Ribopyranosyldiaminomaleonitrile: a Key Intermediate for the Synthesis of Nucleosides

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Summary The preparation of ribopyranosyldiaminomaleonitrile (**2**) and its conversion into imidazole ribopyranosides (**6**) and (**7**) and triazole ribopyranosides (**11**) and (**12**) is described.

Ribosyl derivatives of diaminomaleonitrile (DAMN) (**1**) constitute strategic intermediates for the synthesis of novel nucleoside antitumour agents. We describe herein a simple route to D-ribopyranosyldiaminomaleonitrile (ribosyl-DAMN) (**2**) from DAMN, a substance manufactured from HCN[1], and its conversion into several heretofore inaccessible ribopyranosyl nucleosides.

Reaction of (**1**) (10 mmol) with D-ribose (10 mmol) in 20 ml of MeOH containing 0·2 ml of $MeCO_2H$ for 18 h at 25 °C gave a 51% yield of (**2**) after elution from a silica gel column and crystallization from MeCN (m.p. 125 °C decomp.).† The presence of two anomers was evident from t.l.c. and from the ^1H n.m.r. spectrum which exhibited two H-1′ signals at δ 5·55 (J 10 Hz) and 5·80 (J 1 Hz). A purified sample of the β-anomer (δ 5·55) was obtained by fractional crystallization from MeOH–MeCN. The same anomeric mixture was obtained at a much slower rate when the reaction was performed in aqueous solution at pH 6—7.[2]

It was anticipated the ribosylDAMN would be a useful intermediate for the synthesis of novel nucleosides since a wide array of heterocycles have been synthesized from DAMN (**1**) and other enaminonitriles.[3,4] The limited nucleophilicity of the amino groups of (**2**)[3] permitted its selective *O*-acylation (49%) by reaction with acetic anhydride in pyridine for 2 h at 0—5 °C. The amorphous product was shown to consist of two anomers (**3**) by t.l.c. Treatment of (**3**) with triethyl orthoformate gave the anomeric dicyanoimidazole nucleosides (**6**) and (**7**) which are readily separable by silica gel chromatography. Stereoselectivity was attained by varying the reaction conditions. Heating an anisole solution of (**3**) (3 mmol) and triethyl orthoformate (4·3 mmol) first at 90—100 °C for 30 min, followed by addition of 0·02 g of NaOMe and rapidly increasing the temperature to 150 °C and maintaining it there for 20 min gave a 37% yield of (**7**) (m.p. 169—170 °C)† and a 15% yield of (**6**) (m.p. 151—152 °C).† If the initial heating at 90—100 °C is prolonged to 1—4 h and the temperature is slowly raised to 150 °C a 1 : 3 ratio of (**7**) : (**6**) is obtained in 43% overall yield. These experiments suggest that the α-anomer (**6**) is the product of thermodynamic control. Since control experiments established that (**6**) and (**7**) do not interconvert under the reaction conditions the

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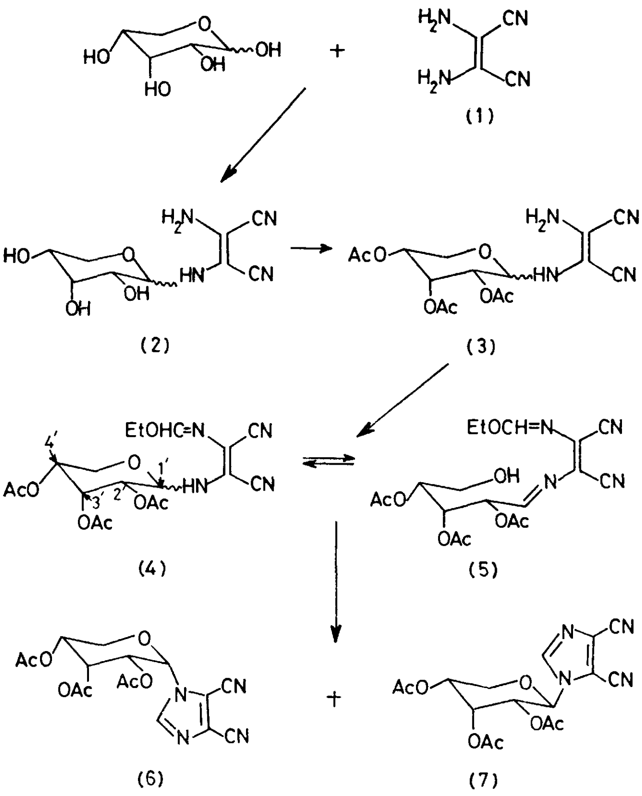
† The i.r., u.v., and ^1H n.m.r. spectra and combustion data were consistent with the assigned structures.

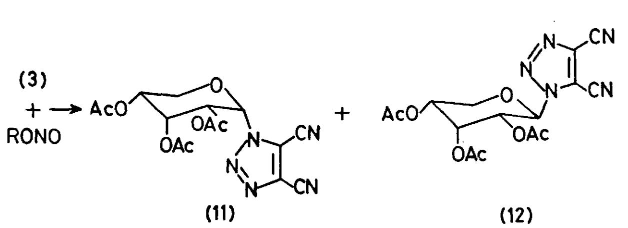
greater yield of (**6**) under conditions of thermodynamic control must be a consequence of the base-catalysed isomerization of (**4**) *via* (**5**).

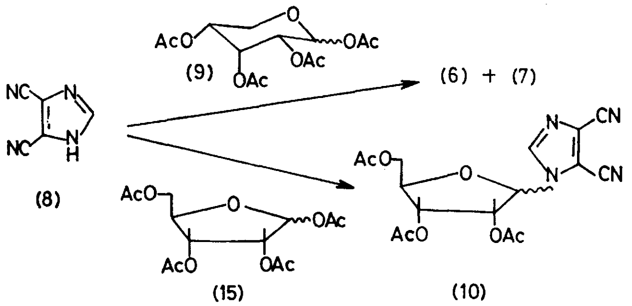


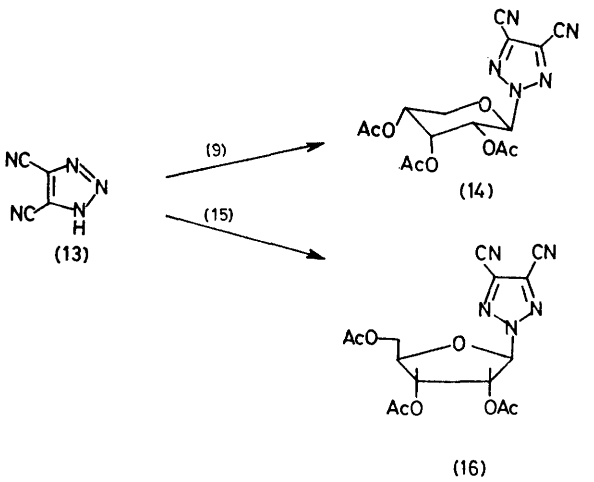
The stereochemistry at C-1′ and the pyranose nature of the ribose unit were established unequivocally by the independent syntheses of (**6**) and (**7**) by the fusion[5] of 4,5-dicyanoimidazole (**8**) (5 mmol)[6] and 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose (**9**) (5 mmol)[7] with $ClCH_2CO_2H$ (0·01 g) at 190 °C *in vacuo* for 5 min. The major product, separated by silica gel chromatography, was (**7**) (26%) along with a 2% yield of (**6**). Neighbouring group participation by the 2′-acetoxy-group of (**9**) directs the nucleophile to the β-side so that the β-pyranoside (**7**) is the major product.[8] A mixture of the ribofuranose derivatives (**10**) was obtained by the reaction of (**8**) with 1,2,3,5-tetra-*O*-acetylribofuranose (**15**)[9] as shown by the ^1H n.m.r. spectrum of the reaction mixture. It was not possible to separate this anomeric mixture.

The triazole nucleosides (**11**) and (**12**) are readily synthesized from ribosylDAMN in the reaction of (**3**) (2 mmol) with 1·5 ml of isopentyl nitrite in MeOH for 20 min at room temperature[10] The anomeric products were separated by silica gel chromatography to give a 37% yield of (**12**) (m.p. 126—127 °C)† and a 20% yield of (**11**) (m.p. 78—85 °C).† A 1 : 3 ratio of (**12**) : (**11**) (48% overall yield) is obtained when the reaction is performed in $CHCl_3$. This solvent effect must be due to the polar interaction between the tetrahydropyranyl oxygen and the nitrogen in the 1′-position (anomeric effect[11]) in the diazo intermediate generated prior to triazole ring formation. Compounds (**11**) and (**12**) were assigned the pyranose structures on the basis of the relative chemical shifts of H(1′) and the H(1′)–H(2′) coupling constants. These were comparable to those of (**6**) and (**7**), respectively.

Attempted synthesis of (**11**) and (**12**) by the fusion of 4,5-dicyanotriazole (**13**) (2 mmol), (**9**) (2 mmol), and $ClCH_2CO_2H$ (0·01 g) at 190 °C for 2 min *in vacuo* gave only the 2-substituted isomer (**14**) (89%; m.p. 53—56 °C).† The ribofuranosyl derivative (**16**) was also formed exclusively in the reaction of (**13**) and (**15**) (78%; m.p. 115—117 °C).† The high yields and specificity observed in these fusion reactions stand in marked contrast to the results obtained in acid-catalysed fusion reactions with other triazoles.[12]







The position of substitution of the triazole ring was confirmed by ^{13}C n.m.r. spectroscopy. Only one signal was observed at 126 p.p.m. for the 2 ring carbons and one signal at 109 p.p.m. for the 2 nitrile groups of the symmetrically substituted triazoles (**14**) and (**16**). The triazoles (**11**) and (**12**) gave 4 signals at 127, 117, 109, and 106 p.p.m.

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