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C-NUCLEOSIDE STUDIES—15[1]

SYNTHESIS OF 3-β-D-ARABINOFURANOSYLPYRAZOLES AND THE D-ARABINOFURANOSYL ANALOGUE OF FORMYCIN

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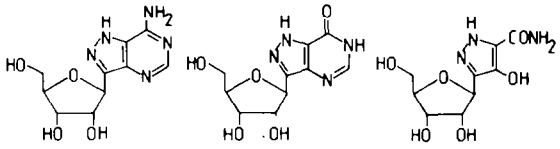
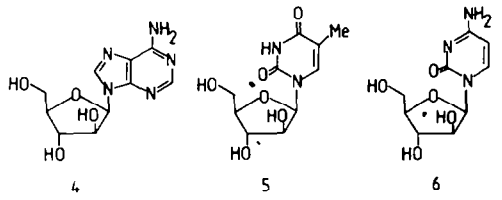
Abstract—A synthesis of 7-amino-3-(β-D-arabinofuranosyl)pyrazolo[4, 3-*d*]pyrimidine (**13**), the D-arabino analogue of formycin (**1**), from D-mannose is described. 1-(2, 4-Dinitrophenyl)-3-(penta-*O*-acetyl-D-*manno*-pentahydroxypentyl)pyrazole was converted into the 4-nitro-derivative **18** in 90% yield using trifluoroacetyl nitrate. In four steps **18** was transformed into the 3-β-D-arabinofuranosylpyrazole **12** which gave the N-nitro derivative **24** in two further stages. *Cine*-substitution of the N-nitro group in **24** by cyanide ion was followed by elaboration of the pyrimidine ring to give **13**. All the reactions proceeded with complete regio and stereoselectivity.

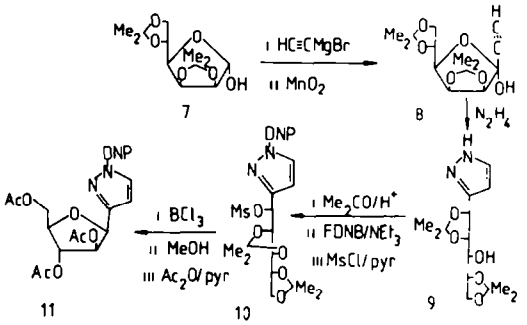
The C-nucleoside antibiotics,[2,3] in which D-ribofuranose is linked to a carbon atom of a heterocyclic ring, have been shown to have antitumour and antiviral properties.[2,4] In recent years the synthesis of the natural antibiotics and analogous compounds has attracted much attention. In particular, the presence of a pyrazole ring in the C-nucleosides formycin (**1**), formycin B(**2**) and pyrazofurin (**3**) has led to the development of methods



for the synthesis of 3-β-D-ribofuranosylpyrazoles and their further elaboration.[1,5-18] Our own synthesis of the pyrazole C-nucleosides,[1,13-16] using acetylenic intermediates, was designed to be flexible and capable of extension to carbohydrate units other than D-ribose. β-D-Arabinofuranose is known as a component of both naturally occurring and synthetic N-nucleosides showing antitumour and antiviral activity. Examples of these are 9-β-D-arabinofuranosyladenine (ara-A, vidarabine) (**4**), 1-β-D-arabinofuranosylthymine (ara-T, spongothymidine) (**5**), and 1-β-D-arabinofuranosylcytosine (ara-C, cytarabine) (**6**).

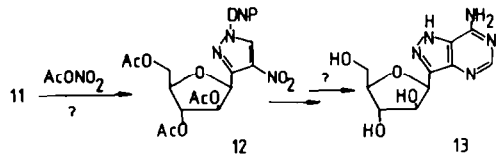


In 1979[19] we reported the synthesis of the β-D-arabinofuranosylpyrazole derivative **11** (Scheme 1), with the intention of converting it into the



Scheme 1.

β-D-arabinofuranosylpyrazolopyrimidine ("araformycin") (**13**), the D-arabino analogue of formycin (**1**) (Scheme 2). Acton and his coworkers had previously described the synthesis of D-*arabino* analogues of oxoformycin B[21] and formycin B(**2**)[22] by routes corresponding to their synthesis of formycin B.[9] Scheme 1 summarises the steps by which the readily available diacetonide (**7**) of D-mannose was converted into **11**. The crystalline lactol **8**,[20] a latent acetylenic ketone, gave the pyrazole **9** on reaction with hydrazine.[14] The *erythro*-isopropylidene group in **9** rearranged into the more stable *threo* compound when treated with acetone and sulphuric acid. Protection of the pyrazole ring nitrogen by a dinitrophenyl group facilitated the formation of the 1'-methanesulphonate **10**. Acidic removal of the acetal protecting groups of **10** was accompanied by ring closure, with inversion of configuration, to give the kinetically favoured furanoid ring. The triacetate



Scheme 2.

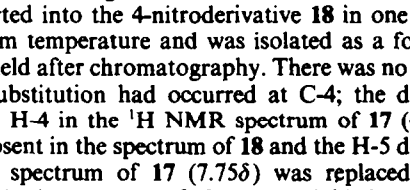
11,[19] obtained after acetylation, appeared to be ideally suited for nitration[15] to the 4-nitro-derivative **12** which could then be subjected to further transformations similar to those used in our synthesis[16] of formycin (**1**) itself.

The synthesis of **11** was improved. The diacetonide **7** was oxidised to the lactone **14**[23] in 82% yield by the Swern method[24] using dimethyl sulphoxide and oxalyl chloride (Scheme 3). Reaction of **14** with lithium acetylide (1.5 equivs) in tetrahydrofuran[25,26] gave the lactol **8** in 68% yield without the need of chromatography. The manganese dioxide oxidation described in the earlier work[19] (Scheme 1) was not readily adapted to a larger scale preparation of **8**.

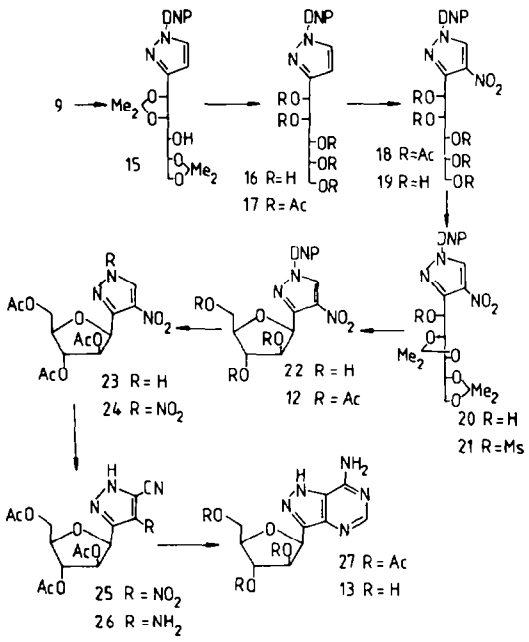
To our surprise and disappointment **11** resisted nitration by acetyl nitrate which had previously proved successful in the ribose series.[15] Trifluoroacetyl nitrate[27,28] was also unreactive, and when a mixture of nitric and sulphuric acids was used gross decomposition took place due, no doubt, to degradation of the carbohydrate moiety. These results are probably due to the "up" 2′-acetoxy group of the arabinose unit, but it is not clear whether the electrophilic attack at C-4 of the pyrazole ring is inhibited by steric or electronic interactions.

We argued that it might be possible to prepare the key intermediate (**12**) by an inverted sequence of reactions, i.e. by carrying out the nitration step before cyclisation of the polyol chain (Scheme 4). The acyclic pentaacetate **17**, the required substrate for nitration, was prepared from **9**. The crystalline dinitrophenyl derivative **15** was easily obtained from **9**, by reaction with fluorodinitrobenzene and triethylamine in refluxing benzene, in 84% yield. Acidic methanolysis of **15** afforded the crystalline pentitol **16** (94%), acetylation of which gave the required crystalline pentaacetate **17** (93%).

In our previous work on nitration of pyrazole derivatives[15,16] the most satisfactory reagent has been a mixture of copper(II) nitrate trihydrate and acetic anhydride,[29] but when it was used for nitration of **17** reaction was slow and even after 5 days at room temperature some starting material remained. We have now used trifluoroacetyl nitrate, generated from ammonium nitrate as described by Crivello,[28] and found it to be the ideal reagent both for C-nitration of dinitrophenylpyrazoles and N-nitration of pyrazoles containing no N-substituent. **17** was easily converted into the 4-nitroderivative **18** in one hour at room temperature and was isolated as a foam in 90% yield after chromatography. There was no doubt that substitution had occurred at C-4; the doublet due to H-4 in the ^{1}H NMR spectrum of **17** (6.62δ) was absent in the spectrum of **18** and the H-5 doublet in the spectrum of **17** (7.75δ) was replaced by a singlet in the spectrum of **18** at appreciably lower field (8.64δ).



Scheme 3.



Scheme 4.

The next stage was the cyclisation of the D-*manno* pentitol chain into a β-D-arabinofuranosyl group. We have previously discussed[19] the problems involved in cyclisation of polyol derivatives to give anhydrides of proved stereochemistry. **18** was converted into the crystalline pentitol **19** (95%) by acidic methanolysis, the more usual alkaline conditions being precluded by the presence of the base-labile dinitrophenyl group. Reaction of **19** with acidic acetone afforded, as expected,[19] the crystalline 2′, 3′: 4′, 5′-di-*O*-isopropylidene derivative **20** in 82% yield. The presence of a free hydroxyl group at C-1′ in **20** was shown by the ^{1}H NMR spectrum in which the H-1′ signal, the lowest field signal of the pentyl side chain, appeared as a double doublet, collapsing to a doublet when the sample was shaken with D_2O. The mesylate **21** (82%) was prepared by treatment of **20** with methanesulphonyl-chloride in pyridine. It crystallised as a solvate with ether, whose presence was shown by ^{1}H NMR and elementary analysis. The ^{13}C NMR spectrum confirmed the existence of two dioxolane rings,[30] showing two quaternary carbon atoms (109.85 and 111.68δ) and four C-Me groups (25.20, 26.28, 27.15 and 27.75δ).

When the isopropylidene groups in **21** were removed by acidic methanolysis ring closure of the intermediate pentitol took place, with inversion of configuration at C-1′, to give the β-D-arabinofuranosyl pyrazole **22**. This was immediately acetylated and the crystalline ether solvate of the triacetate **12** (81%) was fully characterised. The ^{1}H NMR spectra of **12** and later compounds in the synthetic sequence show clearly that they contain a furanoid ring; in particular the chemical shifts of the H-4′ and H-5′ protons in the triacetates are in the relative positions expected of a furanoid and not a pyranoid derivative. The spectrum resembled that of the parent compound **11**,[19]† with the loss of the H-4 signal and the expected deshielding of the signals due to H-1′, H-2′ and H-3′.

†There is a typographical error in Ref. 19. The signal for H-2′ is a double doublet, $J_{1',2'}$4Hz, $J_{2',3'}$1.2Hz.

The removal of the dinitrophenyl group from **12** was effected by methanolic sodium methoxide and the resulting triol reacetylated to give the crystalline triacetate **23** in 91% yield. Complete reaction of **23** with trifluoroacetyl nitrate[28] at room temperature occurred within 30 min affording the crystalline N-nitro derivative **24** in 92% yield. The location of the N-nitro group was clearly indicated by a comparison of the ^{1}H NMR spectra of **23** and **24**. The H-5 signal in **24** (9.03δ) is strongly deshielded relative to that in **23** (8.09δ.), whereas the H-1′ signals are very similar in chemical shift.

Cine-substitution[16,31] of the N-nitro group in **24** by cyanide ion occurred smoothly to give the 5-nitrile **25** (97%) as an oil. The H-5 signal was absent from the ^{1}H NMR spectrum and the IR spectrum showed the presence of a nitrile group. The amine **26** was produced in 86% yield when **25** was reduced with sodium dithionite.

Ring closure of **26** to the required pyrazolopyrimidine **27** was effected by treatment with formamidine acetate in refluxing ethanol. The ^{1}H NMR spectrum of the product showed that **27** was present together with a persistent minor impurity from which it could not be separated by crystallisation or chromatography. **27** was obtained in a reasonable state of purity, judged by its ^{1}H NMR spectrum, after short reaction times. When the ring closure reaction was taken to completion and the crude product deacetylated directly the required C-nucleoside **13** could be isolated in 66% yield. The impurity present in the triacetate **27** may have arisen by partial deacetylation and this is under investigation.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 257 instrument; UV spectra were obtained on a Perkin–Elmer 550 spectrometer. Mass spectrometry was performed using an A.E.I. MS 30 or MS 9 instrument. NMR spectra were recorded on Perkin–Elmer R12B, Jeol MH 100, Bruker WP 200 SY and WH 360 spectrometers. Specific rotations were measured at room temp using a Bendix-NPL 143D automatic polarimeter (path length 1 cm). M.ps were determined in capillaries and are uncorrected. Adsorption chromatography was carried out using Kieselgel H type 60 (Merck); an external pressure was applied to the top of columns. For TLC, pre-coated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)] were used. Light petroleum refers to material of b.p. 40–60°.

2,3:5,6 - *Di* - O - *isopropylidene* - D - mannono - 1,4 - *lactone* (**14**). To a stirred soln of oxalyl chloride (1.40 g, 11 mmole) in CH_2Cl_2 (25 mL) at −60° was added DMSO (1.7 mL, 22 mmole) in CH_2Cl_2 (5 mL); after 2 min, a soln of **7** (2.5 g, 10 mmole) in CH_2Cl_2 (10 mL) was added dropwise over 2 min. After 0.25 hr, Et_3N (15 ml) was added, and after a further 0.25 hr at −60°, the mixture was allowed to warm to room temp, and poured into water (50 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous phase extracted with more CH_2Cl_2. The washed, dried organic layer was evaporated; crystallisation of the residue from ether and recrystallisation from ether–light petroleum gave 2.03 g (82%) of **14**, m.p. 125–126° (lit.[23] m.p. 126°).

1, 2-*Dideoxy*-4, 5: 7, 8-*di*-O-*isopropylidene*-D-manno-*oct*-1-*yl*-3-*ulofuranose* (**8**). Dry acetylene gas was bubbled through dry THF (50 mL) for 15 min at room temp and 15 min at −78°. n-BuLi in ether (38.7 mmol) was then added in drops, with stirring. Passage of acetylene through the soln was continued for 0.5 hr, after which time the lactone (10 g), dissolved in the minimum quantity of dry THF (50 mL) was added to it. The mixture was stirred at −78° for 0.5 hr after which the passage of acetylene was discontinued and the soln maintained at −78° for a further 0.5 hr. The soln was then allowed to warm to room temp and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and to this was added a 10% (w/v) ammonium chloride soln (50 mL). The aqueous layer was then extracted with CH_2Cl_2 until no product was evident by TLC. The dried CH_2Cl_2 soln was concentrated under reduced pressure, and the resultant solid residue crystallised from CH_2Cl_2-light petroleum to give 7.42 g (68%) of **8**, m.p. 126° (lit.[20] m.p. 126–128°).

1-(2, 4-*Dinitrophenyl*)-3-(1, 2: 4, 5-*di*-O-*isopropylidene*-D-manno-*pentahydroxypentyl*)*pyrazole* (**15**). A soln of **9** (5.0 g) and 2,4-dinitrofluorobenzene (3.4 g) in benzene (250 mL) containing Et_3N (3.5 mL) was heated under reflux for 16 hr. Evaporation of solvents gave a dark yellow oil; chromatography on silica eluting with ether–light petroleum (2:1), and crystallisation from ether–light petroleum gave 6.54 g (84%) of **15**, m.p. 116.5–117.5°; $[\alpha]_D$ − 17.7° (c = 1.13, $CHCl_3$); ^{1}H NMR(100 MHz, $CDCl_3$) δ1.32, 1.36, 1.42, 1.60(each 3H, s, CMe_2), 2.4(1H, broad s, exchangeable, OH), 3.3(1H, broad s, 3′-H), 4.02(3H, m, 4′-H, 5′-H), 4.65(1H, d, J = 7Hz, 2′-H), 5.40(1H, d, J = 7Hz, 1′-H), 6.72(1H, d, J = 3Hz, 4-H), 7.78(1H, d, J = 9Hz, 6″-H), 7.81(1H, d, J = 3Hz, 5-H), 8.54 (1H, dd, J = 2, 9Hz, 5″-H), 8.68(1H, d, J = 2Hz, 3″-H); IR(KBr) 3550(OH), 1370, 1385 cm^{-1} (CMe_2). (Found: C, 51.68; H, 5.20; N, 11.71. $C_{20}H_{24}N_4O_9$ requires: C, 51.72; H, 5.17; N, 12.07%.)

1 - (2, 4 - *Dinitrophenyl*) - 3 - (D - manno - *pentahydroxypentyl*)*pyrazole* (**16**). A soln of **15** (5.0 g) in MeOH (100 mL) containing 10 N HCl (1 mL) was left to stand overnight. Evaporation, crystallisation with MeOH–ether and recrystallisation from MeOH gave 3.87 g (94%) of **16**, m.p. 184–186.5°; $[\alpha]_D$ − 70.5°(c = 1.22, DMSO); ^{1}H NMR (100 MHz, DMSO-d_6) δ3.4–4.05 (5H, m, 2′-5′-H), 4.15–4.75(5H, m, becomes 1H, d, J = 9Hz with D_2O, 1′-H and OH), 6.80(1H, d, J = 2.5Hz, 4-H), 8.25 (1H, d, J = 9Hz, 6″-H), 8.50 (1H, d, J = 2.5Hz, 5-H), 8.80(1H, dd, J = 3, 9Hz, 5″-H), 8.95(1H, d, J = 3Hz, 3″-H); IR(KBr) 3550, 3380(OH), 1608, 1535, 1520 cm^{-1}. (Found: C, 44.19; H, 4.24; N, 15.04. $C_{14}H_{16}N_4O_9$ requires: C, 43.98; H, 4.19; N, 15.04%.)

1 - (2, 4 - *Dinitrophenyl*) - 3 - (*penta* - O - *acetyl* - D - manno - *pentahydroxypentyl*)*pyrazole* (**17**). A soln of **16** (3.5 g) in pyridine (50 mL) and Ac_2O (25 mL) was left to stand for 16 hr. The soln was poured on to crushed ice, and extracted with CH_2Cl_2. Evaporation of the dried extracts, crystallisation from ether, and recrystallisation from ether–light petroleum gave 5.06 g (93%) of **17**, m.p. 114–115°; $[\alpha]_D$ +67.9° (c = 1.84, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ1.92, 2.04, 2.06, 2.08, 2.11 (each 3 H, s, COMe), 4.2(2H, m, 5′-H) 5.20 (1H, m, 4′-H), 5.5–5.8(2H, m, 2′-H, 3′-H), 5.84(1H, d, J = 9Hz, 1′-H), 6.62(1H, d, J = 3Hz, 4-H), 7.75(1H, d, J = 3Hz, 5-H), 7.90(1H, d, J = 9Hz, 6″-H), 8.55(1H, d, J = 3, 9Hz, 5″-H), 8.74(1H, d, J = 3Hz, 3″-H). (Found: C, 48.22; H, 4.34; N, 9.55; $C_{24}H_{26}N_4O_{14}$ requires C, 48.48; H, 4.38; N, 9.43%.)

1 - (2, 4 - *Dinitrophenyl*) - 3 - (*penta* - O - *acetyl* - D - manno - *pentahydroxypentyl*) - 4 - *nitropyrazole* (**18**). A soln of **17** (5.0 g) and ammonium nitrate (0.70 g) in trifluoroacetic acid (20 mL) was cooled in ice, and trifluoroacetic anhydride (4 mL) was added dropwise. The mixture was allowed to warm to room temp, and the reaction was monitored by TLC. When no starting material remained (1 hr), the mixture was poured into a separating funnel containing water (100 mL) and CH_2Cl_2 (25 mL). The layers were separated *rapidly* and the aqueous phase extracted with more CH_2Cl_2. Evaporation of the dried organic layers, and chromatography on silica, eluting with ether–light petroleum (2:1) gave 4.84 g (90%) of **18**, as a foam; $[\alpha]_D$ + 113.9° (c = 1.40, $CHCl_3$), ^{1}H NMR (100 MHz, $CDCl_3$) δ1.92, 2.02, 2.04, 2.09, 2.16 (each 3H, s, COMe), 4.2(2H, m, 5′-H), 5.15(1H, m, 4′-H), 5.66(1H, dd, J = 3, 9Hz), 5.84(1H, dd, J = 3, 9Hz), 6.12(1H, d, J = 11Hz, 1′-H), 7.92(1H, d, J = 8Hz, 6″-H), 8.64(1H, s, 5-H), 8.65(1H, dd,

J = 3, 8Hz, 5″-H), 8.86(1H, d, J = 3Hz, 3″-H); IR(KBr) 1740 (CO), 1540, 1350 cm^{-1} (both NO_2). (Found: C, 45.07; H, 4.16; N, 10.48; $C_{24}H_{25}N_5O_{16}$ requires C, 45.07; H, 3.91; N, 10.95%.)

1 - (2, 4 - *Dinitrophenyl*) - 3 - (D - manno - *pentadyroxypentyl*) - 4 - *nitropyrazole* (**19**). A soln of **18** (5.0 g) in MeOH (100 mL) containing conc HCl (1 mL) was left to stand for 16 hr. Evaporation, crystallisation with MeOH–ether, and recrystallisation from MeOH gave 3.20 g, (95%) of **19**, m.p. 192–194°; $[\alpha]_D$ – 52.9° (*c* = 0.6, DMSO); ^1H NMR(60 MHz, DMSO-d_6) δ3.2(3H, m, 3′-5′H), 3.9–4.5 (5H, m, becomes 1H, d, J = 9Hz with D_2O, 2′-H and OH), 4.95–5.55 (2H, m, becomes 1H, d, J = 9Hz with D_2O, 1′-H and OH), 8.25(1H, d, J = 8.5Hz, 6″-H), 8.75(1H, dd, J = 3, 8.5Hz, 5″-H), 8.95(1H, d, J = 3Hz, 3″-H), 9.55(1H, s,.5-H); IR(KBr) 3580, 3300 br (OH), 1610, 1535 cm^{-1}. (Found: C, 39.14; H, 3.46; N, 16.28; $C_{14}H_{15}N_5O_{11}$ requires C, 38.98; H, 3.48; N, 16.24%.)

1-(2, 4-*Dinitrophenyl*)-3(2, 3: 4, 5-*di*-O-*isopropylidene*-D-manno-*pentahydroxypentyl*)-4-*nitropyrazole* (**20**). Pentitol **19** (3.5 g) was stirred with acetone (50 mL) and H_2SO_4 (1 mL) for 6 hr. The acetone was distilled *in vacuo* until the volume remaining was 15 ml. A mixture of water (75 ml) and ether (50 ml) was added, the ether layer immediately separated and washed with fresh water. The dried ethereal soln was evaporated to give a syrup which crystallised in contact with a small amount of ether. Recrystallisation from ether–light petroleum gave 3.39 g (82%) of **20**, m.p. 91.5–93°; $[\alpha]_D$ – 21.4° (*c* = 1.31, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ1.32(9H, s, 3xMe), 1.41(3H, s, Me), 3.7(6H, m, becomes 5H, m, on D_2O shake), 5.21(1H, dd, J = 6.5, 8.5Hz, becomes d, J = 8.5Hz, on D_2O shake, 1′-H), 7.82(1H, d, J = 9Hz, 6″-H), 8.48(1H, dd, J = 3, 9Hz, 5″-H), 8.50(1H, s, 5-H), 8.69(1H, d, J = 3Hz, 3″-H). IR(KBr) 3440 br(OH), 1540, 1350(NO_2), 1385, 1375 cm^{-1} (CMe_2). (Found: C, 46.85; H, 4.85; N, 13.73. $C_{20}H_{23}N_5O_{11}$ requires C, 47.15; H, 4.52; N, 13.75%.)

1 - (2,4 - *Dinitrophenyl*) - 3 - (1 - O - *methylsulphonyl* - 2,3:4, 5-*di*-O-*isopropylidene*-D-manno-*pentahydroxypentyl*)-4-*nitro pyrazole* (**21**). To a soln of **20** (5.0 g) in dry pyridine (50 mL) was added dropwise methanesulphonyl chloride (4.0 g); the mixture was stirred for 16 hr, after which it was partitioned between water and CH_2Cl_2. The dried organic layer was evaporated; trituration of the residue with ether, and crystallisation from ether–CH_2Cl_2 gave 5.02 g (82%) of **21** as a solvate with 0.5 mole of ether, m.p. 113–113.5°; $[\alpha]_D$ + 45.6° (*c* = 1.07, $CHCl_3$); ^1H NMR(100 MHz, $CDCl_3$) δ1.28(6H, s, CMe_2), 1.38(6H, s, CMe_2), 3.04(3H, s, $MeSO_2$-), 3.80(1H, m, 4′-H), 4.12(3H, m, 5′-H, 3′-H), 4.62(1H, m, 2′-H), 6.20(1H, d, J, 6.5Hz, 1′-H), 7.84(1H, d, J, 9.5Hz, 6″-H), 8.60(1H, dd, J, 3, 9.5Hz, 5″-H), 8.64(1H, s, 5-H), 8.76(1H, d, J 3Hz, 3″-H); ^{13}C NMR(50.3MHz, $CDCl_3$) δ25.20, 26.28, 27.15, 27.75(all CMe_2), 38.69(SO_2Me), 67.12(t, 5′-C), 73.09, 76.59, 79.27, 79.36 (each d, 1′-4′-C), 109.85, 111.68 (CMe_2), 121.60, 127.61, 128.17, 131.28(each d, 5-C, 3″, 5″, 6″-C), 135.71, 136.36, 144.07, 146.30, 147.70 (each s, quaternary aromatics); IR(KBr)1340, 1350(NO_2), 1385, 1375(CMe_2), 1175 cm^{-1} (-SO_2-). (Found: C, 44.24; H, 4.98; N, 11.38. $C_{21}H_{25}N_5O_{13}S$. 0.5$C_4H_{10}O$ requires: C, 44.23; H, 4.81; N, 11.22%.) Signals due to ether (0.5 mol.) were present in the NMR spectra.

1-(2, 4-*Dinitrophenyl*-3(2, 3, 5-*tri*-O-*acetyl*-β-D-*arabinofuranosyl*)-4-*nitropyrazole* (**12**). A soln of **21** (5.0 g) in MeOH (100 mL) containing 10 N HCl (1 mL) was heated under reflux for 16 hr. Solvent was removed to give a yellow syrup to which was added pyridine (50 mL) and Ac_2O (25 mL). This soln was left to stand for 16 hr, poured on to crushed ice, and partitioned between water and CH_2Cl_2. The dried organic layer was evaporated, and the residue crystallised with ether; recrystallisation from CH_2Cl_2–ether gave 3.75 g (81%) of **12** as a solvate with 0.5 mole ether, m.p. 81–83°; $[\alpha]_D$ + 81.1° (*c* = 1.06, $CHCl_3$), ^1H NMR(100 MHz, $CDCl_3$) δ1.99, 2.11, 2.16 (each 3H, s, COMe), 4.14(3H, m, 4′-H, 5′-H), 5.20(1H, dd, J = 2, 3Hz, 3′-H), 5.68(1H, dd, J = 3, 4.8Hz, 2′-H), 5.82 (1H, d, J = 4.8Hz, 1′-H), 7.90(1H, d, J = 9.5Hz, 6″-H), 8.62(1H, s, 5-H), 8.64(1H, dd, J = 3, 9.5Hz, 5″-H), 8.82(1H, d, J = 3Hz, 3″-H); ^{13}C NMR(50.3MHz, $CDCl_3$) δ20.23(Me), 20.57(2Me), 62.93(t, 5′-C), 76.36, 76.19, 78.15, 81.70(1′-4′-C), 121.04, 127.91, 128.09, 131.09 (each d, 5, 3″, 5″, 6″-C), 135.34, 135.78, 144.01, 145.80, 147.40 (quaternary aromatics), 169.36, 169.57, 170.57 (C=O); IR(KBr)1750(CO), 1545, 1350 cm^{-1}(NO_2). (Found: C, 45.32; H, 4.16; N, 12.34. $C_{20}H_{19}N_5O_{13}$. 0.5 $C_4H_{10}O$ requires: C, 45.04; H, 4.11; N, 12.51%). Signals due to ether (0.5 mol) were present in the NMR spectra.

3(5) - (2, 3, 5 - *Tri* - O - *acetyl* - β - D - *arabinofuranosyl*) - 4 - *nitropyrazole* (**23**). To a soln of **12** (7.5 g) in MeOH (20 mL) was added a soln of Na (1.2 g) in MeOH (20 mL). After 0.5 hr, solvent was removed under vacuum, and to the residue was added pyridine (30 mL) and Ac_2O (15 mL). The mixture was left to stand overnight, poured onto ice, partitioned between water and CH_2Cl_2, and the dried organic layer evaporated to dryness. The residue was chromatographed on silica, eluting firstly with ether–light petroleum (1:9) to remove dinitroanisole, and then with ether–light petroleum (7:3) to elute the product, which was crystallised from ether–light petroleum to give 4.71 g (91%) of **23**, m.p. 99–101°; $[\alpha]_D$ + 101.8° (*c* = 1.66, $CHCl_3$); ^1H NMR(100 MHz, $CDCl_3$) 1.83, 2.12, 2.16 (each 3H, s, $COCH_3$), 4.24(2H, m, 4′-H, 5′$_a$-H), 4.71(1H, dd, J = 10, 13.5Hz, 5′$_b$-H), 5.06(1H, m, 3′-H), 5.68(1H, dd, J = 1, 4Hz, 2′-H), 5.86(1H, d, J = 4Hz, 1′-H), 8.09(1H, s, 5-H), 9.94(1H, br s, exchangeable, NH); IR(KBr)1750(CO), 1510, 1370 cm^{-1} (NO_2). (Found: C, 45.17; H, 4.65; N, 11.30; $C_{14}H_{17}N_3O_9$ requires: C, 45.53; H, 4.61; N, 11.38%.)

3-(2, 3, 5-*Tri*-O-*acetyl*-β-D-*arabinofuranosyl*)-1, 4-*dinitropyrazole* (**24**). To **23** (3.0 g) was added trifluoroacetic acid (10 mL) and ammonium nitrate (0.65 g). The mixture was stirred until homogeneous, when trifluoroacetic anhydride (4.55 g, 3.1 mL) was added. After 0.5 hr, the mixture was poured on to ice-water and extracted *immediately* with CH_2Cl_2. The dried organic extracts were evaporated to give a solid residue, which was crystallised from CH_2Cl_2–ether to give 3.10 g (92%) of **24**, m.p. 109–111°; $[\alpha]_D$ – 0.9° (*c* = 1.09, $CHCl_3$); ^1H NMR(100 MHz, $CDCl_3$) δ1.91, 2.11, 2.16 (each 3H, s, COMe), 4.30(3H, m, 4′-H, 5′-H), 5.16(1H, m, 3′-H), 5.57(1H, dd, J = 2.5, 4.5Hz, 2′-H), 5.81(1H, d, J = 4.5Hz, 1′-H), 9.03(1H, s, 5-H); IR(KBr) 1740 (CO), 1650 and 1270 (N-NO_2), 1520 and 1275 cm^{-1} (C-NO_2). (Found: C, 40.35; H, 3.88; N, 13.42. $C_{14}H_{16}N_4O_{11}$ requires: C, 40.38; H, 3.85; N, 13.46%.)

3(5) - (2, 3, 5 - *Tri* - O - *acetyl* - β - D - *arabinofuranosyl*) - 5(3) - *cyano* - 4 - *nitropyrazole* (**25**). To a soln of **24** (2.0 g) in EtOAc (20 mL) and EtOH (20 mL) was added a soln of KCN (3 g) in water (15 mL) and EtOH (60 mL), over 5 min. After a further 5 min, the mixture was neutralised with AcOH, and diluted with EtOAc (100 mL) and water (100 mL). The layers were separated, and the organic phase extracted with further EtOAc. The dried organic layers were evaporated, and the residue chromatographed on silica, eluting with ether–light petroleum (3:1) to give 1.85 g (97%) of **25**, as an oil, $[\alpha]_D$ + 107.9° (*c* = 0.70, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 1.87, 2.19, 2.195 (each 3H, s, $COCH_3$), 4.10(1H, dd, J = 2.3, 11.8 Hz, 5′$_a$-H), 4.35(1H, m, 4′-H), 4.92(1H, dd, J = 9.9, 11.8Hz, 5′$_b$-H), 5.03(1H, br.s, 3′-H), 5.68(1H, dd, J = 0.6, 3.7Hz, 2′-H), 5.91(1H, d, J = 3.7Hz, 1′-H); IR(Film) 3200(NH), 2255(C≡N), 1750(C=O), 1590(C=N), 1525, 1370 cm^{-1} (C-NO_2) (Found: C, 45.70; H, 4.38; N, 14.15. $C_{15}H_{16}N_4O_9$ requires: C, 45.45; H, 4.04; N, 14.14%.)

3(5) - (2, 3, 5 - *Tri* - O - *acetyl* - β - D - *arabinofuranosyl*) - 4 - *amino* - 3(5) - *cyano pyrazole* (**26**). To a soln of $KHCO_3$ (3.75 g) in water (25 mL) was added sodium dithionite (3.75 g). When the mixture was homogeneous, EtOH (10 mL) was added, followed by a soln of **25** (2.3 g) in EtOH (5 mL). The mixture was stirred at room temp for 45 min, when TLC indicated that reaction was complete, poured into water, and exhaustively extracted with EtOAc. The dried organic layer was evaporated, and the residue chro-

matographed on silica, eluting with $CHCl_3$–ether (3:2) to give 1.83 g (86%) of **26** as an oil, $[\alpha]_D - 27.9°$ ($c = 1.00$, $CHCl_3$); ^1H NMR(360 MHz, $CDCl_3$) δ1.92, 2.13, 2.14 (each 3H, s, COMe), 3.48(2H, br s, exchangeable, NH_2), 4.20 (1H, m, 4′-H), 4.26(1H, dd, J = 11.7, 3.2Hz, 5′$_a$-H), 4.67(1H, dd, J = 11.7, 7.6Hz, 5′$_b$-H), 5.09 (1H, dd, J = 2.65, 1.1 Hz, 3′-H), 5.28(1H, d, J = 3.8 Hz, 1′-H), 5.43(1H, dd, J = 3.8, 1.1 Hz, 2′-H); IR(Film) 3400–3150(NH), 2215(C≡N), 1750 cm^{-1} (CO); MS m/e 366 (M^+), 324 (M^+-CH_2CO), 187, 137[(Heterocycle + 30)$^+$]; High resolution MS: Found 137.0497; Calc for $[C_5H_5N_4O]^+$ 137.0459.

7 - *Amino* - 3 - (2′, 3′, 5 - *tri* - O - *acetyl* - β - D - *arabinofuranosyl*)*pyrazolo*[4, 3 - d] *pyrimidine* (**27**). To a soln of formamidine acetate (2.5 g) in EtOH (20 mL) at reflux was added **26** (0.75 g). Reflux was continued for 9 min, when the soln was poured on to ice and extracted with EtOAc. The dried organic extracts were evaporated and the residue chromatographed on silica, eluting with EtOAc, to give firstly 0.36 g of recovered starting **26**, followed by 0.29 g (36%, 69% based on recovered starting material) of **27**, containing < 10 mole % of an impurity, as a solid; ^1H NMR (360 MHz, $CDCl_3$) δ1.83, 2.11, 2.13 (each 3H, s, OAc), 4.26(1H, m, 4′-H), 4.36(1H, dd, J = 11.6, 3.8 Hz, 5′$_a$-H), 4.66(1H, dd, J = 11.7, 7.9 Hz, 5′$_b$-H), 5.35(1H, m, 3′-H), 5.59(1H, dd, J = 3.7, 1.2 Hz, 2′-H), 5.79(1H, d, J = 3.7 Hz, 1′-H), 8.30(1H, s, 5-H); the impurity showed 5-H at δ8.19; IR(KBr) 3350(NH). 1740 cm^{-1} (C=O); high resolution MS: Found 164.0574; Calc for $[C_6H_6N_5O]^+$ (heterocycle + 30) 164.0567.

In experiments where the reaction was allowed to proceed to completion, **27** was isolated in *ca* 75% yield, but integration of ^1H NMR signals at δ8.30 and 8.19 indicated ~ 20 mole % of impurity.

7 - *Amino* - 3 - (β - D - *arabinofuranosyl*)*pyrazolo*[4, 3 - *d*] *pyrimidine* (araformycin, **13**)

(a) A soln of **27** (0.36 g) in methanolic NaOMe (0.1 M, 20 mL) was stirred for 1 hr, neutralised with AcOH and evaporated to dryness. The residue, in water (5 mL), was applied to a column of Dowex 50–X8(H^+); after washing the column with water, the product was eluted with dilute aqueous ammonia. Lyophilisation, and crystallisation from water gave 0.20 g (76%) of **13** as a hydrate with 1 mole of water, m.p. 162–163°; $[\alpha]_D + 37.1°$ ($c = 0.87$, H_2O); ^1H NMR(200 MHz, D_2O) δ4.16(1H, dd, J = 12.2, 5.51 Hz, 5′$_a$-H), 4.20(1H, dd, J = 12.2, 3.75 Hz, 5′$_b$-H), 4.37(1H, m, 4′-H), 4.57(1H, dd, J = 4.04, 2.35 Hz, 3′-H), 5.88(1H, d, J = 5.62 Hz, 1′-H), 8.45(1H, s, 5-H); ^1H NMR(200 MHz, DMSO-d_6) δ3.62(2H, m, 5′-H), 3.79(1H, m, 4′-H), 4.08(2H, m, 2′-H, 3′-H), 5.32(1H, d, J = 3.81 Hz, 1′-H), 5.38(1H, d, J = 3.38 Hz, exchangeable OH), 5.6(1H, br, s, exchangeable, NH), 7.5(2H, br.s, exchangeable, NH_2), 8.11(1H, s, 5-H); UV; EtOH, λ_{max} 294 nm (ϵ 9250); in alkali, λ_{max} 237(16360), 304(6390); in acid, λ_{max} 296(9150), 236 nm (6700); IR(KBr) 3480, 3400(NH), 3200(broad, OH), 1670, 1575 cm^{-1}. (Found: C, 42.09; H, 5.38; N, 24.35. $C_{10}H_{13}N_5O_4.H_2O$ requires: C, 42.11; H, 5.26; N, 24.56%.)

(b) A soln of **26** (69.5 mg) and formamidine acetate (0.25 g) in EtOH (5 ml) was heated under reflux until TLC indicated no remaining starting material (0.5 hr). The solvent was evaporated, and the residue chromatographed on silica eluting with ether and then with ether–EtOH 10:1, to elute **27**. To the residue after evaporation was added methanolic NaOMe (2 mL of 1M soln). After 1 hr solvent was removed and the residue in water applied to a column of Dowex 50 – X8(H^+). The column was washed with water; subsequent elution with dilute ammonia, evaporation and crystallisation from water gave 35.4 mg (66%) of **13**, with properties identical to those of material prepared above.

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