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

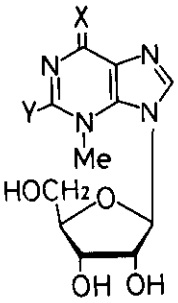
Taisuke Itaya,* Tohru Saito, Tsunehiro Harada, Seiya Kagatani, and Tozo Fujii

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

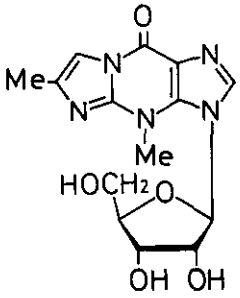
Abstract—— Alkylation of N'-benzyloxy-5-formamido-1-β-D-ribofuranosylimidazole-4-carboxamidine (IV) in the presence of K_2CO_3 followed by hydrogenolysis of the N'-benzyloxy group and alkaline hydrolysis produced the title compounds (X), intermediates adaptable to the syntheses of various 3-alkyl-9-β-D-ribofuranosylpurines.

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-Ribofuranosylwye (II), 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 II 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.

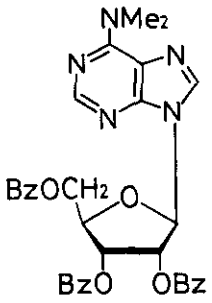
Syntheses of Xa and 2',3'-O-isopropylidene-Xa have been achieved by reductive methylation of appropriate imidazole nucleosides.[5a,6] Alternatively, we have obtained



Ia, X = NH; Y = H
b, X = NH; Y = OH
c, X = O; Y = H
d, X = O; Y = OH
e, X = O; Y = NH_2

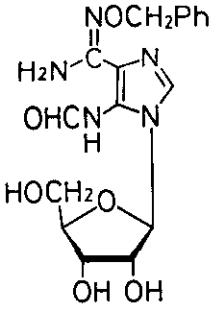


II

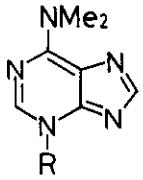


III

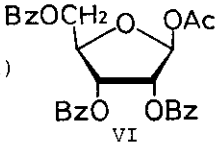
MeI



IV



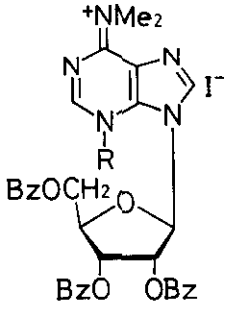
V



VI

i)

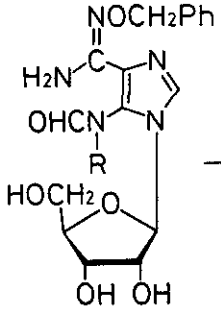
ii) NaI



VII

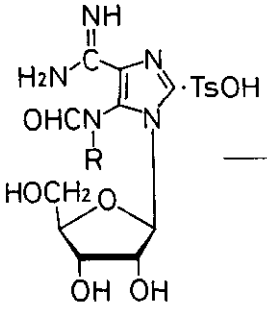
RX
K_2CO_3

NaOH



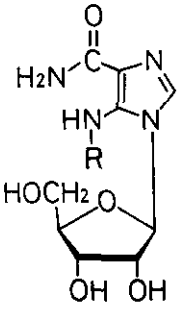
VIII

Raney Ni/H_2
TsOH



IX

NaOH



X

a, R = Me
b, R = Et
c, R = $PhCH_2$
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 $PhCH_2Br$ 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 $ClCH_2CH_2Cl$ in the presence of $SnCl_4$[10] 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 procedure[7] to provide 5-(ethylamino)-1-β-D-ribofuranosylimidazole-4-carboxamide (Xb) as a colorless glass in 30% overall yield; nmr (Me_2SO-d_6) δ: 1.08 (3H, t, J = 7 Hz, CH_3CH_2), 3.15 (2H, m, CH_3CH_2), 6.87 and 7.03 (1H each, broad, NH_2), 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-carboxamidines (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-carboxamidine (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 $HCONMe_2$ in the presence of anhydrous K_2CO_3 at room temperature for 24 h, furnishing N'-benzyloxy-5-(N-ethylformamido)-1-β-D-ribofuranosylimidazole-4-carboxamidine (VIIIb), mp 147–148°C,[14] in 79% yield. Removal of the N'-benzyloxy group[1] 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 $PhCH_2Br$ 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.

REFERENCES

1. T. Saito and T. Fujii, J. Chem. Soc., Chem. Commun., 1979, 135.
2. Will be published elsewhere.
3. T. Itaya and H. Matsumoto, Tetrahedron Lett., 1978, 4047.
4. T. Itaya and T. Harada, Heterocycles, in press.
5. a) S. Nakatsuka, T. Ohgi, and T. Goto, Tetrahedron Lett., 1978, 2579; b) T. Itaya and K. Ogawa, ibid., 1978, 2907; c) T. Itaya, T. Watanabe, and H. Matsumoto, J. Chem. Soc., Chem. Commun., 1980, 1158.
6. P. K. Bridson and C. B. Reese, Bioorg. Chem., 1979, 8, 339.
7. T. Itaya, H. Matsumoto, and T. Watanabe, Chem. Pharm. Bull., 1982, 30, 86.
8. T. Itaya, H. Matsumoto, and K. Ogawa, Chem. Pharm. Bull., 1980, 28, 1920.
9. E. F. Recondo and H. Rinderknecht, Helv. Chim. Acta, 1959, 42, 1171.
10. U. Niedballa and H. Vorbrüggen, J. Org. Chem., 1974, 39, 3654.
11. T. Fujii, T. Saito, and M. Kawanishi, Tetrahedron Lett., 1978, 5007.
12. T. Fujii, T. Saito, and T. Nakasaka, Heterocycles, 1981, 15, 195.
13. T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, Chem. Pharm. Bull., 1973, 21, 1676.
14. Satisfactory elemental analyses and spectral data were obtained for this compound.

Received, 24th February, 1982