

A GENERAL SYNTHESIS OF 5-(ALKYLAMINO)-1- β -D-RIBOFURANOSYL-
IMIDAZOLE-4-CARBOXAMIDES

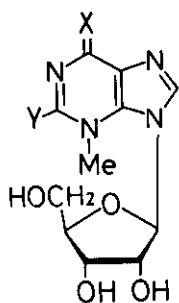
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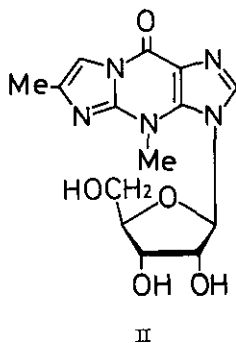
Abstract—Alkylation of N'-benzyloxy-5-formamido-1- β -D-ribofuranosylimidazole-4-carboxamide (IV) in the presence of K_2CO_3 followed by hydrogenolysis of the N'-benzyloxy group and alkaline hydrolysis produced the title compounds (X), intermediates adaptable to the syntheses of various 3-alkyl-9- β -D-ribofuranosylpurines.

Our recent syntheses and hydrolysis studies of 3-methyladenosine (Ia),¹ 3-methylisoguanosine (Ib),² 3-methylinosine (Ic),³ 3-methylxanthosine (Id),⁴ and 3-methylguanosine (Ie)⁵ have revealed unusual lability of the glycosidic bonds of these nucleosides. 3- β -D-Ribofuranosylwe (Π), whose structure is closely related to Ie, also has been shown to be extremely susceptible to acidic hydrolysis.^{5a,c} One plausible explanation for such instability of the glycosidic bonds of I and Π is that release from steric repulsion between the methyl and the ribofuranosyl group would be a major driving force. To judge the validity of this assumption we wish to synthesize the 9- β -D-ribofuranosylpurines substituted by bulkier alkyl groups at the 3-position (type I) and to check their stability. 5-(Alkylamino)-1- β -D-ribofuranosylimidazole-4-carboxamides (X) should be good intermediates for the synthesis of the desired compounds since the 3-methyl homologs (Ib-e) have already been derived from 5-(methylamino)-1- β -D-ribofuranosylimidazole-4-carboxamide (Xa).²⁻⁵ This communication presents the results of our synthesis of X through three routes.

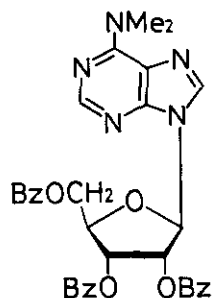
Syntheses of Xa and 2',3'-O-isopropylidene-Xa have been achieved by reductive methylation of appropriate imidazole nucleosides.^{5a,6} Alternatively, we have obtained



- I a, X = NH; Y = H
 b, X = NH; Y = OH
 c, X = O; Y = H
 d, X = O; Y = OH
 e, X = O; Y = NH₂

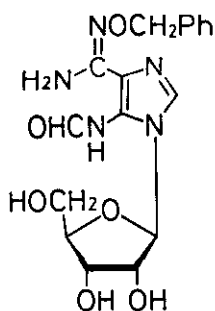


II



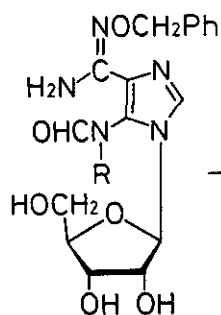
III

MeI



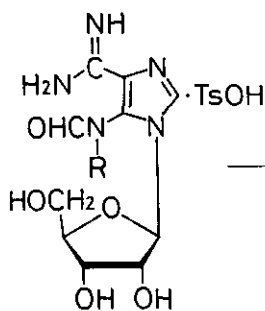
IV

RX
K₂CO₃



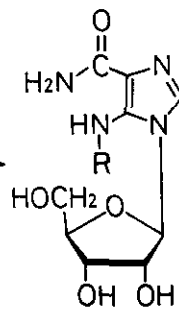
VIII

Raney Ni/H₂
TsOH

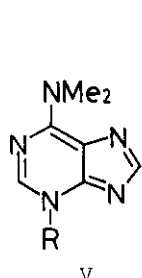


IX

NaOH



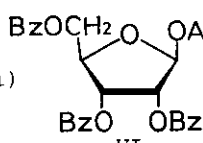
X



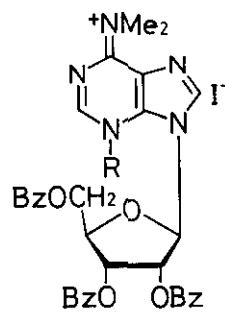
V

i)

ii) NaI



VI



VII

NaOH

- a, R = Me
 b, R = Et
 c, R = PhCH₂
 d, R = iso-Pr

Xa by methylation of 2',3',5'-tri-O-benzoyl-N,N-dimethyladenosine (III) followed by alkaline hydrolysis.^{3,7} In the present study, however, benzylation with PhCH₂Br or ethylation with EtI of III was found to take place so sluggishly that the corresponding quaternary salts (type VII) were not obtained.

On the other hand, condensation of N,N,3-trimethyladenine (Va)⁸ with 1-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (VI)⁹ in ClCH₂CH₂Cl in the presence of SnCl₄¹⁰ at room temperature gave, after treatment with a solution of NaI in EtOH, the desired 2',3',5'-tri-O-benzoyl-N,N,3-trimethyladenosine iodide (VIIa),^{3,7} mp 189–190°C (dec.), in 35% yield. Similar treatment of 3-ethyl-N,N-dimethyladenine (Vb)⁸ gave a colorless solid, which, without further purification, was hydrolyzed according to the reported procedure⁷ to provide 5-(ethylamino)-1-β-D-ribofuranosylimidazole-4-carboxamide (Xb) as a colorless glass in 30% overall yield; nmr (Me₂SO-d₆) δ: 1.08 (3H, t, \underline{J} = 7 Hz, CH₃CH₂), 3.15 (2H, m, CH₃CH₂), 6.87 and 7.03 (1H each, broad, NH₂), 7.60 (1H, s, C(2)-H). 3-Benzyl-N,N-dimethyladenine (Vc),⁸ however, hardly reacted with VI.

We have already established the synthesis of 1-alkyl-5-(N-alkylformamido)imidazole-4-carboxamides (type IX, alkyl for ribofuranosyl),^{11,12} which produce 1-alkyl-5-(alkylamino)imidazole-4-carboxamides (X, alkyl for ribofuranosyl) on alkaline hydrolysis.¹¹ We have also reported the synthesis of 5-(N-methylformamido)-1-β-D-ribofuranosylimidazole-4-carboxamidinium p-toluenesulfonate (IXa)¹ by methylation of N'-benzyloxy-5-formamido-1-β-D-ribofuranosylimidazole-4-carboxamide (IV)¹³ followed by removal of the N'-benzyloxy group. Thus, hydrolysis of IXa should lead to a new synthesis of Xa. In fact, when heated in 1 N aq. NaOH under reflux for 30 min, IXa gave Xa in 39% overall yield based on IV. According to this procedure, IV was treated with EtI in HCONMe₂ in the presence of anhydrous K₂CO₃ at room temperature for 24 h, furnishing N'-benzyloxy-5-(N-ethylformamido)-1-β-D-ribofuranosylimidazole-4-carboxamide (VIIIb), mp 147–148°C,¹⁴ in 79% yield. Removal of the N'-benzyloxy group¹ from VIIIb and successive hydrolysis were conducted in a manner similar to that employed for the synthesis of Xa, and Xb was obtained as a colorless glass in 49% overall yield based on IV. The reactions of IV with PhCH₂Br and with iso-PrI under similar conditions gave the corresponding N-alkylformamido derivatives (VIIIc,d) as oils. These were transformed in a similar manner into 5-(benzylamino)- (Xc), mp 153–154°C,¹⁴ and 5-(isopropylamino)-1-β-D-ribofuranosylimidazole-4-carboxamide (Xd), mp 163–165°C,¹⁴ in 35% and 7% overall yield, respectively.

In conclusion, among the above three synthetic routes to X, the reaction sequence IV→VIII→IX→X has proved to be the most general one, and it should be of great help towards our current efforts on the synthesis of the 3-alkyl homologs of Ib-e.

ACKNOWLEDGMENT This work was supported in part by a Grant-in-Aid for Scientific Research (No. 56470117) from the Ministry of Education, Science and Culture, Japan.

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Received, 24th February, 1982