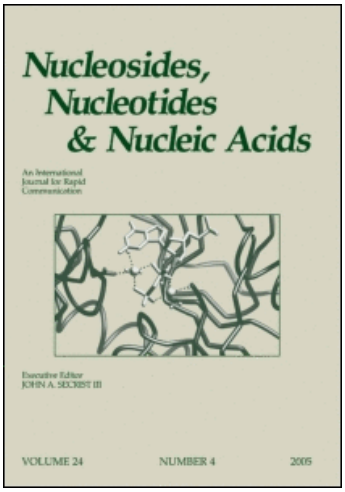

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SYNTHESIS OF BRUNFELSAMIDINE RIBONUCLEOSIDE AND CERTAIN RELATED COMPOUNDS BY THE STEREOSPECIFIC SODIUM SALT GLYCOSYLATION PROCEDURE

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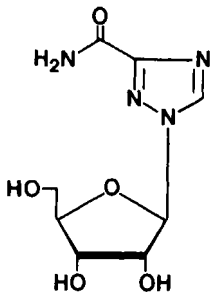
ABSTRACT: A synthesis of 2,4-dideazaribavirin (2), brunfelsamidine ribonucleoside (8c) and certain related derivatives are described for the first time using the stereospecific sodium salt glycosylation procedure. Glycosylation of the sodium salt of pyrrole-3-carbonitrile (4) with 1-chloro-2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-α-D-ribofuranose (5) gave exclusively the corresponding blocked nucleoside (6) with β-anomeric configuration, which on deprotection provided 1-β-D-ribofuranosylpyrrole-3-carbonitrile (7). Functional group tranformation of 7 gave 2, 8c and related 3-substituted pyrrole ribonucleosides. These compounds are devoid of any significant antiviral/antitumor activity in vitro.

INTRODUCTION: Literature repletes with reports on the synthesis and biological evaluation of both C- and N-nucleosides. The broad spectrum antiviral activity of ribavirin[1] (1) has stimulated great interest in the synthesis of ring modified analogues. Of particular interest is the synthesis of nucleoside (2), due to the fact that it is a "dideaza" analogue of ribavirin. Also of interest is the ribonucleoside 8c, since brunfelsamidine, a novel convulsant isolated recently from the roots and bark of Brunfelsia grandiflora is identified[2] as pyrrole-3-carboxamidine (3). The water extracts of Brunfelsia grandiflora is a widely used remedy against rheumatism and arthritis[3]. It has also been used for fevers and snakebite[3]. The above findings provided an excellent rational for the synthesis of certain ribonucleosides of 3-substituted pyrrole.

The present work describes the synthesis of 2,4-dideazaribavirin (2), brunfelsamidine ribonucleoside (8c) and certain related compounds using the regio- and stereospecific sodium salt glycosylation procedure[4]. Utilization of this simple procedure for the synthesis of substituted



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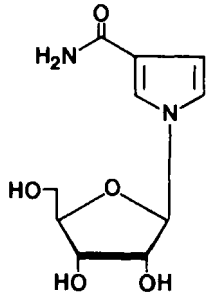

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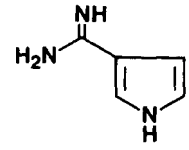

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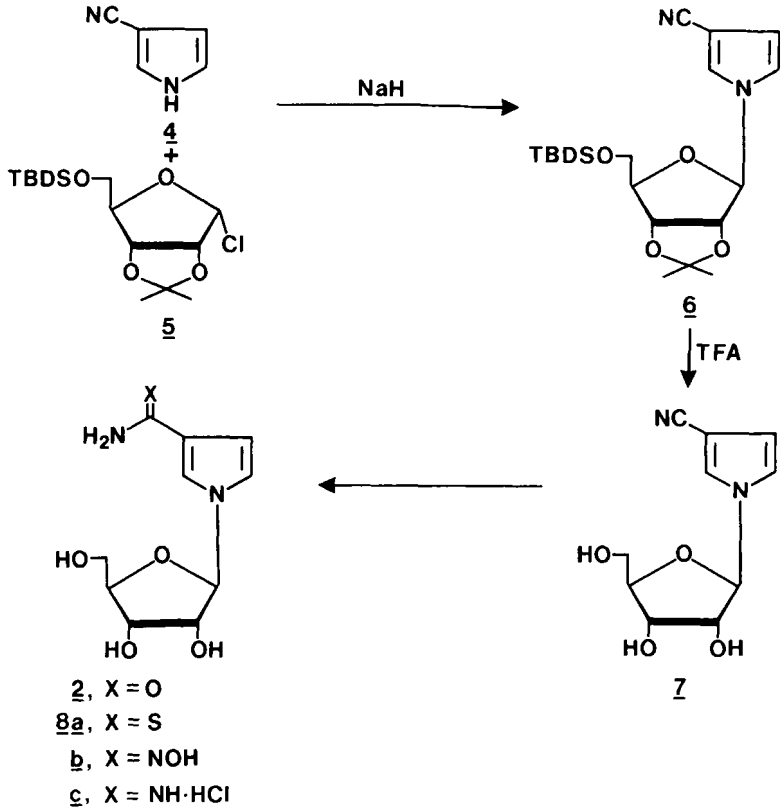
pyrrole nucleosides[5] and pyrrolo[2,3-d]pyrimidine nucleosides[6] has recently been found to be remarkably successful. Reported procedure for the preparation of pyrrole nucleosides[7] are neither straightforward nor simple. Our synthetic pathway involves the direct attachment of a glycon moiety (β-D-ribofuranosyl) to a preformed fully aromatic pyrrole.

RESULTS AND DISCUSSION: Readily available pyrrole-3-carbonitrile[8] (4) was selected for glycosylation studies. The halogenose 1-chloro-2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-α-D-ribofuranose[9a] (5) was generated in situ and used as such without purification since the chloro sugar 5 was found to be unstable during purification. When glycosylation was carried out with 1 equiv each of the sodium salt of 4, produced in situ by NaH in anhydrous CH_3CN, and the chloro sugar 5 gave a 15% yield of glycosylated product (6) accompanied by recoverable starting material 4. Interestingly enough, reaction of 2 equiv of the sodium salt of 4 and 1 equiv of the chloro sugar 5 gave the glycosylated product 6 in 66% yield and 1 equiv of the base 4. However, glycosylation of 1 equiv of 4, and 2 equiv of NaH with 1 equiv of halogenose 5 gave only a trace amount of the desired product 6 and the reactant 4 recovered almost quantitatively. These results could be explained as follows: As the chloro sugar contains a poorly reactive halogene, an excess of the sodium salt of the nucleobase has to be employed to drive the reaction. Excess of NaH may cause side-reactions (e.g. reduction).

The reaction product was purified by flash chromatography over silica gel to furnish 6 as an oil. Treatment of 6 with aqueous tri-

fluoroacetic acid at room temperature gave the desired 1-β-D-ribofuranosylpyrrole-3-carbonitrile (7) in excellent yield, in which the carbonitrile function was available for further transformation reactions. The presence of nitrile function in 7 was confirmed by the IR spectrum which revealed a sharp absorption band at 2220 cm^{-1}. Hydrolysis of 7 with NH_4OH and H_2O_2 (30%) and purification of the reaction product gave one of the target nucleosides viz., 2,4-dideazaribavirin (2) in good yield. Transformation of 7 to the corresponding 3-thiocarboxamide derivative (8a) was effected in 80% yield by treatment of 7 with H_2S in dry pyridine and Et_3N at room temperature.



The target brunfelsamidine ribonucleoside (8c) was prepared in the following manner. When 7 was allowed to react with free NH_2OH in EtOH at reflux temperature, 1-β-D-ribofuranosylpyrrole-3-carboxamidoxime (8b) was formed in almost quantitative yield. Catalytic hydrogenation of 8b in the presence of Raney nickel and NH_4Cl at 45 psi for 12 h furnished a 69% yield of 8c, isolated as the hydrochloride salt. Our attempts to convert 7 directly to 8c with liquid NH_3/NH_4Cl was not fruitful.

The anomeric configuration of the isolated pyrrole ribonucleosides (6, 7, and 8) were assigned as β on the basis of ^{1}H NMR data. ^{1}H NMR spectrum of 6 in DMSO-d_6 exhibited a much smaller coupling constant ($J_{1',2'}$ = 3.1 Hz) than that of 7 ($J_{1',2'}$ = 5.7 Hz) and also revealed the difference between the chemical shift of the two methyl signals of the isopropylidene group as 0.23 ppm, which is characteristic of the β-configuration[10]. Moreover, the ^{1}H NMR of 7 in DMSO-d_6 revealed the anomeric doublet centered at δ 5.48 with a small coupling constant ($J_{1',2'}$= 4.5 Hz), which is within the acceptable limits for β-ribonucleosides[11].

Synthesis of these aromatic pyrrole nucleosides by the stereospecific sodium salt glycosylation procedure has the advantage that it is operationally very smooth and the unreacted base can be recovered quantitatively and reused. This method is very convenient and straightforward and provides a route to the preparation of a wide variety of pyrrole ribonucleosides with different substitution patterns that is not normally possible through the other methods reported in the literature[7].

All compounds 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 compounds are devoid of any significant biological effects in these systems.

EXPERIMENTAL SECTION: Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were determined at 300 MHz with IBM NR/300 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The presence of solvent as indicated by elemental analysis was verified by ^{1}H NMR. Infrared spectra (IR in potassium bromide) were recorded with a Perkin-Elmer 1420-spectrophotometer and ultraviolet spectra (UV; sh = shoulder) with a Beckman DU-50 spectrophotometer. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J. Thin-layer chromatography (TLC) was run on silica gel 60 F-254 plates (EM Reagents). E. Merck silica gel (230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Carbon tet-

rachloride was distilled from P_2O_5 and stored over Linde 3A molecular sieves. Detection of nucleoside components on TLC was by UV light and with 10% sulfuric acid in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30°.

1-(2,3-O-Isopropylidene-5-O-(t-butyl)dimethylsilyl-β-D-ribofuranosyl)pyrrole-3-carbonitrile (6). To a stirred solution of 4 (1.84 g, 20 mmol) in dry CH_3CN (50 ml) was added NaH (60% in oil, 0.8 g, 20 mmol) in small portions. After the addition of NaH, the reaction mixture was stirred at room temperature for 0.5 h. 1-Chloro-2,3-O-isopropylidene-5-O-(t-butyl)dimethylsilyl-α-D-ribofuranose[9b] (5, 3.22 g, 10 mmol, in dry THF) was added and the stirring was continued at room temperature for 15 h. The reaction mixture was evaporated to dryness and the residue was suspended in water (30 ml). The aqueous solution was extracted with EtOAc (2 x 75 ml) and the organic extract was washed with H_2O (50 ml), saturated brine solution (30 ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness to give an oil. The oil was purified on a flash silica gel column using hexane → CH_2Cl_2 gradient to give 2.5 g (66%, based on halogenose) of the title compound; IR (neat) ν 2220 (C ≡ N) cm^{-1}; UV λ_{max} (MeOH) 223 nm (ε 10,940); ^1H NMR (Me_2SO-d_6) δ 0.11 (s, 6, $2CH_3$), 0.92 (s, 9, t-butyl), 1.38 and 1.61 (2 s, 6, isopropylidene), 5.66 (d, 1, J = 3.1 Hz, C_1,H), 6.46 (m, 1, C_4H), 6.89 (t, 1, C_5H), 7.46 (t, 1, C_2H) and other sugar protons. Anal. Calcd for $C_{19}H_{30}N_2SiO_4$ (378.51): C, 60.28; H, 7.99; N, 7.39. Found: C, 60.26, H, 8.13; N, 7.19.

1-β-D-Ribofuranosylpyrrole-3-carbonitrile (7). A solution of 6 (2.1 g, 5.55 mmol) in trifluoroacetic acid (17 ml) and H_2O (3 ml) was stirred at room temperature for 0.5 h. The solvent was evaporated to dryness and the residue was dissolved in MeOH (20 ml) and again evaporated to dryness. This process was repeated for 3 times to remove the last traces of trifluoroacetic acid. The crude product was purified by flash chromatography over silica gel using CH_2Cl_2/acetone (7:3) as eluent. The pure fractions were pooled together, evaporated to dryness and the residue was crystallized from hot acetone/hexane mixture to give 1.2 g (96%) of 7 as colorless powder; mp 140-142°C; IR (KBr) ν 2220 (C≡N) cm^{-1}; UV λ_{max} (pH 1) 222 nm (ε 14,890); (pH 7) 222 nm (ε 15,650); (pH 11) 220 nm (ε 15,780); ^1H NMR (Me_2SO-d_6) δ 5.48 (d, 1, J = 5.7 Hz,

C_1,H), 6.50 (m, 1, C_4H), 7.17 (t, 1, C_5H), 7.84 (t, 1, C_2H) and other sugar protons. Anal. Calcd for $C_{10}H_{12}N_2O_4$ (224.19): C, 53.56; H, 5.39; N, 12.49. Found: C, 53.58; H, 5.37; N, 12.34.

1-β-D-Ribofuranosylpyrrole-3-carboxamide (2,4-Dideazaribavirin, 2). 1-β-D-Ribofuranosylpyrrole-3-carbonitrile (7, 0.25 g, 1.12 mmol) was dissolved in CH_3OH (15 ml), H_2O (5 ml) and treated with NH_4OH (20 ml), H_2O_2 (30%, 5 ml). The reaction mixture was stirred at room temperature in a pressure bottle for 10 h. The pressure bottle was cooled, opened carefully and the contents evaporated to dryness. The residue was purified by flash chromatography over silica gel using CH_2Cl_2/MeOH (9:1) as the eluent. The pure fractions were pooled together and evaporated to give 0.20 g (74%) of 2 as hygroscopic amorphous solid; IR (KBr) ν 1650 ($CONH_2$), 3300-3400 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 231 nm (ε 7,650); (pH 7) 229 nm (ε 7,690); (pH 11) 229 nm (ε 7,550); ^{1}H NMR (Me_2SO-d_6) δ 5.38 (d, 1, J = 5.85 Hz, C_1,H), 6.46 (m, 1, C_4H), 6.94 (m, 1, C_5H), 6.73 and 7.33 (2 br s, 2, $CONH_2$) 7.46 (m, 1, C_2H) and other sugar protons. Anal. Calcd for $C_{10}H_{14}N_2O_5 \cdot 1/2\ H_2O$ (242.21): C, 47.81; H, 6.02; N, 11.15. Found: C, 47.57; H, 5.78; N, 11.22.

1-β-D-Ribofuranosylpyrrole-3-thiocarboxamide (8a). To a stirred solution of 7 (0.30 g, 1.34 mmol) in anhydrous pyridine (50 ml) containing Et_3N (5 ml) was passed H_2S gas at room temperature for 3 h. The reaction mixture was then stirred in a sealed reaction vessel at room temperature for another 12 h. The reaction mixture was purged with nitrogen to remove the excess H_2S and then evaporated to dryness. The residue was adsorbed onto silica gel (2 g) and placed on top of a silica gel column (3 x 30 cm) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2/acetone (1:1, 300 ml) and CH_2Cl_2/MeOH (9:1, 500 ml). The fractions containing the pure product were pooled together and evaporated to dryness. The residue was crystallized from MeOH/CH_2Cl_2 to yield 0.25 g (72%) of 8a; mp 198-201°C; IR (KBr) ν 1260 (C = S), 3200-3400 (NH_2, OH) cm^{-1}; UV λ_{max}(pH 1) 256 nm (ε 12,215), 304 (ε 12,295); (pH 7) 256 nm (ε 12,650), 302 (ε 12,420); (pH 11) 255 nm (ε 11,390), 302 (ε 11,660); ^{1}H NMR (Me_2SO-d_6) δ 5.40 (d, 1, J = 5.8 Hz, C_1,H), 6.60 (m, 1, C_4H), 6.98 (t, 1, C_5H), 7.63 (s, 1, C_2H), 8.82 and 9.01 (2 s, 2, $CSNH_2$) and other sugar protons. Anal. Calcd for $C_{10}H_{14}N_2O_4S$ (258.21): C, 46.51; H, 5.46; N, 10.84; S, 12.39. Found: C, 46.80; H, 5.27; N, 10.68; S, 12.06.

1-β-D-Ribofuranosylpyrrole-3-carboxamidoxime (8b). A solution of 7 (0.8 g, 3.57 mmol) and free NH_2OH (1.2 g, 36.4 mmol) in dry EtOH(35 ml) was heated at reflux for 2 h and stirred at room temperature for 15 h. EtOH was evaporated and the residue was purified by flash chromatography over silica gel using CH_2Cl_2/MeOH (7:3) as eluent to give 0.60 g (65%) of **8b** as hygroscopic amorphous solid; IR (neat) ν 3300-3400 (NH_2, OH) cm^{-1}; UV λ_{max} (MeOH) 206 nm (ε 12,800), 240 (sh) (ε 5,140); ^1H NMR (Me_2SO-d_6) δ 5.35 (d, 1, J = 5.75 Hz, C_1,H), 5.50 (s, 2, C(NOH)NH_2), 6.26 (m, 1, C_4H), 6.91 (t, 1, C_5H), 7.28 (s, 1, C_2H), 9.01 (br s, 1, C(NOH)NH_2) and other sugar protons. Anal. Calcd for $C_{10}H_{15}N_3O_5 \cdot 1/2H_2O$ (257.22): C, 45.12; H, 6.06; N, 15.77. Found: C, 45.48; H, 6.40; N, 15.39.

1-β-D-Ribofuranosylpyrrole-3-carboxamidine Hydrochloride (8c). A solution of **8b** (0.70 g, 2.72 mmol), Raney nickel (1 g) and NH_4Cl (0.15 g, 2.75 mmol) in 50% aqueous EtOH (50 ml) was shaken on a Parr hydrogenator at 45 psi for 6 h. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was purified by HPLC using C_{18} reverse phase column and H_2O as the eluent. The pure fractions were pooled together and lyophilized to give 0.60 g (79%) of **8c** as light pink powder; mp >200°C (dec); IR (KBr) ν 3100-3400 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 236 nm (ε 12,490); (pH 7) 236 nm (ε 12,580); (pH 11) 237 nm (ε 12,160); ^1H NMR (Me_2SO-d_6) δ 5.48 (d, 1, J = 5.70 Hz, C_1,H), 6.83 (s, 1, C_4H), 7.19 (s, 1, C_5H), 8.13 (s, 1, C_2H), 8.59 (s, 2, NH_2), 8.92 (s, 2, NH.HCl) and other sugar protons. Anal. Calcd for $C_{10}H_{16}ClN_3O_4$ (277.73): C, 43.24; H, 5.81; N, 15.12; Cl, 12.78. Found: C, 43.37; H, 5.78; N, 15.19; Cl, 12.83.

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