]-1-methylimidazole-4-carboxamide (VIIc).[4]

However, VIIc was produced in only 39% yield when VIc was heated with EtOCOCl in dioxane in the presence of K_2CO_3.[8] We found that the reaction of VIc with EtOCOCl in H_2O (pH 7) took place smoothly at room temperature, but the yield (34%) of VIIc was not improved owing to the concomitant formation of N-(ethoxycarbonyl)-5-[(ethoxycarbonyl)methylamino]-1-methylimidazole-4-carboxamide (VIII) and N,N-bis-(ethoxycarbonyl)-5-[(ethoxycarbonyl)methylamino]-1-methylimidazole-4-carboxamide (IX). When the reaction was conducted at pH 5 (acetate buffer), neither VIII nor IX was formed and VIIc was produced in 70% yield. Similar treatment of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-(methylamino)imidazole-4-carboxamide (VIb)[3,6,9] gave 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-[(ethoxycarbonyl)methylamino]-imidazole-4-carboxamide (VIIb) as colorless prisms,[10] mp 150–151°C, in 36% yield. Cyclization of VIIb to 2',3',5'-tri-*O*-acetyl-3-methylxanthosine (Vb) was attempted by treatment with NaH in Me_2NCHO according to the synthesis of Vc,[8] but this procedure gave a mixture of products which proved too complex to identify the presence of Vb. We found that treatment of VIIc with 1 *N* NaOH at room temperature also produced Vc in 83% yield. Compound VIIb was successfully converted into Va by this treatment in 69% yield as colorless needles ($C_{11}H_{14}N_4O_6 \cdot 1/3H_2O$),[10] mp *ca.* 200°C (dec.); uv λmax (95% EtOH) 238 nm (ε 10,000), 265 (9500); λmax (H_2O) (pH 2) unstable; λmax (H_2O) (pH 7) 238 nm (ε 10,400), 268 (10,500); λmax (H_2O) (pH 13) 247 nm (ε 8300), 268 (11,300); nmr (Me_2SO-d_6) δ: 3.62 (5H, s, NCH_3 and CH_2), 6.00 (1H, d, J = 4.4 Hz, C(1')-H), 8.12 (1H, s, C(8)-H), 11.18 (1H, broad, NH or OH).[11] The correctness of the structure of Va was supported by comparison of the uv and nmr spectra with those of Vc[8,12] and was confirmed by transformation of Va into 3-methylxanthine (X)[13] with 0.1 *N* HCl at room temperature in 84% yield.

The rate of hydrolysis of the glycosidic bond of Va at pH 1.0 and 25°C [pseudo-first-order rate constant, k 2.8×10^{-1} min^{-1} (half life, $t_{1/2}$ 2.5 min)] was of the same order of magnitude with that of II.[5] Compound Va underwent hydrolysis at a rate [k 8.2×10^{-1} min^{-1} ($t_{1/2}$ 51 sec)] more than 1000 times greater than that [k 6.8×10^{-4} min^{-1} ($t_{1/2}$ 17 h)] of xanthosine in 1.0 *N* HCl at 25°C. Thus, the present results have provided an additional example of the fact that the introduction of methyl group into 9-β-D-ribofuranosylpurines at the 3-position weakens the glycosidic bonds remarkably. Further studies on the hydrolysis of Va are under progress.

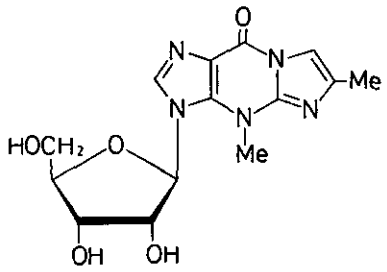


I, X = NH; Y = H

II, X = O; Y = NH_2

III, X = O; Y = H

Va, X = O; Y = OH



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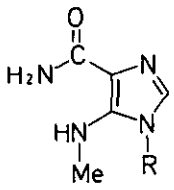

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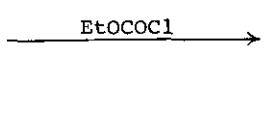
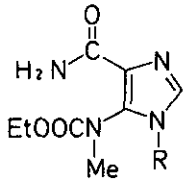
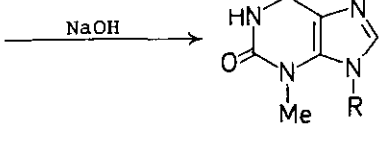




VII

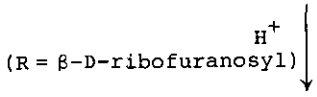


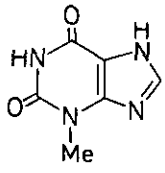
V

a, R = β-D-ribofuranosyl

b, R = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl

c, R = Me





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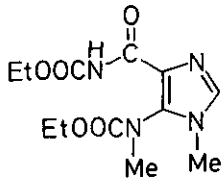
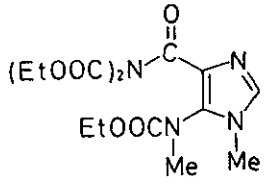


VIII



IX

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Received, 3rd December, 1981