Synthesis of Nucleosides Using Ketene Dithioacetals

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Several unnatural pyrazole and 1,2,4-triazole nucleosides are synthesized in a regio- and stereoselective manner by the reaction of readily available ketene dithioacetals with 1-ribofuranosylhydrazine.

Ketene dithioacetals are conveniently synthesized in large quantities from the reaction of active methylene compounds with carbon disulphide followed by alkylation. These compounds are readily soluble in a variety of organic solvents and the alkylthio groups are convertible into amino, alkyl, and other groups by reaction with the corresponding nucleophiles.

Using these reactions, a wide variety of heterocycles[2] and naturally occurring products[3] have been synthesized. We have also reported the synthesis of pharmaceutically important oxazoles, pyrazoles, pyrimidines,[4] and heterocycles containing an amino acid moiety.[5] In this paper, the work is extended to the synthesis of nucleosides which have recently received considerable attention as antiviral agents.[6]

Results and Discussion

The synthetic methodology of nucleosides is generally classified into two categories: i, direct fusion of the base moiety and ribose derivatives such as ribofuranosyl chloride,[7] ribofuranosyl acetate,[8] or methyl ribofuranoside[9] and ii, construction of the base moiety starting from 1-functionalised riboses such as ribofuranosylamine, ribofuranosyl isocyanate, ribofuranosyl isothiocyanate, ribofuranosylurea, ribofuranosylthiourea, and ribofuranosyl azide.[10] Recently, Townsend *et al.* have reported the synthesis of nucleosides using ribofuranosylhydrazine.[11] From their results, this hydrazine derivative reacts with ketene dithioacetals to afford the corresponding nucleosides regioselectively because it exists mainly in a hydrazone form.[12]

Several nucleosides were prepared starting from ketene dithioacetals. Further, we found that the present reaction formed the β-anomer of nucleosides exclusively, a result that may be attributed to the steric hindrance between the isopropylidene and the hydrazino moieties of the *N,N*-disubstituted hydrazinoribose intermediate (**3**).

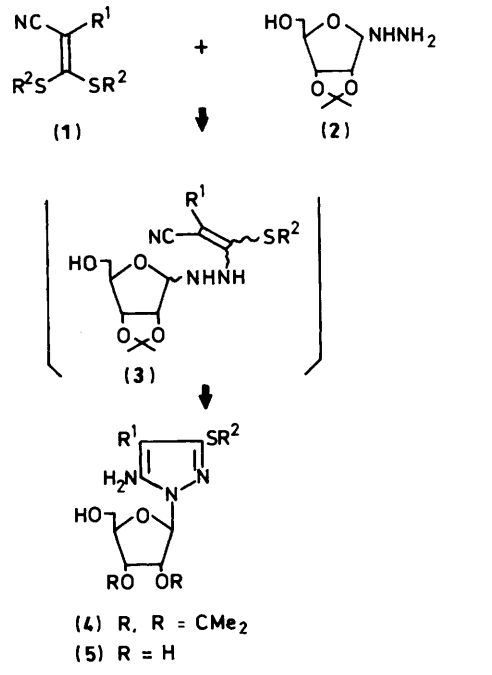
The five ketene dithioacetals (**1**) derived from cyanoacetamide and malononitrile were refluxed with 2,3-*O*-isopropylidene-D-ribofuranosylhydrazine (**2**) in absolute ethanol to give the corresponding nucleosides (**4**) in moderate yields as shown in Table 1 (Scheme 1). The yield is based on the 2,3-*O*-isopropylidene-D-ribose used.

Deprotection of (**4**) was carried out with acetic acid in the usual way to afford the corresponding nucleoside (**5**). In a similar way, compounds (**7**) and (**9**) were synthesized using the modified ketene dithioacetals (**6**) and (**8**), respectively (Schemes 2 and 3).

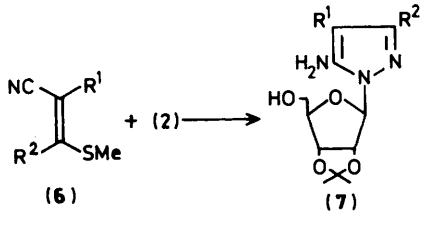
The results for compound (**7**) are summarized in Table 2. Compound (**9**) was further deprotected by treatment with formic acid to give the corresponding nucleoside (**10**). The structures of compounds (**4**), (**7**), and (**9**) were determined by spectral and analytical evidence and their β-anomer structures were assigned on the basis of differences in chemical shifts between the two methyl groups of the isopropylidene moiety in the ^{1}H n.m.r. spectra [$\Delta\delta$ = 0.21 for (**4a**), $\Delta\delta$ = 0.20 for (**7**), and $\Delta\delta$ = 0.12 for (**9**)].[13] The presence of a sugar moiety at position 1 of 1,2-pyrazole or 1,2,4-triazole can be determined on the basis of the $^3J_{C,H}$ splitting in the ^{13}C n.m.r. spectra.[14] The ^{13}C n.m.r. spectrum of (**4a**) which was measured by proton decoupling and n.O.e. showed a quartet peak and a broad peak

Table 1. Preparation of compound (**4**)

(4)	R^1	R^2	M.p. (°C)	Yield (%)
(**4a**)	$CONH_2$	Me	154—155	63
(**4b**)	$CONH_2$	Bn	59—60	51
(**4c**)	CN	CH_2TMS	53—54	34
(**4d**)	CN	Me	159—160	30
(**4e**)	CN	Bn	41—43	27



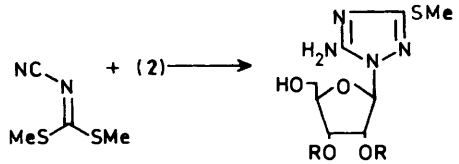
Scheme 1. R^1 and R^2 are given in Table 1



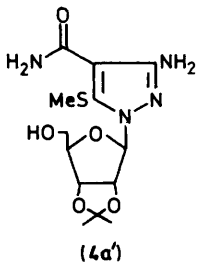
Scheme 2. R^1 and R^2 are given in Table 2

Table 2. Preparation of compound (7)

(7)	R^1	R^2	M.p. (°C)	Yield (%)
(7a)	$CONH_2$	Ph	167—169	20
(7b)	$CONH_2$	Bu	154—155	25
(7c)	CN	Ph	136—137 (decomp.)	23
(7d)	CN	Bu	*ca.* −3	24



for C-3 and C-5, respectively. An alternative structure (**4a'**) is ruled out by this result. The ^{13}C n.m.r. spectrum of (**9**) showed a similar result.



These structures were further supported by the following reactions; compounds (**4a**) and (**9**) were desulphurized with Raney nickel to give 5-amino-1-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carboxamide [15] and 5-amino-1-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,4-triazole, respectively. The latter compound was converted into 5-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole [16] on treatment with acetic acid.

Experimental

Microanalysis was performed with a Perkin-Elmer elemental 240 analyser at the Chemical Analysis Center of Chiba University. I.r., mass, u.v., ^1H n.m.r., and ^{13}C n.m.r. spectra were measured with Hitachi 215, RMU 6MC, EPS-3T, JEOL MH-100, and JMN-GX-270 spectrometers, respectively. Wakogel C-200 was used for column chromatography and Wakogel B-5F was used for t.l.c.

Preparation of Ketene Dithioacetals (**1**).—Compound (**1a**) was prepared by reaction of ethyl cyanoacetate with carbon disulphide followed by methylation.[17] A mixture of ethyl cyanoacetate (120 g, 1.1 mol), carbon disulphide (161 g, 2.1 mol), and aqueous ammonia (28%; 360 ml) was stirred at room temperature for 8 h. The crude product was collected and recrystallized from water–acetone to give light yellow prisms (83 g, 40%), m.p., 147—148 °C. This product was methylated with methyl iodide in water to give pale yellow needles. Recrystallization from ethanol gave white needles (77%), m.p. 84 °C. Similarly, compound (**1b**) was prepared by benzylation instead of methylation. Compounds (**1c**), (**1d**), and (**1e**) were prepared by the alkylation of disodium 2-cyano-3,3-disulphidoacrylonitrile with iodomethyltrimethylsilane, methyl iodide, and benzyl chloride, respectively.

2-*Carbamoyl*-3,3-*bis*(*benzylthio*)*acrylonitrile* (**1b**). White powder (92%), m.p. 125—127 °C (Found: C, 63.45; H, 4.75; N, 8.2. $C_{18}H_{16}N_2OS_2$ requires C, 63.50; H, 4.74; N, 8.23%); $\nu_{max.}$(KBr) 3 350, 3 150 (NH_2), 2 990 (CH), 2 200 (CN), and 1 640 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 4.04 (2 H, s, SCH_2Ph), 4.12 (2 H, s, SCH_2Ph), 5.80—6.10 (2 H, br, $CONH_2$), and 7.00—7.20 (10 H, m, 2 × Ph); *m/z* 340 (M^+).

2-*Cyano*-3,3-*bis*[(*trimethylsilylmethyl*)*thio*]*acrylonitrile* (**1c**). A mixture of disodium 2-cyano-3,3-disulphidoacrylonitrile hydrate [17] (2.4 g, 10 mmol) and iodomethyltrimethylsilane ($TMSCH_2I$) (4.5 g, 21 mmol) was refluxed in water (50 ml) containing a small amount of ethanol (5 ml) for 3 h. The resultant mixture was cooled and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to give yellow plates of (**1c**) (96%) as white plates (recrystallized from hexane–ethyl acetate), m.p. 68—69 °C (Found: C, 45.65; H, 7.0; N, 8.9. $C_{12}H_{22}N_2S_2Si_2$ requires C, 45.81; H, 7.05; N, 8.90%); $\nu_{max.}$(KBr) 2 925, 2860 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 0.18 (18 H, s, 2 × $SiMe_3$), and 2.50 (4 H, s, 2 × SCH_2Si); *m/z* 314 (M^+).

2-*Cyano*-3,3-*bis*(*methylthio*)*acrylonitrile* (**1d**). This compound was prepared according to ref. 17 (86%), m.p. 83—84 °C; $\nu_{max.}$(KBr) 2 980 (CH) and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 2.70 (6 H, s, 2 × Me); *m/z* 170 (M^+).

2-*Cyano*-3,3-*bis*(*benzylthio*)*acrylonitrile* (**1e**). White powder (recrystallized from hexane–ethyl acetate) (75%), m.p. 87—88 °C (Found: C, 67.1; H, 4.4; N, 8.65. $C_{18}H_{14}N_2S_2$ requires C, 67.09; H, 4.34; N, 8.70); $\nu_{max.}$(KBr) 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 4.32 (4 H, s, 2 × SCH_2Ph) and 7.30 (10 H, m, Ph); *m/z* 322 (M^+).

2,3-O-*Isopropylidene*-D-*ribofuranosylhydrazine* (**2**).—The procedure by L.B. Townsend [11] was modified as follows. A mixture of 2,3-*O*-isopropylidene-D-ribose [18] (1.14 g, 6 mmol), anhydrous hydrazine (1.8 ml, 60 mmol; 97% reagent grade), and absolute ethanol (6 ml) was stirred overnight at room temperature under nitrogen. The solvent of the reaction mixture was removed by aspirator and the residue was evaporated with dry ethanol (4 × 4 ml) and dry toluene (1 ml) under a vacuum pump (1 mmHg) below 50 °C in order to remove the excess of hydrazine. The pale yellow syrup thus obtained was used without purification in the next step.

5-*Amino*-4-*carbamoyl*-3-*methylthio*-1-(2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**4a**).—A solution of (**1a**) (376 mg, 2 mmol) and (**2**) (1.22 g, 6 mmol) in absolute ethanol (12 ml) was refluxed for 10 h. The solvent was evaporated off to give a yellow syrup and the syrup was dissolved in methylene dichloride and purified by t.l.c. on silica gel (eluant AcOEt–MeOH, 10:1) to afford white crystals (**8**) (428 mg, 62.4%), m.p. 154 °C (Found: C, 45.1; H, 5.8; N, 16.05. $C_{13}H_{20}N_4O_5S$ requires C, 45.34; H, 5.85; N, 16.27%); $\nu_{max.}$(KBr) 3 380, 3 300 (OH, NH_2), 2 950, 2 900 (CH), and 1 640 cm^{-1} (CO); δ_H(270 MHz, $CDCl_3$) 1.37 (3 H, s, Me), 1.58 (3 H, s, Me), 2.53 (3 H, s, SMe), 3.84, 3.69 (2 H, AB pattern, CH_2OH, $J_{5',5'}$ 12.5 Hz, $J_{4',5'}$ 7 Hz), 4.48 (1 H, s, OH), 4.87 (1 H, dd, 4'-H, $J_{3',4'}$ 3 Hz, $J_{4',5'}$ 7 Hz), 5.02 (1 H, dd, 2'-H, $J_{2',3'}$ 6 Hz, $J_{1',2'}$ 2 Hz), 5.26 (1 H, dd, 3'-H, $J_{2',3'}$ 6 Hz, $J_{3',4'}$ 3 Hz), 5.80 (1 H, d, $J_{1',2'}$ 2 Hz), 5.90 (2 H, br, NH_2 exch. D_2O), and 6.10 (2 H, br, $CONH_2$, exch. D_2O); δ_C (67.8 Hz, $CDCl_3$) 16.0 (SMe), 25.0, 26.9 (2 × Me), 63.6 (C-5'), 81.8 (C-3'), 84.2 (C-2'), 88.1 (C-4'), 91.6 (C-1'), 96.4 (CMe_2), 113.2 (C-5), 145.5 (C-3), 152.2 (C-4), and 166.3 (CO). *m/z* (in beam) 344 $(M + 1)^+$; $\lambda_{max.}$(99% EtOH) 212 (ε 16 000) and 225 nm (5 800); $[\alpha]_D$ −76.8° (*c* 0.35, EtOH).

Compounds (**4b**), (**4c**), (**4d**), and (**4e**) were prepared from compounds (**1b**), (**1c**), (**1d**), and (**1e**) by the same method as above.

5-*Amino*-3-*benzylthio*-4-*carbamoyl*-1-(2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**4b**). White powder (Found: C, 54.1; H, 5.8; N, 13.15. $C_{19}H_{24}N_4O_5S$ requires C, 54.27; H, 5.75; N, 13.32%); $\nu_{max.}$(KBr) 3 400, 3 200 (OH, NH_2), 2 960, 2 920 (CH), and 1 640 cm^{-1} (CO); δ_H(270 MHz, $CDCl_3$) 1.37 (3 H, s, Me), 1.57 (3 H, s, Me), 3.60, 3.76 (2 H, AB pattern, CH_2OH, $J_{5',5'}$ 12.5 Hz, $J_{4',5'}$ 7 Hz), 4.16 (2 H, s, $PhCH_2$), 4.44 (1 H, s, OH), 4.56 (1 H, dd, 4′-H, $J_{3',4'}$ 2 Hz, $J_{4',5'}$ 7 Hz), 4.96 (1 H, dd, 2′-H, $J_{1',2'}$ 2 Hz, $J_{2',3'}$ 6 Hz), 5.17 (1 H, dd, 3′-H, $J_{2',3'}$ 6 Hz, $J_{3',4'}$ 2 Hz), 5.79 (1 H, d, 1′-H, $J_{1',2'}$ 2 Hz), 5.90 (2 H, s, NH_2), 6.20 (2 H, s, $CONH_2$), and 7.26 (5 H, s, Ph); *m/z* (in beam) 420 (M^+); $\lambda_{max.}$(99% EtOH) 210 (ε 91 400) and 260 nm (24 700); $[\alpha]_D$ −44.4° (*c* 0.35, EtOH).

5-*Amino*-4-*cyano*-3-(*trimethylsilyl*)*methylthio*-1-(2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**4c**). White powder (Found: C, 48.05; H, 6.55; N, 13.95. $C_{16}H_{26}N_4O_4SSi$ requires C, 48.22; H, 6.58; N, 14.06%); $\nu_{max.}$(KBr) 3 350, 3 200 (OH, NH_2), 2 950, 2 860 (CH), and 2 220 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 0.12 (9 H, s, $SiMe_3$), 1.30 (3 H, s, Me), 1.48 (3 H, s, Me), 2.16 (2 H, s, CH_2TMS), 3.60 (2 H, m, CH_2OH), 4.20 (1 H, s, OH), 4.30 (1 H, m, 4′-H), 4.70 (1 H, d, 2′-H, $J_{2',3'}$ 4 Hz), 4.90 (1 H, d, 3′-H, $J_{2',3'}$ 4 Hz), 5.20 (2 H, br, NH_2), and 5.50 (1 H, d, 1′-H, $J_{1',2'}$ 2 Hz); *m/z* (in beam) 398 (M^+); $\lambda_{max.}$(99% EtOH) 217 (ε 25 900) and 235 nm (14 400); $[\alpha]_D$ −53.4° (*c* 0.27, EtOH).

5-*Amino*-4-*cyano*-3-*methylthio*-1-(2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**4d**). White powder (Found: C, 47.8; H, 5.55; N, 17.35. $C_{13}H_{18}N_4O_4S$ requires C, 47.84; H, 5.56; N, 17.17%); $\nu_{max.}$(KBr) 3 450, 3 350, 3 180 (OH, NH_2), 2 980, 2 920 (CH), and 2 220 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 1.36 (3 H, s, Me), 1.56 (3 H, s, Me), 2.44 (3 H, s, SMe), 3.70 (2 H, m, CH_2OH), 4.10 (1 H, m, 4′-H), 4.38 (1 H, s, OH), 4.80—5.18 (4 H, m, 2′-H, 3′-H, NH_2), and 5.60 (1 H, d, 1′-H, $J_{1',2'}$ 2 Hz); *m/z* (in beam) 326 (M^+); $\lambda_{max.}$(99% EtOH) 214 (ε 22 000) and 236 nm (10 500); $[\alpha]_D$ −77.9° (*c* 0.65, EtOH).

5-*Amino*-3-*benzylthio*-4-*cyano*-1-(2′-3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**4e**). White powder (Found: C, 56.65; H, 5.5; N, 13.65. $C_{19}H_{22}N_4O_4S$ requires C, 56.70; H, 5.51; N, 13.92%); $\nu_{max.}$(KBr) 3 400, 3 300, 3 200 (OH, NH_2), 2 920, 2 850 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 1.30 (3 H, s, Me), 1.48 (3 H, s, Me), 3.44 (2 H, m, CH_2OH), 4.00 (2 H, s, CH_2Ph), 4.20 (1 H, s, OH), 4.56 (1 H, m, 4′-H), 4.65 (1 H, dd, 2′-H, $J_{1',2'}$ 2 Hz, $J_{2',3'}$ 4 Hz), 4.90—5.10 (3 H, m, 3′-H, NH_2), 5.50 (1 H, d, 1′-H, $J_{1',2'}$ 2 Hz), and 7.00 (5 H, s, Ph); *m/z* (in beam) 402 (M^+); $\lambda_{max.}$(99% EtOH) 215 (ε 62 600) and 258 nm (44 200); $[\alpha]_D$ −37.5° (*c* 0.82, EtOH).

5-*Amino*-4-*carbamoyl*-3-*methylthio*-1-(β-D-*ribofuranosyl*)-*pyrazole* (**5a**).—A mixture of (**4a**) (344 mg, 1 mmol) and 10% acetic acid (2 ml) was refluxed for 3.5 h and then evaporated under reduced pressure with water and ethanol several times to give (**5a**) as a white powder, m.p. 162 °C (decomp.) (Found: C, 39.45; H, 5.3; N, 18.44. $C_{10}H_{16}N_4O_5S$ requires C, 39.47; H, 5.30; N, 18.41%); $\nu_{max.}$(KBr) 3 400—3 150 (NH_2, OH), 2 950—2 870 (CH), and 1 640 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$–C_5D_5N) 2.38 (3 H, s, SMe), 3.98 (2 H, m, CH_2OH), 4.40 (1 H, m, 4′-H), 4.74 (1 H, m, 2′-H), 5.10 (1 H, m, 3′-H), and 5.70—7.40 (6 H, m, 3-OH, 2 × NH_2, 1′-H); *m/z* (in beam) 304 (M^+); $\lambda_{max.}$(99% EtOH) 215 (ε 23 600) and 255 nm (9 500); $[\alpha]_D$ −49.4° (*c* 0.16, EtOH).

Preparation of Modified Ketene Dithioacetals (**6**).—2-*Carbamoyl*-3-*methylthio*-3-*phenylacrylonitrile* (**6a**). A mixture of oil-free sodium hydride (30 mmol), cyanoacetamide (0.84 g, 10 mmol), and dry tetrahydrofuran (20 ml) was refluxed for 1 h. To the reaction mixture was added methyl dithiobenzoate (2.0 g, 12 mmol) below 0 °C. The reaction mixture was quenched by water, washed with benzene, and the resulting aqueous solution was stirred with methyl iodide (1 ml, 15 mmol) at room temperature for 4 h and then extracted with ethyl acetate to give pale yellow crystals (62%), m.p. 202—203 °C (decomp.) (recrystallized from hexane–ethyl acetate) (Found: C, 60.5; H, 4.6; N, 12.8. $C_{11}H_{10}N_2OS$ requires C, 60.53; H, 4.62; N, 12.83%); $\nu_{max.}$(KBr) 3 360, 3 140 (NH_2) 2 200 (CN), and 1 680 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 1.60 (3 H × 1/9, s, SMe), 1.84 (3 H × 8/9, s, SMe), 5.90 (2 H, br, NH_2), 7.10 (2 H, m, Ph), and 7.30 (3 H, m, Ph); *m/z* 218 (M^+). N.m.r. data showed (**6a**) to be a 9:1 mixture of *E*- and *Z*-forms.

3-*Butyl*-2-*carbamoyl*-3-(*methylthio*)*acrylonitrile* (**6b**).—A THF solution of butylmagnesium chloride (2.2 mmol) was added dropwise to a solution of (**1a**) (0.188 g, 1 mmol) in dry THF (10 ml) and the mixture was stirred at the same temperature for 2 h and then at room temperature for 10 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, and the extract was dried (Na_2SO_4) and evaporated to give a pale yellow oil, which was purified by t.l.c. on silica gel (eluant AcOEt–hexane, 1:1) to afford white crystals (40%), m.p. 78—80 °C (Found: C, 54.5; H, 7.1; N, 14.1. $C_9H_{14}N_2OS$ requires C, 54.52; H, 7.11; N, 14.13%); $\nu_{max.}$(KBr) 3 400, 3 280 (NH_2), 2 960, 2 920, 2 860 (CH), 2 200 (CN), and 1 650 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 0.94 [3 H, t, $(CH_2)_3Me$, *J* 4 Hz], 1.20—1.70 (4 H, m, $CH_2CH_2CH_2Me$, *J* 4 Hz), 2.34 (3 H, s, SMe), 2.70 (2 H, br, $CH_2CH_2CH_2Me$), and 5.80 (2 H, br, $CONH_2$); *m/z* 198 (M^+).

2-*Cyano*-3-*methylthio*-3-*phenylacrylonitrile* (**6c**).—Malononitrile (660 mg, 10 mmol) at 0 °C was added to ethanol (50 ml) containing sodium metal (460 mg, 20 mmol) and the mixture was stirred for 30 min at room temperature. Methyl dithiobenzoate (1.68 g, 10 mmol) was added to the reaction mixture at 0 °C, the mixture was stirred for a further 3 h at room temperature and methyl iodide (2 ml) was then added. The resulting solution was stirred at room temperature for 15 h and evaporated to give a yellow oil, which was dissolved in ethyl acetate. The ethyl acetate solution was washed with water several times, dried (Na_2SO_4), and subjected to column chromatography on silica gel (eluant $CHCl_3$) to give (**6c**) (0.62 g, 30%), m.p. 86—87 °C (Found: C, 65.9; H, 4.05; N, 14.0. $C_{11}H_8N_2S$ requires C, 65.98; H, 4.03; N, 13.99%); $\nu_{max.}$(KBr) 3 050 (Ph), 2 900 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 2.16 (3 H, s, SMe) and 7.20—7.50 (5 H, m, Ph); *m/z* 200 (M^+).

Compound (**6d**) was prepared from methyl dithiopentanoate and malononitrile by the method used in the preparation of (**6c**).

3-*Butyl*-2-*cyano*-3-(*methylthio*)*acrylonitrile* (**6d**). Dark red oil (95%), b.p. 125—127 °C/1 mmHg (Found: C, 59.8; H, 6.65; N, 15.55. $C_9H_{12}N_2S$ requires C, 59.97; H, 6.71; N, 15.54%); $\nu_{max.}$(neat) 2 950, 2 920, 2 860 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 0.95 [−3 H, t, $(CH_2)_3Me$, *J* 4 Hz], 1.20—1.60 (4 H, m, $CH_2CH_2CH_2Me$), 2.50 (3 H, s, SMe), and 2.70 (2 H, t, $CH_2CH_2CH_2Me$ *J* 4 Hz); *m/z* 180 (M^+).

Compounds (**7a**), (**7b**), (**7c**), and (**7d**) were prepared from starting compounds (**6a**), (**6b**), (**6c**), and (**6d**) by the method used in the preparation of (**4a**).

5-*Amino*-4-*carbamoyl*-3-*phenyl*-1-(2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**7a**). White powder (from CH_2Cl_2) (Found; C, 57.8; H, 6.0; N, 14.85. $C_{18}H_{22}N_2O_5$ requires C, 57.75; H, 5.92; N, 14.96%); $\nu_{max.}$(KBr) 3 450, 3 350 (OH, NH_2) 2 960, 2 910 (CH), and 1 640 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 1.32 (3 H, s, Me), 1.54 (3 H, s, Me), 3.68 (2 H, m, CH_2OH), 4.36 (1 H, s, OH), 4.92 (1 H, dd, 2′-H, $J_{2',3'}$ 6 Hz, $J_{1',2'}$ 2 Hz), 4.50 (1 H, m, 4′-H), 5.20 (1 H, dd, 3′-H, $J_{2',3'}$ 6 Hz, $J_{2',3'}$ 2 Hz), 5.36 (2 H, s, NH_2), 5.90 (2 H, br, $CONH_2$), and 7.30 (5 H, m, Ph); *m/z* (in beam) 374 (M^+); $\lambda_{max.}$(99% EtOH) 210 (ε 42 800), 231 (31 700), and 255 nm (31 700); $[\alpha]_D$ −86.3° (*c* 0.28, EtOH).

5-*Amino*-3-*butyl*-4-*carbamoyl*-1-(2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**7b**). White powder (from CH_2Cl_2) (Found: C, 54.1; H, 7.3; N, 15.75. $C_{16}H_{26}N_4O_5$ requires C,

54.22; H, 7.39; N, 15.81%); $\nu_{max.}$(KBr) 3 450, 3 330, 3 140 (OH, NH_2), 2 950, 2 910, 2 850 (CH), and 1 630 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 0.92 [3 H, t, $(CH_2)_3Me$, *J* 6 Hz], 1.10—1.60 (4 H, m, $CH_2CH_2CH_2Me$), 1.32 (3 H, s, Me), 1.48 (3 H, s, Me), 2.68 (2 H, t, $CH_2CH_2CH_2Me$, *J* 6 Hz), 3.36 (1 H, s, OH), 3.60 (2 H, m, CH_2OH), 3.80—5.00 (4 H, m, 1'-H, 4'-H, NH_2), and 5.80 (2 H, br, NH_2); *m/z* (in beam) 354 (M^+); $\lambda_{max.}$(99% EtOH) 208.5 (ε 19 500), 225sh (7 400), and 257 nm (9 600); $[\alpha]_D$ −10.2° (*c* 0.29, EtOH).

5-*Amino*-4-*cyano*-3-*phenyl*-1-(2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**7c**). White powder (from AcOEt–hexane) (Found: C, 60.65; H, 5.6; N, 15.65. $C_{18}H_{20}N_4O_4$ requires C, 60.66; H, 5.66; N, 15.72%); $\nu_{max.}$(KBr) 3 400, 3 300, 3 240 (OH, NH_2), 2 960, 2 900, 2 850 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 1.24 (3 H, s, Me), 1.48 (3 H, s, Me), 3.50 (2 H, m, CH_2OH), 4.10 (1 H, s, OH), 4.70 (1 H, m, 4'-H), 4.94 (1 H, s, OH), 5.16 (2 H, br, NH_2), 5.52 (1 H, m, 3'-H), 5.60 (1 H, d, 1'-H, $J_{1',2'}$ 2 Hz), and 7.04 (5 H, m, Ph); *m/z* (in beam) 356 (M^+); $\lambda_{max.}$(99%, EtOH) 236 (ε 9 790) and 275sh; nm $[\alpha]_D$ −34.9° (*c* 0.49, EtOH).

5-*Amino*-3-*butyl*-4-*cyano*-1-(2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)*pyrazole* (**7d**). Pale yellow oil, m.p. *ca.* −3 °C (Found: C, 57.1; H, 7.1; N, 16.55. $C_{16}H_{24}N_4O_4$ requires C, 57.13; H, 7.19; N, 16.66%); $\nu_{max.}$(neat) 3 400—3 150 (NH_2, OH), 2 950—2 830 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 0.90 [3 H, t $(CH_2)_3Me$, *J* 4 Hz], 1.30 (3 H, s, Me), 1.10—1.65 (4 H, m, CH_2CH_2Me), 1.48 (3 H, s, Me), 2.44 (2 H, t, $CH_2CH_2CH_2Me$, *J* 4 Hz), 3.60 (2 H, m, CH_2OH), 4.00 (1 H, m, 4'-H), 4.10—4.50 (3 H, br, NH_2, OH), 4.84 (1 H, d, 2'-H, $J_{2',3'}$ 6 Hz), 5.04 (1 H, d, 3'-H, $J_{2',3'}$ 6 Hz), and 5.60 (1 H, d, 1'-H, $J_{1',2'}$ 2 Hz); *m/z* (in beam) 336 (M^+); $\lambda_{max.}$(99% EtOH) 236 nm (ε 7 830); $[\alpha]_D$ −93.5° (*c* 0.51, EtOH).

Dimethyl N-*Cyanodithiocarbonimidate* (**8**).—Compound (**8**) was readily synthesized from the reaction of cyanamide with carbon disulphide followed by methylation according to the literature;[19] $\nu_{max.}$ (KBr) 2 980, 2 920 (CH), and 2 200 cm^{-1} (CN); δ_H(100 MHz, $CDCl_3$) 2.60 (6 H, s, 2 × Me); *m/z* 146 (M^+).

5-*Amino*-3-*methylthio*-1-(2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)-1,2,4-*triazole* (**9**).—The reaction was carried out by the same procedure as for compound (**4**). Purification was performed by t.l.c. work-up using AcOEt–EtOH (95:5) as eluant; white powder (36%), m.p. 147 °C (Found: C, 43.7; H, 5.95; N, 18.5. $C_{11}H_{18}N_4O_4S$ requires C, 43.70; H, 6.00; N, 18.53%); $\nu_{max.}$(KBr) 3 410, 3 310, 3 210 (NH_2), 2 960, and 2 910 cm^{-1} (CH); δ_H(270 MHz, $CDCl_3$–C_5D_5N) 1.32 (3 H, s, Me), 1.44 (3 H, s, Me), 2.46 (3 H, s, SMe), 3.70, 3.81 (2 H, AB pattern, CH_2OH, $J_{5',5''}$ 12 Hz, $J_{4',5'}$ 3.3 Hz), 4.38 (1 H, dd, 4'-H, $J_{4',5'}$ 3.3 Hz, $J_{3',4'}$ 2 Hz), 4.99 (1 H, dd, 2'-H, $J_{2',3'}$ 6 Hz, $J_{1',2'}$ 2 Hz), 5.21 (1 H, dd, 3'-H, $J_{2',3'}$ 6 Hz, $J_{3',4'}$ 2 Hz), 5.91 (1 H, d, 1'-H, $J_{1',2'}$ 2 Hz), and 6.10 (2 H, br, NH_2, exch. D_2O); δ_C(67.8 MHz, $CDCl_3$–C_5D_5N) 13.4 (SMe), 24.7, 26.5 (2 × Me), 62.7 (CH_2), 81.4 (C-3'), 83.9 (C-2'), 87.7 (C-4'), 91.5 (C-1'), 95.5 (CMe_2), 156.0 (C-5), and 159.1 (C-3); *m/z* (in beam) 302 (M^+); $\lambda_{max.}$(99% EtOH) 236.8 (ε 16 000) and 306.5 nm (1 700); $[\alpha]_D$ −58.2° (*c* 0.52, EtOH).

5-*Amino*-3-*methylthio*-1-(β-D-*ribofuranosyl*)-1,2,4-*triazole* (**10**).—A mixture of compound (**9**) (300 mg, 1 mmol) and 50% formic acid (2 ml) was stirred at room temperature for 5 days. The reaction mixture was evaporated under reduced pressure and then purified by column chromatography on silica gel using AcOEt–EtOH (95:5) as eluant to give a white powder (50%), m.p. 160—161 °C (Found: C, 36.6; H, 5.4; N, 21.4. $C_8H_{14}N_4O_4S$ requires C, 36.64; H, 5.38; N, 21.36%); $\nu_{max.}$(KBr) 3 300, 3 200 (OH, NH_2), and 2 900 cm^{-1} (CH); δ_H(100 MHz, $CDCl_3$–C_5D_5N) 2.22 (3 H, s, SMe), 3.70 (2 H, m, CH_2OH), 4.10 (1 H, m, 4'-H), 4.40 (1 H, m, 2'-H), 4.70 (1 H, m, 3'-H), 5.40—5.60 (3 H, br, 3-OH, together with H_2O), 5.80 (1 H, d, 1'-H, $J_{1',2'}$ 2 Hz), and 6.70 (2 H, s, NH_2); *m/z* (in beam) 262 (M^+); $\lambda_{max.}$(99% EtOH) 207 (ε 11 800), 220sh (7 400), and 240sh nm (3 200); $[\alpha]_D$ −50.5° (*c* 0.16, EtOH).

Desulphurization of Compound (**4a**).—A solution of compound (**4a**) (0.34 g, 1 mmol) and activated Raney nickel[20] (1.5 ml) in 2-methoxyethanol (10 ml) was refluxed for 3 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a white residue which was dried under vacuum (2—3 mmHg). Recrystallization from methanol–hexane gave 5-amino-1-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carboxamide[15] in quantitative yield as white prisms, m.p. 179—180 °C (lit.,[15] 181 °C); δ_H(100 MHz, $CDCl_3$) 1.30 (3 H, s, Me), 1.42 (3 H, s, Me), 3.69 (2 H, m, CH_2OH), 4.32 (1 H, m, 4'-H), 4.98 (1 H, m, 3'-H), 5.25 (1 H, dd, 2'-H), $J_{1',2'}$ 2 Hz, $J_{2',3'}$ 6 Hz), 5.94 (1 H, d, 1'-H, $J_{1',2'}$ 2 Hz), 6.0—6.5 (4 H, br, 2 × NH_2), and 7.50 (1 H, s, 3-H); $\lambda_{max.}$(99%, EtOH) 236.5 (ε 12 300) and 255 nm (13 800); $[\alpha]_D$ −123° (*c* 0.61, EtOH).

5-*Amino*-1-(β-D-*ribofuranosyl*)-1,2,4-*triazole*.—Desulphurization of (**9**) was carried out by the same method as that of (**4a**). The white powder obtained was deprotected by refluxing for 2 days with 50% acetic acid to give a white powder. ^1H N.m.r. and u.v. data were superimposable on those reported by J. T. Witkowski *et al.*[16]

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