Syntheses of D-Arabinofuranosyl and 2'-Deoxy-D-ribofuranosyl Pyrazolecarboxamides

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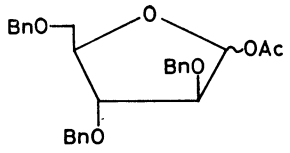
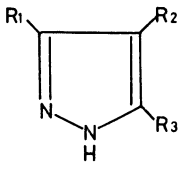
Several D-arabino- and 2'-deoxy-D-ribonucleosides of carbamoylpyrazoles were synthesized by an acid-catalyzed fusion reaction of 1-*O*-acetyl derivatives of the corresponding sugars with pyrazole derivatives. Spectral evidences for their *N*-glycosylation sites and anomeric configurations were presented.

In a previous paper we have reported[1] the synthesis of a cytotoxic nucleoside, 1-(β-D-ribofuranosyl)pyrazole-3-carboxamide, which is closely related to the antiviral antibiotic of pyrazomycin[2] [3-(β-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide]. Our continued interest in the nucleosides of pyrazolecarboxamide has prompted us to synthesize the corresponding nucleosides, *i.e.*, D-arabino- and 2'-deoxy-D-ribonucleosides of pyrazolecarboxamide and related nucleosides.

Since D-arabinosylation of heterocycles has often been successful in yielding antiviral and cytotoxic activities as exemplified[3] by 1-(β-D-arabinofuranosyl)-cytosine and 9-(β-D-arabinofuranosyl)adenine, we undertook a synthetic investigation of the arabinosyl-pyrazolenucleoside (**13β**). The β-nucleoside(1',2'-*cis*) was synthesized by use of 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1**) in which the hydroxyl group at *C*-2 is blocked with benzyl group (a nonparticipating group). The 1-*O*-acetyl sugar **1** was prepared by acetylation of 2,3,5-tri-*O*-benzyl-D-arabinofuranose.[4] Fusion of **1** with ethyl pyrazole-3-carboxylate[5] (**2**) in the presence of bis(*p*-nitrophenyl) hydrogenphosphate[6] gave a mixture of ethyl 1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)pyrazole-3-carboxylate (**5α**) and its β-anomer (**5β**) in a ratio of *ca.* 3 : 5 together with a small amount of 5-ethoxycarbonyl isomer (**6α**). These products were separated by chromatography and then treated with methanolic ammonia to give 1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)pyrazole-3-carboxamide (**9α**), its β-anomer (**9β**), and the α-anomer of 5-carboxamide (**10α**), respectively. Catalytic hydrogenolysis then afforded 1-(α-D-arabinofuranosyl)pyrazole-3-carboxamide (**13α**), its β-anomer (**13β**), and 5-carboxamide (**14α**), respectively.



1
(Bn=$CH_2C_6H_5$)



2, $R_1=CO_2Et$, $R_2=R_3=H$
3, $R_1=R_3=CO_2Et$, $R_2=H$
4, $R_1=R_3=CO_2Et$, $R_2=NO_2$

Chart 1

A similar fusion reaction of diethyl pyrazole-3,5-dicarboxylate[1] (**3**) with **1** afforded an anomeric mixture of (**7**), from which, by treatment with methanolic ammonia followed by chromatographic separation, 1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)pyrazole-3,5-dicarboxamide (**11α**) and its β-anomer (**11β**) were obtained in a ratio of 5 : 1. Catalytic hydrogenolysis of the major product **11α** gave 1-(α-D-arabinofuranosyl)-pyrazole-3,5-dicarboxamide (**15α**).

A fusion of diethyl 4-nitropyrazole-3,5-dicarboxylate[1] (**4**) with **1** followed by chromatographic separation afforded diethyl 1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-nitropyrazole-3,5-dicarboxylate (**8α**) and its β-anomer (**8β**) in a ratio of 11 : 3. The major product (**8α**) was treated with methanolic ammonia to give the carboxamide (**12α**), which was converted by catalytic hydrogenation into 4-amino-1-(α-D-arabinofuranosyl)-pyrazole-3,5-dicarboxamide (**16α**).

The structures of these nucleosides were assigned on the basis of their PMR and UV spectra. Substitution by the anisotropic carbamoyl group at *C*-5 of the pyrazole portion results in the downfield shift of anomeric proton signal[1,10] and it is observed that the anomeric proton signals of **14α** (δ 6.89), **15α** (δ 6.90), and **16α** (δ 6.41) show downfield shifts as compared with those of **13α** (δ 5.82) and **13β** (δ 6.06). The *H*-5 signals of **13α** (δ 8.17) and **13β** (δ 8.04) were observed in lower field than the *H*-3 signal of **14α** (δ 7.75). The anomeric proton signals of 1',2'-*cis* nucleosides have been shown[7] to occur at lower field than those of the corressponding *trans* anomers. The anomeric proton signals of the nucleoside **13α** and **13β** occurred at δ 5.82 and 6.06, respectively. These data suggested α-configuration(1',2'-*trans*) for **13α** and β-configuration(1',2'-*cis*) for **13β**. Comparison of the PMR spectrum of **8α**(1',2'-*trans*) with that of **8β**(1',2'-*cis*) showed a downfield shift for the anomeric proton of **8β** as expected for a 1',2'-*cis* nucleoside. This suggested α-configuration(1',2'-*trans*) for **16α**. The anomeric configuration of **14α** was suggested as α by the coupling constant ($J_{1',2'}=2.8$ Hz) of its benzyl derivative (**10α**).

Syntheses of the 2'-deoxy-D-ribonucleosides were next performed by use of 1-*O*-acetyl-2-deoxy-3,5-di-*O*-(*p*-nitrobenzoyl)-D-*erythro*-pentofuranose (**17**) which was obtained from methyl 2-deoxy-3,5-di-*O*-(*p*-nitro-

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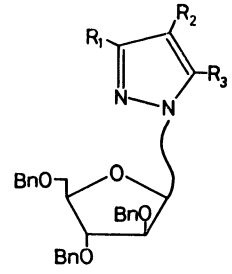
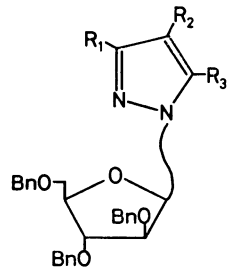
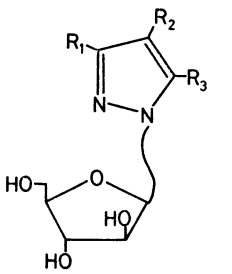


5α, R_1=CO_2Et, R_2=R_3=H
5β, R_1=CO_2Et, R_2=R_3=H
6α, R_3=CO_2Et, R_1=R_2=H
7 (Anomeric mixture)
R_1=R_3=CO_2Et, R_2=H
8α, R_1=R_3=CO_2Et, R_2=NO_2
8β, R_1=R_3=CO_2Et, R_2=NO_2

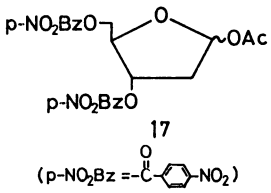


9α, R_1=$CONH_2$, R_2=R_3=H
9β, R_1=$CONH_2$, R_2=R_3=H
10α, R_3=$CONH_2$, R_1=R_2=H
11α, R_1=R_3=$CONH_2$, R_2=H
11β, R_1=R_3=$CONH_2$, R_2=H
12α, R_1=R_3=$CONH_2$, R_2=NO_2
12β, R_1=R_3=$CONH_2$, R_2=NO_2

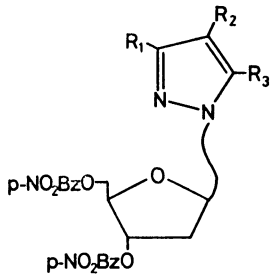


13α, R_1=$CONH_2$, R_2=R_3=H
13β, R_1=$CONH_2$, R_2=R_3=H
14α, R_3=$CONH_2$, R_1=R_2=H
15α, R_1=R_3=$CONH_2$, R_2=H
16α, R_1=R_3=$CONH_2$, R_2=NH_2

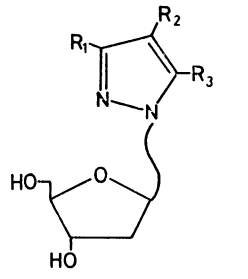
Chart 2



17



18α, R_1=CO_2Et, R_2=R_3=H
18β, R_1=CO_2Et, R_2=R_3=H
19α, R_3=CO_2Et, R_1=R_2=H
19β, R_3=CO_2Et, R_1=R_2=H
20 (Anomeric mixture)
R_1=R_3=CO_2Et, R_2=H
21 (Anomeric mixture)
R_1=R_3=CO_2Et, R_2=NO_2



22α, R_1=$CONH_2$, R_2=R_3=H
22β, R_1=$CONH_2$, R_2=R_3=H
23α, R_3=$CONH_2$, R_1=R_2=H
23β, R_3=$CONH_2$, R_1=R_2=H
24 (Anomeric mixture)
R_1=R_3=$CONH_2$, R_2=H
25 (Anomeric mixture)
R_1=R_3=$CONH_2$, R_2=NO_2

Chart 3

benzoyl)-D-*erythro*-pentofuranoside[8] by acetolysis. The fusion reaction of **17** with **2** gave a mixture of blocked nucleosides, which was subjected to the chromatographic separation on silica gel to give the α- and β-anomers of 1-glycosylpyrazole-3-carboxylate (**18**α, **18**β) and 1-glycosylpyrazole-5-carboxylate (**19**α, **19**β) in yield of 27.4, 20.0, 3.3, and 4.9%, respectively, as crystalline products except for **19**α. It may be noted, in this reaction, that the 3-substituted 1-glycosylpyrazoles (**18**α, **18**β) were formed as major products in accord with the cases of the ribonucleosides[1] and the arabinonucleosides (**5**α, **5**β) syntheses under similar conditions.

Treatment of **18**α, **18**β, **19**α, and **19**β with methanolic ammonia gave 1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-pyrazole-3-carboxamide (**22**α), its β-anomer (**22**β), 1-(2-deoxy-α-D-*erythro*-pentofuranosyl)pyrazole-5-carboxamide (**23**α), and its β-anomer (**23**β), respectively. The chemical shifts for the *H*-5 proton signals of **22**α and **22**β are in agreement with those of the arabinonucleosides **13**α and **13**β, and the chemical shifts for the *H*-3 protons of **23**α and **23**β are comparable with those for **14**α and 1-(β-D-ribofuranosyl)pyrazole-5-carboxamide.[1] Thus, **22**α and **22**β were established as 1-glycosylpyrazole-3-carboxamides, and **23**α and **23**β were as the corresponding 5-carboxamides, respectively. Inspection of the PMR spectra of **22**β and **23**β also revealed that the β-anomers are characterized by each triplet of their anomeric proton signals with a peak width of 12 Hz which is consistent with the β-configuration, and, a quartet with a peak width of 10.7 Hz was observed for the anomeric proton of **23**α. These data were consistent with those reported for 2'-deoxyribonucleosides by Robins and Robins[9], and Witkowski *et al.*[10]

The ultraviolet spectra of the 3-carboxamides (**13**α, **13**β, **22**α, and **22**β) and 5-carboxamides (**14**α, **23**α, and **23**β) showed a characteristic difference each other similar to that reported with respect to the corresponding D-ribofuranosyl derivatives.[1]

Similar fusion of **17** with diethyl pyrazole-3,5-dicarboxylate (**3**) afforded blocked nucleosides (**20**),

which, by treatment with methanolic ammonia, led to an anomeric mixture of 1-(2-deoxy-D-*erythro*-pentofuranosyl)pyrazole-3,5-dicarboxamides (**24**).

Further we similarly synthesized its 2'-deoxy analogue (**25**) as an anomeric mixture since 1-(β-D-ribofuranosyl)-4-nitropyrazole-3,5-dicarboxamide[1] was found cytotoxic.[11]

The downfield shifts of the anomeric proton signals of **24** and **25** were also observed.

Preliminary accounts for structure-activity relationships of the above nucleosides as antiviral agents have already been reported.[11]

Experimental

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

*1-O-Acetyl-2,3,5-tri-O-benzyl-D-arabinofuranose (**1**).* 2,3,5-Tri-O-benzyl-D-arabinofuranose (10.0 g, 23.8 mmol) was dissolved in anhydrous pyridine (50 ml), to which was added acetic anhydride (50 ml) under ice-cooling. The mixture was stirred at room temperature for 12 h. After removal of the solvent by evaporation, the resulting syrup was dissolved in ethyl acetate (10 ml) and chromatographed on a silica gel column (400 g, 5×100 cm, packed with benzene). Elution with 20 : 1 benzene-ethyl acetate afforded a syrup of **1**, 9.48 g (86.4%); PMR ($CDCl_3$) : δ 7.40 (s, 15H, Ar), 6.40 (br s, 1H, H-1'), 4.75—3.95 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.65 (d, 2H, H-5', 5''), 2.00 (s, 2.1H, CH_3), 1.95 (s, 0.9H, CH_3), *ca.* 21 : 9 mixture of α and β. Found: C, 72.49; H, 6.36%. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54%.

*Ethyl 1-(2,3,5-Tri-O-benzyl-β-D-arabinofuranosyl)pyrazole-3-carboxylate (**5β**), Its α-Anomer (**5α**), and Ethyl 1-(2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl)pyrazole-5-carboxylate (**6α**).* A mixture of ethyl pyrazole-3-carboxylate[5] (**2**, 550 mg, 3.93 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-arabinose **1**, 1.70 g, 3.68 mmol) was heated at 140 °C to a melt, to which bis(*p*-nitrophenyl) hydrogenphosphate (3 mg) was added, and the mixture was heated at 140 °C under reduced pressure for 8 min until the evolution of acetic acid ceased. The resulting gum was dissolved in ethyl acetate (5 ml), silica gel (2.5 g) was added, and the resulting suspension was evaporated to dryness. The residue was placed on a column of silica gel (110 g, 2.8×45 cm, packed with 1 : 1 hexane-diisopropyl ether) and eluted with the same solvent system. The effluent was fractionated into 11 mls.

Fraction Nos. 31—38 gave **6α**, a colorless syrup, 165 mg (8.3%). $[\alpha]_D^{25}$+55.3° (*c* 0.77, chloroform). PMR ($CDCl_3$): δ 7.79 (d, 1H, H-3), 7.40 (d, 15H, Ar), 7.10 (d, 1H, $J_{1',2'}$= 3.8 Hz, H-1'), 7.04 (d, 1H, H-4), 5.23 (dq, 1H, H-2'), 4.80—4.20 (m, 10H, CH_2-Ar, H-3', H-4', CH_2-ester), 3.72 (d, 2H, H-5',5''), 1.40 (t, 3H, CH_3-ester). Found: C, 70.85; H, 6.52; N, 4.88%. Calcd for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16%. Fraction Nos. 63—79 gave **5α**, a colorless syrup, 605 mg (30.4%); $[\alpha]_D^{25}$+35.0° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 7.80 (d, 1H, H-5), 7.40 (s, 15H, Ar), 6.90 (d, 1H, H-4), 6.18 (d, 1H, $J_{2',1'}$=2.2 Hz, H-1'), 4.80—4.18 (m, 11H, CH_2-Ar, H-2',H-3',N-4', CH_2-ester), 3.70 (d, 2H, H-5', 5''), 1.42 (t, 3H, CH_3-ester). Found: C, 70.53; H, 6.19; N, 4.83%. Calcd for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16%.

Fraction Nos. 87—102 gave **5β**, a colorless syrup, 957 mg (48.2%); $[\alpha]_D^{25}$+15.0° (*c* 0.50, chloroform). PMR ($CDCl_3$): δ 7.95 (d, 1H, H-5), 7.40 (s, 15H, Ar), 6.88 (d, 1H, H-4), 6.40 (d, 1H, $J_{1',2'}$=4.5 Hz, H-1'), 4.65—4.20 (m, 11H, CH_2-Ar, H-2', H-3', H-4', CH_2-ester), 3.75 (d, 2H, H-5', 5''), 1.38 (t, 3H, CH_3-ester). Found: C, 71.01; H, 6.33; N, 5.07%. Calcd for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16%.

*Diethyl 1-(2,3,5-Tri-O-benzyl-D-arabinofuranosyl)pyrazole-3,5-dicarboxylate (**7**).* By a method similar to that described above, diethyl pyrazole-3,5-dicarboxylate (**3**) (152 mg, 0.715 mmol) was allowed to react with **1** (330 mg, 0.715 mmol) to afford a gum, which was dissolved in ethyl acetate and chromatographed on a column of silica gel (20 g, 1×20 cm, packed with 20 : 1 benzene-ethyl acetate). Elution with the same solvent afforded **7** as a syrup of an anomeric mixture, 334 mg (76%); PMR ($CDCl_3$) : δ 7.38 (d, 16H, Ar, H-4), 7.10 (d, 0.2H, $J_{1',2'}$=5.0 Hz, H-1') 7.08 (d, 0.8H, $J_{1',2'}$=3.7 Hz, H-1'), 5.25 (dq, 1H, H-2'), 4.75—4.17 (m, 12H, CH_2-Ar, CH_2-ester, H-3', N-4'), 3.68 (d, 2H, H-5', 5''), 1.34 (tt, 6H, CH_3-ester). Found: C, 68.10; H, 6.12; N, 4.27%. Calcd for $C_{35}H_{38}O_8N_2$: C, 68.39; H, 6.23; N, 4.56%.

*Diethyl 1-(2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl)-4-nitropyrazole-3,5-dicarboxylate (**8α**) and Its β-Amoner (**8β**).* By a method similar to that described above, diethyl 4-nitropyrazole 3,5-dicarboxylate[1] (**4**) (355 mg, 1.30 mmol) was allowed to react with **1** (600 mg, 1.30 mmol) to give a gum, which was dissolved in ethyl acetate (1 ml), placed on a column of silica gel (70 g, 2.5×40 cm, packed with 2 : 1 hexane-diisopropyl ether) and eluted successively with 2 : 1 (80 ml) and 1 : 1 hexane-diisopropyl ether. The effluent was fractionated into 7.5 mls.

Fraction Nos. 17—26 gave **8α**, a colorless oil, 464 mg (54.2%); $[\alpha]_D^{25}$+129.5° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 7.41 (d, 15H, Ar), 6.69 (d, 1H, $J_{1',2'}$=3.4 Hz, H-1'), 5.19 (dt, 1H, H-2'), 4.72—4.25 (m, 12H, CH_2-Ar, CH_2-ester, H-3', H-4'), 3.70 (d, 2H, H-5',5''), 1.33 (tt, 6H, CH_3-ester). Found: C, 64.01; H, 5.81; N, 6.11%. Calcd for $C_{35}H_{37}O_{10}N_3$: C, 63.72; H, 5.65; N, 6.37%.

Fraction Nos. 32—41 gave **8β**, a colorless oil, 124mg (14.5%); $[\alpha]_D^{25}$−75.0° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 7.40 (d, 15H, Ar), 7.31 (d, 1H, $J_{1',2'}$=5.8 Hz, H-1'), 4.7—3.85 (m, 15H, CH_2-Ar, CH_2-ester, H-2', H-3', H-4', H-5',5''), 1.39 (tt, 6H, CH_3-ester). Found: C, 63.92; H, 5.62; N, 6.19%. 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-α-D-arabinofuranosyl)pyrazole-3-carboxamide (**9α**).* A solution of **5α** (550 mg, 1.01 mmol) in absolute methanol (15 ml) saturated with ammonia at 0 °C was kept at room temperature for 24 h and evaporated. The residual syrup was washed with hexane and dried at 80 °C *in vacuo* for 10 h to give a colorless syrup of **9α**, 415 mg (80%); $[\alpha]_D^{25}$+39.6° (*c* 1.70, chloroform). PMR ($CDCl_3$): δ 7.71 (d, 1H, H-5), 7.38 (d, 15H, Ar), 7.20 (d, 1H, $J_{1',2'}$= 4.0 Hz, H-1'), 6.97 (d, 1H, H-4), 5.13 (dq, 1H, H-2'), 4.8—4.16 (m, 8H, CH_2-Ar, H-3', H-4'), 3.63 (m, 2H, H-5, 5''). Found: C, 70.14; H, 6.15; N, 8.11%. 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-arabinofuranosyl)pyrazole-3-carboxamide (**9β**).* By the same procedure as that for **9α**, **5β** (800 mg, 1.47 mmol) gave **9β**, 635 mg (84%), as a colorless syrup; $[\alpha]_D^{25}$+19.4° (*c* 1.0 chloroform). PMR ($CDCl_3$): δ 7.89 (d, 1H, H-5), 7.42 (m, 15H, Ar), 6.91 (d, 1H, H-4), 6.50 (br d, 2H, $CONH_2$), 6.22 (d, 1H, $J_{1',2'}$=4.5 Hz, H-1'), 4.7—4.2 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.77 (d, 2H, H-5',5''). Found: C, 70.14; H, 6.15; N, 8.07%. 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-arabinofuranosyl)pyrazole-5-carboxamide (**10α**). By a procedure similar to that for **9α**, **6α** (150 mg, 0.28 mmol) gave **10α**, 118 mg (82%), as a colorless syrup; $[\alpha]_D^{25}$ +25.0° (*c* 0.50, chloroform). PMR ($CDCl_3$): δ 7.73 (d, 1H, H-3), 7.40 (d, 15H, Ar), 6.95 (d, 1H, H-4), 6.60 (br d, 2H, $CONH_2$), 6.03 (d, 1H, $J_{1',2'}$=2.8 Hz, H-1'), 4.80 (t, 1H, H-2'), 4.60 (s, 6H, CH_2-Ar), 4.80 (m, 2H, H-3', H-4'), 3.71 (d, 2H, H-5',5''). Found: C, 69.94; H, 6.11; N, 8.13%. 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-arabinofuranosyl)pyrazole-3,5-dicarboxamide (**11α**) *and Its β-Anomer* (**11β**). A solution of **7** (330 mg, 0.537 mmol) in absolute methanol (30 ml) saturated with ammonia at 0 °C was kept at room temperature for 12 h. After removal of methoanol by evaporation, the resulting syrup was dissolved in acetone and chromatographed on a column of silica gel (15 g, 1×10 cm, packed with 6 : 1 chloroform-acetone) with the same solvent system. The effluent was fractionated into 3 mls.

Fraction Nos. 8—10 gave colorless crystals of **11β**, 46 mg (15.4%); mp 200—202 °C. $[\alpha]_D^{25}$ −89.1° (*c* 1.0, dioxane). PMR (CD_3OD): δ 7.50 (m, 16H, Ar, H-4), 7.28 (d, 1H, $J_{1',2'}$=4.9 Hz, H-1'), 4.85—4.20 (m, 9H, CH_2-Ar, H-2', H-3', H-4'), 3.70 (d, 2H, H-5', 5''). Found: C, 66.95; H, 6.01; N, 9.80%. Calcd for $C_{31}H_{32}O_6N_4$: C, 66.89; H, 5.80; N, 10.07%.

Fraction Nos. 13—18 gave a colorless solid of **11α**, 221 mg (74%); $[\alpha]_D^{25}$ +72.8° (*c* 1.0, dioxane). PMR (CD_3OD): δ 7.48 (d, 16H, Ar, H-4), 7.22 (d, 1H, $J_{1',2'}$=3.2 Hz, H-1'), 5.03 (dq, 1H, H-2'), 4.75—4.20 (m, 8H, CH_2-Ar, H-3', H-4'), 3.72 (d, 2H, H-5' H-5''). Found: C, 67.02; H, 5.93; N, 10.04%. Calcd for $C_{31}H_{32}O_6N_4$: C, 66.89; H, 5.80; N, 10.07%.

1-(2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl)-4-nitropyrazole-3,5-dicarboxamide (**12α**). By a method similar to that described above, **8α** (440 mg 0.668 mmol) gave an oil, which was chromatographed on silica gel column (20 g, 1×15 cm, packed with 3 : 1 benzene-ethyl acetate). Evaporation of the portion containing the product gave a colorless syrup of **12α**, 354 mg (88%); $[\alpha]_D^{25}$ +101.3° (*c* 1.0, methanol). PMR (CD_3OD): δ 7.40 (s, 15H, Ar), 6.29 (d, 1H, $J_{1',2'}$=3.2 Hz, H-1'), 5.10 (dt, 1H, H-2'), 4.75—4.00 (m, 8H, CH_2-Ar, H-3', H-4'), 3.69 (d, 2H, H-5',5''). Found: C, 62.06; H, 5.37; N, 11.68%. Calcd for $C_{31}H_{31}O_8N_5$: C, 61.89; H, 5.19; N, 11.64%.

1-(2,3,5-Tri-O-benzyl-β-D-arabinofuranosyl)-4-nitropyrazole-3,5-dicarboxamide (**12β**). By a procedure similar to that described above, **8β** (110 mg, 0.167 mmol) gave **12β**. Its recrystallization from methanol afforded its pure sample (79 mg, 78.5%); mp 188—200 °C. $[\alpha]_D^{25}$ −113° (*c* 0.83, dioxane). PMR (CD_3OD): δ 7.40 (s, 15H, Ar), 6.34 (d, 1H, $J_{1',2'}$=5.2 Hz, H-1'), 3.70 (d, 2H, H-5',5''). Found: C, 62.17; H, 5.39; N, 11.42%. Calcd for $C_{31}H_{31}O_8N_5$: C, 61.89; H, 5.19; N, 11.64%.

1-(α-D-Arabinofuranosyl)pyrazole-3-carboxamide (**13α**). A solution of **9α** (402 mg, 0.78 mmol) in methanol (40 ml) was hydrogenated in the presence of palladium black at 3.5 atm for 24 h. After removal of the catalyst, the methanol was evaporated and the residue was chromatographed on a silica gel column with 4 : 4 : 2 : 3 1-butanol-ethanol-chloroform-17% aqueous ammonia. Evaporation of the portion containing the product gave a colorless glass of **13α** (129 mg, 68%); $[\alpha]_D^{25}$ +30.6° (*c* 0.41, water). PMR (DMSO-d_6): δ 8.17(d, 1H, H-5), 7.50 (br d, 2H, $CONH_2$), 6.84 (d, 1H, H-4), 5.92 (br s, 1H, OH), 5.82 (d, 1H, $J_{1',2'}$=4.7 Hz, H-1'), 5.60 (br s, 1H, OH), 4.85 (br d, 1H, OH), 4.65 (t, 1H, H-2'), 4.30—3.83 (m, H, H-3', H-4'), 3.70 (m, 2H, H-5',5''). UV: λ_{max}^{water} 231 (ε 12800), λ_{max}^{pH1} 198 (ε 13000), λ_{max}^{pH13} 219 nm (ε 11800). Found: C, 42.76; H, 5.51; N, 16.53%. Calcd for $C_9H_{13}O_5N_3$ 1/2H_2O: C, 42.82; H, 5.58; N, 16.65%.

1-(β-D-Arabinofuranosyl)pyrazole-3-carboxamide (**13β**). By a procedure similar to that described above, **9β** (560 mg, 1.09 mmol) gave 13β. Its recrystallization from ethanol and benzene afforded its pure sample (198 mg, 74.6%); mp 126—127.5 °C. $[\alpha]_D^{25}$ −22.4° (*c* 0.67, water). PMR (DMSO-d_6): δ 8.04 (d, 1H, H-5), 7.40 (br d, 2H, $CONH_2$), 6.80 (d, 1H, H-4), 6.06 (d, 1H, $J_{1',2'}$=5.2 Hz, H-1'), 5.50 (d, 2H, OH), 5.02 (t, 1H, OH), 4.25 (m, 2H, H-2', H-3'), 3.75 (m, 3H, H-4', H-5',5''). UV: λ_{max}^{water} 213 (ε 11500), λ_{max}^{pH1} 198 (ε 12000), λ_{max}^{pH13} 219 nm (ε 11000). Found: C, 44.16; H, 5.29; N, 17.13%. Calcd for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28%.

1-(α-D-Arabinofuranosyl)pyrazole-5-carboxamide (**14α**). By a procedure similar to that described above followed by recrystallization from ethanol, **10α** (108 mg, 0.21 mmol) gave crystals of **14α**, 41.2 mg (78%); mp 189—191 °C. $[\alpha]_D^{25}$ +64.0° (*c* 0.88, water). PMR (DMSO-d_6): δ 7.85 (br d, 2H, $CONH_2$), 7.75 (d, 1H, H-3), 7.06 (d, 1H, H-4), 6.89 (d, 1H, $J_{1',2'}$=4.6 Hz, H-1'), 5.58 (q, 2H, OH), 4.80 (m, 2H, OH, H-2'), 4.00 (m, 2H, H-3', H-4'), 3.60 (m, 2H, H-5',5''). UV: λ_{max}^{water} 219 (ε 13700), λ_{max}^{pH1} 221 (ε 10800), 198 (ε 14000), λ_{max}^{pH13} 220 nm (ε 10100). Found: C, 44.42; H, 5.38; N, 17.07%. Calcd for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28%.

1-(α-D-Arabinofuranosyl)pyrazole-3,5-dicarboxamide (**15α**). A solution of **11α** (210 mg, 0.377 mmol) in 21 ml methanol and dioxane (1 : 1) was hydrogenated with palladium black and hydrogen for 48 h to give a solid, which was recrystallized from methanol and benzene to give crystals of **15α** (63 mg, 58%); mp 237—239 °C. $[\alpha]_D^{25}$ +77.4° (*c* 0.5, water). PMR (DMSO-d_6): δ 7.65 (br d, 2H, $CONH_2$), 7.45 (s, 1H, H-4), 6.90 (d, 1H, $J_{1',2'}$=4.5 Hz, H-1',) 5.70 (d, 1H, OH), 6.40 (d, 1H, OH), 4.85 (m, 2H, OH, H-2'), 4.10 (m, 2H, H-3', H-4'), 3.65 (m, 2H, H-5',5''). UV: λ_{max}^{water} 205 (ε 12000), λ_{max}^{pH1} 207 (ε 10600), λ_{max}^{pH13} 219 nm (ε 8900). Found: C, 42.06; H, 5.00; N, 19.35%. Calcd for $C_{10}H_{14}O_6N_4$: C, 41.96; H, 4.93; N, 19.58%.

4-Amino-1-(α-D-arabinofuranosyl)pyrazole-3,5-dicarboxamide (**16α**). A solution of **12α** (300 mg, 0.499 mmol) in methanol (8 ml) was hydrogenated in the same way as described for **13α**. The resulting solid was recrystallized from methanol and benzene to give **16α**, 91.5 mg (61%); mp 208—209 °C. $[\alpha]_D^{25}$ +108.9° (*c* 0.8, water). PMR (DMSO-d_6): δ 7.48 (br s, 4H, $CONH_2$), 6.41 (d, 1H, $J_{1',2'}$= 4.0 Hz, H-1'), 5.65 (d, 1H, OH), 5.31 (br s, 3H, NH_2, OH), 4.85 (m, 2H, OH, H-2'), 3.97 (br d, 2H, H-3', H-4'), 3.60 (m, 2H, H-5',5''). UV: λ_{max}^{water} 204 nm (ε 11000), λ_{max}^{pH1} 207 (ε 98000), 304 (ε 2900), λ_{max}^{pH13} 219 (ε 18000), 302 nm (ε 6800). Found: C, 39.45; H, 4.99; N, 22.98%. Calcd for $C_{10}H_{15}O_6N_5$: C, 39.45; H, 5.02; N, 23.25%.

1-O-Acetyl-2-deoxy-3,5-di-O-(p-nitrobenzoyl)-D-erythro-pentofuranose (**17**). Methyl 2-deoxy-3,5-di-O-(*p*-nitorobenzoyl)-D-*erythro*-pentoside (4.5 g, 10.1 mmol) was dissolved in a mixture of glacial acetic acid (5 ml) and acetic anhydride (10 ml) under cooling at −15 °C, and concentrated sulfuric acid (0.3 ml) was added with stirring, after which the stirring was further continued for 30 min at −15 °C. The mixture was poured onto ice-water (300 ml) and extracted with chloroform (100 ml). The organic layer was washed successively with water (100 ml×2), saturated aqueous sodium hydrogencarbonate solution, and water, and dried over anhydrous sodium sulfate. Evaporation under reduced

pressure gave a syrup, which was dissolved in 20 : 1 benzene-ethyl acetate and chromatographed on a silica gel column (80 g, 2.5×50 cm, packed with the same solvent system). Elution with the same solvent system afforded a pale-yellow glass of **17**, 4.2 g (88%); PMR ($CDCl_3$): δ 8.32 (s, 8H, Ar), 6.60 (m, 1H, H-1), 5.70 (m, 1H, H-3), 4.70 (br s, 3H H-4, H-5,5′), 2.52 (m, 2H, H-2,2′), 2.13 (d, 3H, CH_3). Found: C, 52.89; H, 3.70; N, 5.68%. Calcd for $C_{21}H_{18}O_{11}N_2$: C, 53.17; H, 3.82; N, 5.91%.

*Ethyl 1-(2-Deoxy-3,5-di-*O*-p-nitrobenzoyl-β-*D*-*erythro*-pentofuranosyl)pyrazole-3-carboxylate (**18β**), Its α-Amoner (**18α**), Ethyl 1-(2-Deoxy-3,5-di-*O*-p-nitrobenzoyl-β-*D*-erythro-pentofuranosyl)pyrazole-5-carboxylate (**19β**) and Its α-Anomer (**19α**).* To a mixture of ethyl pyrazole-3-carboxylate (**2**, 539 mg, 4.24 mmol) and 1-*O*-acetyl-2-deoxy-3,5-di-*O*-*p*-nitorobenzoyl-D-*erythro*-pentofuranose (**17**, 1.6 g, 3.38 mmol) heated at 136 °C to a melt, a catalytic amount of bis(*p*-nitrophenyl) hydrogenphosphate (1 mg) was added and the mixture was kept at 136 °C for 3 min under reduced pressure until the evolution of acetic acid ceased. The resulting mixture was triturated with ethyl acetate (5 ml) and chloroform (20 ml). The chloroform solution was evaporated to dryness and the solid was recrystallized from ethyl acetate to give **18α**, 420 mg (22.6%). The mother liquor and the above ethyl acetate layer were combined, and concetrated to about 2 ml. This was chromatographed on a silica gel column (90 g, 2.5×50 cm, packed with 20 : 1 benzene-ethyl acetate) with the same solvent system. The effluent was fractionated into 9 mls.

Fraction Nos. 34—38 gave colorless crystals of **19β**. Recrystallization from benzene and hexane, 94 mg (4.9%); mp 145.5—146.5 °C. $[\alpha]_D^{25}$ −48.0° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 8.34 (d, 8H, Ar), 7.68 (d, 1H, H-3), 7.41 (q, 1H, H-1′), 6.98 (d, 1H, H-4), 6.00 (br t, 1H, H-3′), 4.86 (br s, 3H, H-4′, H-5′,5″), 4.42 (q, 2H, CH_2–ester), 3.75—2.40 (m, 2H, H-2′,2″), 1.40 (t, 3H, CH_3–ester). Found: C, 54.00; H, 4.20; N, 10.16%. Calcd for $C_{25}H_{22}O_{11}N_4$: C, 54.15; H, 4.00; N, 10.10%.

Fraction Nos. 39—42 gave a mixture of **19β** and **19α**, 25.9 mg (1.4%), *ca.* 5 : 8 mixture of **19β** and **19α**, by PMR.

Fraction Nos. 41—44 gave **19α**, a colorless syrup, 62 mg (3.3%); $[\alpha]_D^{25}$ +29.5° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 8.35 (s, 8H, Ar), 7.69 (d, 1H, H-3), 7.32 (q, 1H, H-1′), 7.00 (d, 1H, H-4), 5.70 (q, 1H, H-3′), 5.04—4.60 (m, 3H, H-4′, H-5′,5″), 4.43 (q, 2H, CH_2–ester), 3.11 (t, 2H, H-2′,2″), 1.40 (t, 3H, CH_3–ester). Found: C, 54.73; H, 4.01; N, 9.90%. Calcd for $C_{25}H_{22}O_{11}N_4$: C, 54.15; H, 4.00; N, 10.00%.

Fraction Nos. 64—73 gave colorless crystals of **18β**. Recrystallization of **18β** from ethyl acetate gave a pure sample, 372 mg (20.0%); mp 138—140 °C. $[\alpha]_D^{25}$ −22.5° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 8.38 (s, 8H, Ar), 7.82 (d, 1H, H-5), 6.90 (d, 1H, H-4), 6.43 (t, 1H, H-1′), 5.98 (br t, 1H, H-3′), 4.72 (br s, 3H, H-4′, H-5′,5″), 4.45 (q, 2H, CH_2–ester), 3.72—2.65 (m, 2H, H-2′,2″), 1.39 (t, 3H, CH_3–ester). Found: C, 54.39; H, 4.22; N, 9.95%. Calcd for $C_{25}H_{22}O_{11}N_4$: C, 54.15; H, 4.00; N, 10.10%.

Fraction Nos. 74—77 gave a mixture of **18β** and **18α**, 120 mg (6.7%), *ca.* 1 : 3 mixture of **18β** and **18α**, by PMR.

Fraction Nos. 78—95 gave crystals of **18α**. Recrystallization of **18α** from ethyl acetate gave a pure sample, 90.9 mg (4.8%); mp 183.5—184.5 °C. $[\alpha]_D^{25}$ −6.0° (*c* 1.0, chloroform). PMR ($CDCl_3$): δ 8.25 (m, 8H, Ar), 7.90 (d, 1H, H-5), 6.97 (d, 1H, H-4), 6.45 (q, 1H, H-1′), 5.77 (m, 1H, H-3′), 4.75 (m, 3H, H-4′, H-5′,5″), 4.48 (q, 2H, CH_2–ester), 3.57—2.62 (m, 2H, H-2′,2″), 1.40 (t, 3H, CH_3–ester). Found: C, 54.28; H, 4.03; N, 10.14%. Calcd for $C_{25}H_{22}O_{11}N_4$: C, 54.15; H, 4.00 N, 10.10%.

*Diethyl 1-(2-Deoxy-3,5-di-*O*-p-nitrobenzoyl-*D*-erythro-pentofuranosyl)pyrazole-3,5-dicarboxamide (**20**).* The reaction of diethyl pyrazole-3,5-dicarboxylate (**3**, 630 mg, 2.96 mmol) with **17** (1.4 g, 2.96 mmol) was carried out in a manner similar to that described above. To a solution of the resulting mixture in acetone (5 ml) silica gel (2.2 g) was added and the mixture was evaporated. The residue was chromatographed on a column of silica gel (100 g) packed with 20 : 1 benzene-ethyl acetate. Elution with benzene-ethyl acetate (10 : 1) afforded **20** as an anomeric mixture, 1.18 g (64%); PMR ($CDCl_3$): δ 8.41 (s, 8H, Ar), 7.50 (m, 2H, H-1′, H-4), 6.2—5.5 (m, 1H, H-3′), 4.75 (m, 3H, H-4′, H-5′,5″), 4.50 (q, 4H, CH_2–ester), 3.6—2.1 (m, 2H, H-2′,2″), 1.40 (t, 6H, CH_3–ester). Found: C, 53.39; H, 4.26; N, 9.01%. Calcd for $C_{28}H_{26}O_{13}N_4$: C, 53.67; H, 4.18; N, 8.94%.

*Diethyl 1-(2-Deoxy-3,5-di-*O*-p-nitrobenzoyl-*D*-erythro-pentofuranosyl)-4-nitropyrazole-3,5-dicarboxylate (**21**).* The reaction of diethyl 4-nitropyrazole-3,5-dicarboxylate (**4**) (590 mg, 2.39 mmol) with **17** (1.13 g, 2.39 mmol) was carried out in the similar manner as described above. The resulting mixture was dissolved in ethyl acetate (5 ml), silica gel (1.8 g) was added and the mixture was evaporated to dryness. The residue was placed on a column of silica gel (80 g, 3×60 cm, packed with 1 : 1 hexane-diisopropyl ether) and eluted by the same solvent system. The effluent was fractionated into 8 mls. Fraction Nos. 21—57 gave a colorless syrup of **21**, 664 mg (42%), as an anomeric mixture; PMR ($CDCl_3$): δ 8.40 (s, 8H, Ar), 7.30 (m, 1H, H-1′), 6.2—5.8 (m, 1H, H-3′), 4.75 (m, 3H, H-4′, H-5′,5″), 4.52 (qq, 4H, CH_2–ester), 3.5—2.5 (m, 2H, H-2′, 2″), 1.45 (tt, 6H, CH_3–ester). Found: C, 49.89; H, 3.60; N, 10.18%. Calcd for $C_{28}H_{25}O_{15}N_5$: C, 50.08; H, 3.75; N, 10.43%.

*1-(2-Deoxy-β-*D*-erythro-pentofuranosyl)pyrazole-3-carboxamide (**22β**)* A solution of **18β** (380 mg, 0.686 mmol) in absolute methanol (10 ml) saturated with ammonia at 0 °C was kept at room temperature for 3 days and evaporated. The residual oil was dissolved in water (10 ml) and the solution was extracted with ethyl acetate (3 ml×4). The aqueous layer was evaporated and the residue was chromatographed on a silica gel column (4 g, 0.8×20 cm) packed with 4 : 1 chloroform-methanol. Elution with the same solvent system afforded a glass of **22β**, 129 mg (83%); $[\alpha]_D^{25}$ −17.5° (*c* 1.0, methanol). PMR (CD_3OD): δ 8.09 (d, 1H, H-5), 6.92 (d, 1H, H-4), 6.35 (t, 1H, H-1′), 4.68 (m, 1H, H-3′), 4.11 (m, 1H, H-4′), 3.78 (m, 2H, H-5′,5″), 2.67 (m, 2H, H-2′,2″). UV: λ_{max}^{water} 213 (ε 11900), λ_{max}^{pH1} 198 (ε 12000), λ_{max}^{pH13} 218 nm (ε 11500). Found: C, 47.27; H, 5.90; N, 18.20%. Calcd for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.77; N, 18.49%.

*1-(2-Deoxy-α-*D*-erythro-pentofuranosyl)pyrazole-3-carboxamide (**22α**).* By a procedure similar to that described above, **18α** (580 mg, 1.05 mmol) gave **22α**, 188 mg (79%), as a colorless syrup; $[\alpha]_D^{25}$ +32.5° (*c* 1.0, methanol). PMR (CD_3OD): δ 8.17 (d, 1H, H-5), 6.96 (d, 1H, H-4), 6.32 (q, 1H, H-1′), 4.39 (m, 2H, H-3′, H-4′), 3.72 (m, 2H, H-5′,5″), 3.12—2.34 (m, 2H, H-2′,2″). UV: λ_{max}^{water} 212 nm (ε 12800), λ_{max}^{pH1} 198 nm (ε 12500), λ_{max}^{pH13} 218 nm (ε 11800). Found: 47.26; H, 5.95; N, 18.19%. Calcd for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.77; N, 18.49%.

*1-(2-Deoxy-β-*D*-erythro-pentofuranosyl)pyrazole-5-carboxamide (**23β**).* By a procedure similar to that described above, **19β** (102 mg, 0.546 mmol) gave **23β**, a colorless glass, 36 mg (82%); $[\alpha]_D^{25}$ −69.5° (*c* 1.0, methanol). PMR (CD_3OD): δ 7.82 (d, 1H, H-3) 7.33 (t, 1H, H-1′), 7.03 (d, 1H, H-4), 4.7—4.18 (m, 2H, H-3′, H-4′), 3.90 (m, 2H, H-5′, 5″), 3.23—2.30 (m, 2H, H-2′,2″). UV: λ_{max}^{water} 220 (ε 12800), λ_{max}^{pH1} 198 (ε 13000), λ_{max}^{pH13} 220 nm (ε 11000).

Found: C, 47.45; H, 5.80; N, 18.64%. Calcd for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.77; N, 18.49%.

*1-(2-Deoxy-α-*D*-erythro-pentofuranosyl)pyrazole-5-carboxamide (**23α**).* By a procedure similar to that described above, **19α** (68 mg, 0.123 mmol) gave **23α**, 21.2 mg (76%), as a colorless glass; $[\alpha]_D^{25}$ +18.3° (*c* 1.0, methanol). PMR (CD_3OD): δ 7.80 (d, 1H, H-3), 7.29 (q, 1H, H-1′), 7.00 (d, 1H, H-4), 4.7—4.2 (m, 2H, H-3′, H-4′), 3.85 (m, 2H, H-5′,5″), 3.20—2.25 (m, 2H, H-2′,2″). UV: λ_{max}^{water} 219 (ε 8300), λ_{max}^{pH1} 200 (ε 8100), λ_{max}^{pH13} 220 nm (ε 9000). Found: C, 47.38; H, 5.85; N, 18.60%. Calcd for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.77; N, 18.49%.

*1-(2-Deoxy-*D*-erythro-pentofuranosyl)pyrazole-3,5-dicarboxamide (**24**).* A solution of **20** (800 mg, 1.28 mmol) in absolute methanol (120 ml) saturated with ammonia at 0 °C was kept at room temperatuer for 12 h, and then heated at 90 °C for 30 h in a sealed tube. The solution was evaporated and the resultant syrup was chromatographed on a silica gel column (40 g, 2×30 cm, packed with 4 : 1 chloroform–methanol): Elution by the same solvent system afforded a syrup of **24**, 218 mg (63%); PMR (DMSO-d_6): δ 7.30 (d, 1H, H-4), 7.00 (tq, 1H, H-1′), 4.8—4.2 (m, 2H, H-3′, H-4′), 3.80 (m, 2H, H-5′,5″), 2.80 (m, 2H, H-2′,2″). Found: C, 44.19; H, 5.18; N, 20.61%. Calcd for $C_{10}H_{14}O_5N_4$: C, 44.44; H, 5.22; N, 20.73%.

*1-(2-Deoxy-*D*-erythro-pentofuranosyl)-4-nitropyrazole-3,5-dicarboxamide (**25**).* By a procedure similar to that described above, **21** (600 mg, 0.91 mmol) gave **25** as an anomeric mixture, 179 mg (61%); PMR (CD_3OD): δ 6.40 (tq, 1H, H-1′), 4.40 (m, 2H, H-3′, H-4′), 3.78 (m, 2H, H-5′,5″), 2.80 (m, 2H, H-2′,2″). Found: C, 38.01; H, 4.00; N, 22.09%. Calcd for $C_{10}H_{13}O_7N_5$: C, 38.10; H, 4.16;N, 22.22%.

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