Synthesis of D-Ribofuranosylpyrazolecarboxamides

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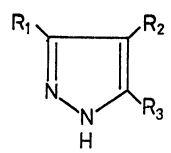
Several carbamoylpyrazole-nucleosides were synthesized by fusion of 1-*O*-acetyl derivatives of ribofuranoses with pyrazole derivatives in the presence of bis(*p*-nitrophenyl) hydrogen phosphate as an acidic catalyst. NMR and UV spectral studies revealed the orientation in *N*-glycosylation of the substituted pyrazoles.

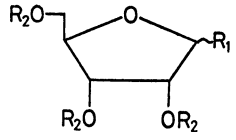
The pyrazole-nucleoside antibiotic pyrazomycin[1] (3-(β-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide) has been found to be an inhibitor of virus multiplication. On the other hand, 1-β-D-ribofuranosyl-1,2,3-triazole-4-carboxamide, previously synthesized in our laboratory,[2] was found to possess activity against vaccinia viruses, and, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole), synthesized by Witkowski *et al.*,[3] was reported to possess activity against DNA and RNA viruses. These facts prompted us to investigate the structure-activity relationship of pyrazolecarboxamide nucleosides. This paper describes the synthesis of several carbamoylpyrazoles and related nucleosides.

In the present synthesis, blocked derivatives of pyrazoles were coupled with 1-*O*-acetyl derivatives of blocked ribofuranoses by the fusion procedure in the presence of bis(*p*-nitrophenyl)hydrogen phosphate (BNPP)[4] to give blocked nucleosides. Another purpose of the present investigation was to study the orientation in the *N*-glycosylation of pyrazole derivatives.

Fusion of ethyl pyrazole-3-carboxylate[5] (**1**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[6] (**4**) in the presence of BNPP gave a mixture of two major nucleosides, namely ethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole-3-carboxylate (**6**) and -5-carboxylate (**7**), which were separated by chromatography to give **6** and **7** in a ratio of approximatly 8: 1. Treatment of **6** and **7** with methanolic ammonia gave 1-β-D-ribofuranosylpyrazole-3-carboxamide (**18β**) and 5-carboxamide (**19β**), respectively.

In an attempt to prepare the corresponding α-nucleosides, 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-ribofuranose





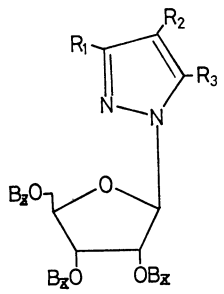
1, R_1=CO_2Et, R_2=R_3=H
2, R_1=R_3=CO_2Et, R_2=H
3, R_1=R_3=CO_2Et, R_2=NO_2

4, R_1=β-OAc, R_2=Bz
5, R_1=OAc, R_2=Bn

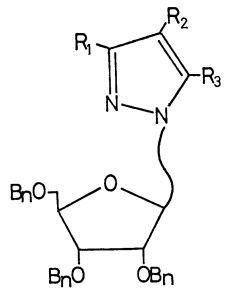
Chart 1.

(**5**), which has a benzyl group at *C*-2 as a non-participating group, was prepared and condensed with **1** by the fusion procedure to give ethyl 1-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)pyrazole-3-carboxylate (**10α**), its β-anomer (**10β**), and β-5-carboxylate (**11β**) in a ratio of approximately 2.6: 1.6: 1. Upon treatment with methanolic ammonia, these gave the carboxamide derivatives, (**14α**), (**14β**), and (**15β**), respectively. Catalytic hydrogenolysis of these products afforded 1-α-D-ribofuranosylpyrazole-3-carboxamide (**18α**), its β-isomer (**18β**), and β-5-carboxamide (**19β**), respectively.

Next, several pyrazole-3,5-dicarboxamide nucleosides, namely, 1-β-D-ribofuranosylpyrazole-3,5-dicarboxamide (**20β**), 4-nitro-1-(β-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (**21β**), 4-amino-1-(β-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (**22β**), and its α-anomer (**22α**) were synthesized. The fusion of ethyl pyrazole-3,5-dicarboxylate (**2**) with **4** gave ethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole-3,5-dicarboxylate (**8**), which led to **20β** by the treatment with methanolic ammonia. Similar condensation of **2** with the benzyl sugar **5** also afforded a

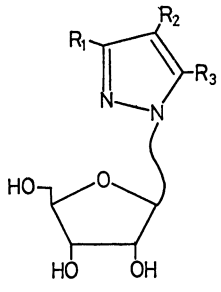


6, R_1=CO_2Et, R_2=R_3=H
7, R_3=CO_2Et, R_1=R_2=H
8, R_1=R_3=CO_2Et, R_2=H
9, R_1=R_3=CO_2Et, R_2=NO_2



10β, R_1=CO_2Et, R_2=R_3=H
10α, R_1=CO_2Et, R_2=R_3=H
11β, R_3=CO_2Et, R_1=R_2=H
12β, R_1=R_3=CO_2Et, R_2=H
13β, R_1=R_3=CO_2Et, R_2=NO_2
13α, R_1=R_3=CO_2Et, R_2=NO_2

14β, R_1=$CONH_2$, R_2=R_3=H
14α, R_1=$CONH_2$, R_2=R_3=H
15β, R_3=$CONH_2$, R_1=R_2=H
16β, R_1=R_3=$CONH_2$, R_2=H
17β, R_1=R_3=$CONH_2$, R_2=NO_2
17α, R_1=R_3=$CONH_2$, R_2=NO_2



18β, R_1=$CONH_2$, R_2=R_3=H
18α, R_1=$CONH_2$, R_2=R_3=H
19β, R_3=$CONH_2$, R_1=R_2=H
20β, R_1=R_3=$CONH_2$, R_2=H
21β, R_1=R_3=$CONH_2$, R_2=NO_2
22β, R_1=R_3=$CONH_2$, R_2=NH_2
22α, R_1=R_3=$CONH_2$, R_2=NH_2

Chart 2

β-nucleoside (**12β**) which led to **20β** through **16β**. In an attempt to prepare 4-amino nucleosides, ethyl 4-nitropyrazole-3,5-dicarboxylate (**3**) was prepared and coupled with **4** to give ethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-nitropyrazole-3,5-dicarboxylate (**9**); subsequent amidation yielded the 4-nitro-3,5-dicarbamoyl derivative (**21β**), and catalytic reduction afforded the 4-amino derivative (**22β**). Similar fusion of **3** with the benzyl sugar **5** gave a mixture (approximately 1:1) of (**13α**) and (**13β**), which were separated by chromatography; subsequent amidation gave (**17α**) and (**17β**), respectively, and catalytic reduction yielded the 4-amino nucleosides (**22α**) and **22β**.

The structures of the above mentioned pyrazole-nucleosides were assigned on the basis of their NMR spectral data. An apparent difference in the chemical shift for the anomeric proton signals in the 3-carboxamides (**18α, 18β**) and 5-carboxamide (**19β**) is consistently observed. The large downfield shift of the latter is attributable to the close location of the anisotropic carbamoyl group. The same effect has been observed in other nucleosides.[7-9] The proton of 3,5-dicarboxamide (**20β**) also showed a similar downfield shift. The ultraviolet spectra of the 3-carboxamides (**18α, 18β**) and 5-carboxamide (**19β**) also showed a characteristic difference, as shown in Table 1.

Table 1. Ultraviolet absorption data for pyrazole-3- and 5-carboxamide derivatives

Compound No.	Solvents λ_{max} nm and ε					
	pH 7 H_2O		pH 1 HCl		pH 13 NaOH	
	λ_{max}	ε	λ_{max}	ε	λ_{max}	ε
18α	214	11500	215	12700	227	11000
18β	212	11100	213	11200	227	12200
19β	220	12500	221	12200	227	8400

Assignment of the anomeric configuration is also supported by the NMR spectral data. The *H*-1′ signal for 1′,2′-*trans*-nucleosides has been shown[10] to appear at higher field than the *H*-1′ signal of the corresponding 1′,2′-*cis*-nucleosides. No formation of α-anomers corresponding to **11β** and **12β** was detected in this procedure; however, their β-configurations were characterized by the small $J_{1'2'}$ values (2.0 Hz).

The data of the NMR spectra also shows that *N*-glycosylation causes a chemical shift: the proton at *C*-5 adjacent to glycosylated nitrogen is at a lower field than that of the proton at *C*-3 adjacemt to nitrogen which is not glycosylated. A similar trend has been observed in the case of the proton at *C*-5 of 1,2,3-triazoles glycosylated at *N*-1.[11]

Among the pyrazole-nucleosides prepared in this paper, the 3-carboxamide (**18β**), which is a carbon bioisostere of virazole, and 3,5-dicarbamoyl-4-nitro derivative (**21β**) were found to have antileuchemic and antitumor activities.[12]

Experimental

Melting points were determined on a micro hot stage and were uncorrected. Thin layer chromatography (tlc) was conducted by the use of a Wakogel B-5. Silica gel column chromatography was carried out by using a Wakogel G-200. UV-Spectra were taken with a Hitachi Perkin-Elmer UV-VIS spectrometer 139. The NMR spectra were measured with a Varian A-60D spectrometer (TMS as an internal standard).

Ethyl Pyrazole-3-carboxylate (1). Prepared by the method of K. V. Auewrs[5]; NMR ($CDCl_3$): δ 7.95 (d, 1H, H-5), 7.01 (d, 1H, H-4), 4.55 (q, 2H, CH_2-ester), 1.47 (t, 3H, CH_3-ester).

Ethyl Pyrazole-3,5-dicarboxylate (2). Pyrazole-3,5-dicarboxylic acid[13] (10.0 g, 64 mmol) was dissolved in a 70% hydrogen chloride ethanol solution (100 ml) and refluxed for 4 hr. After removal of the solvent, the residue was dissolved in ethyl acetate and chromatographed on a silica gel column (200 g) using benzene–ethyl acetate (3:1) as a solvent. The main fraction was evaporated to give colorless crystals of **2**, 9.8 g (72%); mp 49—51 °C. NMR ($CDCl_3$): δ 7.50 (s, 1H, H-4), 4.52 (q, 4H, CH_2-ester), 1.41 (q, 6H, CH_3-ester). Found: C, 50.80; H, 5.72; N, 13.14%. Calcd for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20%.

Ethyl 4-Nitropyrazole-3,5-dicarboxylate (3). 3-Methyl-4-nitropyrazole-5-carboxylic acid[14] (10.0 g, 58.5 mmol) was dissolved in water (100 ml), to which powdered potassium permanganate (0.13 mol) was gradually added for 30 min under stirring. The solution was heated at 100 °C for 8 hr under stirring. After filtration, the solution was evaporated to dryness. 3 M Sulfulic acid (30 ml) was added and the precipitate was filtered. The dried crude precipitate was suspended in a 70% ethanolic hydrogen chloride solution (65 ml) and the solution was refluxed for 4 hr. After evaporation of the solvent, the residual syrup was dissolved in acetone (10 ml) and silica gel (6.5 g) was added; the mixture was evaporated and the crude product was purified by chromatography on a column (2.5×90 cm) of silica gel (130 g) using benzene–ethyl acetate (4:1) as a solvent, to give pale yellow crystals of **3**, 6.3 g (42%); mp 82—84 °C. Found: C, 41.96; H, 4.11; N, 16.18%. Calcd for $C_9H_{11}O_6N_3$: C, 42.03; H, 4.31; N, 16.34%.

1-O-Acetyl-2,3,5-tri-O-benzyl-D-ribofuranose (5). 2,3,5-Tri-*O*-benzyl-D-ribose[15] (10.0 g, 23.8 mmol) was dissolved in anhydrous pyridine (50 ml) and acetic anhydride (5 ml) was added. The mixture was stirred at room temperature for 12 hr. After evaporation of the solvent, the crude syrup was dissolved in ethyl acetate and chromatographed on a column of silica gel (400 g, 5×100 cm, packed with benzene) and eluted with benzene–ethyl acetate (20:1). The main fraction was evaporated to give a syrup of **5** (9.55 g, 87%); NMR ($CDCl_3$): δ 7.40 (s, 15H, Ar), 6.38 (s, 1H, H-1′), 4.8—3.9 (m, 9H, CH_2-Ar, H-2′, H-3′, H-4′), 3.71 (m, 2H, H-5′, 5″), 1.90 (s, 2.9H, CH_3), 1.87 (s, 0.1H, CH_3), α: β=1:29 (from acetyl peak). Found: C, 72.65; H, 6.50%. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54%.

Ethyl 1-(2, 3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)pyrazole-3-carboxylate (6) and Ethyl 1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)pyrazole-5-carboxylate (7). A mixture of ethyl pyrazole-3-carboxylate[5] (**1**) (0.62 g, 4.43 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[6] (**4**) (2.0 g, 3.97 mmol) was heated to 140 °C. To the melt was added BNPP (4 mg) and the mixture was heated at 140 °C under reduced pressure about 20 min until the evolution of acetic acid ceased. The resulting mixture was dissolved in ethyl acetate and was placed on a column of silica gel (130 g, 2.5×90 cm, packed with benzene) and eluted succesively with benzene (150 ml) and benzene–ethyl acetate (20:1). The effluent was fractionized into 12 mls.

Fraction Nos 11—21 gave **7**, colorless syrup, 255 mg (11%); $[\alpha]_D^{25}$ −6.7° (*c* 1.73, chloroform). NMR ($CDCl_3$): δ 8.15

(m, 6H, Ar), 7.73 (d, 1H, H-3), 7.51 (m, 10H, Ar, H-1'), 7.02 (d, 1H, H-4), 6.50 (m, 2H, H-2', H-3'), 4.80 (m, 3H, H-4', H-5', 5''), 4.40 (q, 2H, CH_2-ester), 1.40 (t, 3H, CH_3-ester). Found: C, 65.49; H, 5.01; N, 4.58%. Calcd for $C_{32}H_{28}O_9N_2$: C, 65.75; H, 4.83; N, 4.79%.

Fraction Nos 31—49 gave **6**, colorless syrup, 1.92 g (83.5%); $[\alpha]_D^{25}$ −40.0° (*c* 3.2, chloroform). NMR ($CDCl_3$): δ 8.15 (m, 6H, Ar), 7.85 (d, 1H, H-5), 7.55 (m, 10H, Ar, H-1'), 6.95 (d, 1H, H-4), 6.30 (m, 2H, H-2', H-3'), 4.85 (m, 3H, H-4', H-5', 5''), 4.46 (q, 2H, CH_2-ester), 1.40 (t, 3H, CH_3-ester). Found: C, 65.49; H, 5.01; N, 4.58%. Calcd for $C_{32}H_{28}O_9N_2$: C, 65.75; H, 4.85; N, 4.79%.

*Ethyl 1-(2,3,5-Tri-*O*-benzoyl-β-*D*-ribofuranosyl)pyrazole-3,5-dicarboxylate (**8**).* A mixture of ethyl pyrazole-3,5-dicarboxylate (**2**) (630 mg, 2.97 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.50 g, 2.97 mmol) was fused in the presence of BNPP (2 mg) in the same manner as described for the preparation of **7**. The resulting mixture was dissolved in hot acetone (50 ml) and 1.5 g charcoal was added. After heating the mixture on boiling water, the charcoal was filtered off and the filtrate was evaporated under reduced pressure. The syrup was crystallized from isopropylalcohol to give **8**, 1.66 g (85.1%); mp 106—107 °C. $[\alpha]_D^{25}$ −25.6° (*c* 0.96, chloroform). NMR ($CDCl_3$): δ 8.15 (m, 6H, Ar). 7.50 (m, 11H, Ar, H-4, H-1'), 6.45 (m, 2H, H-2', H-3'), 4.81 (m, 3H, H-4', H-5', 5''), 4.48 (q, 4H, CH_2-ester), 1.40 (t, 6H, CH_3-ester). Found: C, 64.24; H, 5.09; N, 4.06%. Calcd for $C_{35}H_{32}O_{11}N_2$: C, 64.02; H, 4.91; N, 4.27%.

*Ethyl 1-(2,3,5-Tri-*O*-benzoyl-β-*D*-ribofuranosyl)-4-nitropyrazole-3,5-dicarboxylate (**9**).* A mixture of ethyl 4-nitropyrazole-3,5-dicarboxylate (**3**) (765 mg, 2.98 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**) (1.5 g, 2.98 mmol) was fused at 138 °C in the presence of BNPP in the same manner as described for the preparation of **7**. The resulting mixture was dissolved in hot acetone (40 ml) and treated with charcoal. After removal of the charcoal, the acetone solution was evaporated under reduced pressure. The resulting syrup was crystallized from isopropylalcohol to give **9**, 1.38 g (66%); mp 92—93 °C. $[\alpha]_D^{25}$ −51.2° (*c* 1.0, chloroform). NMR ($CDCl_3$): δ 8.15 (m, 6H, Ar), 7.60 (m, 9H, Ar), 7.12 (d, 1H, $J_{1',2'}$=2.0 Hz, H-1'), 6.5—6.2 (m, 2H, H-2', H-3'), 4.80 (m, 3H, H-4', H-5', 5''), 4.49 (dq, 4H, CH_2-ester), 1.39 (t, 6H, CH_3-ester). Found: C, 60.01; H, 4.53; N, 5.83%. Calcd for $C_{35}H_{31}O_{13}N_3$: C, 59.91; H, 4.45; N, 5.99%.

*Ethyl 1-(2, 3, 5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole-3-carboxylate (**10β**), Its α-anomer (**10α**) and Ethyl 1-(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole-5-carboxylate (**11β**).* A mixture of **1** (525 mg, 3.04 mmol) and **5** (1.40 g, 3.03 mmol) and a catalytic amount of BNPP were fused for 10 min in the same manner as described for the preparation of **7**. The resulting residue was dissolved in chloroform (5 ml) and silica gel (2 g) was added. The mixture was evaporated and then chromatographed on a column of silica gel (120 g) using *n*-hexane–isopropylether (2: 1) as a solvent. The effluent was fractionized into 13 mls.

Fraction Nos 31—43 gave **11β**, a colorless syrup, 282 mg (17.2%); $[\alpha]_D^{25}$ −1.4° (*c* 5.0, chloroform). NMR ($CDCl_3$): δ 7.65 (d, 1H, H-3), 7.41 (s, 15H, Ar), 7.15 (d, 1H, $J_{1',2'}$= 2.0 Hz, H-1'), 6.99 (d, 1H, H-4), 4.78—4.25 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 4.45 (q, 2H, CH_2-ester), 3.72 (m, 2H, H-5', 5''), 1.38 (t, 3H, CH_3-ester). Found: C, 70.53; H, 6.02; N, 4.64%. Calcd for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16%.

Fraction Nos 49—53 gave **10β**, a colorless syrup, 455 mg (27.2%); $[\alpha]_D^{25}$ −30.1° (*c* 1.0, chloroform). NMR ($CDCl_3$): δ 7.88 (d, 1H, H-5), 7.40 (s, 15H, Ar), 6.83 (d, 1H, H-4), 6.17 (d, 1H, $J_{1',2'}$=2.4 Hz, H-1'), 4.80—4.20 (m, 11H, CH_2-Ar, H-2', H-3', H-4', CH_2-ester), 3.77 (t, 2H, H-5', 5''), 1.40 (t, 3H, CH_3-ester). Found: C, 70.51; H, 6.26; N, 4.97%. Calcd for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16%.

Fraction Nos 56—67 gave **10α**, a colorless syrup, 727 mg (44.4%); $[\alpha]_D^{25}$ +35.8° (*c* 0.98, chloroform). NMR ($CDCl_3$): δ 8.17 (d, 1H, H-5), 7.40 (s, 15H, Ar), 6.95 (d, 1H, H-4), 6.44 (d, 1H, $J_{1',2'}$=4.9 Hz, H-1'), 4.70—4.15 (m, 11H, CH_2-ester, CH_2-Ar, H-2', H-3', H-4'), 3.62 (t, 2H, H-5', 5''), 1.38 (t, 3H, CH_3-ester). Found: C, 70.63; H, 6.37; N, 5.08%. Calcd for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16%.

*Ethyl 1-(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole-3,5-dicarboxylate (**12β**).* A mixture of ethyl pyrazole-3,5-dicarboxylate (**2**) (286 mg, 1.35 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-ribofuranose (**5**) (622 mg, 1.35 mmol) was fused in the presence of BNPP (2 mg) in the same manner as described for the preparation of **7**. The resulting mixture was dissolved in ethyl acetate and chromatographed on a column of silica gel (40 g, 2.5×30 cm) using *n*-hexane–isopropylether (2: 1) as a solvent. The effluent was fractionized into 8 mls. Fractjon lNos 38—64 gave **12β**, a colorless syrup, 530 mg (63%); $[\alpha]_D^{25}$ −28.3° (*c* 1.0, chloroform). NMR ($CDCl_3$): δ 7.42 (t, 16H, H-4, Ar), 7.10 (d, 1H, $J_{1',2'}$=2.0 Hz, H-1'), 4.77—4.25 (m, 13H, CH_2-ester, CH_2-Ar, H-2', H-3', H-4'), 3.73 (m, 2H, H-5', 5''), 1.40 (t, 6H, CH_3-ester). Found: C, 68.08; H, 6.11; N, 4.36%. Calcd for $C_{35}H_{38}O_8N_2$: C, 68.39; H, 6.23; N, 4.57%.

*Ethyl 1-(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-4-nitropyrazole-3,5-dicarboxylate (**13β**) and Its α-Anomer (**13α**).* A mixture of ethyl 4-nitropyrazole-3,5-dicarboxylate (**3**) (599 mg, 2.32 mmol) and the sugar component **5** (1.07 g, 2.32 mmol) was fused in the presence of BNPP (2 mg) and worked up in a similar manner to the above, using a silica gel column (80 g, 2.8×35 cm). The effluent was fractionized into 11 mls.

Fraction Nos 38—46 gave **13β**, a colorless syrup, 550 mg (36%); $[\alpha]_D^{25}$ −55.8° (*c* 2.0, chloroform), NMR ($CDCl_3$): δ 7.40 (t, 15H, Ar), 6.52 (d, 1H, $J_{1',2'}$=2.0 Hz, H-1'), 4.8—4.5 (m, 9H, H-2', H-3', H-4', CH_2-Ar), 4.42 (q, 4H, CH_2-ester), 3.52 (d, 2H, H-5', 5''), 1.35 (t, 6H, CH_3-ester). Found: C, 64.03; H, 5.56; N, 6.10%, Calcd for $C_{35}H_{37}O_{10}N_3$: C, 63.72; H, 5.65; N, 6.37%.

Fraction Nos 49—61 gave **13α**, a colorless syrup, 580 mg (38%); $[\alpha]_D^{25}$ −9.3° (*c* 3.0, chloroform). NMR ($CDCl_3$): δ 7.42 (t, 15H, Ar), 6.77 (d, 1H, $J_{1',2'}$=3.3 Hz, H-1'), 4.75—4.50 (m, 9H, H-2', H-3', H-4', CH_2-Ar), 4.42 (q, 4H, CH_2-ester), 3.65 (d, 2H, H-5', 5''), 1.35 (t, 6H, CH_3-ester). Found: C, 63.98; H, 5.46; N, 6.13%. Calcd for $C_{35}H_{37}O_{10}N_3$: C, 63.72; H, 5.65; N, 6.37%.

*1-(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)pyrazole-3-carboxamide (**14β**).* A sample of **10β** (400 mg, 0.785 mmol) in absolute methanol (40 ml) saturated with ammonia at 0°C was kept at room temperaturefor 12 hr, and evaporated under reduced pressure at 40 °C. The residual syrup was washed with *n*-hexane and dried at 80 °C for 10 hr to give a colorless oil of **14β**, 318 mg (84%); $[\alpha]_D^{25}$ −22.5° (*c* 1.0, chloroform). NMR ($CDCl_3$): δ 7.75 (d, 1H, H-5), 7.38 (d, 15H, Ar), 6.87 (d, 1H, H-4), 6.60 (br s, 2H, $CONH_2$), 6.03 (d, 1H, $J_{1',2'}$=3.2 Hz, H-1'), 4.70—4.20 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.70 (t, 2H, H-5', 5''). Found: C, 70.14; H, 6.14; N, 8.22%. Calcd for $C_{30}H_{31}O_5N_3$: C, 70.16; H, 6.08; N, 8.18%.

*1-(2,3,5-Tri-*O*-benzyl-α-*D*-ribofuranosyl)pyrazole-3-carboxamide (**14α**).* The same procedure as described above was applied to **10α** (700 mg, 1.29 mmo.) in absolute methanol saturated with ammonia (70 ml) to give a colorless oil of **14α**, 546 mg (82%); $[\alpha]_D^{25}$ +45.2° (*c* 0.92, chloroform). NMR

($CDCl_3$): δ 8.25 (d, 1H, H-5), 7.40 (m, 15H, Ar), 7.00 (d, 1H, H-4), 6.45 (br s, 2H, $CONH_2$), 6.31 (d, 1H, $J_{1'2'}$=5.2 Hz, H-1'), 4.80—4.13 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.67 (d, 2H, H-5', 5''). Found: C, 70.15; H, 6.12; N, 8.24%. Calcd for $C_{30}H_{31}O_5N_3$: C, 70.16; H, 6.08; N, 8.18%.

1-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)pyrazole-5-carboxamide (15β). The same procedure as described above was applied to **11β** (260 mg, 0.48 mmol) in absolute methanol saturated with ammonia (26 m.) to give a colorless oil of **15β**, 196 mg (80%); $[\alpha]_D^{25}$ −2.5° (*c* 3.0, chloroform), NMR ($CDCl_3$): δ 7.60 (d, 1H, H-3), 7.40 (d, 15H, Ar), 7.18 (d, 1H, H-4), 6.60 (br d, 3H, $CONH_2$, $J_{1'2'}$=1.8 Hz, H-1'), 4.95—4.30 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.74 (m, 2H, H-5', 5''). Found: C, 70.47; H, 6.24; N, 8.27%, Calcd for $C_{30}H_{31}O_5N_3$: C, 70.16; H, 6.08; N, 8.18%.

1-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (16β). The same procedure as described above was applied to **12β** (420 mg, 0.685 mmol) in absolute methanol (42 ml) saturated with ammonia. The residual syrup was chromatographed on a column of silica gel (30 g) using benzene–ethyl acetate (3:1) as a solvent, to give a colorless glass of **16β**, 351 mg (92%); $[\alpha]_D^{25}$ −23.3° (*c* 1.0, dioxane). NMR (CD_3OD): δ 7.40 (t, 16H, Ar, H-4), 7.20 (d, 1H, $J_{1'2'}$=1.8 Hz, H-1'), 4.8—4.3 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.30 (d, 2H, H-5', 5''). Found: C, 66.66; H, 5.79; N, 9.96%. Calcd for $C_{31}H_{32}O_6N_4$: C, 66.89; H, 5.80; N, 10.07%.

4-Nitro-1-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (17β). A sample of **13β** (400 mg, 0.606 mmol) was led to its amide in a similar manner to that described above. The residual oil was washed with *n*-hexane and crystallized from benzene to give **17β**, 314 mg (81%); mp 82—83° C. $[\alpha]_D^{25}$ −27.5° (*c* 1.0, chloroform). NMR (CD_3OD): δ 7.42 (s, 15H, Ar), 6.27 (d, 1H, $J_{1'2'}$=3.1 Hz, H-1'), 4.8—4.4 (m, 9H, H-2', H-3', H-4', CH_2-Ar), 3.70 (m, 2H, H-5', 5''). Found: C, 61.78; H, 5.23; N, 11.58%. Calcd for $C_{31}H_{31}O_8N_5$: C, 61.89; H, 5.19; N, 11.64%.

4-Nitro-1-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (17α). By the same procedure as described above, **15α** gave **17α**, 296 mg (81%), crystallized from benzene–isopropylether; mp 161—162 °C. $[\alpha]_D^{25}$ −14.5° (*c* 1.0, chloroform). NMR (CD_3OD): δ 7.40 (d, 15H, Ar), 6.52 (d, 1H, $J_{1'2'}$=4.9 Hz, H-1'), 4.70—4.10 (m, 9H, H-2', H-3', H-4', CH_2-Ar), 3.68 (m, 2H, H-5', 5''). Found: C, 62.01; H, 5.22; N, 11.47%. Calcd for $C_{31}H_{31}O_8N_5$: C, 61.89; H, 5.19; N, 11.64%.

1-α-D-Ribofuranosylpyrazole-3-carboxamide (18α). A sample of **14α** (500 mg, 0.975 mmol) in 10 ml methanol was hydrogenated over a palladium black catalyst at 50 lb/sq inch for 24 hr. After removal of the catalyst, the methanol layer was evaporated and recrystallized from ethanol and benzene to give **18α**, 187 mg (79%); mp 175.5 °C. $[\alpha]_D^{25}$ +33.4° (*c* 1.0, water). NMR (DMSO-d_6): δ 8.15 (d, 1H, H-5), 7.44 (br d, 2H, $CONH_2$), 6.78 (d, 1H, H-4), 6.14 (d, 1H, $J_{1'2'}$=5.3 Hz, H-1'), 5.32 (t, 2H, OH), 4.47 (t, 1H, OH), 4.57—4.13 (m, 3H, H-2', H-3', H-4'), 3.60 (m, 2H, H-5', 5''). Found: C, 44.61; H, 5.41; N, 17.48%. Calcd for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28%.

1-β-D-Ribofuranosylpyrazole-3-carboxamide (18β).

A. From 14β: A sample of **14β** (300 mg, 0.585 mmol) was hydrogenated and worked up in a similar manner to that described above. It was recrystallized from methanol to give **18β**, 111 mg (78%); mp 137 °C. $[\alpha]_D^{25}$ −41.6° (*c* 0.5, water). NMR (DMSO-d_6): δ 8.20 (d, 1H, H-5), 7.47 (br d, 2H, $CONH_2$), 6.83 (d, 1H, H-4), 5.85 (d, 1H, $J_{1'2'}$=4.0 Hz, H-1'), 5.50 (d, 1H, OH), 5.18 (d, 1H, OH), 4.95 (t, 1H, OH), 4.55—3.90 (m, 3H, H-2', H-3', H-4'), 3.71 (m, 2H, H-5', 5''). Found: C, 44.14; H, 5.37; N, 17.09%. Calcd for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28%.

B. From 6: A sample of **6** (1.2 g, 2.06 mmol) in absolute methanol (120 ml) saturated with ammonia at 0 °C was kept at room temperature for 3 days and then evaporated under reduced pressure at 40 °C. The residual syrup was dissolved in water (30 ml) and washed with ether (5 ml×10). The aqueous layer was evaporated to dryness to give 18β, 370 mg (72%).

1-β-D-Ribofuranosylpyrazole-5-carboxamide (19β).

A. From 15β: A sample of **15β** (180 mg, 0.351 mmol) was debenzylated by catalytic hydrogenation in a similar manner to that described above, in (A) of **18β**. After removal of methanol, the residual syrup was dissolved in aqueous ammonia and chromatographed on a column of silica gel (8 g, 1×10 cm) using butanol–ethanol–chloroform–17% aqueous ammonia (4:4:2:3) as a solvent, to give **19β**, colorless crystals, 61.5 mg (72%); mp 150—151 °C. $[\alpha]_D^{25}$ −64.5° (*c* 1.91, water). NMR (DMSO-d_6): δ 7.85 (br d, 2H, $CONH_2$), 7.72 (d, 1H, H-3), 7.00 (d, 1H, H-4), 6.86 (d, 1H, $J_{1'2'}$=3.0 Hz, H-1'), 5.28 (d, 1H, OH), 5.02 (d, 1H, OH), 4.83—3.80 (m, 4H, OH, H-2', H-3', H-4'), 3.58 (m, 2H, H-5', 5''). Found: C, 44.73; H, 5.52; N, 17.43%. Calcd for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28%.

B. From 7: A sample of **7** (230 mg, 0.394 mmol) in absolute methanol (50 m.) saturated with ammonia at 0 °C was kept at room temperature for 3 days. After removal of the methanol, water (10 ml) was added and the aqueous solution was extracted with ether (5 ml×10). The aqueous layer was evaporated and the residual syrup was chromatographed in a similar manner as described above to give **19β**, 74 mg (75%).

1-β-D-Ribofuranosylpyrazole-3,5-dicarboxamide (20β).

A. From 8: A sample of **8** (600 mg, 0.91 mmol) was subjected to ammonolysis in a similar manner to that described for the preparation (*B*) of **19β**. The residual syrup was chromatographed on a column of silica gel (30 g), using butanol–ethanol–chloroform–17% aqueous ammonia (4:4:2:3) as a solvent. The main fraction was evaporated to give a colorless glass of **20β**, 188 mg (72%); $[\alpha]_D^{25}$ −31.3° (*c* 1.0, water); NMR (DMSO-d_6): δ 7.80 (br d, 2H, $CONH_2$), 7.40 (s, 1H, H-4), 6.89 (d, 1H, $J_{1'2'}$=3.0 Hz, H-1'), 5.40 (d, 1H, OH), 5.00 (d, 1H, OH), 4.60 (m, 3H, OH, H-2', H-3'), 3.90 (m, 1H, H-4'), 3.60 (m, 2H, H-5', 5''). UV: λ_{max}^{water} 205 nm (ε 19700), λ_{max}^{pH1} 207 nm (ε 20600), λ_{max}^{pH13} 219 nm (ε 12500). Found C, 42.06; O, 5.00; N, 19.35%. Calcd for $C_{10}H_{14}O_6N_4$: C, 41.96; H, 4.93; N, 19.58%.

B. From 16β: A sample of **16β** (300 mg, 0.54 mmol) in 8 ml methanol was hydrogenated over a palladium black catalyst at 50 lb/sq inch for 70 hr. After filtration of the catalyst, the filtrate was evaporated and chromatographed on a column of silica gel with butanol–ethanol–chloroform–17% aqueous ammonia (4:4:2:3) to give **20β**, 94.3 mg (61%).

4-Nitro-1-(β-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (21β). A sample of 9 (800 mg, 1.14 mmol) was subjected to ammonolysis and worked up in a similar manner to that described for the preparation (*A*) of **20β** to give a colorless glass of **21β**, 272 mg (72%); $[\alpha]_D^{25}$ −23.5° (*c* 1.0, water); NMR (DMSO-d_6): δ 8.04 (br d, 4H, $CONH_2$), 5.82 (d, 1H, $J_{1'2'}$=3.7 Hz, H-1'), 5.55 (d, 1H, OH), 5.52 (d, 1H, OH), 4.80—3.90 (m, 4H, OH, H-2', H-3', H-4'), 3.60 (d, 2H, H-5', 5''). UV: λ_{max}^{water} 201 nm (ε 24500), 270 nm (ε 11200), λ_{max}^{pH1} 207 nm (ε 21200), 268 nm (ε 10600), λ_{max}^{pH13} 219 nm (ε 17300), 276 nm (ε 11100). Found: C, 35.98; H, 4.21; N, 20.90%. Calcd for $C_{10}H_{13}O_8N_5$: C, 36.26; H, 3.96; N, 21.14%.

4-Amino-1-(β-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (22β).

A. From 17β: A sample of **17β** (200 mg, 0.332 mmol) in 6 ml methanol was hydrogenated over a palladium black

catalyst at 50 lb/sq inch for 24 hr. The catalyst was filtered off and the filtrate was evaporated. Recrystallization from water gave **22β**, 74 mg (74%); mp 227—229 °C. $[\alpha]_D^{25}$ −68.2° (*c* 1.0, water). NMR (DMSO-d_6): δ 7.50 (br s, 4H, $CONH_2$), 6.45 (d, 1H, $J_{1'2'}$=3.6 Hz, H-1'), 5.40 (br d, 3H, OH, NH_2), 5.00 (d, 1H, OH), 4.70 (m, 2H, H-2', OH), 4.45—3.80 (m, 2H, H-3', H-4'), 3.50 (m, 2H, H-5', 5''). UV: λ_{max}^{water} 210 nm (ε 26000), 301 nm (ε 6330), $\lambda_{max}^{pH\ 1}$ 208 nm (ε 21200), 304 nm (ε 2470), $\lambda_{max}^{pH\ 13}$ 219 nm (ε 19300), 303 nm (ε 6620). Found: C, 39.50; H, 4.98; N, 23.10%. Calcd for $C_{10}H_{15}O_6N_5$: C, 39.37; H, 5.02; N, 23.25%.

B. From 21β: A sample of **21β** (200 mg, 0.604 mmol) was hydrogenated in the same way as above to give **22β**, 82 mg (82%).

4-Amino-1-(α-D-ribofuranosyl)pyrazole-3,5-dicarboxamide (22α). A sample of **17α** (250 mg, 0.415 mmol) was hydrogenated in the same manner as above. Recrystallization from methanol and benzene gave **22α**, 100 mg (80%); mp 206—207 °C. $[\alpha]_D^{25}$ +35.0° (*c* 0.5, water). NMR (DMSO-d_6): δ 7.55 (br d, 4H, $CONH_2$), 6.80 d, 1H, $J_{1'2'}$=5.7 Hz, H-1'), 5.25 (br s, 2H, NH_2), 5.2—4.8 (m, 3H, OH), 4.5—4.0 (m, 3H, H-2', H-3', H-4'), 3.60 (d, 2H, H-5', 5''). UV: λ_{max}^{water} 211 nm (ε 27700), 300 nm (ε 6900), $\lambda_{max}^{pH\ 1}$ 208 nm (ε 22500), 300 nm (ε 28600), $\lambda_{max}^{pH\ 13}$ 219 nm (ε 20100), 302 nm (ε 6800). Found: C, 39.64; H, 5.03; N, 23.01%. Calcd for $C_{10}H_{15}O_6N_5$: C, 39.37; H, 5.02; N, 23.25%.

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