Synthesis of some D-Mannofuranosyl and D-Lyxofuranosyl Imidazole and Adenine Nucleosides and Anomalous ^{1}H Nuclear Magnetic Resonance Spectra of Related Anomers

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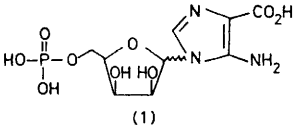
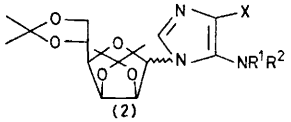
Summary Ethyl 1-α- and -β-D-2′,3′-*O*-isopropylidene mannofuranosyl imidazole-4-carboxylates have been prepared from corresponding 2′,3′:5′,6′-di-*O*-isopropylidene derivatives and, after *N*-acetylation, converted by periodate and borohydride into the corresponding 1-α- and -β-D-2′,3′-*O*-isopropylidene lyxofuranosyl imidazole-4-carboxylates; the anomeric configuration of the nucleosides was confirmed by ^{1}H n.m.r. and optical rotation studies and by conversion of the 2′,3′:5′,6′-*O*-isopropylidene mannoside esters with ammonia into the corresponding amides which were converted by sequences of reactions into the corresponding 1-α- and -β-D-mannofuranosyl adenines.

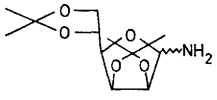
As part of a project designed to prepare inhibitors of the enzyme duet phosphoribosylaminoimidazole carboxylase (E.C. 4.1.1.21) and phosphoribosylaminoimidazolesuccinocarboxamide synthetase (E.C. 6.3.2.6.)[1] we have been interested to prepare 5-amino-1-α- and -β-D-lyxofuranosylimidazole-4-carboxylic acid 5′-phosphates, (**1a**) and (**1b**), which are analogues of 5-amino-1-α- and -β-D-ribofuranosylimidazole 4-carboxylic acid 5′-phosphates, respectively, the latter being a central intermediate in the *de novo* biosynthetic pathway to purine nucleotides. We have previously recorded[2] the synthesis of the 1-β-D-imidazole carboxamide (**2d**) and the corresponding esters, (**2a**) and (**2b**). We now report the synthesis of D-lyxose imidazole nucleosides from the corresponding mannose derivatives.



(1)
a; α-anomer
b; β-anomer

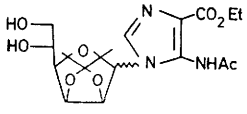


(2)
a; X = CO_2Et, R^1 = R^2 = H, α-anomer
b; X = CO_2Et, R^1 = R^2 = H, β-anomer
c; X = $CONH_2$, R^1 = R^2 = H, α-anomer
d; X = $CONH_2$, R^1 = R^2 = H, β-anomer
e; X = CO_2Et, R^1 = R^2 = Ac, α-anomer
f; X = CO_2Et, R^1 = R^2 = Ac, β-anomer
g; X = CO_2Et, R^1 = H, R^2 = Ac, α-anomer
h; X = CO_2Et, R^1 = H, R^2 = Ac, β-anomer
i; X = CN, R^1 = R^2 = H, α-anomer
j; X = CN, R^1 = R^2 = H, β-anomer

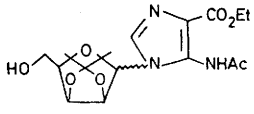


(3)

EtOCH=N•CH(CN)COX
(4)
a; X = OEt
b; X = NH_2



(5)
a; α-anomer
b; β-anomer



(6)
a; α-anomer
b; β-anomer

Reaction of the D-mannofuranosylamine (**3**)[2] with the formimidate (**4a**)[3] gave the α- (**2a**),[2] m.p. 225—226 °C (23%) and β- (**2b**),[2] m.p. 190—192 °C (19%) mannosides. The 5-amino-group of the aforementioned nucleosides was protected by acetylation with acetyl chloride in pyridine to give, in each case, the *N*-di- and *N*-mono-acetylated derivatives (**2e**), m.p. 139 °C (37%); (**2g**) m.p. 194 °C (36%); (**2f**), m.p. 177 °C (31%), and (**2h**), m.p. 169 °C (25%), respectively, which were purified by chromatography on silica gel. Conversion of the *N*-diacetylated derivatives into the *N*-monoacetylated derivatives was achieved in good yield by treatment with ammonia in methanol.

Selective hydrolysis of the 5′,6′-*O*-isopropylidene group of the *N*-monoacetylated derivatives (**2g**) and (**2h**) with water–acetic acid (3:7) gave, respectively, the α- (**5a**) (85%) and β- (**5b**) (83%) 2′,3′-*O*-isopropylidene derivatives as solids (pure on t.l.c.).

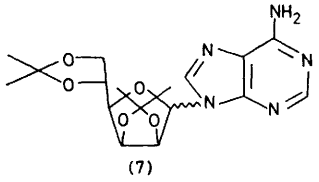
The mannosides (**5a**) and (**5b**) on treatment with sodium periodate followed by sodium borohydride gave the respective α- (**6a**) (59%) and β- (**6b**) (56%) lyxosides as solids (pure on t.l.c.).

In order to establish, unequivocally, the anomeric configuration of the foregoing imidazole mannosides and lyxosides it was decided to convert them into the corresponding adenine nucleosides for comparison with authentic specimens.

The mannosylamine (**3**) with the formimidate (**4b**) gave, after chromatography on silica gel, the crystalline α- (**2c**), m.p. 178 °C (11%) and β- (**2d**),[2] m.p. 218 °C (28%) imidazole carboxamide mannosides. The relationship assumed between the esters and amides was confirmed by reaction of the α- and β-ester derivatives (**2a**) and (**2b**) with aqueous ethanolic ammonia to produce the corresponding amides (**2c**) and (**2d**) which were readily distinguishable on t.l.c.

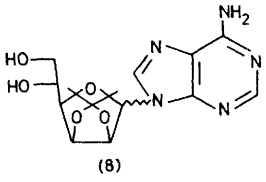
Dehydration of the amides with phosphoryl chloride in chloroform gave the corresponding α- (**2i**), m.p. 234 °C (18%) and β- (**2j**), m.p. 235 °C (22%) nitriles. The nitriles with triethylorthoformate and ammonia in ethanol gave the corresponding α- (**7a**), m.p. 233 °C (68%) and β- (**7b**), m.p. 285 °C (76%) adenine mannosides. The 5′,6′-*O*-isopropylidene group of each mannosyl adenine was selectively hydrolysed with water–acetic acid (3:7) to give (**8a**), m.p. 248 °C (74%) and (**8b**), m.p. 265 °C (69%). The former compound was identical with an authentic sample.[4] Removal of the 2′,3′-*O*-isopropylidene group of (**8a**) and (**8b**) with water–acetic acid (3:1) gave the unprotected nucleoside (**9a**), m.p. 237 °C (45%) and (**9b**), (hydrate) m.p. 94 °C (34%), respectively. The former compound was identical with an authentic sample.[4] To establish further the anomeric configuration of the foregoing mannosyl and lyxosyl nucleosides, the adenines (**9a**) and (**9b**) were

each treated with sodium periodate followed by sodium borohydride using a method described earlier[5] to give products which had specific rotations of $-64°$[6] and $+70°$, respectively. When adenosine was treated in the same manner, the product was found to have a specific rotation of $+67°$.



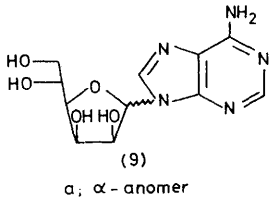
(7)

a; α-anomer
b; β-anomer



(8)

a; α-anomer
b; β-anomer



(9)

a; α-anomer
b; β-anomer

The ^{1}H n.m.r. spectra of the foregoing compounds (Table), excluding (**7a**,**b**) and (**9a**,**b**) showed that the shift in anomeric proton signals for a pair of corresponding anomers was not in accordance with the empirical rule[7] which states that H-1′ resonates at lower fields when the 1′,2′-substituents are *cis* than when they are *trans*. It is also interesting to note that for a pair of related anomers, with the exception of the unprotected mannosides (**9a**) and (**9b**), the H-1′ signal for the α-anomers appeared as a singlet whereas the H-1′ signal for the β-anomers appeared as a doublet having a $J_{1',2'}$ value of 3—4 Hz. According to the Karplus equation,[8] as modified for furanose systems, a singlet in the ^{1}H n.m.r. spectrum assigned to H-1′ is good evidence for a *trans* H-1′, H-2′ arrangement and hence for the α-configuration in the case of mannose and lyxose nucleosides.

TABLE. ^{1}H N.m.r. spectra of D-mannose and D-lyxose nucleosides (δ values).

Compound	H-1′ ($J_{1',2'}$/Hz)	Isopropylidene methyl groups	Δδ
(**2a**)[a]	5·72 (s)	1·45 (m)	—
(**2b**)[a]	5·44 (3)	1·45 (m)	—
(**2c**)[b]	5·86 (s)	1·38 (m)	—
(**2d**)[b]	5·51 (3)	1·35 (m)	—
(**2e**)[a]	5·50 (s)	1·52, 1·36	0·16
(**2f**)[a]	5·10 (3)	1·52, 1·36	0·16
(**2g**)[a]	6·02 (s)	1·45 (m)	—
(**2h**)[a]	5·49 (3)	1·45 (m)	—
(**2i**)[b]	5·88 (s)	1·35 (m)	—
(**2j**)[b]	5·48 (3)	1·31 (m)	—
(**5a**)[a]	5·88 (s)	1·48, 1·34	0·14
(**5b**)[a]	5·42 (3)	1·50, 1·34	0·16
(**6a**)[a]	5·99 (s)	1·50, 1·34	0·16
(**6b**)[a]	5·44 (s)	1·56, 1·36	0·20
(**7a**)[a]	5·93 (s)	1·46 (m)	—
(**7b**)[a]	6·06 (3)	1·46 (m)	—
(**8a**)[b]	6·14 (s)	1·50, 1·36	0·14
(**8b**)[b]	6·06 (4)	1·49, 1·30	0·19
(**9a**)[b]	5·90 (8)	—	
(**9b**)[b]	6·17 (8)	—	

[a] In Me_2SO. [b] In $CDCl_3$.

Further examination of the ^{1}H n.m.r. spectra of the 2′,3′-*O*-isopropylidene derivatives (**2e**,**f**), (**5a**,**b**), (**6a**,**b**), and (**8a**,**b**) revealed that for a pair of corresponding anomers, the chemical shifts of the isopropylidene methyl groups were not in accordance with the limitations set by J.-L. Imbach[9] for ribose nucleosides, that the difference in chemical shifts (Δδ) for the *endo*- and *exo*-methyl groups are $>0{\cdot}15$ p.p.m. for β-anomers and $<0{\cdot}15$ p.p.m. for α-anomers. It might be expected that 2′,3′-*O*-isopropylidene lyxose and mannose nucleosides would show the opposite trend to the corresponding ribose derivatives.†

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† Satisfactory analytical, t.l.c., and spectral data were obtained for all new compounds.

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