General Synthesis of Imidazole C-Nucleosides From Carbohydrate Adducts of Diaminomaleonitrile

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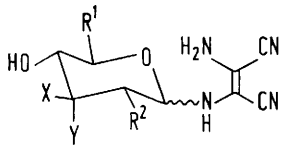
Summary The preparation of the imidazole C-nucleosides (**14**), (**15**), (**20**), and (**21**) from the adducts of ribose, arabinose, glucose, and mannose with diaminomaleonitrile is described.

RIBOSYL derivatives of diaminomaleonitrile are useful intermediates for the synthesis of imidazole and triazole ribopyranosides.[1] We describe herein an efficient and simple synthesis of C-nucleoside analogues of the antitumour and antiviral agents pyrazomycin (pyrazofurin) (**23**)[2] and bredinin (**22**)[3] using readily available carbohydrates and diaminomaleonitrile as the starting materials. The novel oxidative cyclization of a carbohydrate–diaminomaleonitrile adduct to an imidazole is a key step in the synthesis. The configuration at each asymmetric centre and the number of carbon atoms in the C-nucleoside can easily be varied using this synthetic approach.

Reaction of amino(ribosylamino)maleonitrile (**1**)[1] (52 mmol) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (54·5 mmol) in 325 ml of MeOH for 1·5 h at room temperature resulted in the formation of 4-cyano-5-methoxy-2-(D-*ribo*-tetrahydroxybutyl)imidazole (**4**) (64%) [m.p. 179—180 °C (decomp.); u.v. λ_{max} (MeOH) 246 nm (ϵ 12,900); i.r. (Nujol) 2212 (CN) and 1567 (C=C, C=N) cm^{-1};

^{1}H n.m.r. [$(CD_3)_2SO$] δ 5·68 (d, 1H, *J* 4 Hz, H-1′) and 3·90 (s, 3H, OMe); mass spectrum *m/e* 243 (M^+)].† The imino-(ribosylimino)succinonitrile adduct (**3**) is probably the initial oxidation product[4] which then adds methanol[5] to give an imidate ester that cyclizes to the imidazole (**4**). The oxidative cyclizations of the *o*-phenylenediamine adducts of sugars to benzimidazoles have been reported.[6]



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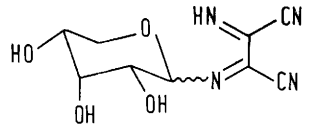
(2) R^1 = CH_2OH, R^2 = ~OH
X = OH, Y = H



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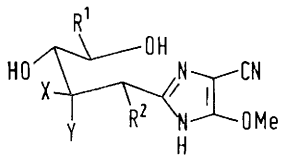
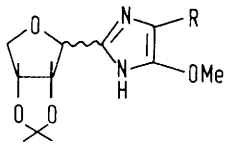
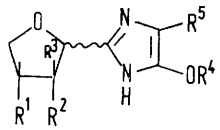


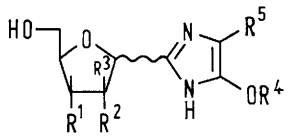
(4) R^1 = H, R^2 = OH, X = H, Y = OH
(5) R^1 = CH_2OH, R^2 = ~OH,
X = OH, Y = H



(6) α, R = CN
(7) β, R = CN
(8) α, R = $CONH_2$
(9) β, R = $CONH_2$

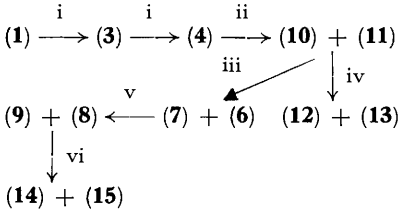


(**10**) α, R^1 = R^2 = OH, R^3 = H, R^4 = Me, R^5 = CN
(**11**) β, R^1 = R^2 = OH, R^3 = H, R^4 = Me, R^5 = CN
(**12**) α, R^1 = R^2 = O_2CMe, R^3 = H, R^4 = Me, R^5 = CN
(**13**) β, R^1 = R^2 = O_2CMe, R^3 = H, R^4 = Me, R^5 = CN
(**14**) α, R^1 = R^2 = OH, R^3 = R^4 = H, R^5 = $CONH_2$
(**15**) β, R^1 = R^2 = OH, R^3 = R^4 = H, R^5 = $CONH_2$



(**16**) α, R^1 = R^3 = OH, R^2 = H, R^4 = Me, R^5 = CN
(**17**) β, R^1 = R^3 = OH, R^2 = H, R^4 = Me, R^5 = CN
(**18**) α, R^1 = R^3 = OH, R^2 = H, R^4 = Me, R^5 = $CONH_2$
(**19**) β, R^1 = R^3 = OH, R^2 = H, R^4 = Me, R^5 = $CONH_2$
(**20**) α, R^1 = R^3 = OH, R^2 = R^4 = H, R^5 = $CONH_2$
(**21**) β, R^1 = R^3 = OH, R^2 = R^4 = H, R^5 = $CONH_2$

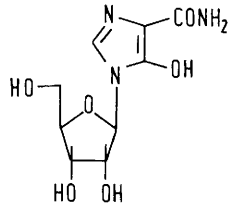
An anomeric mixture of D-erythrofuranosylimidazoles (**10**) and (**11**) was obtained in 77% yield by heating 7·5 mmol of (**4**) for 3 h at 150 °C in a mixture of 15 ml of 2-ethoxyethanol and 0·1 ml of acetic acid.[7] This mixture was converted into the corresponding isopropylidene acetals which were separated by chromatography on silica gel to give the β-anomer (**7**) in 62% yield [m.p. 110–111 °C; u.v. λ_{max} (MeOH) 245 nm (ε 14,070); mass spectrum *m/e* 265 (M^+)]† and the α-anomer (**6**) in 21% yield [m.p. 75—83 °C; u.v. λ_{max} 244 nm (ε 16,200); mass spectrum *m/e* 265 (M^+)].† Treatment of the mixture of (**10**) and (**11**) with acetic anhydride–pyridine yielded the diacetates (**12**) (13%) and (**13**) (46%) which were separated by h.p.l.c. on silica gel. The diacetates (**12**) and (**13**) were also obtained when amino(arabinosylamino)maleonitrile was the starting point in the synthesis, a result consistent with the loss of stereochemistry at C-1′ during the acid-catalysed cyclization of (**4**) and the corresponding *arabino*-tetrahydroxybutyl derivative. Hydrolysis of (**6**) and (**7**) with KOH–Bu^tOH[14] gave the amides (**8**) [35%; m.p. 104—106 °C (amorphous); i.r. 1640 cm^{-1} ($CONH_2$); mass spectrum *m/e* 283 (M^+)]† and (**9**) [52%; m.p. 230—232 °C; i.r. 1640 cm^{-1} ($CONH_2$); mass spectrum *m/e* 283 (M^+)] (Scheme 1).



SCHEME 1. *Reagents:* i, (**1**) (52 mmol), DDQ (54·5 mmol), MeOH (325 ml), 1·5 h, r.t.; ii, (**3**) (7·5 mmol), $EtO[CH_2]_2OH$ (15 ml)–AcOH (0·1 ml), 150 °C, 3 h; iii, $Me_2C(OMe)_2$; iv, acetic anhydride–pyridine; v, KOH–Bu^tOH; vi, Me_3SiI.

The anomeric configurations of compounds (**6**)—(**9**) were assigned from their ^{13}C n.m.r. spectra using the following criteria. (i) The isomer with the *trans*-relationship between the aglycone and the C-2′ hydroxyl group (β-anomer in the erythrofuranose series) has C-1′ at lower field than the corresponding *cis*-isomer.[8] (ii) The difference in chemical shifts between the gem-dimethyl groups of the acetal is greater in the β-anomers than in the α-anomers.[9] The chemical shift of C-1′ in (**7**) is δ 83·91 and the Δδ (Me) is 1·63 p.p.m. while the corresponding values for (**6**) are 81·24 and Δδ (Me) 1·33 p.p.m., consistent with the assignment of (**7**) as the β-anomer and (**6**) as the α-anomer. Similar ^{13}C n.m.r. spectral data lead to the assignment of the β-configuration to (**9**) [C-1′ δ 83·57, Δδ (Me) 1·68 p.p.m.] and the α-configuration to (**8**) [C-1′ δ 81·28, Δδ (Me) 1·13 p.p.m.].

Both the isopropylidene and methyl ether groups of (**8**) and (**9**) were cleaved with trimethylsilyl iodide[10] to give (**14**) (47%) and (**15**) (46%), respectively; these are erythrofuranosyl C-nucleoside analogues of bredinin (**22**) and pyrazomycin (**23**).[2,3] The structures of (**14**) and (**15**) were established from their characteristic u.v. [λ_{max} 240 nm



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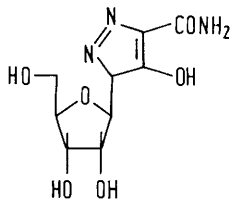
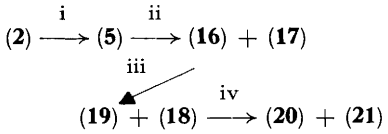


(23)

† The i.r., u.v., and n.m.r. spectra and combustion data were consistent with the assigned structures.

(ϵ 5500) and 280 nm (ϵ 12,000)] and mass spectra [*m/e* 229, (M^+)]. The ^{1}H n.m.r. spectrum of (**15**) is very similar to that of 4-carboxamido-5-hydroxy-2-(β-D-ribofuranosyl)-imidazole and the two compounds exhibit almost identical chemical shifts and $J_{1'2'}$ values for H-1'.[11]

The synthesis of the corresponding arabinofuranosyl-imidazole was initiated by the reaction of diaminomaleonitrile (0·05 mol) and either D-glucose[12] or D-mannose in a mixture of methanol and acetic acid (75:10) to give a 75% yield of (**2**).† The DDQ (0·01 mol) oxidation of 0·01 mol of (**2**) in 75 ml MeOH gave a 52% yield of (**5**) [u.v. λ_{max} (MeOH) 246 nm (ϵ *ca.* 15,000)].† The structure of (**5**), the oxidation product of glucosyldiaminomaleonitrile, was supported by its conversion into the penta-*O*-acetyl derivative by acetic anhydride and pyridine [m.p. 159—160 °C; mass spectrum *m/e* 483 (M^+)].† Heating (**5**) in a mixture of 30 ml of 2-ethoxyethanol and 10 ml of acetic acid for 12 h at 150 °C resulted in the formation of (**16**) and (**17**). The β-anomer, (**17**), was obtained in 38% yield by a combination of fractional crystallization followed by chromatography [m.p. 215—216 °C; u.v. λ_{max} (MeOH) 243 nm (ϵ 14,920); mass spectrum *m/e* 225 (M^+)].† The α-anomer (**16**) (13%) was purified by column chromatography [m.p. 94—97 °C (amorphous); u.v. λ_{max} (MeOH) 245 nm (ϵ 13,280)]. The β-configuration was assigned to (**17**) [^{1}H n.m.r. δ 4·66 (s, H-1); ^{13}C n.m.r. δ 71·72 p.p.m. (C-1')] and the α-configuration to (**16**) [^{1}H n.m.r. δ 4·2—3·8 (H-1' overlaps with the signals from the other protons); ^{13}C n.m.r. δ 76·48 p.p.m. (C-1')].[8,13] The nitriles (**16**) and (**17**) were hydrolysed[14] to the corresponding amides (**18**) (80%) [m.p. 172—174 °C (decomp.); u.v. λ_{max} (MeOH) 259·5 nm (ϵ 14,140); ^{1}H n.m.r. δ 4·2—3·5 (H-1' overlaps with signals from the other protons); ^{13}C n.m.r. δ 71·13 p.p.m. (C-1'); mass spectrum *m/e* 273 (M^+); hygroscopic, no combustion analyses]† and (**19**) (45%) [m.p. 243—244 °C (decomp.); u.v. λ_{max} (MeOH) 259 nm (ϵ 16,645); ^{1}H n.m.r. δ 4·62 (s, H-1'); ^{13}C n.m.r. δ 76·48 p.p.m. (C-1'); mass spectrum *m/e* 273 (M^+)].† Reaction with trimethylsilyl iodide gave a 52% yield of (**20**) [m.p. 235 °C (decomp.); u.v. λ_{max} (H_2O) 280·5 nm (ϵ 14,910) and 240 nm (ϵ 6507); ^{1}H n.m.r. δ 4·1—3·5 (H-1' overlaps with the signals from the other protons); mass spectrum *m/e* 259 (M^+)]† and a 42% yield of (**21**) [m.p. 225 °C (decomp.); u.v. λ_{max} (H_2O) 281 nm (ϵ 16,000) and 240 nm (ϵ 6865); ^{1}H n.m.r. δ 4·67 (s, H-1'); mass spectrum *m/e* 259 (M^+)] (Scheme 2).† It was surprising and gratifying that the primary hydroxy-groups in (**18**) and (**19**) were not converted into the corresponding iodides with trimethylsilyl iodide.[15]



SCHEME 2. *Reagents:* i, (**2**) (0·01 mol), DDQ (0·01 mol), MeOH (75 ml); ii, EtO[CH_2]$_2$OH (30 ml)–AcOH (10 ml), 150 °C, 12 h; iii, KOH; iv, Me_3SiI.

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