A Facile Synthesis of Certain 4- and 4,5-Disubstituted 1-β-D-Ribofuranosylpyrazoles

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A number of pyrazole ribonucleosides, structurally related to AICA riboside and ribavirin have been prepared and evaluated for their biological activity *in vitro*. Deisopropylidenation of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**6**) with aqueous trifluoroacetic acid gave 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**7**). Conventional transformation of the carbonitrile function of **7** gave the AICA riboside congener (**2**) and related 5-amino-1-(β-D-ribofuranosyl)-pyrazoles (**8-10**). Acetylation of **7** at low temperature gave the versatile intermediate 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**15**). Non-aqueous diazotization of **15** with isoamylnitrite in dibromomethane or diiodomethane gave the corresponding C_5-bromo **13** and C_5-iodo **16** derivatives. Compounds **13** and **16** were subsequently transformed into 5-bromo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**11**) and the 5-iodo analog **25**. However, a similar nonaqueous diazotization of **15** in dichloromethane afforded the deaminated product 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**22**). Treatment of **22** with ammonium hydroxide/hydrogen peroxide gave the ribavirin congener 1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**18**). Similar treatment of **22** with hydrogen sulfide in pyridine or hydroxylamine in ethanol gave the 4-thiocarboxamide **19** and 4-carboxamidoxime **20** derivatives, respectively. Catalytic hydrogenation of **20** afforded 1-(β-D-ribofuranosyl)pyrazole-4-carboxamidine (**21**). These pyrazole nucleosides are devoid of any significant antiviral or antitumor activity *in vitro*.

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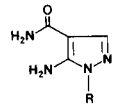
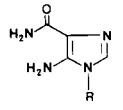
3(5)-Aminopyrazole-4-carboxamide (**1**) [1] is a ring isomer of the normal metabolite 5-aminoimidazole-4-carboxamide (AICA, **3**) and differs from it only by the position of the nitrogen atoms in the heterocyclic ring. The corresponding β-D-ribonucleoside **2** is a structural analog of AICA-riboside (5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide, **4**), which is the key intermediate in the *de novo* purine biosynthetic pathway [2]. Both **1** and **2** exhibit significant biological activity [3]. Their inhibitory effects on several enzymes has been investigated as well [4-6]. It has been found that 3(5)-aminopyrazole-4-carboxamide (**1**) enhances the immunogenicity of L1210, 6C3HED leukemia an AKR spontaneous lymphoma [7]. However, 3(5)-aminopyrazole-4-carbonitrile (**5**) [1], the precursor for **1**, was found to exhibit plaque reduction and inhibition of the cytopathic effect of mengovirus (an RNA virus) *in vitro* by suppression of the virus multiplication [8,9]. Furthermore, 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidine (**10**), prepared by the ring-opening of 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine [10] was found to be quite cytotoxic, having an ED_{50} value of 1.9 μMoles/l.

Although several pyrazole nucleosides in which the sugar is attached to a ring nitrogen have been reported [10-14], the pyrazole ribonucleosides structurally related to the broad spectrum antiviral agents ribavirin [15] and pyrazofurin [16] are very sparse. Moreover, pyrazolecarboxamide nucleosides with a halogen substituent at C-5 position have not yet been reported. The synthesis of these and related substituted 1-β-D-ribofuranosylpyrazoles is the subject of the present study.

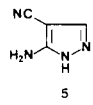
The key starting material 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**6**) was prepared as reported by Townsend and co-workers [17]. Although deisopropylidenation of **6** by Amberlite IR-120 (H^+ form) is reported [18] to give 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**7**) in a 76% yield, use of aqueous trifluoroacetic acid was found to be much more convenient, which provided a 92% yield of the desired **7** as the crystalline material. Oxidative hydrolysis of **7** by the treatment with ammonium hydroxide in the presence of hydrogen peroxide gave the AICA riboside analog 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**2**) in a 78% yield. The preparation of **2** has been reported by the pyrimidine ring fission of allopurinol ribonucleoside [11], as well as by the catalytic hydrogenation (Raney nickel) of 5-(3,3-dimethyl-1-triazeno)-1-(β-D-ribofuranosyl)-pyrazole-4-carboxamide [19]. However, the preparation of **2** by the ring opening of allopurinol ribonucleoside by aqueous sodium hydroxide at elevated temperature is inconvenient and sometimes not reproducible. Similarly, the glycosylation of the trimethylsilyl 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide, and separation of the glycosylated products is cumbersome [19] and provides



1, R = H
2, R = β-D-ribofuranosyl



3, R = H (AICA)
4, R = β-D-ribofuranosyl (AICA riboside)



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poor overall yield of the desired **2**. The presently described procedure for the preparation of **2** is rather straightforward and suitable for large-scale synthesis.

Treatment of **7** with nucleophiles such as hydrogen sulfide in dry pyridine, and hydroxylamine in absolute ethanol furnished 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-thiocarboxamide (**8**) and 5-amino-1-(β-D-ribofuranosyl)-pyrazole-4-carboxamidoxime (**9**), respectively. It was found that thiation of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**6**) with hydrogen sulfide in dry pyridine resulted in the formation of a single major product, which on deisopropylidenation with trifluoroacetic acid afforded **8** in a 87% yield. Direct thiation of **7**, however, resulted in an intractable reaction mixture from which the isolation of the desired nucleoside **8** was found to be difficult. It is of particular interest that Schmidt and co-workers have reported [18] the synthesis of 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-4-thiocarboxamide which was isolated in an 9.6% yield. Catalytic reduction of **9** in the presence of Raney nickel gave 5-amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidine (**10**), which was isolated as the monohydrochloride salt.

In view of the potent antiviral activity of certain C-5 halogen substituted 1-β-D-ribofuranosylimidazole-4-carboxamides [20], we undertook the synthesis of the corresponding pyrazole nucleoside congeners. Acetylation of **7** with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) at -25° ± 3° gave 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**15**) as crystalline material in a 63% yield. A nonaqueous diazotization of **15** with isoamylnitrite in dibromomethane at 60°, according to the general procedure of Nair and Richardson [21] and as modified by Ueda *et al.* [22,23], gave 5-bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**13**) in a 61% yield. Deacetylation of **13** with methanolic ammonium hydroxide at 0-4° afforded 5-bromo-1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**14**) in excellent yield. A similar nonaqueous diazotization of **15** with isoamylnitrite in diiodomethane (in the absence of iodine or cuprous iodide) gave 5-iodo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**16**) in almost quantitative yield, which on subsequent deacetylation with methanolic ammonium hydroxide at 0° furnished 5-iodo-1-(β-D-ribofuranosyl)-pyrazole-4-carbonitrile (**17**) in a 93% yield. Our attempts to prepare **13** and **16** *via* aqueous diazotization of **15** following the previously reported procedure [20] were unsuccessful. When the nucleoside **13** was treated with methanolic ammonium hydroxide in the presence of hydrogen peroxide at room temperature for 18 hours, 5-bromo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**11**) was formed, which was isolated in excellent yield. Reaction of **13** with hydroxylamine in ethanol at reflux temperature, followed by the treatment of the reaction product with methanolic ammonium hydroxide at room temperature gave 5-bromo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidoxime (**12**). In a similar manner, treatment of the protected nucleoside **16** with ammonium hydroxide/hydrogen peroxide furnished a 87% yield of 5-iodo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**25**), whereas the deprotected **17** with hydroxylamine in ethanol at reflux temperature gave 5-iodo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidoxime (**26**). In an attempt to prepare the corresponding thiocarboxamide derivative, **25** was acetylated with acetic anhydride in the presence of DMAP to obtain 5-iodo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxamide (**24**), which was then treated with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] [24]. A clean reaction was observed and a crystalline nucleoside material was isolated in 65% yield. This product was found to be identical with **16**, prepared unambiguously as described above. Thus, it seems to us an interesting procedure to convert a carbamoyl group into a carbonitrile function. Further attempts towards synthesis of the corresponding thiocarboxamide analogs of **11** and **25** by the treatment of **13** and **16** with hydrogen sulfide in pyridine in the presence of triethylamine were unsuccessful.

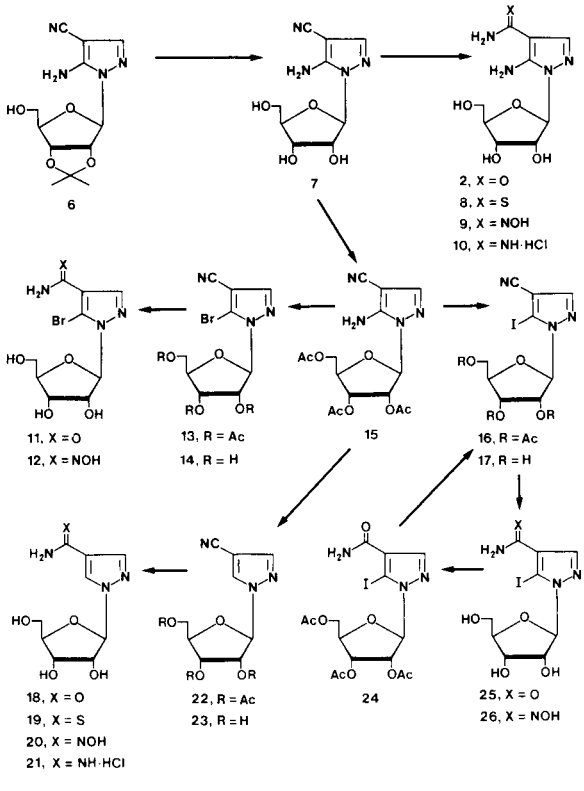
Our attempts to prepare 5-chloro-1-(β-D-ribofuranosyl)-pyrazole-4-carboxamide from **15** *via* nonaqueous diazotization procedure using isoamylnitrite in dichloromethane were also unsuccessful, and resulted in the formation of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**22**), which was isolated in a 74% yield. This hydrogenodediazoniation probably arises *via* the formation of an aryl (pyrazolyl) radical which can abstract a proton from the solvent. Deacetylation of **22** with methanolic ammonium hydroxide at 0° for 1 hour gave 1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**23**) in a 90% yield. Hydrolysis of **22** with ammonium hydroxide/hydrogen peroxide, and subsequent purification of the reaction product gave the ribavirin congener 1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**18**) in excellent yield. Transformation of **23** to the corresponding 4-thiocarboxamide derivative, 1-(β-D-ribofuranosyl)pyrazole-4-thiocarboxamide (**19**), was effected in 56% yield by the treatment of **23** with hydrogen sulfide in dry pyridine and triethylamine at room temperature. When the protected nucleoside **22** was allowed to react with hydroxylamine in ethanol at reflux temperature, and subsequent deprotection of the reaction product with ammonium hydroxide, 1-(β-D-ribofuranosyl)-pyrazole-4-carboxamidoxime (**20**) was formed, which was isolated in a 48% yield as analytically pure crystalline material. Catalytic hydrogenation of **20** in the presence of Raney nickel and ammonium chloride at 50 psi for 4 hours

furnished a 74% yield of 1-(β-D-ribofuranosyl)pyrazole-4-carboxamidine hydrochloride (**21**). Our attempts to convert **22** directly to **21** with liquid ammonia/ammonium chloride at elevated temperature was not fruitful.

Thus, a successful manipulation of the functional groups in **7** afforded a series of hitherto inaccessible pyrazole ribonucleosides structurally related to the broad-spectrum antiviral agent ribavirin and AICA riboside.

All the ribonucleosides prepared during this study have been evaluated *in vitro* for their ability to inhibit the growth of L1210-leukemia, WI-L2 and CCRF-CEM (for antitumor effects), as well as against HSV-1, para-3, VV and Cox B-1 viruses (for antiviral effects). These nucleosides are devoid of any significant biological effects in these systems.

Scheme I



EXPERIMENTAL

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Robertson Laboratory, Madison, NJ. The presence of water as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy. Thin layer chromatography (tlc) was performed on plates of silica gel 60F-254 (EM Reagents). Silica gel (E. Merck; 230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in tlc was by uv light, and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30°. Infrared (ir) spectra were recorded in potassium bromide with a Perkin-Elmer 1420 spectrophotometer and ultraviolet spectra (uv) were recorded on a Beckman DU-50 spectrophotometer. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as the internal standard (key: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad).

5-Amino-1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**7**).

A solution of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**6**) [17] (12.0 g, 42.8 mmoles) in trifluoroacetic acid (75 ml) and water (18 ml) was stirred at room temperature for 30 minutes. The reaction mixture was evaporated to dryness and the residue was coevaporated with ethanol (3 x 35 ml). The residue was washed with ether (3 x 30 ml), air dried and crystallized from water to yield 9.5 g (92%) of **7** as needles, mp 218-219° (Lit [18] 219°); ir: ν max 2240 (C≡N), 3100-3400 (NH_2 and OH) cm^{-1}; uv (*p*H 1): λ max 234 nm (ε 9,300); (*p*H 7): λ max 233 nm (ε 10,100); (*p*H 11): λ max 234 nm (ε 9,700); ^{1}H nmr (DMSO-d_6): δ 3.55 (m, 2H, $C_{5'}CH_2$), 3.85 (q, 1 H, $C_{4'}H$), 4.1 (q, 1 H, $C_{3'}H$), 4.42 (q, 1 H, $C_{2'}H$), 4.96 (t, 1 H, $C_{5'}OH$), 5.09 (d, 1 H, $C_{3'}OH$), 5.30 (d, 1 H, $C_{2'}OH$), 5.65 (d, 1 H, J = 4.17 Hz, $C_{1'}H$), 6.91 (br s, 2 H, NH_2), and 7.61 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{12}N_4O_4$ (240.22): C, 44.09; H, 5.03; N, 23.33. Found: C, 44.94; H, 4.90; N, 23.11.

5-Amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**2**).

To a solution of **7** (0.60 g, 2.49 mmoles) in methanol (25 ml) and water (10 ml) was added ammonium hydroxide (35 ml) and 30% hydrogen peroxide (2 ml). The mixture was stirred in a pressure bottle at room temperature for 18 hours. the pressure bottle was cooled, opened carefully and the volatile products were evaporated to dryness. The residue thus obtained was coevaporated with ethanol (3 x 20 ml) and purified by flash chromatography using dichloromethane:methanol (7:3, v/v) as the eluent to give 0.50 g (78%) of **2** as a crystalline compound. An analytical sample was obtained by recrystallization of the pure compound from a mixture of methanol/hexane, mp 162-163° (Lit [19] 226-235°, the low mp is due to the hydrated form of the compound); ir: ν max 1650 (C=O of amide), 3300-3400 (NH_2 and OH) cm^{-1}; uv (*p*H 1): λ max 253 nm (ε 7,700), 234 (7,600); (*p*H 7): λ max 252 nm (ε 7,700), 235 (7,700); (*p*H 11): λ max 254 nm (ε 7,900), 235 (7,600); ^{1}H nmr (DMSO-d_6): δ 3.57 (m, 2H, $C_{5'}CH_2$), 3.86 (q, 1 H, $C_{4'}H$), 4.11 (q, 1 H, $C_{3'}H$), 4.43 (q, 1 H, $C_{2'}H$), 4.94 (t, 1 H, $C_{5'}OH$), 5.05 (d, 1 H, $C_{3'}OH$), 5.28 (d, 1 H, $C_{2'}OH$), 5.63 (d, 1 H, J = 3.99 Hz, $C_{1'}H$), 6.51 (br s, 2 H, NH_2), 6.71 and 7.26 (2 br s, 2 H, $CONH_2$), and 7.69 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{14}N_4O_5 \cdot \frac{3}{4}H_2O$ (271.71): C, 39.71; H, 5.74; N, 20.62. Found: C, 39.72; H, 5.40; N, 20.61.

5-Amino-1-(β-D-ribofuranosyl)pyrazole-4-thiocarboxamide (**8**).

To a stirred solution of **6** (1.5 g, 5.35 mmoles) in anhydrous pyridine (80 ml) containing triethylamine (4 ml), dry hydrogen sulfide gas was bubbled for 3 hours. The reaction mixture was stirred at room temperature in a sealed flask for 14 hours and then purged with nitrogen for 30 minutes before it was evaporated to dryness. The residue on purification by flash chromatography over silica gel using dichloromethane →

methanol gradient and further crystallization of the homogeneous product from dichloromethane/methanol gave 0.95 g (56%) of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-pyrazole-4-thiocarboxamide as a light yellow crystalline product, mp 105-106°; ir: ν max 1220 (C=S), 3300-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 309 nm (ε 9,100), 271 (7,000), 225 (11,200); (*p*H 7): λ max 309 nm (ε 10,500), 274 (7,400), 226 (12,300); (*p*H 11): λ max 309 nm (ε 10,700), 272 (7,800), 224 (12,600); ^1H nmr (DMSO-d_6): δ 1.30 and 1.48 (2s, 6 H, isopropylidene), 3.40 (m, 2 H, $C_{5'}CH_2$), 4.07 (t, 1 H, $C_{4'}H$), 4.84 (t, 1 H, $C_{3'}H$), 4.92 (br s, 1 H, $C_{5'}OH$), 5.24 (d, 1 H, $C_{2'}H$), 6.04 (s, 1 H, $C_{1'}H$), 7.73 (br s, 2 H, NH_2), 7.90 (s, 1 H, C_3H), 8.61 and 8.68 (2 br s, 2 H, $CSNH_2$).

Anal. Calcd. for $C_{12}H_{18}N_4O_4S$ (314.35): C, 45.86; H, 5.73; N, 17.83; S, 10.19. Found: C, 45.64; H, 5.71; N, 17.60; S, 10.27.

The above protected nucleoside (0.25 g, 0.79 mmole) was treated with 90% aqueous trifluoroacetic acid (6 ml) and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was evaporated to dryness and coevaporated with ethanol (4 x 20 ml). The residue on purification by flash chromatography using dichloromethane:methanol (10:2, v/v) as the eluent and crystallization from methanol/dichloromethane gave 0.19 g (87%) of **8**, mp 180-181°; ir: ν max 1260 (C=S), 3300-3400 (NH_2 and OH) cm^{-1}; uv (*p*H 1): λ max 323 nm (ε 6,400), 253 (16,000), 230 (21,600); (*p*H 7): λ max 310 nm (ε 19,100), 272 (14,000), 224 (21,400); (*p*H 11): λ max 309 nm (ε 18,800), 271 (13,700), 224 (21,100); ^1H nmr (DMSO-d_6): δ 3.56 (m, 2 H, $C_{5'}CH_2$), 3.87 (q, 1 H, $C_{4'}H$), 4.12 (q, 1 H, $C_{3'}H$), 4.47 (q, 1 H, $C_{2'}H$), 4.93 (t, 1 H, $C_{5'}OH$), 5.07 (d, 1 H, $C_{3'}OH$), 5.31 (d, 1 H, $C_{2'}OH$), 5.66 (d, 1 H, J = 4.11 Hz, $C_{1'}H$), 7.68 (br s, 2H, NH_2), 7.85 (s, 1 H, C_3H), 8.58 and 8.63 [2s, 2 H, C(S)NH_2].

Anal. Calcd. for $C_9H_{14}N_4O_4S$ (274.29): C, 39.42; H, 5.12; N, 20.44; S, 11.68. Found: C, 39.16; H, 4.83; N, 20.23; S, 11.82.

5-Amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidoxime (**9**).

A mixture of **7** (0.10 g, 0.41 mmole), absolute ethanol (10 ml) and hydroxylamine (0.18 g, 5.42 mmoles) was heated under reflux for 3 hours and the reaction mixture was allowed to stand at room temperature for 24 hours. The solution was evaporated to dryness and the residue on purification by flash chromatography using dichloromethane → methanol gradient gave 0.085 g (75%) of **9** as a foam. An analytical sample was prepared by crystallization of pure compound from methanol/dichloromethane, mp 165-167°; ir: ν max 3300-3350 (NH_2 and OH) cm^{-1}; uv (*p*H 1): λ max 261 nm (ε 7,700); (*p*H 7): λ max 244 nm (ε 10,600); (*p*H 11): λ max 244 nm (ε 10,700); ^1H nmr (DMSO-d_6): δ 3.57 (m, 2 H, $C_{5'}CH_2$), 3.86 (q, 1 H, $C_{4'}H$), 4.15 (q, 1 H, $C_{3'}H$), 4.45 (q, 1 H, $C_{2'}H$), 4.94 (q, 1 H, $C_{5'}OH$), 5.03 (t, 1 H, $C_{3'}OH$), 5.25 (t, 1 H, $C_{2'}OH$), 5.63 (t, 3 H, NH_2 and $C_{1'}H$, after deuterium oxide exchange, d, J = 4.08 Hz), 6.12 [br s, 2 H, C(NOH)NH_2], 7.57 (s, 1 H, C_3H), and 8.92 (s, 1 H, NO*H*).

Anal. Calcd. for $C_9H_{15}N_5O_5$ (273.25): C, 39.56; H, 5.49; N, 25.64. Found: C, 39.50; H, 5.30; N, 25.69.

5-Amino-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidine Hydrochloride (**10**).

A mixture of **9** (0.15 g, 0.55 mmole), Raney nickel (0.50 g, wet weight), ammonium chloride (0.18 g) and 50% aqueous ethanol (20 ml) was shaken on a Parr hydrogenator at 50 psi for 8 hours. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated to dryness. The residue was purified by hplc using C-18 reverse phase column and water:methanol (98:2, v/v) as solvent. The pure fractions were lyophilized to give 0.11 g (68%) of **10** as a white powder, mp 185-188°; ir: ν max 3300-3350 (NH_2 and OH) cm^{-1}; uv (*p*H 1): λ max 288 nm (ε 6,000); (*p*H 7): 285 nm (ε 5,400); (*p*H 11): 270 nm (ε 5,900); ^1H nmr (DMSO-d_6): δ 3.55 (m, 2 H, $C_{5'}CH_2$), 3.86 (q, 1 H, $C_{4'}H$), 4.11 (q, 1 H, $C_{3'}H$), 4.44 (q, 1 H, $C_{2'}H$), 4.92 (q, 1 H, $C_{5'}OH$), 5.03 (d, 1 H, $C_{3'}OH$), 5.25 (d, 1 H, $C_{2'}OH$), 5.63 (d, 1 H, J = 4.17 Hz, $C_{1'}H$), 6.51-7.41 [3 br s, 6 H, NH_2, C(N*H*·*H*Cl)NH_2], and 7.69 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{15}N_5O_4$·HCl·$2H_2O$ (329.745): C, 32.78; H, 6.10; N, 21.24; Cl, 10.75. Found: C, 32.65; H, 6.12; N, 21.33; Cl, 10.61.

5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**15**).

To a solution of **7** (5.0 g, 20.81 mmoles) in anhydrous *N*,*N*-dimethylformamide (60 ml) was added 4-dimethylaminopyridine (DMAP) (0.3 g) and the mixture was cooled to -25° ± 3° in a cooling bath. To this mixture, acetic anhydride (4.1 ml) was added portionwise under nitrogen atmosphere and the reaction mixture was stirred at -25 ± 3° for 3 hours. The reaction was quenched by addition of methanol (35 ml) and allowed to warm up to room temperature. The reaction mixture was evaporated to dryness and the residue was coevaporated with methanol (3 x 35 ml). The dry residue was dissolved in dichloromethane (50 ml) and washed with water (2 x 70 ml). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The residue on purification by flash chromatography using dichloromethane → methanol gradient and crystallization from dichloromethane/ether gave 4.8 g (63%) of **15**, mp 95-96°; ir: ν max 2180 (C≡N), 1730 (C=O of acetate), 3200-3400 (NH_2) cm^{-1}; uv (*p*H 1): λ max 235 nm (ε 9,500); (*p*H 7 and *p*H 11): λ max 234 nm (ε 9,600); ^1H nmr (DMSO-d_6): δ 1.97, 2.06 and 2.08 (3s, 9 H, $C_{2'}$, $C_{3'}$, $C_{5'}$ acetyls), 4.00 (q, 1 H, $C_{4'}H$), 4.33 (m, 2 H, $C_{5'}CH_2$), 5.51 (t, 1 H, $C_{3'}H$), 5.66 (q, 1 H, $C_{2'}H$), 6.06 (d, 1 H, J = 2.25 Hz, $C_{1'}H$), 7.06 (br s, 2 H, NH_2), and 7.72 (s, 1 H, C_3H).

Anal. Calcd. for $C_{15}H_{18}N_4O_7$ (366.32): C, 49.18; H, 4.95; N, 15.29. Found: C, 49.00; H, 4.78; N, 15.24.

5-Bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**13**).

To an ice-cooled (0-5°) solution of **15** (4.0 g, 10.91 mmoles) in dibromomethane (65 ml) was added isoamyl nitrite (13 ml) portionwise over a period of 30 minutes. The mixture was stirred for 30 minutes at room temperature and then at 60° for 1 hour. The reaction mixture was evaporated to dryness and the residue was dissolved in dichloromethane (50 ml). The organic phase was washed with water (2 x 80 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane → ethyl acetate gradient to give **13** as a light-yellow foam which was crystallized from dichloromethane/ether. Yield 2.85 g (61%), mp 105-106°; ir: ν max 2240 (C≡N), 1750 (C=O of acetate) cm^{-1}; uv (*p*H 1): λ max 226 nm (ε 8,800); (*p*H 7): λ max 225 nm (ε 9,500); (*p*H 11): λ max 224 nm (ε 9,400); ^1H nmr (DMSO-d_6): δ 1.94, 2.07 and 2.10 (3s, 9 H, $C_{2'}$, $C_{3'}$ and $C_{5'}$ acetyls), 4.04 (q, 1 H, $C_{4'}H$), 4.43 (m, 2 H, $C_{5'}CH_2$), 5.59 (t, 1 H, $C_{3'}H$), 5.78 (t, 1 H, $C_{2'}H$), 6.12 (s, 1 H, $C_{1'}H$), and 8.42 (s, 1 H, C_3H).

Anal. Calcd. for $C_{15}H_{16}BrN_3O_7$ (430.21): C, 41.88; H, 3.75; Br, 18.57; N, 9.77. Found: C, 41.93; H, 3.74; Br, 18.72; N, 9.79.

5-Bromo-1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**14**).

To a stirred solution of **13** (0.65 g, 1.51 mmoles) in methanol (5 ml) was added ammonium hydroxide (15 ml) and the stirring was continued for 5 hours at 0-4°. The reaction mixture was evaporated to dryness and the residue on purification by flash chromatography using dichloromethane → methanol gradient and crystallization from methanol gave 0.32 g (71%) of **14**, mp 143-144°; ir: ν max 2240 (C≡N), 3400-3460 (OH) cm^{-1}; uv (*p*H 1): λ max 226 nm (ε 9,600); (*p*H 7): λ max 227 nm (ε 10,100); (*p*H 11): λ max 223 nm (ε 10,900); ^1H nmr (DMSO-d_6): δ 3.52 (m, 2 H, $C_{5'}CH_2$), 3.94 (q, 1 H, $C_{4'}H$), 4.16 (d, 1 H, $C_{3'}H$), 4.55 (t, 1 H, $C_{2'}H$), 4.77 (t, 1 H, $C_{5'}OH$), 5.29 (d, 1 H, $C_{3'}OH$), 5.56 (s br, 1 H, $C_{2'}OH$), 5.76 (d, 1 H, J = 4.26 Hz, $C_{1'}H$), and 8.32 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{10}BrN_3O_4$ (304.1): C, 35.55; H, 3.31; Br, 26.28; N, 13.82. Found: C, 35.59; H, 3.43; Br, 26.50; N, 13.64.

5-Bromo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**11**).

To a solution of **13** (0.60 g, 1.39 mmoles) in methanol (5 ml) was added ammonium hydroxide (35 ml) and hydrogen peroxide (30%, 3 ml). The reaction mixture was stirred at room temperature in a pressure bottle for 18 hours. The pressure bottle was opened carefully and the mixture was evaporated to dryness. The residue was coevaporated with methanol (3 x 20 ml) and the dry solid thus obtained was crystallized from methanol to give 0.38 g (85%) of **11**, mp 200-202°; ir: ν max 1670 (C=O of amide), 3240-3450 (OH) cm^{-1}; uv (*p*H 1 and *p*H 7): λ max 227 nm (ε 12,700); (*p*H 11): λ max 228 nm (ε 12,500), 214 (11,700); ^1H nmr (DMSO-d_6): δ 3.52 (m, 2 H, $C_{5'}CH_2$), 3.91 (q, 1 H, $C_{4'}H$), 4.15 (s, 1 H, $C_{3'}H$), 4.54 (s, 1 H, $C_{2'}H$), 4.76 (s, 1 H, $C_{5'}OH$), 5.20 (s, 1 H, $C_{3'}OH$), 5.48 (s, 1 H, $C_{2'}OH$), 5.83 (d, 1 H, J = 4.19 Hz, $C_{1'}H$), 7.27 and 7.61 (2s, 2 H, $CONH_2$), and 8.11 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{12}BrN_3O_5$ (322.11): C, 33.55; H, 3.76; Br, 24.81; N, 13.05. Found: C, 33.46; H, 3.77; Br, 24.62; N, 12.85.

5-Bromo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidoxime (**12**).

To a solution of **13** (0.60 g, 1.39 mmoles) in absolute ethanol (15 ml), hydroxylamine (0.058 g, 1.75 mmoles) was added and the reaction mixture was heated under reflux for 1 hour. Additional hydroxylamine (0.058 g, 1.75 mmoles) was added and the clear solution was refluxed for further two hours and then left at room temperature overnight. The reaction mixture was evaporated to dryness and the residue was purified by flash chromatography on silica gel using dichloromethane → ethyl acetate as the gradient. The pure syrupy product was treated with concentrated ammonium hydroxide (10 ml) in methanol (5 ml) at 0° and stirred at room temperature for 5 hours. The reaction mixture was evaporated to dryness and the residue was coevaporated with ethanol (3 x 15 ml). The dry residue on purification by flash chromatography using dichloromethane → methanol gradient and crystallization from methanol gave 0.31 g (66%) of **12**, mp 122-124°; ir: ν max 3300-3340 (OH and NH_2) cm^{-1}; uv (*p*H 1): λ max 219 nm (ε 12,700); (*p*H 7): λ max 210 nm (ε 12,200); (*p*H 11): λ max 212 nm (ε 12,500); ^1H nmr (DMSO-d_6): δ 3.52 (m, 2 H, $C_{5'}CH_2$), 3.89 (d, 1 H, $C_{4'}H$), 4.16 (d, 1 H, $C_{3'}H$), 4.57 (q, 1 H, $C_{2'}H$), 4.78 (q, 1 H, $C_{5'}OH$), 5.19 (d, 1 H, $C_{3'}OH$), 5.46 (d, 1 H, $C_{2'}OH$), 5.70 (s, 2 H, NH_2), 5.80 (d, 1 H, J = 4.2 Hz, $C_{1'}H$), 7.87 (s, 1 H, C_3H), and 9.55 (s, 1 H, NOH).

Anal. Calcd. for $C_9H_{13}BrN_4O_5$ (337.13): C, 32.06; H, 3.89; Br, 23.70; N, 16.62. Found: C, 32.05; H, 4.08; Br, 23.71; N, 16.33.

5-Iodo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**16**).

Method A.

To a solution of **15** (5.0 g, 13.01 mmoles) in diiodomethane (60 ml) was added isoamylnitrite (15 ml) portionwise over a period of 30 minutes at 0° under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 minutes and then heated to 100° in an oil bath for 2 hours. The solvent was evaporated and the residue was purified by flash chromatography using dichloromethane → ethyl acetate gradient and cyrstallized from dichloromethane/ether to give 5.85 g (94%) of **16** as a light pink crystalline material, mp 126-128°; ir: ν max 2240 (C≡N), 1740 (C=O of acetate) cm^{-1}; uv (*p*H 1 and *p*H 7): λ max 232 nm (ε 10,300); (*p*H 11): λ max 231 nm (ε 11,600); ^1H nmr (DMSO-d_6): δ 1.93, 2.07 and 2.10 (3s, 9 H, $C_{5'}$, $C_{3'}$, $C_{5'}$ acetyls), 4.02 (m, 1 H, $C_{4'}H$), 4.42 (m, 2 H, $C_{5'}CH_2$), 5.60 (t, 1 H, $C_{3'}H$), 5.78 (q, 1 H, $C_{2'}H$), 6.07 (d, 1 H, J = 2.30 Hz, $C_{1'}H$), and 8.37 (s, 1 H, C_3H).

Anal. Calcd. for $C_{15}H_{16}IN_3O_7$ (477.21): C, 37.75; H, 3.38; I, 26.59; N, 8.81. Found: C, 38.06; H, 3.31; I, 26.40; N, 8.67.

Method B.

A solution of **24** (0.20 g, 0.40 mmole) in dry toluene (10 ml) was treated with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide [24] (Lawesson's reagent, 0.49 g, 1.21 mmoles) and the mixture was heated under reflux for 3 hours. The reaction mixture was cooled, poured into water (50 ml) and extracted with ethyl acetate (3 x 25 ml). The organic layer was washed with water (2 x 35 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified on flash silica gel column by using hexane:ethyl acetate (8:2, v/v) as the eluent. The homogeneous fractions were pooled and evaporated to give a foam which on crystallization from dichloromethane/ether yielded 0.13 g (65%) of **16**, mp 126-128°. This product was found to be identical with **16** prepared by Method A.

5-Iodo-1-(β-D-ribofuranosyl)pyrazole-4-carbonitrile (**17**).

A solution of **16** (3.0 g, 6.29 mmoles) in methanol (10 ml) was treated with concentrated ammonium hydroxide (35 ml) and the mixture was stirred at 0° for 5 hours. The solvent was removed by evaporation and the residue thus obtained was crystallized from methanol to give 2.05 g (93%) of **17**, mp 208-210°; ir: ν max 2240 (C≡N), 3300-3440 (OH) cm^{-1}; uv (*p*H 1, *p*H 7 and *p*H 11): λ max 231 nm (ε 8,800); ^1H nmr (DMSO-d_6): δ 3.54 (m, 2 H, $C_{5'}CH_2$), 3.94 (q, 1 H, $C_{4'}H$), 4.16 (d, 1 H, $C_{3'}H$), 4.53 (d, 1 H, $C_{2'}H$), 4.78 (t, 1 H, $C_{5'}OH$), 5.27 (d, 1 H, $C_{3'}OH$), 5.54 (d, 1 H, $C_{2'}OH$), 5.76 (d, 1 H, J = 4.25 Hz, $C_{1'}H$), and 8.29 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{10}I\ N_3O_4$ (351.10): C, 30.79; H, 2.84; I, 36.14; N, 11.97. Found: C, 30.84; H, 2.84; I, 36.43; N, 11.80.

5-Iodo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**25**).

To an ice-cooled (0-5°) solution of **16** (0.50 g, 1.047 mmoles) in methanol (5 ml) was added ammonium hydroxide (20 ml) followed by hydrogen peroxide (30%, 2 ml). The reaction mixture was stirred at 0° for 20 hours. The solvent was evaporated and the residual product was coevaporated with methanol (2 x 20 ml). The dry residue was purified by flash chromatography using dichloromethane → methanol gradient. The pure product was crystallized from methanol to give 0.34 g (87%) of **25**, mp 135-136°; ir: ν max 1650 (C=O of amide), 3320-3440 (NH_2 and

OH) cm^{-1}; uv (*p*H 1 and *p*H 11): λ max 232 nm (ε 10,900); (*p*H 7): λ max 233 nm (ε 9,900); ^1H nmr (DMSO-d_6): δ 3.54 (m, 2 H, $C_{5'}CH_2$), 3.91 (q, 1 H, $C_{4'}H$), 4.17 (d, 1 H, $C_{3'}H$), 4.54 (d, 1 H, $C_{2'}H$), 4.77 (t, 1 H, $C_{5'}OH$), 5.18 (d, 1 H, $C_{3'}OH$), 5.44 (d, 1 H, $C_{2'}OH$), 5.89 (d, 1 H, J = 4.09 Hz, $C_{1'}H$), 7.16 and 7.57 (2 br s, 2 H, $CONH_2$), and 8.10 (s, 1 H, C_3H).

Anal. Calcd. for $C_9H_{12}IN_3O_5$ (369.15): C, 29.29; H, 3.28; I, 34.38; N, 11.38. Found: C, 29.49; H, 3.40; I, 34.37; N, 11.30.

5-Iodo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamidoxime (**26**).

To a solution of **17** (0.56 g, 1.59 mmoles) in absolute ethanol (10 ml) was added hydroxylamine (0.065 g, 1.96 mmoles) and heated under reflux for 1 hour. Additional hydroxylamine (0.065 g, 1.96 mmoles) was added to the mixture and heating was continued for additional 2 hours. The reaction mixture was allowed to stand at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography using dichloromethane → methanol gradient and the pure product was crystallized from methanol to give 0.39 g (64%) of **26**, mp 195-197°; ir: ν max 3200-3440 (OH and NH_2) cm^{-1}; uv (*p*H 1, *p*H 7 and *p*H 11): λ max 230 nm (ε 10,700); ^1H nmr (DMSO-d_6): δ 3.54 (m, 2 H, $C_{5'}CH_2$), 3.91 (q, 1 H, $C_{4'}H$), 4.17 (q, 1 H, $C_{3'}H$), 4.58 (q, 1 H, $C_{2'}H$), 4.78 (q, 1 H, $C_{5'}OH$), 5.20 (t, 1 H, $C_{3'}OH$), 5.47 (t, 1 H, $C_{2'}OH$), 5.7 (br s, 2 H, NH_2), 5.80 (d, 1 H, J = 4.27 Hz, $C_{1'}H$), 7.87 (s, 1 H, C_3H), and 9.55 (s, 1 H, NO*H*).

Anal. Calcd. for $C_9H_{13}IN_4O_5 \cdot \frac{1}{2}C_2H_5OH$ (407.15): C, 29.50; H, 3.96; I, 31.17; N, 13.76. Found: C, 29.27; H, 3.91; I, 31.17; N, 13.59.

5-Iodo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxamide (**24**).

To a solution of **25** (1.0 g, 2.71 mmoles) in anhydrous *N*,*N*-dimethylformamide (35 ml) was added 4-dimethylaminopyridine (DMAP, 0.1 g) and the mixture was cooled to -25° ± 3° in a cooling bath. To this mixture, acetic anhydride (1.1 g, 10.77 mmoles) was added portionwise under nitrogen atmosphere and the reaction mixture was stirred at -25° ± 3° for 2 hours. The reaction mixture was quenched by addition of methanol (25 ml) and allowed to warm up to room temperature. The reaction mixture was evaporated to dryness, and the residue was coevaporated with methanol (3 x 25 ml). The dry residue was dissolved in dichloromethane (35 ml) and the organic phase was washed with water (2 x 60 ml). After drying the organic phase over anhydrous sodium sulfate for 15 hours, was evaporated to dryness. The residue on purification by flash chromatography using dichloromethane → ethyl acetate gradient gave **24** as a white foam, which was crystallized from dichloromethane/hexane. Yield 1.15 g (86%), mp 141-142°; ir: ν max 1675 ($CONH_2$), 1730 (C = O of acetate), 3350-3460 (NH_2) cm^{-1}; uv (*p*H 1, *p*H 7 and *p*H 11): λ max 231 nm (ε 14,000); ^1H nmr (DMSO-d_6): δ 1.96, 2.08 and 2.10 (3s, 9 H, $C_{2'}$, $C_{3'}$, $C_{5'}$ acetyls), 4.00 (m, 1 H, $C_{4'}H$), 4.40 (m, 2 H, $C_{5'}CH_2$), 5.61 (t, 1 H, $C_{3'}H$), 5.80 (q, 1 H, $C_{2'}H$), 6.13 (d, 1 H, J = 2.65 Hz, $C_{1'}H$), 7.24 and 7.64 (2 br s, 2 H, $CONH_2$) and 8.17 (s, 1 H, C_3H).

Anal. Calcd. for $C_{15}H_{18}IN_3O_8$ (495.21): C, 36.38; H, 3.66; I, 25.62; N, 8.48. Found: C, 36.66; H, 3.73; I, 25.52; N, 8.30.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**22**).

To a solution of **15** (4.0 g, 10.91 mmoles) in dry dichloromethane (60 ml) was added isoamylnitrite (14 ml) portionwise and stirred under nitrogen at 0° for 30 minutes. After stirring for another 30 minutes at room temperature, the reaction mixture was heated at 70° for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography by using dichloromethane → ethyl acetate gradient. The pure fractions were collected and concentrated to give 2.85 g (74%) of **22** as a syrup; ir: ν max 1755 (C = O of acetate), 2240 (C ≡ N) cm^{-1}; uv (*p*H 1, 7 and 11): λ max 212 nm (ε 10,400); ^1H nmr (DMSO-d_6): δ 1.98, 2.07 and 2.08 (3s, 9 H, $C_{2'}$, $C_{3'}$, $C_{5'}$ acetyls), 4.09 (q, 1 H, $C_{4'}H$), 4.40 (m, 2 H, $C_{5'}CH_2$), 5.55 (t, 1 H, $C_{3'}H$), 5.66 (q, 1 H, $C_{2'}H$), 6.18 (d, 1 H, J = 3.04 Hz, $C_{1'}H$), 8.26 (s, 1 H, C_3H), and 8.79 (s, 1 H, C_5H).

Anal. Calcd. for $C_{15}H_{17}N_3O_7$ (351.31): C, 51.27; H, 4.87; N, 11.96. Found: C, 51.09; H, 4.83; N, 11.88.

1-(β-D-Ribofuranosyl)pyrazole-4-carbonitrile (**23**).

A mixture of **22** (1.1 g, 3.13 mmoles), ammonium hydroxide (25 ml) and methanol (4 ml) was stirred at 0° for 1 hour and then evaporated to dryness. The residue was coevaporated with methanol (3 x 20 ml) and the syrup thus obtained was purified by flash chromatography using dichloromethane → methanol gradient. The pure fractions were collected, solvents evaporated and the residue was crystallized from aqueous ethanol to yield 0.64 g (90%), mp 101-102°; ir: ν max 2240 (C ≡ N), 3100-3460 (OH) cm^{-1}; uv (*p*H 1): λ max 214 nm (ε 10,900); (*p*H 7): λ max 213 nm (ε 12,000); (*p*H 11): λ max 207 nm (ε 16,700); ^1H nmr (DMSO-d_6): δ, 3.65 (m, 2 H, $C_{5'}CH_2$), 3.95 (q, 1 H, $C_{4'}H$), 4.11 (q, 1 H, $C_{3'}H$), 4.31 (q, 1 H, $C_{2'}H$), 4.95 (t, 1 H, $C_{5'}OH$), 5.19 (d, 1 H, $C_{3'}OH$), 5.55 (d, 1 H, $C_{2'}OH$), 5.71 (d, 1 H, J = 3.97 Hz, $C_{1'}H$), 8.14 (s, 1 H, C_3H), and 8.82 (s, 1 H, C_5H).

Anal. Calcd. for $C_9H_{11}N_3O_4$ (225.20): C, 48.00; H, 4.92; N, 18.66. Found: C, 47.71; H, 4.83; N, 18.29.

1-(β-D-Ribofuranosyl)pyrazole-4-carboxamide (**18**).

In a similar manner as described for **25**, treatment of **22** (0.35 g, 0.99 mmoles) in methanol (5 ml) with ammonium hydroxide (5 ml) and hydrogen peroxide (30%, 0.5 ml) gave 0.21 g (86%) of crystalline **18** (from aqueous ethanol), mp 160-161°; ir: ν max 1650 ($CONH_2$), 3200-3400 (OH) cm^{-1}; uv (*p*H 1): 223 nm (ε 19,800); (*p*H 7): λ max 223 nm (ε 20,400); (*p*H 11): λ max 216 nm (sh) (ε 20,800); ^1H nmr (DMSO-d_6): δ 3.60 (m, 2 H, $C_{5'}CH_2$), 3.92 (q, 1 H, $C_{4'}H$), 4.10 (q, 1 H, $C_{3'}H$), 4.30 (q, 1 H, $C_{2'}H$), 4.91 (q, 1 H, $C_{5'}OH$), 5.15 (d, 1 H, $C_{3'}OH$), 5.45 (d, 1 H, $C_{2'}OH$), 5.65 (d, 1 H, J = 4.2 Hz, $C_{1'}H$), 7.06 and 7.59 (2 br s, 2 H, $CONH_2$), 7.90 (s, 1 H, C_3H), and 8.37 (s, 1 H, C_5H).

Anal. Calcd. for $C_9H_{13}N_3O_5$ (243.21): C, 44.44; H, 5.39; N, 17.28. Found: C, 44.31; H, 5.05; N, 17.04.

1-(β-D-Ribofuranosyl)pyrazole-4-thiocarboxamide (**19**).

Hydrogen sulfide gas was bubbled through a solution of **23** (0.30 g, 1.33 mmoles) in anhydrous pyridine (15 ml) containing triethylamine (0.5 ml) for 3 hours. The saturated reaction mixture was stirred in a tightly stoppered flask for 15 hours. The reaction mixture was purged with nitrogen for 2 hours and the solvent was evaporated to dryness. The residue was coevaporated with ethanol (3 x 15 ml) to remove last trace of pyridine and was purified by flash chromatography using dichloromethane → methanol gradient. The homogeneous product was crystallized from aqueous ethanol to give 0.19 g (56%) of **19**, mp 105-106°; ir: ν max 1260 (C = S) cm^{-1}; uv (*p*H 1): λ max 294 nm (ε 9,400), 248 (9,200), 212 (7,000); (*p*H 7): λ max 294 nm (ε 9,800), 249 (9,600); (*p*H 11): λ max 291 nm (ε 10,300), 249 (9,700); ^1H nmr (DMSO-d_6): δ 3.62 (m, 2 H, $C_{5'}CH_2$), 3.92 (q, 1 H, $C_{4'}H$), 4.10 (q, 1 H, $C_{3'}H$), 4.31 (q, 1 H, $C_{2'}H$), 4.89 (q, 1 H, $C_{5'}OH$), 5.15 (d, 1 H, $C_{3'}OH$), 5.46

(d, 1 H, $C_{2'}OH$), 5.65 (d, 1 H, J = 4.2 Hz, $C_{1'}H$), 7.97 (s, 1 H, C_3H), 8.4 (s, 1 H, C_5H), 9.16 and 9.36 [2 br s, 2 H, C(S)NH_2].

Anal. Calcd. for $C_9H_{13}N_3O_4S \cdot \frac{1}{2}H_2O$ (268.28): C, 40.25; H, 5.21; N, 15.65; S, 11.92. Found: C, 39.99; H, 5.31; N, 15.35; S, 11.72.

1-(β-D-Ribofuranosyl)pyrazole-4-carboxamidoxime (**20**).

In a similar manner as described for **12**, treatment of a solution of **22** (0.52 g, 1.49 mmoles) in ethanol (20 ml) with hydroxylamine (2 x 0.056 g, 3.4 mmoles) at reflux temperature for 3 hours gave 0.19 g (48%) of crystalline **20** (from methanol), mp 135-136°; ir: ν max 3100-3500 (OH and NH_2) cm^{-1}; uv (*p*H 1): λ max 226 nm (ε 18,000); (*p*H 7): λ max 228 nm (ε 12,200); (*p*H 11): λ max 230 nm (sh) (ε 12,300); ^1H nmr (DMSO-d_6): δ 3.61 (m, 2 H, $C_{5'}CH_2$), 3.91 (q, 1 H, $C_{4'}H$), 4.10 (q, 1 H, $C_{3'}H$), 4.31 (q, 1 H, $C_{2'}H$), 4.88 (t, 1 H, $C_{5'}OH$), 5.13 (d, 1 H, $C_{3'}OH$), 5.41 (d, 1 H, $C_{4'}OH$), 5.62 (d, 1 H, J = 4.3 Hz, $C_{1'}H$), 5.66 (s, 2 H, NH_2), 7.71 (s, 1 H, C_3H), 8.17 (s, 1 H, C_5H), and 9.19 (s, 1H, NO*H*).

Anal. Calcd. for $C_9H_{14}N_4O_5$ (258.23): C, 41.86; H, 5.46; N, 21.70. Found: C, 41.50; H, 5.39; N, 21.69.

1-(β-D-Ribofuranosyl)pyrazole-4-carboxamidine (**21**).

In a similar manner as described for the preparation of **10**, hydrogenation of a solution of **20** (0.28 g, 1.08 mmoles) in 50% aqueous ethanol (25 ml) in the presence of Raney nickel (0.60 g, wet weight) for 4 hours gave 0.22 g (74%) of crystalline **21** (from aqueous ethanol), mp 205-207°; ir: ν max 3100-3400 (OH and NH_2) cm^{-1}; uv (*p*H 1): λ max 228 nm (ε 10,500); (*p*H 7): λ max 228 nm (ε 11,200); (*p*H 11): λ max 221 nm (sh) (ε 10,500); ^1H nmr (DMSO-d_6): δ 3.59 (m, 2 H, $C_{5'}CH_2$), 3.94 (d, 1 H, $C_{4'}H$), 4.06 (s, 1 H, $C_{3'}H$), 4.28 (s, 1 H, $C_{2'}H$), 5.05 (s, 1 H, $C_{5'}OH$), 5.27 (s, 1 H, $C_{3'}OH$), 5.63 (d, 1 H, $C_{2'}OH$), 5.68 (d, 1 H, J = 3.90 Hz, $C_{1'}H$), 7.5 (br s, 4 H, [C(N*H*·*H*Cl)NH_2], 8.41 (s, 1 H, C_3H), and 9.13 (s, 1 H, C_5H).

Anal. Calcd. for $C_9H_{14}N_4O_4 \cdot HCl \cdot 1\frac{1}{2}\ H_2O$(305.71): C, 35.35; H, 5.93; N, 18.32; Cl, 11.59. Found: C, 35.31; H, 5.61; N, 17.99; Cl, 11.56.

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REFERENCES AND NOTES

[1] R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

[2] L. B. Townsend, *Chem. Rev.*, **67**, 584 (1967).

[3] K. Nakayama and H. Tanaka, *German Offen.*, 1,939,030 (1970).

[4] T. A. Krenitsky, S. M. Neil, G. B. Elion and G. H. Hitchings, *J. Biol. Chem.*, **244**, 4779 (1969).

[5] T. A. Krenitsky, Ph. Papaioannou and G. B. Elion, *J. Biol Chem.*, **244**, 1263 (1969).

[6] V. Massy, H. Komai and G. Palmer, *J. Biol. Chem.*, **245**, 2837 (1970).

[7] A. Nicolin, S. Vadlamudi and A. Goldin, *Cancer Chemother. Rep.*, **57**, 3 (1973).

[8] H. Willitzer, M. Tonew and E. Lippmann, *Antimicrob. Agents Chemother.*, **9**, 367 (1976).

[9] M. Tonew, E. Lippmann and H. Willitzer, *Antimicrob. Agents Chemother.*, **9**, 371 (1976).

[10] J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972).

[11] H. Tanaka, T. Hayashi and K. Nakayama, *Agr. Biol. Chem.*, **37**, 1731 (1973).

[12] J. L. Barascut, C. Tamby and J-L. Imbach, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 77 (1974).

[13] I. A. Korbukh, M. N. Preobrazhenskaya and O. N. Judina, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 363 (1974).

[14] O. Makabe, M. Nakamura and S. Umezawa, *Bull. Chem. Soc. Japan*, **48**, 3210 (1975).

[15] R. W. Sidwell, G. R. Revankar and R. K. Robins, *intl. Enc. Pharmacol. Therapy*, Chapter 3/section 116, "Viral Chemotherapy", Vol **2**, D. Shugar, ed, Pergamon Press, (1985) pp 49-108.

[16] C. R. Petrie, G. R. Revankar, N. K. Dalley, R. D. George, P. A. McKernan, R. L. Hamill and R. K. Robins, *J. Med. Chem.*, **29**, 268 (1985).

[17] O. L. Acevedo, S. H. Krawczyk and L. B. Townsend, *J. Org. Chem.*, **51**, 1050 (1986).

[18] R. R. Schmidt, W. Guilliard and J. Karg, *Chem. Ber.*, **110**, 2445 (1977).

[19] R. A. Earl, R. P. Panzica and L. B. Townsend, *J. Chem. Soc., Perkin Trans I*, 2672 (1972).

[20] P. C. Srivastava, D. G. Streeter, T. R. Matthews, L. B. Allen, R. W. Sidwell and R. K. Robins, *J. Med. Chem.*, **19**, 1020 (1976).

[21] V. Nair and S. G. Richardson, *Synthesis*, 670 (1982).

[22] A. Matsuda and T. Ueda, *Nucleosides Nucleotides*, **6**, 85 (1987).

[23] A. Matsuda, N. Minakawa and T. Ueda, *Nucleic Acids Res.*, Symposium Series No. 20, 13 (1988).

[24] Commercially available from Aldrich Chemical Co. Inc., Milwaukee, Wisconsin.