Purines, Pyrimidines, and Imidazoles. Part 52.[1] New Syntheses of Some 1-β-D-Arabinofuranosylaminoimidazoles and of Related Purine Nucleosides, including 9-β-D-Arabinofuranosyladenine

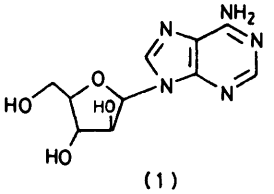
By **Kamaliah Kadir, Grahame Mackenzie,** and **Gordon Shaw,*** School of Chemistry, University of Bradford, Bradford BD7 1DP

Ethyl 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxylate and the corresponding carboxamide have been prepared by reaction of ethyl 5-aminoimidazole-4-carboxylate or the carboxamide, respectively with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (but not the bromide or iodide) and deblocking. Reaction of the nucleoside ester with formamidine acetate gave 9-β-D-arabinofuranosylhypoxanthine. 5-Amino-4-cyano-1-β-D-arabinofuranosylimidazole obtained by dehydration of the benzylated carboxamide or by direct glycosylation of 5-amino-4-cyanoimidazole and debenzylation of the product, when heated with triethyl orthoformate and ammonia, gave 9-β-D-arabinofuranosyladenine. 2,3,5-Tri-*O*-benzylarabinofuranosyl chloride with sodium azide, followed by reduction of the glyosyl azide formed with platinic oxide, and condensation of the arabinosylamine produced with ethyl *N*-(carbamoylcyanomethyl)formimidate gave a mixture of 2,3,5-tri-*O*-benzyl 1-α- and -β-D-arabinofuranosylimidazole 4-carboxamides. Reduction of the azide with lithium aluminium hydride followed by debenzylation of the product gave, in addition to the two anomers, 5-amino-1-D-arabinitylimidazole-4-carboxamide.

ARABINOFURANOSYL-PURINES and -pyrimidines including especially the adenine (Ara-A) (1) and cytosine (Ara-C) derivatives have proven anti-tumour and anti-viral activity.[2] We have been interested in preparing the corresponding 1-β-D-arabinofuranosylimidazoles both as synthetic precursors of various types of arabinosylpurines and as biochemical precursors of the purines *in vivo* and hence with potential activity. We have earlier recorded the synthesis of 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxylic acid 5′-phosphate (2), an analogue of the ribonucleotide CAIR (3) which is a central intermediate in purine nucleotide *de novo* biosynthesis, and also the inhibition of the enzyme AIR-carboxylase by this nucleotide.[3] The activity of Ara-A is commonly considered to be due to its structural analogy to deoxyadenosine.[2] However, the marked inhibitory activity of the arabinosylimidazoles in the pathway enzyme inhibition studies is unlikely to be due to their analogy to 2′-deoxyribosylimidazoles since the latter compounds are not involved in the pathway. Nevertheless, the arabinose derivative is markedly more active than any of the other analogues, including sugar variations, which have so far been examined.

Unfortunately the arabinosyl nucleoside ester (4a), from which the nucleotide (2) was prepared, could only be obtained in low yield by reaction of the arabinofuranosylamine (5a), prepared by, in turn, reduction of the arabinofuranosyl azide (5b) with platinic oxide, with the formimidate[4] (6a) and deblocking the benzoylated nucleoside (4b). The major product in this reaction was the α-anomer (7a). Moreover the total yield of imidazole nucleoside was diminished by O→N migration of the benzoyl group in the amine (5a) to form the *N*-benzoyl-3,5-di-*O*-benzoylarabinosylamine derivative, and additionally, by *O*-alkyl fission during the exceptionally difficult removal of benzoyl groups in (4b) with methanolic sodium methoxide. We have, accordingly, sought alternative routes to (4a) since we require relatively large amounts of both the nucleoside and nucleotide for further enzyme studies and for appropriate biological tests.

In order to exclude the undesirable O→N migration we examined the use of alternative tri-*O*-benzylarabinofuranosyl derivatives. In preliminary experiments we



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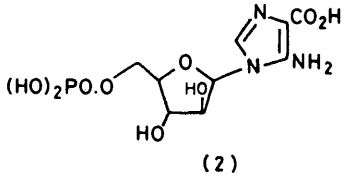

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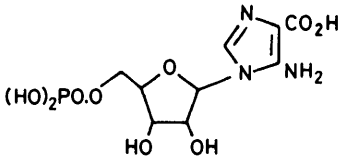

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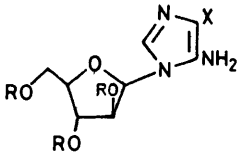
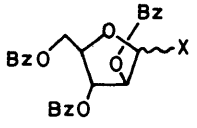


(4) a; X = CO_2Et, R = H
b; X = CO_2Et, R = Bz
c; X = $CONH_2$, R = CH_2Ph
d; X = CO_2Et, R = CH_2Ph
e; X = $CONH_2$, R = H
f; X = CN, R = CH_2Ph
g; X = CN, R = H



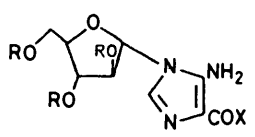
(5) a; X = NH_2
b; X = N_3

NC·CHN(:CHOEt)COX

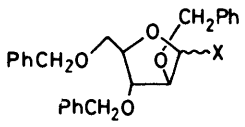
(6) a; X = OEt
b; X = NH_2

examined the preparation of the corresponding arabinofuranosylamine (8a) by reaction of the arabinosyl chloride (8b)[5] with ammonia followed by reaction of the intermediate amine (8a) with the formimidate[6] (6b). From the reaction mixture was isolated by chromato-

graphy on silica gel, a mixture of nucleosides which could not be separated but whose mass spectra suggested that they were the α- and β-anomeric nucleosides (4c) and (7b) respectively. Similarly, reaction of the chloride



(7) a; R = H, X = OEt
b; R = CH_2PH, X = NH_2

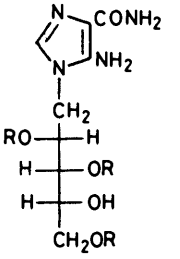


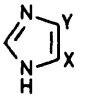
(8) a; X = NH_2
b; X = Cl
c; X = N
d; X = Br
e; X = I

with sodium azide gave a product which was not crystallised but had properties [strong i.r. band at 2 135 cm^{-1}, *m/e* 403 ($M - N_3$)] consistent with the arabinosyl azide structure (8c). This was confirmed since after hydrogenation over platinic oxide and condensation of the product, presumably (8a), with the formimidate (6b), the same mixture of α- and β-imidazole nucleosides (4c) and (7b) was obtained as in the previous experiment. In both cases, however, apart from the difficulty in separating the anomers, the yields were low. As an alternative to the use of catalytic hydrogenation we have also examined the reduction of the azide (8c) with lithium aluminium hydride in dry ether. After 45 min the azide band had disappeared (followed by i.r. spectroscopy), and the product was condensed with the imidate (6b). In this case three materials with positive Bratton–Marshall tests [7] were observed on t.l.c. Of these, two corresponded to the mixture of anomers produced in the earlier experiments. The third compound was readily separated, however, and obtained as a homogeneous gum (t.l.c.). It had a mass spectrum consistent with the arabinityl structure (9a) and this was confirmed by removal of the benzyl groups with palladium–hydrogen to give the arabinityl-imidazole (9b) which was obtained as a crystalline picrate. This is a novel route to such compounds and could possibly be extended. The failure of the above reactions to give reasonable yields of the desired β-anomer (4a) in pure form prompted us to re-examine the synthesis of aminoimidazole nucleosides by direct condensation of a suitable imidazole with a glycosyl halide.

Earlier attempts to prepare aminoimidazole nucleosides by direct condensation of a sugar derivative with an imidazole have proved very unrewarding. Various heavy-metal salts of the nitroimidazole ester (10a) with acylated glycosyl halides give mixtures of the 1- and (mainly) 3-glycosyl derivatives, the required 1-isomer being produced in very low yields.[8,9] Similarly fusion of the nitro-imidazole (10a) with tetra-acetyl-α-D-ribofuranose gave only the 3-isomer.[10] In our hands several attempts to condense heavy-metal salts or silyl derivatives of several aminoimidazole derivatives with tri-*O*-benzoylribofuranosyl or arabinofuranosyl halides produced only small amounts of condensation products, and similar results were obtained in a variety of fusion reactions. These results are in sharp contrast to those obtained with most purines and pyrimidines when good yields are frequently obtained by fusion reactions or by the use of silyl derivatives and acylated glycosyl halides. We now record a simple improved synthesis of the arabinosyl nucleosides (4a) and (4c). A preliminary account has been recorded.[11]

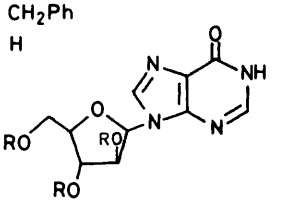
Reaction of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride [5] (8b) with the aminoimidazole ester [12] (10b) in





(10) a; X = NO_2, Y = CO_2Me
b; X = NH_2, Y = CO_2Et
c; X = NH_2 Y = $CONH_2$
d; X = NH_2, Y = CN

(9) a; R = CH_2Ph
b R = H



(11) a; R = CH_2Ph
b; R = H

hot acetonitrile containing triethylamine was complete in less than 1 h and produced ethyl 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazole-4-carboxylate (4d) which rapidly crystallised without chromatography in pure form (25—30%). The structure of the compound was confirmed by elemental analysis, mass and n.m.r. spectroscopy, and by its reaction with excess of formamidine acetate in refluxing butanol–ethanol to produce the arabinosyl-hypoxanthine (11a). The latter after palladium-catalysed hydrogenolysis of the benzyl groups gave 9-β-D-arabinofuranosylhypoxanthine (11b) as a crystalline solid, identical with an authentic specimen.[13] Hydrogenation of the imidazole nucleoside (4d) was similarly achieved with a palladium–barium sulphate catalyst to produce the aminoimidazole nucleoside (4a). The reaction permits the preparation of relatively large amounts of aminoimidazole arabinosides in the desired β-configuration without chromatography and, at the same time, offers an alternative route to purine β-D-arabinosides. The same compound (4d) was also produced by reaction in dichloromethane at room temperature over a longer period of time, or from a silyl derivative prepared from the aglycone (10b) and hexamethyldisilazane and the arabinosyl chloride (8b); in each case, however, lower yields of product were obtained. In contrast to the ease of reaction of the arabinosyl chloride with the aglycone (10b), attempts to bring about

reaction of the corresponding arabinosyl bromide (8d) or iodide (8e) (produced like the chloride from 2,3,5-tri-*O*-benzylarabinofuranosyl *p*-nitrobenzoate with hydrogen halide) gave, even after long heating, only traces of nucleosides. It seems reasonable to assume that using the glycosyl chloride direct glycosylation under the conditions given largely, but not entirely, proceeds *via* an S_N2 reaction involving displacement of the α-chlorine atom. In the case of the bromo- or iodo-derivatives an S_N1 mechanism presumably operates with dehydrohalogenation as the major reaction.

In order to test the generality of the reaction we have in preliminary experiments examined the condensation of the chloride (8b) with the amide aglycone (10c). A similar reaction occurred to produce the crystalline carboxamide (4c). The structure of this compound was confirmed by its identity with the compound produced by amination of the ester (4d) with aqueous alcoholic ammonia. In this last reaction it was found that alcoholic ammonia with the nucleoside (4d) at 120 °C over 2 days produced very little conversion into the amide as revealed by t.l.c. However, using the maximum ratio of aqueous ammonia (*d* 0.88) to alcohol consistent with achieving dissolution of the benzylated nucleoside (1 : 1.5) at 120 °C over 4 days, a *ca.* 30% yield of the carboxamide (4e) resulted; some 20% of unchanged ester was recovered. The remainder of the imidazole could not be accounted for and it must presumably have suffered degradation, probably to acyclic products. The possibility of an equilibrium reaction between the amide and the ester in this reaction can be excluded since, when the pure amide was heated with alcoholic ammonia under the same condition, no evidence for ester formation could be found.

The cyano-aglycone (10d) is not readily accessible but a solution prepared from aminomalononitrile, triethyl orthoformate, and ammonia was found to react with (8b) to produce the arabinosyl nitrile derivative (4f). The structure of this compound was confirmed by its identity with the compound produced by dehydration of the carboxamide (4c) with phosphoryl chloride. In addition, the nitrile (4f) was smoothly debenzylated in high yield by treatment with boron trichloride in dichloromethane to produce the crystalline nucleoside (4g) which, when heated with triethyl orthoformate and ethanolic ammonia in a modification of an earlier adenine synthesis, produced a good yield of crystalline arabinofuranosyladenine (1), identical with an authentic specimen.

EXPERIMENTAL

Evaporations were carried out with a Büchi rotary evaporator, under a water-pump vacuum with a flask temperature ⩽40 °C unless otherwise stated. U.v. absorption spectra were measured with a Unicam SP 800 spectrophotometer and i.r. spectra with a Perkin-Elmer 157 spectrophotometer, ^{1}H n.m.r. spectra with a JEOL JNM-MH-100 spectrophotometer (δ in p.p.m. with $SiMe_4$ as internal standard), and mass spectra with an A.E.I. MS-903 spectrometer. Silica gel (0.05—0.20 mm, 325—70 mesh Machery Nagel and Co.) was used for column chromatography and silica gel 60 F 0.25 mm pre-coated aluminium 254 plates (Merck) was used for t.l.c. with (A) $CHCl_3$–MeOH (9 : 1), (B) toluene–ethyl acetate (4 : 1), (C) n-butanol–acetic acid–water (6 : 6 : 1), and (D) $CHCl_3$–MeOH (1 : 1) as development solvent systems. Imidazoles were detected on t.l.c. plates by u.v. absorbance or the Bratton–Marshall test.

Ethyl 5-*Amino*-1-(2,3,5-*tri*-O-*benzyl*-β-D-*arabinofuranosyl*)-*imidazole*-4-*carboxylate* (4d).—(*a*) A solution of 2,3,5-tri-*O*-benzyl-D-arabinose [5] (30 g) in dichloromethane (115 ml) was added to a solution of *p*-nitrobenzoyl chloride (14.5 g) in dichloromethane (75 ml) and anhydrous pyridine (22.5 ml). The mixture was set aside at room temperature overnight and then washed successively with 2M-hydrochloric acid (3 × 50 ml), aqueous sodium hydrogencarbonate (3 × 50 ml), and water (50 ml). The solution was dried (Na_2SO_4) and concentrated to give a waxy crystalline solid (44 g) of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinose [5] which was dissolved in dichloromethane (800 ml) pre-saturated with anhydrous hydrogen chloride at 0 °C. Anhydrous hydrogen chloride was then passed through the solution for 10 min which was then set aside at 0 °C overnight. The precipitated *p*-nitrobenzoic acid (12 g) was removed and the filtrate concentrated to a syrup which was kept at 1 mmHg/30 °C for 2 h. A solution of the 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride thus prepared in dry acetonitrile (50 ml) was added to a solution of ethyl 5-aminoimidazole-4-carboxylate (11.1 g) [12] and triethylamine (7.2 g) in dry acetonitrile (200 ml). The solution was refluxed for 1 h, cooled, and evaporated to leave a gum. T.l.c. examination (system A) showed a major Bratton–Marshall active spot (R_F 0.67) and some aglycone (R_F 0.32). Further t.l.c. examination (system B) revealed two Bratton–Marshall active spots (R_F 0.25, 0.15) and some aglycone (R_F 0.0). A solution of the foregoing gum in dichloromethane (200 ml) was washed with 2M-sodium hydroxide (3 × 20 ml) and water (20 ml) respectively. The organic phase was separated, dried (Na_2SO_4), and evaporated to leave a gum which crystallised from a mixture of benzene (5 ml) and ether (50 ml) to give the *arabinose nucleoside* as needles (9.6 g), m.p. 98 °C (Found: C, 68.75; H, 6.7; N, 7.35%; M^+, 557. $C_{32}H_{35}N_3O_6$ requires C, 68.9; H, 6.35; N, 7.55%; *M*, 557); ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 5.73 (H-1′, $J_{1,2}$, 5 Hz), 7.15 (H-1, s), 5.40 (NH_2, s), 1.37 (CH_3, t); $\lambda_{max.}$ 268 nm (ε 10 800) in MeOH.

(*b*) Two samples of the foregoing 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinose (1 g) were separately treated with saturated solutions of anhydrous hydrogen bromide and hydrogen iodide, respectively, in dichloromethane (25 ml). After 2 h at 0 °C, the precipitated nitrobenzoic acid (92 and 86% respectively) from each reaction was removed and each filtrate evaporated to a gum which was kept at 1 mmHg/30 °C for 2 h. A solution of each of the foregoing gums in acetonitrile (5 ml) was added to a solution of ethyl 5-aminoimidazole-4-carboxylate (0.25 g) and triethylamine (0.25 g) in acetonitrile (10 ml) and each mixture boiled under reflux.

T.l.c. examination (system A) of the reaction involving hydrogen bromide showed the presence of a small amount of benzylated arabinose nucleoside (R_F 0.67) after prolonged heating (5 h). However, t.l.c. examination (system A) of the reaction involving hydrogen iodide showed only a trace of nucleoside (R_F 0.67) after 10 h.

(*c*) A suspension of ethyl 5-aminoimidazole-4-carboxylate [14] (5.5 g) in hexamethyldisilazane (12 g) was refluxed for 6 h.

The imidazole gradually dissolved and at the end of the period a homogeneous solution was obtained which was evaporated to leave a thick oil. A solution of this and freshly prepared 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (18 g) in dry acetonitrile (50 ml) was refluxed for 1 h. The mixture was cooled and evaporated to leave a gum, a solution of which in dichloromethane was washed successively with 2M-sodium hydroxide and water. The organic phase was separated, dried (Na_2SO_4), and evaporated to dryness. The residue crystallised from benzene–ether as needles (4 g), m.p. 98 °C, identical (t.l.c., m.p., mixed m.p., and i.r.) to those obtained in (*a*).

(*d*) A mixture of ethyl 5-aminoimidazole-4-carboxylate (1.55 g) and 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (5 g) was heated in an oil-bath at 110 °C for 1 min. T.l.c. examination (system A) showed the appearance of a strong Bratton–Marshall active spot (R_F 0.67), much aglycone (R_F 0.32), and a u.v. absorbing spot (R_F 0.80) which corresponded to the arabinosyl chloride. The fusion mixture was cooled, dissolved in dichloromethane, and the solution washed successively with 2M-sodium hydroxide and water. The organic phase was separated, dried (Na_2SO_4), and evaporated to dryness. The residue in chloroform (2 ml) was applied to a silica-gel column (2.5 × 60 cm) equilibrated with ethanol–chloroform (1 : 100). The product (R_F 0.67) was eluted with ethanol–chloroform (2 : 100) and evaporated to leave a gum, which crystallised from benzene–ether as needles (0.4 g), m.p. 98 °C, identical (t.l.c., m.p., mixed m.p., and i.r.) to those prepared in (*a*) and (*c*).

Ethyl 5-Amino-1-β-D-arabinofuranosylimidazole-4-carboxylate (4a).—Palladium (10%) on barium sulphate (7.5 g) and a solution of ethyl 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazole-4-carboxylate (5 g) in ethanol–acetic acid–water (8 : 1 : 1) (250 ml) were shaken under hydrogen for 30 h. The catalyst was filtered off and washed with methanol. The filtrate and washings were combined and evaporated to dryness. The *hydrated arabinose nucleoside* crystallised from water as needles (2.3 g), m.p. 101 °C (Found: C, 42.4; H, 6.2; N, 13.0%; M^+, 287. $C_{11}H_{17}N_3O_6,1.5H_2O$ requires C, 42.05; H, 6.35; N, 13.35%; *M*, 287). The ^1H n.m.r. spectrum in $(CD_3)_2SO$ had signals at δ 5.80 (H-1′, $J_{1',2'}$ 5 Hz), 7.30 (H-1, s), 5.99 (NH_2, s), and 1.24 (CH_3, t). It had $\lambda_{max.}$ 269 nm (ε 11 100) in water.

9-β-D-*Arabinofuranosylhypoxanthine* (11b).—To a refluxing solution of ethyl 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazole-4-carboxylate (0.2 g) in butanol (20 ml) and ethanol (5 ml) were added 50-mg portions of formamidine acetate at 15-min intervals; the reaction was followed by t.l.c. A total of 1.2 g of formamidine acetate was required to remove the starting material. The solution was cooled and evaporated to leave a gum, which was freed from traces of butanol by repeated evaporation with water. A solution of the residue in chloroform (1 ml) was applied to a silica-gel column (2 × 60 cm) equilibrated with ethanol–chloroform (1 : 100). The product was eluted with ethanol–chloroform (5 : 100) and evaporated to give a foam (0.19 g), M^+, 538 ($C_{31}H_{30}N_4O_5$ requires *M*, 538). Palladium (10%) on barium sulphate (0.25 g) was added to a solution of the foregoing material in methanol–acetic acid–water (8 : 1 : 1) (20 ml) and the mixture was shaken under hydrogen for *ca.* 30 h. The catalyst was filtered off and washed with methanol. The filtrate and washings were combined and evaporated to dryness. The residue crystallised from water as needles (20 mg; 20%) identical (m.p., mixed m.p., and i.r.) with an authentic sample of 9-β-D-arabinofuranosylhypoxanthine, m.p. 239—241 °C.

5-Amino-1-(2,3,5-tri-O-benzyl-α- and -β-D-arabinofuranosyl)imidazole-4-carboxamide (4c) *and* (7b).—(*a*) A solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (2.2 g) in methanol (50 ml) pre-saturated with ammonia was set aside for 18 h. The precipitated ammonium chloride (2.3 g) was removed and the filtrate evaporated to leave a gum which was re-evaporated with methanol (2 × 10 ml) and then kept at 1 mmHg/30 °C for 45 min. A solution of the residue *N*-(carbamoylcyanomethyl)formimidate [6] (1.5 g) and triethylamine (0.1 g) in acetonitrile (40 ml) was set aside at room temperature overnight. T.l.c. examination (system A) showed the presence of two Bratton–Marshall active spots (R_F 0.46 and 0.48), much aglycone (R_F 0.32), and a u.v.-absorbing spot (R_F 0.78) which corresponded to the arabinosyl chloride. The reaction mixture was evaporated to a gum which was dissolved in chloroform and the solution washed successively with 2M-sodium hydroxide and water. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue in chloroform (2 ml) was applied to a silica-gel column (2.5 × 70 mm) equilibrated with ethanol–chloroform (1 : 100). Elution with ethanol–chloroform (1 : 100) failed to achieve satisfactory separation of products (R_F 0.46 and 0.48). Evaporation of the fractions containing the foregoing products gave the α- and β-arabinose nucleosides as a hard gum (0.4 g), the mass spectrum of which showed a molecular ion (M^+, 528; $C_{30}H_{32}N_4O_5$ requires *M*, 528) and an aglycone peak (*m/e* 155) $\lambda_{max.}$ (MeOH) 268 nm.

(*b*) A solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (2.2 g) and dry finely powdered sodium azide (5 g) in dry acetonitrile (50 ml) was refluxed for 1.75 h. The resulting mixture was filtered whilst hot and the solid washed with hot acetonitrile (3 × 10 ml). The combined filtrates were evaporated to give a syrup (2.3 g) which showed a strong band at 2 135 cm^{-1} (N_3) in the i.r. spectrum and, in the mass spectrum, *m/e* of 403 ($M - N_3$). The 2,3,5-tri-*O*-benzyl-D-arabinosylazide thus prepared in ethyl acetate (100 ml) was added to a suspension of pre-reduced Adam's platinum catalyst (0.25 g) in ethyl acetate (25 ml). The mixture was shaken under hydrogen for 1 h. The catalyst was filtered off and a solution of *N*-(carbamoylcyanomethyl)formimidate (1.5 g) and triethylamine (0.1 g) in ethyl acetate (40 ml) was added. The reaction mixture was set aside at room temperature overnight. T.l.c. examination (system A) showed the presence of two Bratton–Marshall active spots (R_F 0.46 and 0.48) and much aglycone (R_F 0.32). The solvent was evaporated and a solution of the residue in dichloromethane was washed with 2M-sodium hydroxide and water. The organic phase was separated, dried, and evaporated to dryness. A solution of the residue in chloroform (2 ml) was applied to a silica-gel column (2.5 × 80 cm) equilibrated with ethanol–chloroform (1 : 100). Elution with ethanol–chloroform failed to achieve satisfactory separation of products and no crystalline material was recovered from the evaporated fractions. The fractions corresponding to the products (R_F 0.46 and 0.48) were evaporated to give a hard gum of the α- and β-*arabinose nucleosides* which was identical (t.l.c. and mass spectrum) to that obtained in (*a*).

5-Amino-1-D-arabinitylimidazole-4-carboxamide (9b).—A suspension of lithium aluminium hydride (0.75 g) in a solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranosylazide (1.5 g) in dry ether (25 ml) was shaken at room temperature. The reaction was followed by i.r. spectroscopy [*i.e.* disappearance

of $\nu_{max.}$ 2 135 cm^{-1} (N_3)] of the reaction mixture at 15-min intervals; it was complete in 45 min. Water (10 ml) was added to the mixture and the organic phase was separated, dried (Na_2SO_4), and added to a solution of *N*-(carbamoylcyanomethyl)formimidate (1 g) and triethylamine (75 mg) in ethyl acetate (50 ml). The mixture was set aside at room temperature overnight. T.l.c. examination (system A) showed the presence of three Bratton–Marshall active spots (R_F 0.46, 0.48, and 0.38) and some aglycone (R_F 0.32). The solvent was evaporated and a solution of the residue in dichloromethane washed with 2M-sodium hydroxide and water. The organic phase was separated, dried, and evaporated. The residue in chloroform (2 ml) was applied to a silica-gel column (2.5 × 80 cm) equilibrated with ethanol–chloroform (1 : 100). The products (R_F 0.46 and 0.48) were eluted with ethanol–chloroform (1 : 100) but no separation was achieved. The fractions were evaporated to leave a hard gum (0.125 g) which was identical (t.l.c. and mass spectrum M^+, 528) to that obtained in the foregoing synthesis of the 5-amino-1-(2,3,5-tri-*O*-benzyl-α- and -β-D-arabinofuranosyl)imidazole-4-carboxamides. The product (R_F 0.38) was eluted with ethanol–chloroform (5 : 100) and obtained as a hard gum (0.325 g) (homogeneous on t.l.c. in systems A and B) of 5-amino-1-(2,3,5-*O*-benzyl-D-arabinityl)imidazole-4-carboxamide which showed M^+ 530 ($C_{30}H_{34}N_4O_5$ requires: *M*, 530) and an aglycone peak (*m/e* 155) in the mass spectrum; it had $\lambda_{max.}$ 267 nm (MeOH). A suspension of palladium (10% on barium sulphate) in a solution of the foregoing compound in methanol–acetic acid–water (8 : 1 : 1) was shaken under hydrogen for 40 h. T.l.c. examination (system C) showed one Batton–Marshall active spot (R_F 0.42). The catalyst was filtered off and the filtrate evaporated to dryness; the residue was re-evaporated with water (3 × 5 ml). An excess of saturated methanolic picric acid was added to a solution of the foregoing residue in methanol (2 ml). The crystalline precipitate, which rapidly separated, was collected and recrystallised from methanol to give the hydrated *arabinityl imidazole picrate* as yellow needles (14 mg), m.p. 210 °C (decomp.) (Found: C, 33.7; H, 4.75; N, 18.0%; *m/e*, 260. $C_{15}H_{19}N_7O_{12}\cdot 2.5H_2O$ requires C, 33.7; H, 4.5; N, 18.35%; $M - C_6H_3N_3O_7$ 260. A solution of the free base in water was liberated from the picrate using Dowex AG1 × 2 resin OH^- form; it had $\lambda_{max.}$ 267 nm (ε 9 500).

5-Amino-1-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)-imidazole-4-carboxamide (4c).—(*a*) Ethyl 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazole-4-carboxylate (9 g) was dissolved in saturated ethanolic ammonia (90 ml) and aqueous ammonia solution (*d* 0.88; 135 ml). The reaction mixture was heated at 120 °C for 4 days. Evaporation of the solution afforded a gum which was dissolved in methanol (5 ml) and applied to a silica-gel column (3 × 50 cm) and the products eluted by chloroform–methanol (98 : 2). The *carboxamide* (3.3 g, 39%) crystallised from toluene as needles, m.p. 101 °C (Found: C, 67.9; H, 5.8; N, 10.5%; M^+, 528. $C_{30}H_{32}N_4O_5$ requires C, 68.15; H, 6.10; N, 10.6%; *M*, 528), $\lambda_{max.}$ (MeOH) 266 nm (ε 12 400); δ ($CDCl_3$) 5.72 (H-1′, $J_{1'2'}$ 4 Hz), 5.33 (NH_2), and 7.20 (C_6H_5). Unchanged imidazole ester (2 g) was recovered and crystallised from benzene–ether as needles, m.p. 98 °C.

Use of alcoholic ammonia in the above experiment at 120 °C over 2 days resulted in very little amide formation.

(*b*) A mixture of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (12 g), 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride (4.5 g), and triethylamine (5.5 g) in acetonitrile (150 ml) was refluxed for 1.25 h. T.l.c. examination in system A showed a u.v. and Bratton–Marshall active spot (R_F 0.61). The cooled solution was evaporated and the residue in dichloromethane (100 ml) was washed with 2M-sodium hydroxide solution (2 × 40 ml). The dried (Na_2SO_4) organic layer was filtered and evaporated to dryness. The residue in chloroform (5 ml) was applied to a silica-gel column (2 × 60 cm). The product was eluted by chloroform–methanol (98 : 2) to give a hard gum, homogeneous on t.l.c. Crystallisation from toluene afforded the arabinofuranosylimidazoleamide as needles (3.5 g), m.p. 101 °C. The product was identical (t.l.c., m.p., mixed m.p., and i.r.) with the product prepared under (*a*).

5-Amino-4-cyano-1-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)imidazole (4f).—(*a*) A solution of 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazole-4-carboxamide (3 g) in chloroform (200 ml) containing triethylamine (2.87 g) and phosphoryl chloride (1.74 g) was refluxed for 2 h. T.l.c. examination (system A) showed a single spot (R_F 0.70) and absence of starting material. The cooled solution was poured into ice–sodium hydrogencarbonate solution and the organic phase dried (Na_2SO_4) and evaporated to a gum. A solution of this in chloroform (2 ml) was applied to a silica-gel column (2 × 30 cm). The product was eluted with chloroform–methanol (97 : 3). The *cyanoimidazole arabinoside hemihydrate* (1.8 g) crystallised from benzene as needles, m.p. 97—99 °C (Found: C, 69.5; H, 5.9; N, 10.5%; M^+, 510. $C_{30}H_{30}N_4O_4\cdot 0.5H_2O$ requires C, 69.35; H, 5.95; N, 10.7%; *M*, 510), $\lambda_{max.}$ (MeOH) 254 nm (ε 11 800); ν_{CN} 2 230 cm^{-1}.

(*b*) Dry ammonia was passed through a suspension of aminomalononitrile toluene-*p*-sulphonate [15] (3 g) in dry acetonitrile (100 ml) with stirring and cooling for 20 min. Precipitated ammonium toluene-*p*-sulphonate was removed and the filtrate evaporated to *ca.* 50 ml; triethyl orthoformate (1.8 g) was then added to it and the solution refluxed for 10 min. The cooled solution was treated with a saturated solution of ammonia in dry acetonitrile (25 ml) and then set aside at room temperature for 5 h. Excess of ammonia was removed *in vacuo*. To the cyano-imidazole solution was added 2,3,4-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (4.9 g) in acetonitrile (10 ml) and triethylamine (1.5 g) and the reaction mixture was refluxed for 2 h. T.l.c. examination in system A showed the presence of a spot (R_F 0.70). The cooled solution was evaporated to dryness. The residue in dichloromethane (50 ml) was washed with 2M-sodium hydroxide (2 × 20 ml). The dried (Na_2SO_4) organic layer was filtered and evaporated to dryness and a solution of the residue in chloroform (1 ml) applied to a silica-gel column (1 × 25 cm). The tri-*O*-benzylarabinofuranosylimidazole carbonitrile was eluted by chloroform–methanol (97 : 3). The compound (0.6 g) was identical (t.l.c. in systems A and C) with material prepared under (a).

5-Amino-4-cyano-1-β-D-arabinofuranosylimidazole (4g).—To a solution of 5-amino-4-cyano-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazole (0.8 g) in dry distilled dichloromethane (8 ml), maintained at 0 °C, was added a dichloromethane solution of boron trichloride (3.2 ml; 25 g per 100 ml). The solution was allowed to come to room temperature. A solid precipitate was observed after *ca.* 5 min. T.l.c. examination of the solid in system D showed a major spot (R_F 0.59). After 2 h, the solid was collected, washed with dry dichloromethane (2 × 5 ml) and then dissolved in ethanol (5 ml); the solution was evaporated to dryness. A

solution of the residue in ethanol (0.5 ml) was applied to a silica gel column (1 × 27 cm). The product was eluted with chloroform–methanol (80 : 20). The cyano-imidazole nucleoside (0.2 g) crystallised from ethanol as *needles*, m.p. 151—152 °C (Found: C, 45.1; H, 5.0; N, 23.1%; M^+, 240. $C_9H_{12}N_4O_4$ requires C, 45.0; H, 5.05; N, 23.3%; *M*, 240), $\lambda_{max.}$ (MeOH) 250 nm (ε 11 040); ν_{CN} 2 230 cm^{-1}; δ (Me_2SO) 5.77 (H-1′, $J_{1'2'}$ 4 Hz), 6.08 (NH_2, s), and 7.34 (H-1, s).

9-β-D-*Arabinofuranosyladenine* (1).—A mixture of 5-amino-4-cyano-1-β-D-arabinofuranosylimidazole (0.05 g), ethanol (3 ml) saturated with ammonia, and triethyl orthoformate (0.031 g) was heated at 150 °C for 6 h. T.l.c. examination (system D) showed a single spot at R_F 0.49 and absence of starting material. On cooling, a dark amorphous solid precipitated, which was removed. The filtrate was evaporated to leave a solid residue which was dissolved in hot water (30 ml) and the solution treated with decolourising charcoal. The clarified filtrate was evaporated to a small volume which gave crystals when cooled. The arabinofuranosyladenine (0.038 g, 68%) had m.p. 254—257 °C and was identical (t.l.c., mixed m.p., i.r.) with an authentic specimen.

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REFERENCES

[1] Part 51, T. Brown, K. Kadir, G. Mackenzie, and G. Shaw, *J.C.S. Perkin I*, 1979, 3107.
[2] R. J. Suhadolnik in 'Nucleoside Antibiotics', Wiley-Interscience, 1970; G. A. LePage, L. S. Worth and A. P. Kimball, *Cancer Res.*, 1976, **36**, 1481; G. D. Diana and F. Panck, *Angew. Chem.*, 1976, **88**, 458.
[3] G. Mackenzie and G. Shaw, *J. Chem. Research* (*S*), 1977, 184; (*M*), 1977, 2145.
[4] D. H. Robinson and G. Shaw, *J.C.S. Perkin I*, 1972, 1715.
[5] C. P. J. Glaudemans and H. G. Fletcher, jun., in 'Synthetic Procedures in Nucleic Acid Chemistry', eds. W. W. Zorbach and R. S. Tipson, Wiley–Interscience, New York, 1968, 126.
[6] G. Shaw, R. N. Warrener, R. K. Ralph, and D. Butler, *J. Chem. Soc.*, 1959, 1648.
[7] A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, 1939, **128**, 537.
[8] J. Baddiley, J. G. Buchanan, F. E. Hardy and J. Stewart, *Proc. Chem. Soc.*, 1957, **149**, *J. Chem. Soc.*, 1959, 2893.
[9] H. Guglielmi, *Annalen*, 1973, 1286.
[10] R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, 1968, **90**, 2661.
[11] G. Mackenzie and G. Shaw, *J.C.S. Chem. Comm.*, 1978, 882.
[12] A. H. Cook and I. M. Heilbron, *J. Chem. Soc.*, 1949, 1071.
[13] E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, 1962, **27**, 3274.
[14] E. Shaw and D. W. Woolley, *J. Biol. Chem.*, 1949, **181**, 89.
[15] J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.*, 1968, **88**, 3829.