Purines, Pyrimidines, and Imidazoles. Part 49.[1] Adenine and Imidazole Nucleosides of D-Mannofuranose

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Reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosylamine with ethyl *N*-[carbamoyl(cyano)methyl]-formimidate gave crystalline 5-amino-1-(2,3:5,6-di-*O*-isopropylidene-α- and -β-D-mannofuranosyl)imidazole-4-carboxamides, treatment of which with phosphoryl chloride in chloroform produced 5-amino-4-cyano-1-(2,3:5,6-di-*O*-isopropylidene-α- and -β-D-mannofuranosyl)imidazoles. The anomeric aminonitriles with triethyl orthoformate followed by ethanolic ammonia led directly to 9-(2,3:5,6-di-*O*-isopropylidene-α- and -β-D-mannofuranosyl)adenines which with acid gave sequentially 9-(2,3-*O*-isopropylidene-α- and -β-D-mannofuranosyl)-adenines and 9-α- and -β-D-mannofuranosyladenines. The two latter α-anomers were identical with specimens prepared by another route. The structures of the mannofuranosyladenines were confirmed by periodate oxidation followed by reduction with sodium borohydride and comparison of the specific rotations of derived glycerol derivatives with those produced by adenosine, and by n.m.r. and c.d. studies. ^{1}H N.m.r. spectra of comparable pairs of anomeric mannofuranosyl imidazoles and 2',3'-*O*-isopropylidenemannofuranosyladenines showed that they did not accord with an empirical rule relating anomer configuration with the field positions of 1'-H whereas 9-(2,3:5,6-di-*O*-isopropylidene-α- and -β-D-mannofuranosyl)adenine or 9-α- and -β-D-mannofuranosyl-adenine anomer pairs had spectral relationships in accord with the rule.

ADENOSINE analogues including especially adenine 9-β-D-nucleosides are of considerable interest as potential antimetabolites and several such compounds including 9-β-D-arabinofuranosyl- and 9-β-D-xylofuranosyl-adenine are active as anti-viral and anti-cancer agents and the former compound is widely used clinically for the treatment of diseases in these categories.[2] The only 9-β-D-glycofuranosyladenine derived from a common sugar for which there is no recorded preparation is 9-β-D-mannofuranosyladenine (1b). The preparation of a mannofuranosyladenine has been recorded by Lerner[3] who condensed 2,3:5,6-di-*O*-isopropylidenemannofuranosyl chloride with chloromercuri-6-benzamidopurine to produce, after deblocking the intermediates, 9-α-D-mannofuranosyladenine (1a). The author points out that the reaction might reasonably have been expected to produce a mixture of α- and β-anomers but paper chromatographic examination in two solvent systems of the mother liquors remaining after crystallization of the α-anomer revealed the presence of only a trace of another nucleoside apart from (1a). The structure (1a) assigned to the nucleoside was confirmed by elemental analysis, u.v. absorption spectroscopy, and periodate oxidation to give 0.98 mole of formaldehyde which was isolated as a dimedone derivative. In addition[4] the 2,3-*O*-isopropylidenemannofuranosyladenine (2a) produced by mild acid hydrolysis of the 2,3:5,6-di-*O*-isopropylidene derivative (3a) when treated with periodate followed by sodium borohydride gave 9-(2,3-*O*-isopropylidene-α-D-lyxofuranosyl)adenine (4a) which together with the deblocked nucleoside (5a) were found to be different from a previously described 9-(2,3-*O*-isopropylidene-β-D-lyxofuranosyl)adenine (4b) which had in turn been synthesised[5] from 9-β-D-xylofuranosyladenine and the deblocked β-anomer (5b), respectively.

In addition, treatment of the proposed α-anomer (1a) with periodate followed by sodium borohydride gave 2-*O*-[1-(9-adenyl)-2-hydroxyethyl]glycerol which had a specific rotation of −65°. Under the same conditions adenosine produced material with a specific rotation of +68.1°.

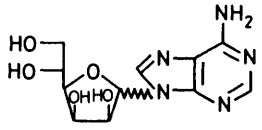
We have recently outlined[6] a useful new route to mannofuranosyl-5-aminoimidazole derivatives in which di-*O*-isopropylidenemannofuranosylamine (6) is employed as the source of the glycosyl unit. Aminoimidazole nucleosides are useful intermediates for the synthesis of purine nucleosides and we have been interested to use our methods to investigate the synthesis of both the α- and β-anomeric adenine mannofuranosides. A preliminary account[7] of some of the work has been published.

Reaction of the mannofuranosylamine[6] (6) with the formimidate[8] (7), prepared from α-aminocyanoacetamide and triethyl orthoformate, gave after chromatography on silica gel, the α- and -β-D-imidazolecarboxamide nucleosides (8a and b), respectively, as crystalline solids. We have earlier recorded[6] a similar preparation of the two anomeric imidazole ester mannofuranosides (8c and d) and of one crystalline carboxamide, shown to be the β-anomer (8b). The relationship between the two sets of anomers (esters and amides) was confirmed by amination of each ester (8c and d) with aqueous ethanolic ammonia to produce corresponding amides (8a and b) respectively, which were indistinguishable on t.l.c. from the compounds prepared by the direct route.

The carboxamides (8a and b) were readily dehydrated by phosphoryl chloride in chloroform to produce the

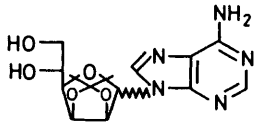
[1] Part 48, R. Lofthouse, G. Mackenzie, G. Shaw, and N. J. Cusack, *J. Chem. Research*, 1978 (*S*), 56; (*M*), 664.
[2] R. J. Suhadolnik in 'Nucleoside Antibiotics,' Wiley–Interscience, New York, 1970.
[3] L. M. Lerner and P. Kohn, *J. Org. Chem.*, 1966, **31**, 339.
[4] P. Kohn, L. M. Lerner, and B. D. Kohn, *J. Org. Chem.*, 1967, **32**, 4076.
[5] E. J. Reist, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, 1967, **32**, 169.
[6] N. J. Cusack, D. H. Robinson, P. W. Rugg, G. Shaw, and R. Lofthouse, *J.C.S. Perkin I*, 1974, 73.
[7] G. Mackenzie and G. Shaw, *J.C.S. Chem. Comm.*, 1977, 753.
[8] D. H. Robinson and G. Shaw, *J.C.S. Perkin I*, 1972, 1715.

corresponding aminonitrileimidazole nucleosides (8e and f) as crystalline solids. The conversion of an aminoimidazole nitrile, namely 5-amino-1-methylimidazole-4-carbonitrile (9) into an adenine derivative, namely 9-methyladenine, was first accomplished [9] by reaction of



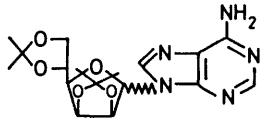
(1)

a; α—anomer
b; β—anomer



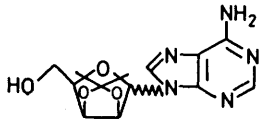
(2)

a; α—anomer
b; β—anomer



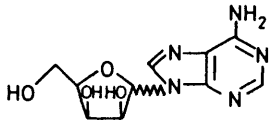
(3)

a; α—anomer
b; β—anomer



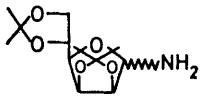
(4)

a; α—anomer
b; β—anomer



(5)

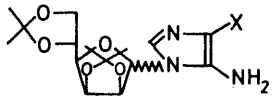
a; α—anomer
b; β—anomer



(6)

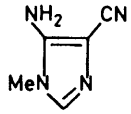
EtOCH=N·CH(CN)CONH$_2$

(7)

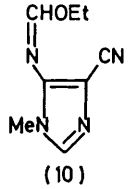


(8)

a; X = CONH$_2$, α—anomer
b; X = CONH$_2$, β—anomer
c; X = CO$_2$Et, α—anomer
d; X = CO$_2$Et, β—anomer
e; X = CN, α—anomer
f; X = CN, β—anomer



(9)



(10)

the aminoimidazole with triethyl orthoformate followed by amination of the intermediate ethoxymethylidene derivative (10) with ethanolic ammonia to produce 9-methyladenine directly, and the reaction could be carried out in good yield without isolation of the intermediate (10). In a similar manner the mannofuranosylimidazoles (8e and f) with triethyl orthoformate and ammonia at 150° gave the corresponding 9-(2,3:5,6-di-*O*-isopropylidenemannofuranosyl)adenines (3a and b) respectively as crystalline solids. Mild aqueous acid treatment of the di-*O*-isopropylidene derivatives produced corresponding 2,3-*O*-isopropylidene derivatives (2a and b) respectively as crystalline solids. The first of the compounds (2a) was identical (t.l.c., i.r., mixed m.p.) with the specimen prepared by Lerner [3,4] and was designated the α-anomer. Further, more vigorous acid treatment of the monoisopropylidene derivatives readily produced the deblocked mannofuranosyladenines (1a and b) respectively as crystalline compounds, and the former compound was identical (t.l.c., i.r., mixed m.p.) to the material prepared by Lerner. When each mannofuranosyladenine (1a and b) was treated with periodate followed by sodium borohydride [10] the products obtained had specific rotations respectively of −64 and +70°. Under the same conditions adenosine gave a product with a specific rotation of +67°. These results clearly confirm the anomeric configurations which we have assigned to the two mannofuranosyladenines and at the same time further confirm in a more direct manner the original configuration assigned to the α-anomer (1a).

The ability to be able to relate anomer configuration to that of a nucleoside of known structure is especially important. ^{1}H N.m.r. spectroscopy has been used [11] to assign anomer configurations in a given pair of anomeric nucleosides by use of an empirical rule which states that 1′-H resonates at lower fields when the 1′,2′-substituents are *cis* rather than *trans*. However examination of the ^{1}H n.m.r. spectra of various anomeric pairs of mannofuranosyl nucleosides (Table) reveals that all the mannofuranosylimidazoles and the partially blocked mannofuranosyladenines (2a and b) showed shifts in the anomeric proton signals for a pair of corresponding anomers which was not in accordance with the empirical rule. On the other hand the fully blocked (3a and b) or fully deblocked (1a and b) pairs of mannofuranosyladenines had a ^{1}H n.m.r. spectral relationship which accorded with the empirical rule. It is also noteworthy that with the exception of the deblocked mannofuranosyladenines (1a and b), for a pair of related anomers, the 1′-H signal for the α-anomer appears as a singlet whereas that for the β-anomer appears as a doublet having a $J_{1'2'}$ value of 3—4 Hz. According to the Karplus equation [12] as modified for furanose systems, a singlet in the ^{1}H n.m.r. spectrum assigned to 1′-H provides good evidence for a *trans*-1′-H, 2′-H arrangement and hence for the α-configuration in the case of the mannofuranosyl nucleosides.

It is also of interest to compare the chemical shifts of the isopropylidene methyl groups for pairs of anomeric mannofuranosides. In the case of 2,3-*O*-isopropylidene ribosides Imbach [13] has pointed out that the difference ($\Delta\delta$) in chemical shifts for the *endo*- and *exo*-methyl groups is <0.15 for α-anomers and >0.15 for β-anomers. It might be expected that the 2′,3′-*O*-isopropylidenemannofuranosyladenines would show the opposite trend

[9] G. Shaw and D. N. Butler, *J. Chem. Soc.*, 1959, 4040.
[10] R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Amer. Chem. Soc.*, 1958, **80**, 2004.
[11] L. B. Townsend in ' Synthetic Procedures in Nucleic Acid Chemistry,' eds. W. W. Zorbach and R. S. Tipson, Wiley–Interscience, New York, 1973.
[12] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[13] J.-L. Imbach, *Ann. New York, Acad. Sci.*, 1975, **255**, 177.

to those shown by ribonucleosides but this does not appear to be the case.

The optical rotations for the pairs of imidazole amides (8a and b), imidazole nitriles (8e and f), and fully

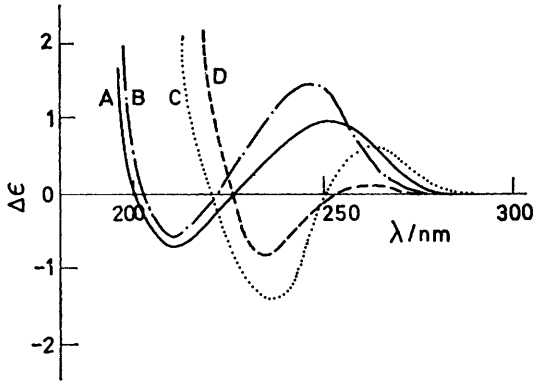


FIGURE 1 C.d. spectra of some mannofuranosylimidazoles: A, (8a); B, (8e); C, (8b); D, (8f)

deblocked adenines (1a and b) were in agreement with Hudson's rules.[14] However, Hudson's rules could not be applied, satisfactorily, to the anomeric pairs of partially and fully protected mannosyladenines (2a and b) and (3a and b).

The c.d. curves for the mannosyladenine nucleosides (Figure 2) showed the expected [15] negative Cotton effects for the β-anomers and positive effects for the α-anomers. A conformation approaching *anti* can, therefore, be related to a negative Cotton effect for the adenine β-D-mannosides. The c.d. spectra of the cyanoimidazole α- and β-mannosides (8e and f) (Figure 1) also showed positive and negative Cotton effects respectively but in the latter a blue shift of 10 nm was observed in the c.d. maximum. It is noteworthy that the α-amide (8a) has the same general shape of c.d. curve as the corresponding β-anomer (8b) (Figure 1). This observation is in agreement with that previously reported for the corresponding esters (8c and d).

It is hoped that most of the nucleosides mentioned in this paper will ultimately be tested for anti-viral and anti-tumour activity.

[14] C. S. Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66.

[15] J. L. V. Ulbricht in ' Synthetic Procedures in Nucleic Acid Chemistry,' eds. W. W. Zorbach and R. S. Tipson, Wiley–Interscience, New York, 1973.

EXPERIMENTAL

Evaporations were carried out with a Büchi rotary evaporator, under water-pump vacuum with a flask temperature ≤40°, unless otherwise stated. U.v. absorption spectra were measured with a Unicam SP 800 spectrophotometer, i.r. spectra with a Perkin-Elmer 157 spectrophotometer, n.m.r. spectra with a JEOL JNM-MN-100 spectrometer (tetramethylsilane as internal standard), mass spectra with an A.E.I. MS902 spectrometer, and optical rotations with a Perkin-Elmer 141 polarimeter; c.d. spectra were provided by Professor W. Klyne and Dr. P. M. Scopes, Westfield College, University of London, whom we thank. Silica gel (0.05—0.20 mm; 325—370 mesh; Machery Nagel and Co.) was used for column chromatography, and silica gel $60F_{254}$ 0.25 mm precoated glass plates (Merck) were used for t.l.c. with (A) chloroform–methanol (9 : 1) and (B) n-butanol–acetic acid–water (12 : 3 : 5) as development systems.

5-Amino-1-(2,3:5,6-di-O-isopropylidene-α- and β-D-mannofuranosyl)imidazole-4-carboxamide (8a *and* b).—A solution of ethyl *N*-[carbamoyl(cyano)methyl]formimidate [8] (5 g, 0.032 mol) in a mixture of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosylammonium toluene-*p*-sulphonate [6] (13 g, 0.03 mol) and ethanolic sodium ethoxide (50 ml containing 0.03 mol) was set aside overnight. T.l.c. examination in system (A) showed two major Bratton–Marshall [16] active products, R_F 0.47 and 0.38. The solution was filtered and evaporated to a red gum which was dissolved in chloroform (100 ml) and the solution washed with 2M-sodium hydroxide (20 ml). The organic phase was dried (Na_2SO_4) and eva-

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

Compound	1'-H ($J_{1',2'}$/Hz)	$CHMe_2$	Δ	$CONH_2$	NH_2	2-H	8-H
(1a) [b]	5.86 (s)	1.38 (m)		6.72	5.94	7.24	
(1b) [b]	5.51 (3)	1.35 (m)		6.72	5.82	7.16	
(2a) [b]	5.88 (s)	1.35 (m)			6.34	7.34	
(2b) [b]	5.48 (3)	1.31 (m)			6.08	7.16	
(3a) [a]	5.93 (s)	1.46 (m)			5.90	8.26	7.76
(3b) [a]	6.06 (3)	1.46 (m)			5.94	8.30	8.09
(4a) [b]	6.14 (s)	1.50, 1.36	0.14		7.29	8.28	8.20
(4b) [b]	6.06 (4)	1.49, 1.30	0.19		7.31	8.21	8.12
(5a) [b]	5.90 (8)				7.25	8.40	8.20
(5b) [b]	6.17 (8)				7.14	8.38	8.13

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

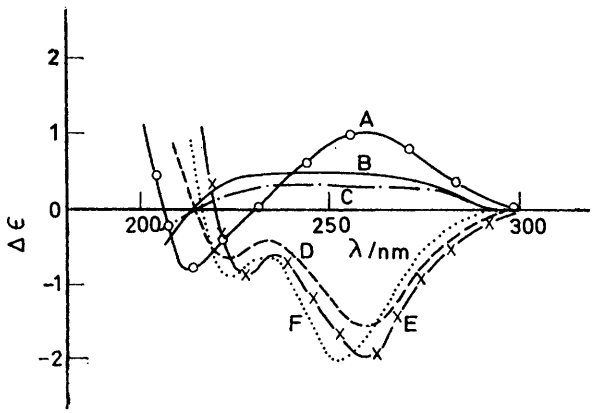


FIGURE 2 C.d. spectra of some mannofuranosyladenines: A, (1a); B, (3a); C, (2a); D, (1b); E, (2b); F, (3b)

[16] A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, 1939, **128**, 537.

porated to a gum which readily crystallised from chloroform. The β-*mannofuranosylimidazole* (8b), R_F 0.38 (A) crystallised from methanol as laths (3.1 g, 28%), m.p. 218°, $[\alpha]_D^{20}$ +35° (*c* 1.0 in Me_2SO) (Found: C, 52.35; H, 6.6; N, 15.35%; M^+, 368. Calc. for $C_{16}H_{24}N_4O_6$: C, 52.15; H, 6.5; N, 15.2%; *M*, 368), $\lambda_{max.}$ (MeOH) 265 nm (ε 11 900). The mother liquors were evaporated to a gum which was dissolved in chloroform (3 ml) and applied to a silica gel column (60 × 3 cm). The α-mannofuranosylimidazole R_F 0.47 (A) and β-anomer R_F 0.38 (A) were separated by elution with methanol–chloroform (2 : 98). The fractions were separately evaporated to give the α-*nucleoside* (8a) which crystallised from methanol as needles (1.2 g, 11%), m.p. 178°, $[\alpha]_D^{20}$ +88° (*c* 1.0 in Me_2SO) (Found: C, 51.95; H, 6.65; N, 15.0%; M^+, 368. $C_{16}H_{24}N_4O_6$ requires C, 52.15; H, 6.5; N, 15.2%; *M*, 368), $\lambda_{max.}$ (MeOH) 266 nm (ε 11 400).

5-*Amino*-4-*cyano*-1-(2,3:5,6-*di*-O-*isopropylidene*-α-D-*mannofuranosyl*)*imidazole* (8e).—Phosphoryl chloride (1.2 g, 0.008 mol) was added dropwise, over 3 h, to a stirred, cooled solution of 5-amino-1-(2,3 : 5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)imidazole-4-carboxamide (2.4 g, 0.007 mol) and triethylamine (2.5 g, 0.025 mol) in chloroform (60 ml). The cooled solution was stirred for a further 1.5 h. T.l.c. [system (A)] showed a single spot (R_F 0.47) and the absence of starting material. The solution was poured over ice–sodium hydrogencarbonate solution and the organic phase was dried (Na_2SO_4) and evaporated to a gum. A solution of the gum in chloroform (2 ml) was applied to a silica gel column (40 × 2 cm). The product was eluted by chloroform–methanol (97 : 3). Crystallisation from methanol gave the *cyanoimidazole* α-*nucleoside* as needles (0.41 g, 18%), m.p. 234°, $[\alpha]_D^{20}$ +115° (*c*. 1.0 in Me_2SO) (Found: C, 54.7; H, 6.3; N, 15.95%; M^+, 350. $C_{16}H_{22}N_4O_5$ requires C, 54.85; H, 6.3; N, 16.0%; *M*, 350), $\lambda_{max.}$ (MeOH) 242 nm (ε 11 200), ν_{CN} 2 210 cm^{-1}.

5-*Amino*-4-*cyano*-1-(2,3:5,6-*di*-O-*isopropylidene*-β-D-*mannofuranosyl*)*imidazole* (8b).—Phosphoryl chloride (1.8 g, 0.012 mol) was added dropwise, over 3 h, to a stirred, cooled solution of 5-amino-1-(2,3 : 5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)imidazole-4-carboxamide (3.6 g, 0.01 mol) and triethylamine (3.8 g, 0.038 mol) in chloroform (100 ml). The cooled solution was stirred for a further 3 h. T.l.c. [system (A)] showed a single spot (R_F 0.45) and the absence of starting material. The solution was poured over ice–sodium hydrogencarbonate solution and the organic phase dried (Na_2SO_4) and evaporated to a gum. A solution of the gum in chloroform (2 ml) was applied to a silica gel column (40 × 2 cm). The product was eluted by chloroform–methanol (97 : 3). Crystallisation from methanol gave the *cyanoimidazole* β-*nucleoside* as needles (2.6 g, 76%), m.p. 235°, $[\alpha]_D^{20}$ +53° (*c* 1.0 in Me_2SO) (Found: C, 54.9; H, 6.35; N, 15.95%; M^+, 350. $C_{16}H_{22}N_4O_5$ requires C, 54.85; H, 6.3; N, 16.0%; *M*, 350), $\lambda_{max.}$ (MeOH) 245 nm (ε 11 400), ν_{CN} 2 215 cm^{-1}.

9-(2,3:5,6-*di*-O-*isopropylidene*-α-D-*mannofuranosyl*)-*adenine* (3a).—A mixture of 5-amino-4-cyano-1-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)imidazole (1 g, 0.029 mol), ethanol (15 ml) saturated with ammonia, and triethyl orthoformate (4.3 g, 0.29 mol) was held for 6 h at 150°. T.l.c. [system (A)] showed a single spot (R_F 0.52) and absence of starting material. On cooling, a dark amorphous solid precipitated which was separated by filtration. A solution of the residue in chloroform (20 ml) was passed through a Supercel–charcoal pad and the filtrate evaporated to give a solid. The α-*mannosyladenine* crystallised from chloroform as plates (0.73 g, 68%), m.p. 233°, $[\alpha]_D^{20}$ +8° (*c* 0.25 in Me_2SO) (Found: C, 54.2; H, 6.05; N, 18.35%; M^+, 377. $C_{17}H_{23}N_5O_5$ requires C, 54.1; H, 6.1; N, 18.55%; *M*, 377), $\lambda_{max.}$ (MeOH) 259 nm (ε 14 200).

9-(2,3:5,6-*Di*-O-*isopropylidene*-β-D-*mannofuranosyl*)-*adenine* (3b).—A mixture of 5-amino-4-cyano-1-(2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)imidazole (1 g, 0.029 mol), ethanol (15 ml) saturated with ammonia, and triethyl orthoformate (4.3 g, 0.29 mol) was held for 6 h at 150°. T.l.c. [system (A)] showed a single spot (R_F 0.50) and absence of starting material. The reaction mixture was then worked up as for the α-isomer. The β-*mannosyladenine* crystallised from chloroform as plates (0.82 g, 76%), m.p. 285°, $[\alpha]_D^{20}$ +38° (*c* 1.0 in Me_2SO) (Found: C, 53.85; H, 6.1; N, 18.65%; M^+, 377. $C_{17}H_{23}N_5O_5$ requires C, 54.1; H, 6.1; N, 18.55%; *M*, 377), $\lambda_{max.}$ (MeOH) 260 nm (ε 13 800).

9-(2,3-O-*Isopropylidene*-α-D-*mannofuranosyl*)*adenine* (2a).—A solution of 9-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)adenine (0.5 g) in acetic acid–water (7 : 3) was heated at 55° for 4 h. T.l.c. [system (A)] showed the presence of a single spot (R_F 0.21) and absence of starting material. The cooled solution was evaporated and the residue re-evaporated with water (2 × 10 ml). A solution of the residual gum in water (1 ml) soon produced the crystalline α-*mannosyladenine* which formed needles (0.33 74%), m.p. 248°, $[\alpha]_D^{20}$ +31° (*c* 1.0 in Me_2SO) {lit.,[3] $[\alpha]_D^{21}$ +32.5° (*c* 1.26 in 0.1N-HCl)} (Found: C, 49.65; H, 5.6; N, 20.5%; M^+, 377. Calc. for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.65; N, 20.75%; *M*, 337), $\lambda_{max.}$ (MeOH) 260 nm (ε 14 000). The product was identical (m.p., mixed m.p., and i.r.) with an authentic specimen.[3]

9-(2,3-O-*Isopropylidene*-β-D-*mannofuranosyl*)*adenine* (2b).—A solution of 9-(2,3 : 5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)adenine (0.5 g) in acetic acid–water (7 : 3) was heated at 55° for 4 h, cooled, and evaporated. The residue was re-evaporated with water (2 × 10 ml) to give the crystalline β-*mannosyladenine* which formed needles (0.31 g, 69%), m.p. 265°, $[\alpha]_D^{20}$ +29° (*c* 0.5 in Me_2SO) (Found: C, 49.8; H, 5.7; N, 20.85%; M^+, 337. $C_{14}H_{19}N_5O_5$ requires C, 49.85; H, 5.65; N, 20.75%; *M*, 337), $\lambda_{max.}$ (MeOH) 259 nm (ε 14 300).

9-α-D-*Mannofuranosyladenine* (1a).—A solution of 9-(2,3-*O*-isopropylidene-α-D-mannofuranosyl)adenine (0.25 g) in acetic acid–water (1 : 3) was heated at 100° for 3 h. The cooled solution was evaporated and the residue re-evaporated with water (2 × 10 ml). A solution of the residual gum in ethanol–water gave the α-*mannofuranosyladenine* as rods (0.10 g, 45%), m.p. 237°, $[\alpha]_D^{20}$ +79° (*c* 1.0 in Me_2SO){lit.,[3] $[\alpha]_D^{21}$ +74.8° (*c* 3.05 in 1N-HCl)} (Found: C, 44.2; H, 5.1; N, 23.4%; M^+, 297. Calc. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.05; N, 23.55%; *M*, 297), $\lambda_{max.}$ (MeOH) 259 nm (ε 14 600). The product was identical (m.p., mixed m.p., and i.r.) with an authentic sample.[3]

9-β-D-*Mannofuranosyladenine* (1b).—A solution of 9-(2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)adenine (0.5 g) in trifluoroacetic acid–water (9 : 1) (10 ml) was set aside at room temperature for 4 h. The solution was evaporated to dryness and the residue dissolved in methanolic ammonia and the solution evaporated to a gum. A solution of the gum in aqueous ethanol slowly gave a microcrystalline solid precipitate of 9-β-D-*mannofuranosyladenine* (0.2 g), m.p. 136° which retained water, $[\alpha]_D^{20}$ −70° (*c* 0.2% in Me_2SO) (Found: C, 43.8; H, 5.15; N,

23.25%; M^+, 297. $C_{11}H_{15}N_5O_5,1/4H_2O$ requires C, 44.4; H, 5.05; N, 23.55%; *M*, 297), $\lambda_{max.}$ (MeOH) 260 nm (ε 14 900). The same compound was similarly obtained from the 2,3-*O*-isopropylidene derivative.

Determination of Anomeric Configuration of D-*Mannofuranosyl Nucleosides*.—Samples (22.2, 22.2, and 20 mg) of 9-α- and -β-D-mannofuranosyladenine and authentic adenosine respectively, were each treated with 0.08M-sodium periodate and the mixture kept for 15 min at room temperature. Sodium borohydride (40 mg) was added to each solution, followed, after 0.5 h, by the slow addition of water–acetic acid (9 : 1) (0.5 ml). When the evolution of gas ceased (*ca.* 1 h) the specific rotation of each solution was determined. The solutions initially containing 9-α- and β-D-mannofuranosyladenine and adenosine had $[\alpha]_D^{20}$ values of −64, +70, and +67° respectively, based upon weights of the starting materials.

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