# Purines, Pyrimidines, and Imidazoles. Part 46.[1] Some Acyclic D-Arabinose Imidazole and Purine Nucleosides

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The reaction of D-arabinopyranosylamine with acetone, 2,2-dimethoxypropane, and toluene-*p*-sulphonic acid gave 3,4-*O*-isopropylidene-D-arabinopyranosylamine as a crystalline toluene-*p*-sulphonate, which with ethyl *N*-(α-cyano-β-ethoxyacryloyl)-*N*-methylcarbamate gave 1-α- and -β-D-arabinopyranosyl-5-cyano-3-methyluracils and with ethyl *N*-(carbamoylcyanomethyl)formimidate, after removal of the isopropylidene groups, 5-amino-1-α- and -β-D-arabinopyranosylimidazole-4-carboxamides. D-Ribopyranosylamine with dimethylformamide dimethyl acetal produced *NN*-dimethyl-*N'*-D-ribopyranosylformamidine; when this was heated with methanolic acetic acid and the product condensed with α-amino-α-cyanoacetamide, 5-amino-1-α-D-ribofuranosylimidazole-4-carboxamide and 5-amino-1-α- and -β-D-ribopyranosylimidazole-4-carboxamides were obtained, the structures of which were confirmed by conversion into the respective ribosylhypoxanthines by reaction with ethyl formate and sodium methoxide. D-Arabinopyranosylamine with dimethylformamide dimethyl acetal gave *N*-D-arabinopyranosyl-*N'N'*-dimethylformamidine; treatment of this with methanolic acetic acid followed by condensation with α-amino-α-cyanoacetamide produced 5-amino-1-α- and -β-D-arabinopyranosylimidazole-4-carboxamides, which were converted into the corresponding arabinosylhypoxanthines and 1-(5-amino-4-carbamoylimidazol-1-yl)-1-*O*-methyl-D-arabinitol. The acyclic imidazolylarabinitol was converted by ethyl formate and sodium methoxide into 1-(hypoxanthin-9-yl)-1-*O*-methyl-D-arabinitol, which after acetylation, thiation with phosphorus pentasulphide, and deacylation produced 1-(6-mercaptohypoxanthin-9-yl)-1-*O*-methyl-D-arabinitol; this gave 1-(adenin-9-yl)-1-*O*-methyl-D-arabinitol by reaction with chlorine followed by ammonia.

Structures of the nucleosides were confirmed by periodate titration and u.v., mass, c.d., and $^1$H n.m.r. spectroscopy, and a mechanism for the formation of the acyclic nucleosides is proposed.

CRITERIA for the formation of isopropylideneglycofuranosylamines by the reaction of glycopyranosylamines with acetone, 2,2-dimethoxypropane, and toluene-*p*-sulphonic acid are satisfied by all the common pentoses except arabinose. We have already described syntheses of glycofuranosylamine toluene-*p*-sulphonates from D-ribose,[2] D-xylose,[3,4] D-glucose,[3] D-mannose,[3] and L-rhamnose.[3] Treatment of D-arabinopyranosylamine (1) with the above reagents, however, produced the crystalline toluene-*p*-sulphonate of the isopropylidene-D-arabinopyranosylamine (2), identified by acidic hydrolysis to give acetone and by reaction with the *N*-methylacrylamide (3) to produce the 5-cyanouracil α- and β-nucleosides (4a and b). Mild treatment with acid removed the isopropylidene groups with formation of the corresponding nucleosides (5a and b), each of which absorbed 2 equiv. of periodate. The specific assignments of anomeric configuration made here are tentative and based on optical rotation measurements.

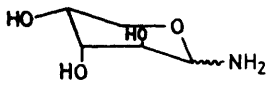
The importance of D-arabinofuranosyl derivatives of purines and pyrimidines as antitumour and antiviral agents[5] has encouraged us to investigate the preparation of related 5-amino-1-D-arabinofuranosylimidazoles.

One approach to the 1-D-arabinofuranosylimidazoles seemed to be afforded by a method described earlier[4] for the preparation of a 5-amino-1-D-xylofuranosylimidazole. D-Xylopyranosylamine (6) was converted by reaction with dimethylformamide dimethyl acetal into the acyclic formamidine (7), which with α-amino-α-cyanoacetamide produced the 5-amino-1-D-xylopyranosylimidazole (8). If however the formamidine (7) was first heated with methanolic acetic acid and the product then condensed with α-amino-α-cyanoacetamide, in addition to the pyranosylimidazole (8), the α-D-xylofuranosylimidazole (9) was obtained.

It was suggested that the reaction proceeded by formation of an intermediate oxazoline (10) which could only

[1] Part 45, R. Lofthouse, G. Shaw, P. S. Thomas, G. Mackenzie, D. H. Robinson, and P. W. Rugg, *J.C.S. Perkin I*, 1976, 997.
[2] N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg, and G. Shaw, *J.C.S. Perkin I*, 1973, 1720.
[3] N. J. Cusack, D. H. Robinson, P. W. Rugg, G. Shaw, and R. Lofthouse, *J.C.S. Perkin I*, 1974, 73.
[4] D. H. Robinson and G. Shaw, *J.C.S. Perkin I*, 1974, 774.
[5] R. J. Suhadolnik in 'Nucleoside Antibiotics,' Wiley–Interscience, New York, 1970.

produce one anomer. Confirmation of such a mechanism came from the preparation of the analogous isopropylidene D-*xylo*-oxazoline (11) as a crystalline solid and its



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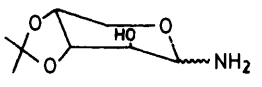

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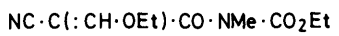

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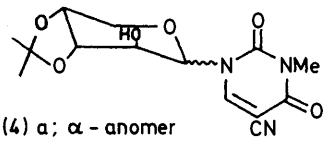
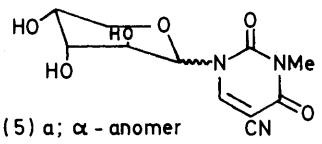
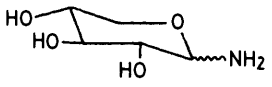


(4) a; α - anomer
b; β - anomer



(5) a; α - anomer
b; β - anomer



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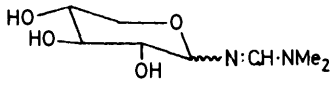

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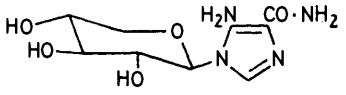

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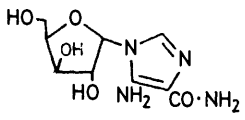
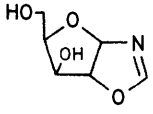
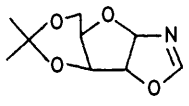


(9)



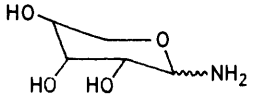
(10)



(11)

reaction with α-amino-α-cyanoacetic acid derivatives to produce stereospecifically the α-nucleosides. It might be expected that other glycopyranosylamines, including the ribose and arabinose derivatives, would produce a similar type of oxazoline derivative which could then only lead in these cases to α- or β-nucleosides, respectively.

The reaction of D-ribopyranosylamine (12) with dimethylformamide dimethyl acetal gave the D-ribopyranosylformamidine (13), identified by mass and i.r. (strong C:N band at 1 640 $cm^{-1}$) spectra and comparison of the $^1H$ n.m.r. spectrum with that of the analogous xylose derivative (7). Treatment of the formamidine derivative with methanolic acetic acid and condensation of the product with α-amino-α-cyanoacetamide gave three Bratton–Marshall-positive compounds.[6] The major component readily crystallised and was shown to be the α-D-ribofuranosylimidazole (14) by comparison (t.l.c., i.r. spectrum, and mixed m.p.) of its crystalline picrate with that of an authentic specimen. Further confirmation of the furanose structure came from its conversion with ethyl formate and sodium methoxide



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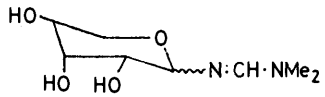

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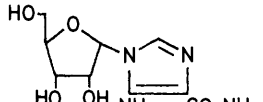

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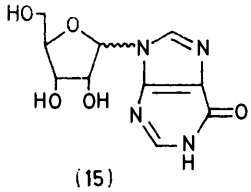
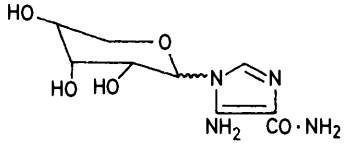
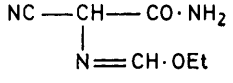


(15)
a; α - anomer
b; β - anomer



(16)
a; α - anomer
b; β - anomer

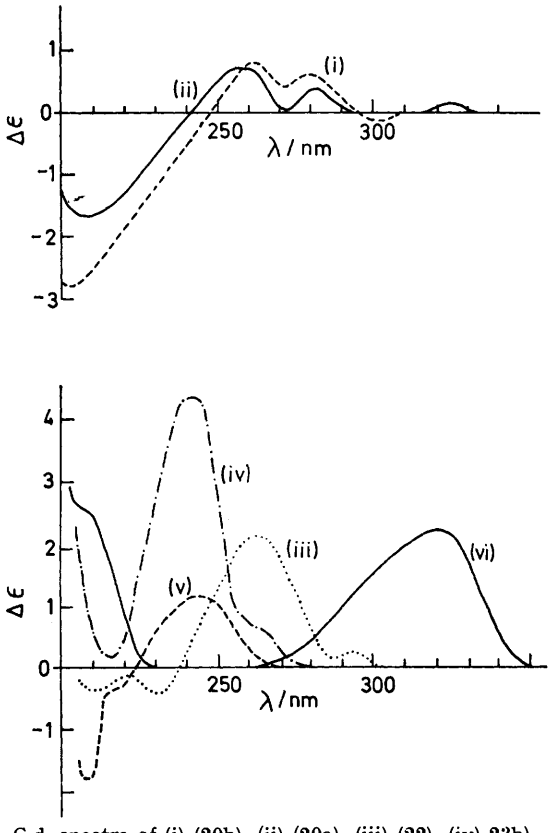


(17)

[6] C. Bratton and F. K. Marshall, *J. Biol. Chem.*, 1939, **128**, 537.

into α-inosine (15a) as a crystalline solid which absorbed 1 mol. equiv. of periodate. A comparison of the $^1$H n.m.r. spectra of α-inosine (15a) and inosine (15b) showed the chemical shifts of H-1′ to be δ 6.26 and 5.88, respectively, in agreement with the empirical rule [7] that H-1′ resonates at a lower field when the 1′- and 2′-substituents have a *cis*- rather than *trans*-relationship.

The c.d. spectra (Figure) of the α- and β-inosines showed




C.d. spectra of (i) (20b), (ii) (20a), (iii) (22), (iv) 23b), (v) (23a), and (vi) (23c)

a positive and a negative Cotton effect, respectively, in accord with most anomeric pairs of purine nucleosides. Also, comparison of optical rotations (Table 2) showed that the two inosines obeyed Hudson's Rules. α-Inosine has been previously recorded [8] as a by-product of a synthesis of inosine, the identification following from u.v. absorption data and paper chromatographic behaviour. α-Inosine has also been reported [9] as a gum of unstated purity from ring closure of the ribosylimidazole (14).

The two remaining components which accompanied the ribofuranosylimidazole (14) in the above reaction were the α- and β-D-ribopyranosylimidazoles (16a and b). Their identity was confirmed by comparison with products of the reaction of D-ribopyranosylamine with the formimidate (17). The isomers were difficult to separate by chromatography but their identity was confirmed by mass and u.v. spectra, comparative t.l.c. in several solvent systems, and $^1$H n.m.r. spectroscopy. For each case two sets of signals were observed for the anomeric protons, at δ 5.82 ($J_{1',2'}$ *ca.* 2 Hz) and 5.10 ($J_{1',2'}$ 9 Hz) in the ratio *ca.* 1 : 4. The large $J_{1',2'}$ value for one isomer suggests that H-1′ and -2′ are *trans*-diaxially related and this is only possible when the $^4C_1$ conformation and the β-configuration are adopted. The mixture therefore appears to comprise the α- and β-isomers in the ratio 1 : 4, respectively.

Treatment of D-arabinopyranosylamine (1) with dimethylformamide dimethyl acetal under dry conditions readily gave the crystalline D-arabinosylformamidine (18) identified by elemental analysis and mass ($M^+$ 204), i.r. ($\nu_{C=N}$ 1 640 cm$^{-1}$), and $^1$H n.m.r. spectroscopy. In the presence of moisture the *N*-formyl derivative (19) was isolated from this last reaction and identified by elemental analysis and i.r. ($\nu_{CO}$ at 1 685 cm$^{-1}$) and $^1$H n.m.r. spectra. When the arabinosylformamidine (18) was heated with methanolic acetic acid for 45 min and the solution then treated with α-amino-α-cyanoacetamide, chromatography of the mixture on Amberlite CG-400 ($OH^-$ form) gave the α- and β-D-arabinopyranosylimidazoles (20b and a). Their structures were confirmed by positive Bratton–Marshall reactions, u.v. absorption spectra characteristic of similar glycosylimidazoles (Table 1), and

TABLE 1

Optical rotation and light absorption data for some 5-aminoimidazole nucleosides

| Compound | $[\alpha]_D^{20}$ (°) † | $\lambda_{max.}$/nm ($\varepsilon \times 10^{-3}$) ‡ | B.–M. $\lambda_{max.}$/nm § |
|---|---|---|---|
| (22) | −35 (1.0) | 267 (10.21) | 518 |
| (20b) | −25 (1.0) | 267 (11.02) | 516 |
| (20a) | −3 (1.0) | 267 (10.66) | 520 |
| (14) | +36 (1.0) | 262 (12.38) | 507 |

† *c* 1 in $Me_2SO$. ‡ In methanol. § Absorption of the dyestuff produced in the Bratton–Marshall assay.

conversion with ethyl formate and sodium methoxide into the known α- and β-arabinopyranosylhypoxanthines (21b and a).[10] The pyranose nature of the two imidazole nucleosides was further confirmed by periodate titration of each of the derived hypoxanthine arabinosides: in each case 2 mol. equiv. were absorbed. The same arabinopyranosylimidazoles (20a and b) were also produced by the reaction of D-arabinopyranosylamine with the formimidate (17) or, as 3,4-*O*-isopropylidene derivatives by the reaction of 3,4-*O*-isopropylidene-D-arabinopyranosylamine with the imidate (17) or with dimethylformamide dimethyl acetal followed by α-amino-α-cyanoacetamide.

The conformation of the sugar moiety of the imidazole isomers (20a and b) was confirmed by $^1$H n.m.r. spectroscopy. The signal for H-1′ of the α-anomer (20b) has a large coupling constant ($J_{1',2'}$ 9 Hz), which shows that

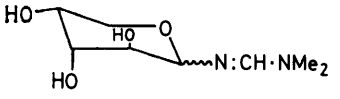
[7] T. Nishimura and B. Shimizu, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 803; G. T. Rodgers and T. L. V. Ulbricht, *J. Chem. Soc.*, 1968, 1929.

[8] K. Imai, A. Nohara, and M. Honjo, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 1377.

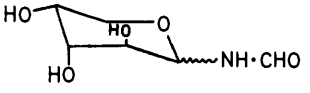
[9] C. G. Beddows and D. V. Wilson, *J. Chem. Soc.*, 1972, 1773.

[10] A. P. Martinez and W. W. Lee, *J. Org. Chem.*, 1969, **34**, 416.

H-1′ and -2′ are *trans*-diaxially related; this is only possible when the $^1C_4$ conformation is adopted. However, the signal assigned to H-1′ of the β-anomer (20a) shows a singlet which is downfield from the H-1′ signal of the α-anomer. This suggests that the H-1′ and -2′ are axial–equatorial for the β-anomer and that the $^4C_1$ conformation may be adopted. The same coupling constant ($J_{1',2'}$) values [8] were also observed for the corresponding α- and β-hypoxanthine derivatives (21b and a), and $^1C_4$ and $^4C_1$ conformations, respectively, were likewise assigned.




(18)

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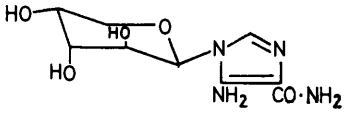
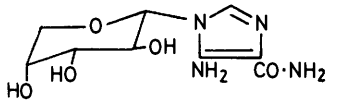
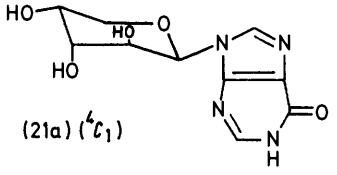


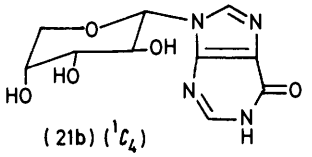

(20a) ($^4C_1$)



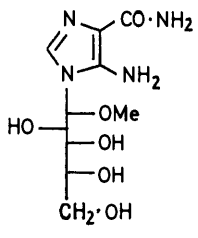

(20b) ($^1C_4$)



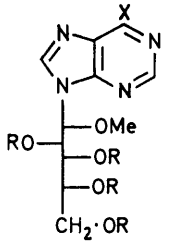

(21a) ($^4C_1$)



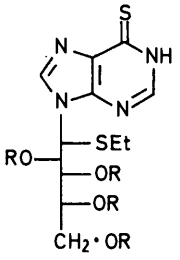

(21b) ($^1C_4$)




(22)




(23) a; R = H, X = OH
b; R = Ac, X = OH
c; R = Ac, X = SH
d; R = H, X = SH
e; R = H, X = $NH_2$




(26) a; R = Ac
b; R = H

If the foregoing assignments are correct, the optical rotation data (Tables 1 and 2) for the imidazole and hypoxanthine arabinopyranosides are not in agreement with Hudson's [11] rules. It is known that the magnitudes and signs of optical rotations are influenced by the degree of solvation of the solute and changes in population of various dissymmetric conformations. The latter includes changes in conformation of the sugar ring and in freedom of rotation about the glycosidic bond. It seems likely, therefore, that differences in conformation of the α- and β-anomers of the imidazole and hypoxanthine arabinopyranosides may contribute to the disagreement with Hudson's rules.

In addition to the two arabinopyranosylimidazoles a third compound was isolated from the chromatographic separation as a crystalline solid, for which we suggest the acyclic structure (22).[12] The structure is confirmed by elemental analysis, mass spectrum, u.v. spectrum characteristic of glycosylimidazoles of this type (Table 1), and a positive reaction in the Bratton–Marshall test for primary aromatic amines. In addition, the reaction of the acyclic nucleoside (22) with ethyl formate and sodium methoxide gave the acyclic hypoxanthine nucleoside (23a) in 80% yield, identified by elemental analysis, mass spectrum ($M^+$ 300 and a major aglycone peak, *m/e* 136), and u.v. spectrum similar to those of inosine and other 9-glycosylhypoxanthines in acidic, neutral, or basic solution (Table 2). The $^1$H n.m.r. spectrum of the nucleoside showed the presence of H-2 and -8 signals typical of purines and a

TABLE 2

Optical rotation and light absorption data for some purine nucleosides

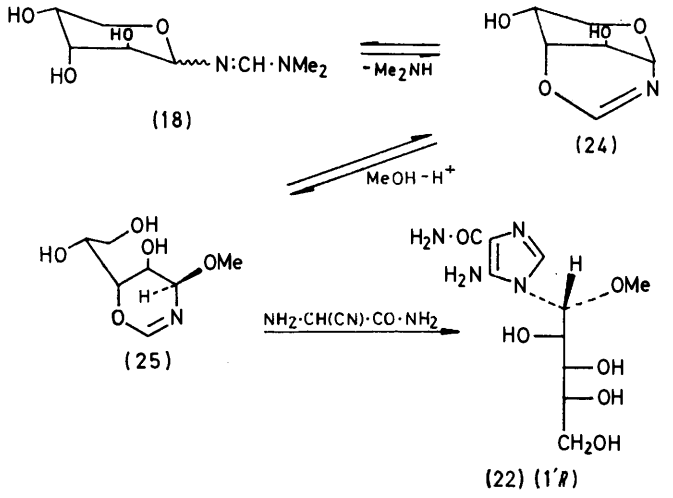
| Compound | $[a]_D^{20}$ (°) † | $\lambda_{max.}$/nm (ε × $10^{-3}$) pH 1 | pH 7 | pH 13 |
|---|---|---|---|---|
| (23a) | −15 (*c* 1.0) | 249 (11.46) | 249 (11.83) | 253 (12.40) |
| (21b) | −61 (*c* 0.25) | 248 (11.08) | 248 (11.82) | 253 (12.10) |
| (21a) | +77 (*c* 0.25) | 248 (12.96) | 248 (12.85) | 253 (13.21) |
| (23b) | +36 (*c* 1.0) | 249 (10.98) | 249 (11.42) | 253 (12.01) |
| (23c) | +28 (*c* 1.0) | 325 (18.10) | 323 (17.78) | 310 (17.47) |
| (23d) | | 325 | 323 | 310 |
| (15a) | +71 (*c* 1.0) | 249 (12.10) | 249 (12.20) | 253 (13.10) |
| (23e) | | 258 | 259 | 259 |
| (15b) | −60 (*c* 1.0) | 250 (12.00) | 250 (12.10) | 253 (12.80) |

† In $Me_2SO$.

[11] C. S. Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66.
[12] Preliminary report, G. Mackenzie and G. Shaw, *J.C.S. Chem. Comm.*, 1975, 48.

methoxy-singlet at δ 3.16. Periodate titration of the derivative resulted in absorption of 3 equiv. Confirmation that the arabinose configuration had not altered during the reaction sequence came from hydrolysis of the nucleosides with dilute hydrochloric acid: D-arabinose was the only sugar detected by t.l.c. Attempts to convert the nucleoside (23a) into a furanose or pyranose analogue by even milder treatment with acids in aqueous or alcoholic solution still resulted in cleavage of the sugar from the aglycone.

The reaction involving the formation of the acyclic nucleoside (22) appears to proceed stereospecifically to




SCHEME 1

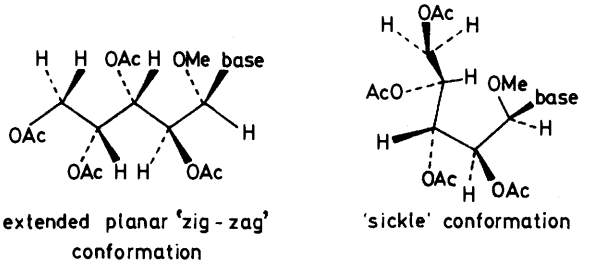
produce a single C-1′ epimer since the $^1$H n.m.r. spectrum of the product shows only one set of signals for the aglycone. Likewise, the $^1$H n.m.r. spectrum of the hypoxanthine derivative (23a) shows one set of signals corresponding to the aglycone. For reasons advanced later, C-1′ has been assigned the *R*-configuration. If this assignment is correct, a stereospecific route to the acyclic nucleoside (22) may involve initial formation of an oxazine intermediate (24). This may be brought about by the proximity of the 3′-OH and the dimethylaminomethylene group when the sugar adopts a $^4C_1$ conformation and an α-configuration. The oxazine (24) with methanolic acetic acid would then produce a methoxyoxazine (25). This with α-amino-α-cyanoacetamide would then give the (1′*R*)-acyclic arabinose imidazole nucleoside (22) (Scheme 1).

Treatment of compound (23a) with acetic anhydride–pyridine gave the acetylated hypoxanthine nucleoside (23b), which with phosphorus pentasulphide in dry pyridine gave the 6-mercaptopurine acyclic arabinoside (23c), isolated as a crystalline solid in 50% yield. This compound was identified by elemental analysis, mass spectrum ($M^+$ 484, and aglycone peak at *m/e* 152), and u.v. spectrum in acidic, basic, and neutral solvents (Table 2). Deacetylation of the 6-mercaptopurine acyclic arabinoside (23c) with methanolic sodium methoxide gave (23d).

Analogous sulphur-containing compounds have been prepared [13] by condensation of an unstable acyclic D-arabinose bromo-derivative with 6-chloro-9-chloromercuriopurine and thiation of the resultant 6-chloropurine nucleoside with thiourea to give (26a), which was deacetylated to (26b). Only a single epimer was obtained in the arabinose series, the structure of which was confirmed by *X*-ray crystal structure analysis. Related *O*-alkyl acyclic nucleosides of pyrimidines and purines have also been prepared in a similar fashion, but only from hexoses.[14]

Treatment of a dry methanolic solution of the unprotected nucleoside (23d) with chlorine gas resulted in a solution which, after removal of the excess of chlorine, showed one spot on t.l.c. and had a u.v. spectrum similar to that of the known cyclic arabinosyl 6-chloropurine analogues.[15] The chlorinated product was treated directly with aqueous ammonia at 100 °C for 5 h. T.l.c. of the resulting solution showed the presence of one major u.v. absorbing product and some free adenine. The material was purified by formation of a picrate followed by chromatography to give the acyclic adenine nucleoside (23e) as a crystalline solid free from picric acid, characterised by elemental analysis, mass ($M^+$ 299, and aglycone peak at *m/e* 135), and u.v. spectra (Table 2).

It has been established by *X*-ray crystallography and $^1$H n.m.r. studies that the molecule (26a) has an extended planar ' zig-zag ' structure.[13,14] The $^1$H n.m.r. spectra of compounds (23b and c) (26a) show similarities except that H-3′ is deshielded in the former two compounds; this implies a deviation from the extended ' zig-zag ' structure, perhaps to a ' sickle ' structure (Scheme 2).




SCHEME 2

$^1$H N.m.r. spectra of the unprotected nucleosides (22) and (23a) are significantly different from that of (26a), indicating that a folded structure for (22) and (23a) is more likely.

It has been predicted [16] that dextrorotatory compounds have the (1*R*)-configuration whether the carbohydrate moiety is acetylated or unprotected. However, specific

[13] D. C. Baker, A. Ducruix, D. Horton, and C. Pascard-Billy, *J.C.S. Chem. Comm.*, 1974, 729.
[14] D. Horton, D. C. Baker, and S. S. Kokrady, *Ann. New York Acad. Sci.*, 1975, **225**, 131.
[15] E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, 1962, **27**, 3274.
[16] H. El Khadem and Z. M. ElShafei, *Tetrahedron Letters*, 1963, **27**, 1887.

rotation studies (Tables 1 and 2) have shown that the unprotected nucleosides (22) and (23a) are laevorotatory whereas the acetylated nucleosides (23b and c) are dextrorotatory. A constant factor observed for each acyclic nucleoside was a positive Cotton effect. From an o.r.d. study [14] of 6-mercaptopurine 1′-ethylthiopentose nucleosides, including compound (26a), a positive Cotton effect was found to be indicative of a (1′*R*)-configuration and a negative Cotton effect a (1′*S*)-configuration. Analogously it appears that the acyclic arabinosyl imidazole nucleoside (22) and its purine derivatives all have the (1′*R*)-configuration.

## EXPERIMENTAL

Evaporations were carried out with a Buchi rotary evaporator, under water pump vacuum with a flask temperature below 40 °C unless otherwise stated. U.v. spectra were measured with a Unicam SP 800 spectrophotometer, i.r. spectra with a Perkin-Elmer 157 spectrophotometer, $^1$H n.m.r. spectra with a JEOL JNM-MH-100 spectrometer (tetramethylsilane or 3-trimethylsilylpropane-1-sulphonic acid as internal standard), mass spectra with an A.E.I. MS-903 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; Macherey Nagel and Co.) was used for column chromatography. Thin-layer chromatograms were run on Silica Gel $60F_{254}$ (0.025 mm thick) precoated glass plates from (Merck) in the systems (A) chloroform–methanol (9 : 1); (B) butan-1-ol–acetic acid–water (12 : 3 : 5); (C) propan-1-ol–ammonia–water (6 : 6 : 1); (D) propan-1-ol–ammonia–water (3 : 6 : 1); and (E) butan-1-ol saturated with water.

Ion-exchange separations were preformed in all-Teflon or glass apparatus equipped with a Buchler micropump and an LKB Uvicord 470 1A u.v. absorptiometer, with a flow cell of 3 mm light path for continuous recording of column eluates at 253.7 nm.

3,4-O-*Isopropylidene*-D-*arabinopyranosylammonium Toluene*-p-*sulphonate*.—A solution of dry toluene-*p*-sulphonic acid monohydrate (13.5 g, 0.071 mol) in dry dimethoxypropane (45 ml, 0.35 mol) and dry acetone (65 ml) was stirred at room temperature for 15 min. Finely powdered D-arabinopyranosylamine [17] (5 g, 0.033 mol) was added with stirring. After 2 h the undissolved amine (0.8 g) was filtered off, the filtrate was evaporated to *ca.* 60 ml, dry ether (*ca.* 100 ml) was added to incipient turbidity, and the mixture was stored at 4 °C overnight. The resulting crystalline precipitate was collected, washed with acetone, and ether, and then dried. The *product* (6.6 g, 56%) had m.p. 123—124° (decomp.), $[\alpha]_D^{20}$ −44° after 5 min (*c* 2 in $Me_2SO$) (Found: C, 50.1; H, 6.3; N, 3.85. $C_{15}H_{23}NO_7S$ requires C, 49.85; H, 6.4; N, 3.9%) and was soluble in water: $\lambda_{max.}$ ($H_2O$) 223s, 248, 256, 261, and 272w nm (characteristic of the toluene-*p*-sulphonic acid group).

A solution of the product (100 mg) in 2N-hydrochloric acid (3 ml) was warmed at 80 °C for 5 min. Brady's reagent (3 ml) was added to the cooled solution; the mixture was set aside at 0 °C for 1 h and the precipitate (36 mg) collected, washed with water, and recrystallised from methanol to give bright yellow-orange needles, m.p. and mixed m.p. (with acetone 2,4-dinitrophenylhydrazone) 126—127°.

5-*Cyano*-1-(3,4-O-*isopropylidene*-α- *and* -β-D-*arabinopyranosyl*)-3-*methyluracil* (4a *and* b).—α-Cyano-β-ethoxycarbonyl-*N*-methylacrylamide [18] (4.5 g, 0.02 mol) was added to a stirred solution of 3,4-*O*-isopropylidene-D-arabinopyranosylammonium toluene-*p*-sulphonate (7.2 g, 0.02 mol) in ethanolic sodium ethoxide (40 ml) [from sodium (0.02 mol)] and the mixture was set aside at room temperature overnight. T.l.c. [system (A)] showed one major u.v. absorbing spot, $R_F$ 0.94. The yellow solution was filtered from sodium toluene-*p*-sulphonate and evaporated to a foam, a solution of which in chloroform (5 ml) was applied to a silica gel column (2 × 40 cm). The u.v.-absorbing product (pale yellow band) was eluted by ethanol–chloroform (1 : 99). Evaporation gave a gum (5.3 g), a solution of which in ethanol soon yielded a crystalline precipitate. The solid (1.8 g) was collected and recrystallised from ethanol to give 5-*cyano*-(3,4-O-*isopropylidene*-α-D-*arabinopyranosyl*)-3-*methyluracil* as fine needles, m.p. 190—191° (Found: C, 52.15; H, 5.35; N, 13.15%; $M^+$, 323. $C_{14}H_{17}N_3O_6$ requires C, 52.00; H, 5.30; N, 13.0%; *M*, 323).

The mother liquors gave a gum (3.5 g) which yielded no further crystalline material from ethanol. The mass spectrum showed $M^+$ 323, suggesting that it consisted mainly of the β-anomer.

1-α-D-*Arabinopyranosyl*-5-*cyano*-3-*methyluracil* (5a).—A solution of the foregoing crystalline isopropylidene-α-arabinosyluracil (200 mg) in 20% acetic acid (10 ml) was heated on a steam-bath for 20 min. T.l.c. showed the absence of starting material and a new u.v.-absorbing spot at $R_F$ 0.32 [system (A)] or 0.5 [system (C)]. The mixture was evaporated and the residue re-evaporated with water (2 × 5 ml) and ethanol (5 ml) to a crystalline solid. Recrystallisation from aqueous ethanol yielded the α-*arabinosyl nucleoside* (165 mg, 97%) as short rods, m.p. 238—239° (Found: C, 46.6; H, 4.65; N, 15.0%; $M^+$, 283. $C_{11}H_{13}N_3O_6$ requires C, 46.65; H, 4.65; N, 14.85%, *M*, 283). In 24 h at room temperature the nucleoside consumed 2.01 mol. equiv. of 0.1M-periodate. It had $[\alpha]_D^{20}$ −63° (*c* 2.0 in $Me_2SO$), $\lambda_{max.}$ (MeOH) 274 (ε 11 600) and 214 nm (9 500), $\lambda_{min.}$ 235 nm (ε 1 500).

1-β-D-*Arabinopyranosyl*-5-*cyano*-3-*methyluracil* (5b).—A solution of the residual gum (500 mg) containing the isopropylidene-β-D-arabinopyranosyluracil in aqueous 20% acetic acid (15 ml) was heated on a water-bath for 15 min. T.l.c. showed the presence of a trace of starting material and two new u.v.-absorbing spots at $R_F$ 0.40 and 0.32 [system (A)]. The latter, less intense spot corresponded to the isopropylidene-free α-arabinopyranosyluracil. The solution was heated for a further 15 min and evaporated, and the residue was re-evaporated with water (2 × 8 ml) and ethanol (2 × 8 ml). A solution of the resulting gum in 50% ethanolic chloroform soon yielded a crystalline solid. Recrystallisation from aqueous ethanol gave the β-D-*arabinopyranosyluracil* (5b) as prisms, m.p. 220—221°. The product ran as one spot, $R_F$ 0.40 on t.l.c. [system (A)] (Found: C, 46.65; H, 4.65; N, 15.1%; $M^+$, 283. $C_{11}H_{13}N_3O_6$ requires C, 46.65; H, 4.65; N, 14.85%; *M*, 283). In 24 h at room temperature the nucleoside consumed 2.02 mol. equiv. of 0.1M-periodate. It had $[\alpha]_D^{20}$

[17] C. A. Lobry de Bruyn and F. H. Van Leent, *Rec. Trav. chim.*, 1895, **14**, 134.
[18] R. K. Ralph and G. Shaw, *J. Chem. Soc.*, 1956, 1877.

+50° (*c* 1.2 in $Me_2SO$); $\lambda_{max.}$ 277 (ε 1 300) and 216 nm (9 300), $\lambda_{min.}$ 239 nm (ε 1 400).

N-*Dimethylaminomethylene*-D-*ribopyranosylamine* (13).—A suspension of D-ribopyranosylamine [2] (3 g, 0.02 mol) in absolute methanol (100 ml) and dimethylformamide dimethyl acetal (3 g) was refluxed for 1 h. The mixture was evaporated to a cream solid (3.8 g, 93%), $M^+$ 204, $\nu_{C=N}$ 1 640 $cm^{-1}$, δ [$(CD_3)_2SO$] 7.68 (N:CH), 4.02 (H-1′, $J_{1',2'} < 1$ Hz), and 2.90 (s, $NMe_2$). The D-xylopyranosyl derivative had δ [$(CD_3)_2SO$] 7.60 (N:CH), 4.02 (H-1′, $J_{1',2'}$ 8 Hz), and 2.85 (s, $NMe_2$).

5-*Amino*-1-α-D-*ribofuranosylimidazole*-4-*carboxamide* (14).—A solution of *N*-dimethylaminomethylene-D-ribopyranosylamine (2.5 g) and glacial acetic acid (0.6 g, 0.01 mol) in absolute methanol (40 ml) was heated under reflux for 0.75 h. The solution was cooled, α-amino-α-cyanoacetamide (1 g, 0.01 mol) was added, and the mixture was set aside at room temperature overnight. T.l.c. [system (B)] showed one major red Bratton–Marshall active spot ($R_F$ 0.36) and two much fainter purple Bratton–Marshall-active spots ($R_F$ 0.40 and 0.30). The mixture yielded a crystalline precipitate which was collected after 24 h. 5-*Amino*-1-α-D-*ribofuranosylimidazole*-4-*carboxamide* crystallised from methanol as prisms (670 mg, 34%), m.p. 206° (softening at 170 °C) (Found: C, 41.0; H, 5.55; N, 21.55%; $M^+$, 258. $C_9H_{14}N_4O_5$ requires C, 41.85; H, 5.45; N, 21.7%, *M*, 258).

The mother liquors were evaporated to a gum (2.7 g) which was dissolved in water (3 ml) and applied to a column (80 × 2.7 cm) of Amberlite CG-400 resin ($OH^-$ form). One u.v.-absorbing and Bratton–Marshall-active fraction was eluted with water–methanol (1 : 9). The fraction was evaporated to a foam (150 mg) which crystallised from methanol to yield a further crop (80 mg) of the foregoing α-D-ribofuranosylimidazole.

Evaporation of the mother liquors gave a solid mixture of 5-amino-1-α- and -β-D-ribopyranosylimidazole-4-carboxamides (16a and b), $M^+$ 258, *m/e* 126, δ 5.82 (H-1′, $J_{1',2'}$ 2 Hz), 5.10 (H-1′, $J_{1',2'}$ 9 Hz), 7.21 and 7.36 (H-2′), 5.8 ($NH_2$), and 6.66 ($CO{\cdot}NH_2$).

Excess of saturated methanolic picric acid was added to a solution of the foregoing α-ribofuranosylimidazole nucleoside (200 mg) in methanol (4 ml). The picrate crystallised from methanol as yellow needles (290 mg, 75%), identical (m.p. and mixed m.p., i.r. spectrum, and t.l.c.) with an authentic specimen,[2] m.p. 168—170°.

9-α-D-*Ribofuranosylhypoxanthine* (15a).—A solution of 5-amino-1-α-D-ribofuranosylimidazole-4-carboxamide (500 mg, 1.9 mmol), freshly distilled ethyl formate (0.65 g, 8.8 mmol), and methanolic sodium methoxide (10 ml) [from sodium (10 mmol)] was refluxed for 1 h. T.l.c. showed a single spot at $R_F$ 0.30 and disappearance of the starting material ($R_F$ 0.36). The cooled mixture was adjusted to pH 7 with Amberlite IR-120 resin ($H^+$ form) then clarified by filtration through a pad of Supercel, which was washed with methanol (3 × 10 ml). The filtrate and washings were evaporated to a gum, a solution of which in methanol yielded a crystalline precipitate. α-*Inosine* crystallised from methanol (yield 390 mg, 75%); m.p. 214° (Found: C, 44.5; H, 4.7; N, 20.65%; $M^+$, 268. $C_{10}H_{12}N_4O_5$ requires C, 44.8; H, 4.5; N, 20.9%; *M*, 268); it consumed 1 mol. equiv. of periodate in 24 h; δ [$(CD_3)_2SO$] 6.26 (d, $J_{1',2'}$ 5 Hz), 8.27 (H-2), and 8.06 (H-8).

5-*Amino*-1-α- *and* -β-D-*ribopyranosylimidazole*-4-*carboxamides* (16a *and* b).—A solution of ethyl *N*-(carbamoylcyanomethyl)formimidate [19] (3.1 g, 0.02 mol) and D-ribopyranosylamine (3 g, 0.02 mol) in methanol (60 ml) was set aside at room temperature overnight. T.l.c. [system (B)] showed the presence of two Bratton–Marshall-active products at $R_F$ 0.40 and 0.30 and some aglycone at $R_F$ 0.03. The mixture was evaporated and the residue dissolved in water (3 ml) and applied to an Amberlite CG-400 resin ($OH^-$ form) column (80 × 2.7 cm). One u.v.-absorbing and Bratton–Marshall-active fraction was eluted with water–methanol (9 : 1). T.l.c. [system (B)] showed the presence of both products. The fraction was rechromatographed to give a white solid identical [t.l.c. in systems (B)—(E)] with the mixture of 5-amino-1-(α- and -β-D-ribopyranosyl)imidazole-4-carboxamides obtained during the preparation of 5-amino-1-α-D-ribofuranosylimidazole-4-carboxamide. The mass spectrum of the purified mixture showed $M^+$ 258 and a major (heterocyclic base + H) peak (*m/e* 126).

N-*Dimethylaminomethylene*-D-*arabinopyranosylamine* (18).—A suspension of D-arabinopyranosylamine (3 g, 0.02 mol) in dimethylformamide dimethyl acetal (3 g, 0.025 mol) and dry methanol (75 ml) was refluxed for 1 h. The mixture was evaporated to a glass which was dissolved in a solution of acetonitrile (1 ml) in absolute methanol (2 ml). The *amidine derivative* (1.6 g, 39%) separated after about 1 week as spars, m.p. 126—128°, $[\alpha]_D^{20}$ −9° (*c* 1% in $Me_2SO$) (Found: C, 47.0; H, 7.9; N, 13.7%; $M^+$, 204. $C_8H_{16}N_2O_4$ requires C, 47.05; H, 7.85; N, 13.75%; *M*, 204), $\nu_{C=N}$ 1 640 $cm^{-1}$, δ [$(CD_3)_2SO$] 7.60 (N:CH), 4.15 (H-1′, $J_{1',2'}$ 4 Hz), and 2.90 (s, $NMe_2$).

N-D-*Arabinopyranosylformamide* (19).—A suspension of D-arabinosylamine (3 g, 0.02 mol) in dimethylformamide dimethyl acetal (3 g, 0.025 mol) and methanol (150 ml) was refluxed for 1 h. The mixture was evaporated and the residue triturated with 95% ethanol. A crystalline solid (1.9 g, 75%) soon precipitated. The *formyl derivative* crystallised from ethanol as spars, m.p. 156—157° (Found: C, 41.0; H, 6.15; N, 7.95%. $C_6H_{11}NO_5$ requires C, 40.65; H, 6.2; N, 7.9%), $\nu_{CO}$ 1 685 $cm^{-1}$, δ [$(CD_3)_2SO$] 4.66 (H-1′, $J_{1',2'}$ 4 Hz) and 8.12 (s, N·CHO).

5-*Amino*-1-(3,4-O-*isopropylidene*-α- *and* -β-D-*arabinopyranosyl*)*imidazole*-4-*carboxamides* (22b *and* a).—Ethyl *N*-(carbamoylcyanomethyl)formimidate [19] (3.1 g, 0.02 mol) was dissolved in a solution of 3,5-*O*-isopropylidene-D-arabinopyranosylammonium toluene-*p*-sulphonate (7.2 g, 0.02 mol) and triethylamine (2 g, 0.02 mol) in acetonitrile (60 ml), and the solution was set aside overnight. T.l.c. [system (A)] showed the presence of two Bratton–Marshall-active products at $R_F$ 0.34 and 0.26 and much aglycone at $R_F$ 0.03. The mixture was evaporated and the residue dissolved in ethanol–chloroform (1 : 1; 5 ml) and applied to a silica gel column (2 × 40 cm). The first Bratton–Marshall-active product ($R_F$ 0.34) was eluted by ethanol–chloroform (3 : 22). This fraction was evaporated to a gum (720 mg, 11%). An excess of methanolic picric acid was added to a solution of the gum in methanol (10 ml), whereupon a solid rapidly separated. The β-*arabinopyranosylimidazolecarboxamide picrate* crystallised from acetonitrile as small yellow prisms, m.p. 195—196° (decomp. from 180 °C), $[\alpha]_D^{20}$ −29° (*c* 1.8 in $Me_2SO$) (Found: C, 40.75; H, 4.25; N, 18.35%; $M^+$, 298. $C_{12}H_{18}N_4O_5,C_6H_3N_3O_7$ requires C, 41.0; H, 4.0; N, 18.6%; *M*, 298).

Elution of the foregoing column with ethanol–chloroform (3 : 17) produced a second Bratton–Marshall active product ($R_F$ 0.26). This fraction was evaporated to a gum (1.24 g,

[19] G. Shaw, R. N. Warrener, D. N. Butler, and R. K. Ralph, *J. Chem. Soc.*, 1959, 1648.

19%). A solution of the gum in methanol with an excess of methanolic picric acid soon yielded a crystalline solid. The *α-arabinopyranosylimidazolecarboxamide picrate* crystallised from much acetonitrile as small yellow prisms, m.p. 177—178° (decomp. from 160 °C), $[\alpha]_D^{20}$ −40.5° (*c* 2.2 in $Me_2SO$) (Found: C, 40.95; H, 4.1; N, 18.55%; $M^+$, 298).

1-(5-*Amino*-4-*carbamoylimidazol*-1-*yl*)-1-O-*methyl*-D-*arabinitol* (22).—A solution of *N*-dimethylaminomethylene-D-arabinopyranosylamine (2.04 g, 0.01 mol) and acetic acid (0.6 g, 0.01 mol) in dry methanol (50 ml) was heated under reflux for 0.75 h, then cooled; α-amino-α-cyanoacetamide (1 g, 0.01 mol) was added and the mixture was set aside at room temperature overnight. T.l.c. [system (D)] showed three Bratton–Marshall-active spots at $R_F$ 0.37, 0.29, and 0.27. The mixture was evaporated to a gum (3.1 g) which was dissolved in water (3 ml) and applied to a column (80 × 2.7 cm) of Amberlite CG-400 resin ($OH^-$ form). The first two u.v.-absorbing and Bratton–Marshall-active fractions were eluted with water–methanol (9 : 1) and the third fraction with water–methanol (3 : 2). T.l.c. of each fraction (20 × 1.5 cm plates) showed three separate Bratton–Marshall-active spots: fraction (1), $R_F$ 0.29 (D), 0.67 (F); fraction (2), $R_F$ 0.27 (D), 0.61 (F); fraction (3), $R_F$ 0.37 (D), 0.68 (F).

Evaporation of each fraction separately gave a foam (112, 404, and 413 mg, respectively). Each fraction was re-chromatographed on an Amberlite CG-400 resin ($OH^-$ form) column (80 × 2.7 cm) with elution as before. The first fraction gave a solid foam which when dissolved in a little methanol soon produced a crystalline precipitate. 1-(5-*Amino*-4-*carbamoylimidazol*-1-*yl*)-1-O-*methyl*-D-*arabinitol* (94 mg) crystallised from methanol as rods, m.p. 198° (Found: C, 41.25; H, 6.4; N, 19.2%; $M^+$, 290. $C_{10}H_{18}N_4O_6$ requires C, 41.4; H, 6.2; N, 19.3%; *M*, 290). The compound had a u.v. absorption spectrum (Table 1) similar to that of related imidazole nucleosides and gave a positive test in the Bratton–Marshall assay; $\nu_{OH}$ 3 450 (sugar OH), $\nu_{CO}$ 1645 $cm^{-1}$ (C:O); *m/e* 290 ($M^+$) and 126 (aglycone +H); δ [$(CD_3)_2SO$] 5.08 (H-1′, $J_{1',2'}$ 9 Hz), 3.26 ($OCH_3$), 7.26 (H-2), 5.66 ($NH_2$), and 6.8 ($CONH_2$).

The second fraction gave 5-*amino*-1-α-D-*arabinopyranosylimidazole*-4-*carboxamide* (22b) (0.4 g) as a solid, homogeneous on t.l.c. (Found: C, 41.55; H, 5.75; N, 21.45%; $M^+$, 258. $C_9H_{14}N_4O_5$ requires C, 41.85; H, 5.45; N, 21.7%; M, 258), δ [$(CD_3)_2SO$] 4.92 (H-1′, $J_{1',2'}$ 9 Hz), 7.22 (H-2), 5.76 ($NH_2$), and 6.77 ($CONH_2$).

The third fraction produced 5-*amino*-1-β-D-*arabinopyranosylimidazole*-4-*carboxamide* (20a) (0.402 g) as a white solid, homogeneous on t.l.c. (Found: C, 41.7; H, 5.7; N, 21.45%; $M^+$, 258), δ [$(CD_3)_2SO$] 5.44 (H-1′, $J_{1',2'} < 1$ Hz), 7.38 (H-2), 5.78 ($NH_2$), and 6.74 ($CONH_2$).

5-*Amino*-1-α- *and* -β-D-*arabinopyranosylimidazole*-4-*carboxamides* (20b *and* a) *and* 3′,4′-O-*Isopropylidene Derivatives*. —(*a*) A solution of ethyl *N*-(carbamoylcyanomethyl)-formimidate [19] (3.1 g, 0.02 mol) and D-arabinopyranosylamine (3 g, 0.02 mol) in methanol (60 ml) was set aside at room temperature overnight. T.l.c. [system (B)] showed two Bratton–Marshall-active spots at $R_F$ 0.29 and 0.37 and some aglycone ($R_F$ 0.03). The mixture was evaporated to a gum, which was dissolved in water (3 ml) and applied to an Amberlite CG-400 resin ($OH^-$ form) column (80 × 2.7 cm). 5-*Amino*-1-α-D-*arabinosylimidazole*-4-*carboxamide* ($R_F$ 0.29) was eluted by water–methanol (9 : 1) and the corresponding β-anomer ($R_F$ 0.37) by water–methanol (3 : 2). The fractions were separately evaporated to give the α-arabinoside as a white solid (0.9 g), $M^+$ 258 and the β-arabinoside also as a white solid (0.65 g), $M^+$ 258 (each isomer also showed an aglycone peak at *m/e* 126). The imidazole α- and β-arabinosides were homogeneous on t.l.c. and identical with the samples described above.

(*b*) A solution of 3,4-*O*-isopropylidene-D-arabinopyranosylammonium toluene-*p*-sulphonate (3.6 g, 0.01 mol), dimethylformamide dimethyl acetal (1.5 g, 0.013 mol), and triethylamine (1.4 ml, 0.01 mol) in acetonitrile (30 ml) was heated under reflux for 1 h. The solution was cooled and evaporated to a gum. The gum in chloroform (25 ml) was washed with water (15 ml), dried, and evaporated. A solution of the residue and acetic acid (0.6 g, 0.01 mol) in dry methanol was heated under reflux for 45 min and cooled; α-amino-α-cyanoacetamide (1.0 g, 0.01 mol) was added and the mixture set aside at room temperature overnight. T.l.c. [system (B)] showed four Bratton–Marshall-active spots at $R_F$ 0.29, 0.37, 0.46, and 0.49. The mixture was evaporated and the residue dissolved in water (3 ml) and applied to a column (70 × 2.7 cm) of Amberlite CG-400 resin ($OH^-$ form). Four u.v.-absorbing and Bratton–Marshall fractions (A—D) were eluted by water–methanol (4 : 1). Fractions A and C were separately evaporated to give white solids (120 mg) and (20 mg) which were characterised as 5-amino-1-(α- and -β-D-arabinopyranosyl)imidazole-4-carboxamides, respectively. The mass spectrum of each showed $M^+$ 258 and an aglycone peak at *m/e* 126. Each was identical with the corresponding sample described above. Fractions B and D were separately evaporated to gums (80 and 60 mg, respectively). Excess of picric acid was added to a solution of each gum in methanol (1 ml) whereupon a solid rapidly separated. The products were characterised as picrates of 5-amino-1-(3,4-*O*-isopropylidene-α- and -β-D-arabinopyranosyl)imidazole-4-carboxamides, respectively. The mass spectrum of each showed $M^+$ 298 and an aglycone peak at *m/e* 126. Each isomer was identical (m.p., mixed m.p., and t.l.c.) with the corresponding authentic sample described above.

9-α-D-*Arabinopyranosylhypoxanthine* (21b).—A solution of 5-amino-1-α-D-arabinopyranosylimidazole-4-carboxamide (260 mg, 1.0 mmol) freshly distilled ethyl formate (0.33 g, 4.4 mmol), and methanolic sodium methoxide (7 ml) [from sodium (5 mmol)] was refluxed for 1 h, cooled, and neutralised to pH 7 with Amberlite IR-120 resin ($H^+$ form). The solution was clarified by filtration through a pad of Supercel which was then washed with methanol (3 × 5 ml). The filtrate and washing were combined and evaporated. A solution of the residue in methanol gave a crystalline precipitate, which was collected and recrystallised from methanol to give the arabinopyranosylhypoxanthine methanolate m.p. 217—219° (lit.,[8] 219—220°), $M^+$ 268. The compound consumed 2 mol. equiv. of periodate in 24 h and showed δ [$(CD_3)_2SO$] 5.3 (H-1′, d, $J_{1',2'}$ 9 Hz), 8.19 (H-2, s), and 8.04 (H-8, s).

9-β-D-*Arabinopyranosylhypoxanthine* (21a).—A solution of 5-amino-1-β-D-arabinopyranosylimidazole-4-carboxamide (260 mg, 1.0 mmol), freshly distilled ethyl formate (0.33 g, 4.4 mmol), and methanolic sodium methoxide (7 ml) [from sodium (5 mmol)] was refluxed for 1 h, then worked up as for the α-isomer. A solution of the final residue in water gave a crystalline precipitate. The β-arabinopyranosylhypoxanthine crystallised from water as spars (150 mg, 56%), m.p. 260—261° (lit.,[8] 260—261°), $M^+$ 268. The compound consumed 2 mol. equiv. of periodate in 24 h and showed δ [$(CD_3)_2SO$] 6.03 (H-1′, s), 8.19 (H-2, s), and 8.11 (H-8, s).

2-(*Hypoxanthin*-9-*yl*)-1-O-*methyl*-D-*arabinitol* (23).—A solution of the alditol (22) (450 mg, 1.55 mmol), freshly distilled ethyl formate (0.65 g, 8.8 mmol), and methanolic sodium methoxide (10 ml) [from sodium (11 mmol)] was refluxed for 1 h. T.l.c. showed the appearance of a new spot at $R_F$ 0.34 with complete disappearance of the starting material ($R_F$ 0.29). The cooled mixture was adjusted to pH 7 with Amberlite IR-120 resin ($H^+$ form). The solution was clarified by filtration through a pad of Supercel which was then washed with methanol (3 × 10 ml). The filtrate and washings were combined and concentrated to *ca.* 5 ml. Crystallisation soon commenced to give the acyclic *nucleoside* (370 mg, 80%) as needles, m.p. 214—215° (softening at 208 °C) (Found: C, 43.9; H, 5.45; N, 18.6%; $M^+$, 300 $C_{11}H_{16}N_4O_6$ requires C, 44.0; H, 5.35; N, 18.65%; *M*, 300), *m/e* 300 and 136 (base + H). The product consumed 3 mol. equiv. of periodate in 24 h and showed δ [$(CD_3)_2SO$] 5.5 (H-1', d, $J_{1',2'}$ 8.5), 4.28 [t, *J* 8.5, H-2' ($J_{2',3'}$) or H-3' ($J_{3',4'}$)], 3.55 (H-2' or -3' and H-4', -5a', and -5b', m), 3.16 ($OCH_3$), 8.13 (H-2, s), and 8.02 (H-8, s).

(*a*) A solution of the arabinitol (23a) (3 mg) in aqueous 0.01M-hydrochloric acid (2 ml) was heated at 100 °C for 1 h. The mixture was evaporated to dryness and the residue on t.l.c. [system (B)] showed one u.v.-absorbing spot, $R_F$ 0.36, and one anisaldehyde-active spot at $R_F$ 0.21. The two spots corresponded to hypoxanthine and arabinose, respectively. D-Xylose, D-ribose, and D-lyxose had $R_F$ 0.31, 0.30, and 0.31, respectively.

(*b*) Samples of the arabinitol (23a) (5 mg) were dissolved separately in (i) aqueous 0.01M-hydrochloric acid (2 ml), (ii) methanolic 0.05M-hydrogen chloride (2 ml), and (iii) acetic acid. (1) Each reaction mixture was warmed at 100 °C for 5 min; t.l.c. [system (D)] then showed the presence of much aglycone ($R_F$ 0.57) and some starting material ($R_F$ 0.46). After 15 min each mixture showed the presence of the aglycone and disappearance of the starting material. (2) Each mixture was set aside at room temperature for 3 h; t.l.c. [system (D)] then showed the presence of some aglycone ($R_F$ 0.57) and much starting material ($R_F$ 0.46).

Reference samples of 9-α- and -β-D-arabinofuranosyl- and 9-α- and -β-D-arabinopyranosyl-hypoxanthine had $R_F$ [system (D)] 0.50, 0.50, 0.44, and 0.39, respectively.

2,3,4,5-*Tetra*-O-*acetyl*-1-(*hypoxanthin*-9-*yl*)-1-O-*methyl*-D-*arabinitol* (23b).—A suspension of the alditol (23a) (350 mg, 1.2 mmol) in dry pyridine (30 ml) and acetic anhydride (0.9 g, 8.8 mmol) was shaken overnight at room temperature. T.l.c. [system (A)] showed a single spot ($R_F$ 0.41) and the absence of starting material. The excess of acetic anhydride was decomposed with methanol (5 ml) and the solution evaporated to dryness; the residue was then evaporated with methanol (2 × 5 ml) to remove pyridine. A solution of the residue in methanol (2 ml) soon gave a crystalline solid. The *tetra-acetate* crystallised from methanol as needles (390 mg, 71%), m.p. 207—209° (Found: C, 48.5; H, 5.20; N, 11.8%; $M^+$, 468. $C_{19}H_{24}N_4O_{10}$ requires C, 48.7; H, 5.15; N,11.95%; *M*, 468), *m/e* 468 and 136 (base + H); δ [$(CD_3)_2SO$] 5.48 (H-1', d, $J_{1',2'}$ 8.5 Hz), 4.18 ($J_{5'a,5'b}$ 12.5 Hz, m, H-5'a and -5'b), 5.08 (m, *J* 6 and 4 Hz, H-4'), 5.6 (m, H-2' and -3'), 1.76, 2.06, 2.08, and 2.2 (4 × Ac), 3.27 ($OCH_3$), 8.38 (H-2, s), and 7.96 (H-8, s).

2,3,4,5-*Tetra*-O-*acetyl*-1-(6-*mercaptopurin*-9-*yl*)-1-O-*methyl* D-*arabinitol* (23c).—Freshly purified (by Soxhlet extraction with carbon tetrachloride) phosphorus pentasulphide (250 mg, 1.1 mmol) was added to a solution of the tetra-acetate (23b) (100 mg, 0.21 mmol) in dry pyridine (5 ml). The mixture was refluxed with stirring for 2 h with protection from moisture. T.l.c. [system (B)] showed a major spot ($R_F$ 0.64) together with several minor by-product spots and no starting material ($R_F$ 0.49). The solution was poured into hot water (100 ml) and the mixture evaporated to dryness. The residue was triturated with cold water (3 ml) to give a solid (66 mg, 63%), m.p. 148—152°. The *acyclic* 6-*mercaptopurine arabinoside monohydrate* crystallised from methanol as rods (52 mg, 50%), m.p. 177—178° (Found: C, 45.45; H, 5.05; N, 10.9; S, 6.5%; $M^+$, 484. $C_{19}H_{24}N_4O_9S,H_2O$ requires; C, 45.4; H, 5.2; N, 11.15; S, 6.4%; *M*, 484), *m/e* 484 and 152; δ [$(CD_3)_2SO$] 5.52 (H-1, d, $J_{1',2'}$ 9 Hz), 4.24 ($J_{5'a,5'b}$ 12.5 Hz, m, H-5'a and -5'b), 5.14 (m, *J* 6 and 4 Hz, H-4'), 5.8 (m, H-2' and -3'), 1.82, 2.05, 2.08, and 2.2 (4 × Ac), 3.34 ($OCH_3$), 8.7 (H-2, s), and 8.52 (H-8, s).

1-(6-*Mercaptopurin*-9-*yl*)-1-O-*methyl*-D-*arabinitol* (23d).—A solution of 2,3,4,5-tetra-O-acetyl-1-(6-mercaptopurin-9-yl)-1-*O*-methyl-D-arabinitol (200 mg, 0.41 mmol) in methanolic sodium methoxide (10 ml) [from sodium (100 mg)] was set aside at room temperature overnight. T.l.c. [system (B)] showed a single spot ($R_F$ 0.34) and complete disappearance of starting material ($R_F$ 0.64). The mixture was adjusted to pH 7 with acetic acid, and evaporated to a gum (310 mg). The gum was dissolved in ammonia–methanol (1 : 4, 3 ml) and shaken at room temperature for 1 min with activated charcoal (*ca.* 2 mg). The resulting mixture was filtered through Supercel and the filtrate evaporated to a gum (280 mg). This in water (1 ml) was applied to a Bio-Gel P-2 (<400 mesh) column (2.5 × 60 cm) equilibrated with aqueous ammonia (pH 10.3). The product-containing fraction was eluted with aqueous ammonia (pH 10.3) to produce the acyclic nucleoside as a gum (182 mg), homogeneous on t.l.c. [systems (B) and (D); $R_F$ values 0.34 and 0.72, respectively], *m/e* 316 ($M^+$) and 152; δ [$(CD_3)_2SO$] 5.51 (H-1', d, $J_{1',2'}$ 8.5), 3.3 ($OCH_3$), 8.65 (H-2), and 8.47 (H-8).

1-(*Adenin*-9-*yl*)-1-O-*methyl*-D-*arabinitol* (23e).—A solution of the foregoing acyclic thiopurine nucleoside (120 mg) in dry methanol (5 ml) was cooled to −10 °C with protection from moisture. Chlorine gas was slowly bubbled through the mixture for 2 min. The resulting solution was stirred at −10 °C for a further 5 min, then dry nitrogen was bubbled through it for 15 min; the excess of chlorine had then been removed (loss of yellow colour). (If this is not done, the subsequent neutralisation with ammonia may cause the mixture to ignite spontaneously.) T.l.c. showed a new u.v.-absorbing product ($R_F$ 0.49) ($\lambda_{max.}$ 264, 264, and 266 nm at pH 1, 7, and 13) but no starting material ($R_F$ 0.34). Concentrated ammonia was added to the mixture, which was then heated in a sealed tube at 100 °C for 5 h, and evaporated to a gum. T.l.c. [system (B)] showed a major product ($R_F$ 0.30) and some aglycone ($R_F$ 0.32). Excess of aqueous picric acid was added to a solution of the residue in water (2 ml). The resulting crystalline precipitate (35 mg) was dissolved in acetone–water (1 : 1; 40 ml) and passed through a column (2.5 × 60 cm) of Amberlite CG-400 resin ($CO_3^{2-}$ form). The picric acid-free product was eluted with acetone–water (1 : 1) and the resulting fraction was evaporated. A solution of the residue in water (1 ml) was applied to a Bio-Gel P-2 (<400 mesh) column (2.5 × 60 cm) equilibrated with aqueous ammonia (pH 10.3). The product-containing fraction was eluted with aqueous ammonia (pH 10.3) and evaporated to a gum (9 mg). The *acyclic adenine nucleoside* (6 mg) crystallised from methanol as partially

hydrated spars, m.p. 192—193° (Found: C, 43.35; H, 5.8; N, 23.1%; $M^+$, 299. $C_{11}H_{17}N_5O_5$, $0.25H_2O$ requires C, 43.5; H, 5.75; N, 23.05%; $M$, 299), $m/e$ 299 and 135.

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