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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 HCN¹, 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 MeCO₂H 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 $^{\circ}$ 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 $150 \,^{\circ}$ 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

† 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 fusion⁵ of 4,5-dicyanoimidazole (8) (5 mmol)⁶ and 1,2,3,4-tetra-Oacetyl- β -D-ribopyranose (9) (5 mmol)⁷ with ClCH₂CO₂H (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-Oacetylribofuranose (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 temperature¹⁰ 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 CHCl₃. This solvent effect must be due to the polar interaction between the tetrahydropyranyl oxygen and the nitrogen in the 1'-position (anomeric effect¹¹) 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 ClCH₂CO₂H (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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