Synthesis of 2'-Deoxyribofuranosyl Indole Nucleosides Related to the Antibiotics SF-2140 and Neosidomycin

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Dedicated to Professor Norman H. Cromwell

The 2'-deoxyribofuranose analog of the naturally occurring antibiotics SF-2140 and neosidomycin were prepared by the direct glycosylation of the sodium salts of the appropriate indole derivatives, with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*pentofuranose (**5**). Thus, treatment of the sodium salt of 4-methoxy-1*H*-indol-3-ylacetonitrile (**4a**) with **5** provided the blocked nucleoside, 4-methoxy-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**6a**), which was treated with sodium methoxide to yield the SF-2140 analog, 4-methoxy-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**7a**). The neosidomycin analog (**8**) was prepared by treatment of the sodium salt of 1*H*-indol-3-ylacetonitrile (**4b**) with **5** to obtain the blocked intermediate 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**6b**) followed by sodium methoxide treatment to give 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**7b**) and finally conversion of the nitrile function of **7b** to provide 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetamide (**8**). In a similar manner, indole (**9a**) and several other substituted indoles including 1*H*-indole-4-carbonitrile (**9b**), 4-nitro-1*H*-indole (**9c**), 4-chloro-1*H*-indole-2-carboxamide (**9d**) and 4-chloro-1*H*-indole-2-carbonitrile (**9e**) were each glycosylated and deprotected to provide 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**11a**), 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-4-carbonitrile (**11b**), 4-nitro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**11c**), 4-chloro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carboxamide (**11d**) and 4-chloro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carbonitrile (**11e**), respectively.

The 2'-deoxyadenosine analog in the indole ring system was prepared for the first time by reduction of the nitro group of **11c** using palladium on carbon thus providing 4-amino-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**16**, 1,3,7-trideaza-2'-deoxyadenosine).

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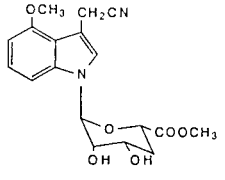
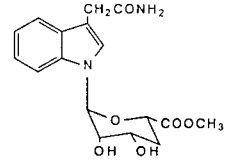
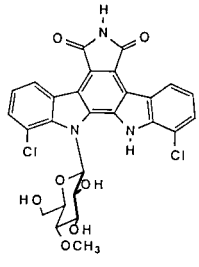
The naturally occurring antibiotics SF-2140 (**1**) [1] and neosidomycin (**2**) [2] are the only examples of simple indole-*N*-glycosides of biological origin so far reported. The antibiotic rebeccamycin (**3**) contains an *N*-glycoside of a fused indole (indolocarbazole) moiety and exhibits *in vivo* antitumor activity against P388 and L1210 leukemias and B16 melanoma in mice [3]. SF-2140 exhibits good *in vitro* and *in vivo* antiviral activity against several strains of influenza virus as well as weak *in vitro* antibacterial activity against certain Gram-positive and Gram-negative bacteria [1]. Neosidomysin shows weak activity against certain Gram-negative organisms [2]. SF-2140 and neosidomycin have related aglycons and spectral data indicate that they share a common glycosyl moiety; methyl (4-deoxy-α-D-*lyxo*hexopyranosid)uronate [1].



1
SF-2140



2
NEOSIDOMYCIN



3
REBECCAMYCIN

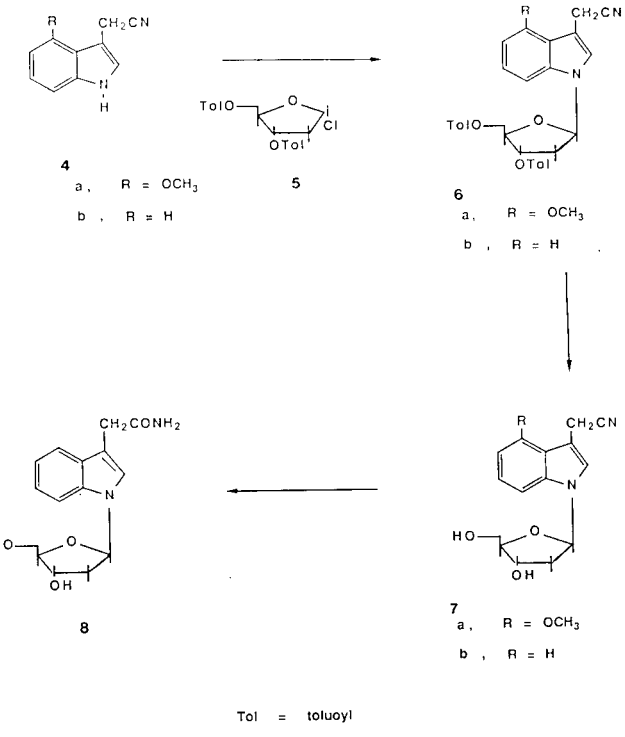
Our interest in the synthesis of analogs of SF-2140 as possible antiviral agents was generated by the report [1] that SF-2140 was reported to be superior to amantadine with respect to percent survivors when given orally to influenza virus (A_0/PR-8) infected mice. We now report the synthesis of 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-4-methoxy-1*H*-indol-3-ylacetonitrile (**7a**) and 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetamide (**8**) (the 2'-deoxyribofuranose analog of SF-2140 and neosidomycin, respectively) as well as the 2'-deoxyadenosine analog in the indole ring system, 4-amino-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**16**).

Indole nucleosides have previously been synthesized primarily by the indoline-indole method [4,5]. Recently however, we have found the sodium salt glycosylation procedure to be generally applicable to several pyrrole [6,7] and fused pyrrole [8-11] ring systems for the direct preparation of cetain 2'-deoxyribo and arabinofuranosyl nucleosides without the required hydrogenation-dehydrogenation steps as in the indoline-indole procedure. The application of this stereospecific sodium salt glycosylation procedure to a variety of substituted indoles was found to be remarkably successful and represents the first report of the formation of an *N*-glycoside by direct attachment of a 2-deoxyribose moiety to a fully aromatic preformed indole.

The sodium salt of 4-methoxy-1*H*-indol-3-ylacetonitrile (**4a**) [12], generated *in situ* by treatment of **4a** with sodium hydride in dry acetonitrile, was reacted with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*pentofuranose (**5**) [13] at room temperature to yield 4-methoxy-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**6a**) in 90% yield (Scheme I). No α-isomer product was detected in this reaction mixture or in any of the other glycosylation reactions performed in this study. Removal of the ester protective groups of **6a** by sodium methoxide treatment gave the target SF-2140 analog, 1-(2-deoxy-β-D-ribofuranosyl)-4-methoxy-1*H*-indol-3-ylacetonitrile (**7a**), in 87% yield. The anomeric configuration of **7a** was verified as β by ^{1}H nmr spectroscopy in which the characteristic pseudotriplet pattern was observed for the anomeric proton signal. A pseudotriplet pattern has been observed for the anomeric proton of many other 2'-deoxy-β-D-ribofuranosyl nucleosides [7,9-11,14,15].

The synthesis of the neosidomycin analog was accomplished in a manner similar to that for the SF-2140 analog, **7a**, (Scheme I). The sodium salt of 1*H*-indol-3-ylacetonitrile (**4b**) [16] was treated with the α-chlorosugar, **5**, to provide the blocked β-nucleoside, 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-ribofuranosyl)-1*H*-indol-3-ylacetonitrile (**6b**) in 70% yield. Reaction of **6b** with sodium methoxide provided a 75% yield of 1-(2-deoxy-β-D-ribofuranosyl)-1*H*-indol-3-ylacetonitrile (**7b**). The target analog of neosidomycin, 1-(2-deoxy-β-D-ribofuranosyl)-1*H*-indol-3-ylacetamide (**8**), was then obtained in 56% yield by treatment of **6b** with a mixture of sodium hydroxide and hydrogen peroxide. The structural assignment of the anomeric configuration was again made on the basis of ^{1}H nmr.

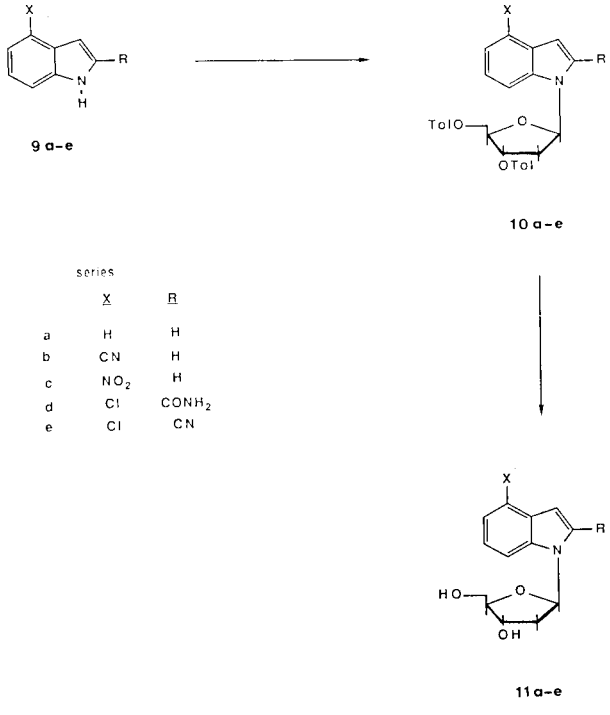
Scheme I



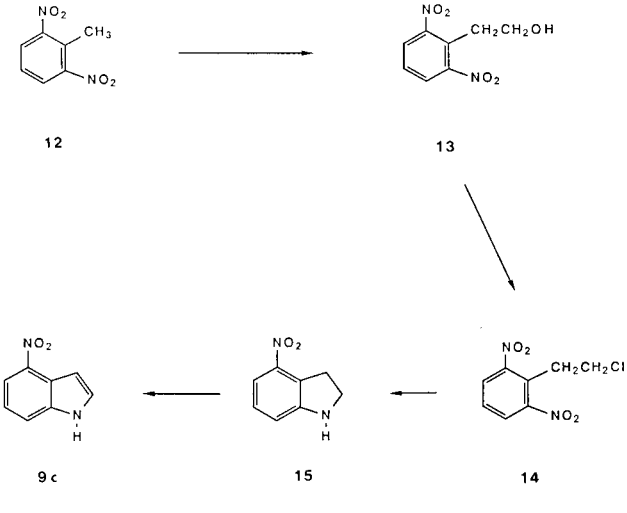
This sodium salt glycosylation procedure was extended to several other indoles including indole itself (**9a**), 1*H*-indole-4-carbonitrile (**9b**) [17], 4-nitro-1*H*-indole (**9c**) [18], 4-chloro-1*H*-indole-2-carboxamide (**9d**) [19], and 4-chloro-1*H*-indole-2-carbonitrile (**9e**) [20] (Scheme II). Thus, indole was glycosylated in 70% yield to give 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indole (**10a**). Deprotection of **10a** with sodium methoxide provided 1-(2-deoxy-β-D-*erythro*pentofuranosyl-1*H*-indole (**11a**) in 85% yield. Similarly, glycosylation of 1*H*-indole-4-carbonitrile (**9b**) gave 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-1*H*-indole-4-carbonitrile (**10b**) in 79% yield. Removal of the blocking groups of **10b** by sodium methoxide treatment provided 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-4-carbonitrile (**11b**). When 4-nitro-1*H*-indole (**9c**) was employed as the aglycon for glycosylation, an 82% yield of 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-4-nitro-1*H*-indole (**10c**) was obtained. The sugar protective groups were then removed to yield 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-4-nitro-1*H*-indole (**11c**) in 96% yield. The starting aglycon itself, 4-nitro-1*H*-indole (**9c**), was prepared (Scheme III) by a procedure similar to the general procedure described by Bakke [18] (although Bakke did not actually report 4-nitro-1*H*-indole). Thus, 2,6-dinitrotoluene was treated with paraformaldehyde and potassium *t*-butoxide to yield 2-(2,6-di-

nitrophenyl)ethanol (**13**) in 77% yield. Treatment of **13** with thionyl chloride in pyridine furnished 1-(2-chloroethyl)-2,6-dinitrobenzene (**14**) in 74% yield. Ring closure of **14** with hydrochloric acid in the presence of iron provided a 73% yield of 4-nitro-2,3-dihydro-1*H*-indole (**15**). The desired 4-nitro-1*H*-indole (**9c**) was obtained in 70% yield by catalytic dehydrogenation using palladium on carbon, or by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Scheme II

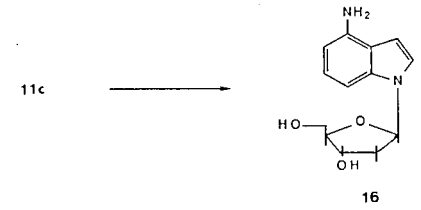


Scheme III



In the 2,4-disubstituted series, 4-chloro-1*H*-indole-2-carboxamide (**9d**) was glycosylated in 60% yield to furnish 4-chloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl-1*H*-indole-2-carboxamide (**10d**). Treatment of **10d** with sodium methoxide provided a 77% yield of 4-chloro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carboxamide (**11d**). Finally, glycosylation of 4-chloro-1*H*-indole-2-carbonitrile (**9e**) resulted in a 57% isolated yield of protected nucleoside, 4-chloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carbonitrile (**10e**), which, upon treatment with sodium methoxide gave 4-chloro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carbonitrile (**11e**) in 75% yield.

The 2'-deoxyadenosine indole ring analog (1,3,7-trideaza-2'-deoxyadenosine) was prepared by treating 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-4-nitro-1*H*-indole (**11c**) with palladium on carbon in a hydrogen atmosphere providing a 74% yield of 4-amino-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**16**). It should be noted that the β-D-ribofuranosyl derivatives of both **16** [21] and **11c** [22], have been prepared by the indoline-indole method.



The exclusive formation of the 2'-deoxyribofuranosyl-nucleosides possessing the β-configuration in the glycosylation reactions of these indoles by this sodium salt procedure is predicted from previous studies published from our laboratory [6-11]. The stereospecific attachment of the 2-deoxy-β-D-ribofuranosyl moiety to these indoles appears to be due to a Walden inversion at the C_1 sugar carbon by the anionic heterocyclic nitrogen (S_N2 mechanism).

EXPERIMENTAL

General Procedures.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H nmr) spectra were determined at 300.1 MHz with an IBM NR300AF spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Ultraviolet spectra (uv: sh = shoulder) were recorded on a Beckman DU-50 spectrophotometer. Elemental analyses were performed by Robertson Laboratories, Madison, N.J. Evaporations were carried out under reduced pressure with the bath temperature below 40°. 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.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-4-methoxy-1*H*-indol-3-ylacetonitrile (**6a**).

A solution of 4-methoxy-1*H*-indol-3-ylacetonitrile (**4a**, 1.12 g, 6 mmoles) [12] in dry acetonitrile (125 ml) was treated with sodium hydride (0.32 g, 7.2 mmoles, 60% in oil) and the mixture stirred at room temperature for 30 minutes. The sugar 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*pentofuranose (**5**, 2.8 g, 7.2 mmoles) was then added and the reaction mixture was stirred overnight at room temperature, filtered and

evaporated to dryness under reduced pressure. The crude product was purified by flash silica gel column chromatography using petroleum ether-ethyl acetate (4:1, v/v) to give a colorless solid which was crystallized from methanol to afford **6a** (2.9 g, 90%) as colorless needles, mp 129-130°; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.00-6.58 (m, 11H, aromatic protons), 7.44 (s, 1H, C_2H), 6.52 ("t", 1H, C_1·H), 3.97 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), and other sugar protons.

Anal. Calcd. for $C_{32}H_{30}N_2O_4 \cdot H_2O$: C, 69.06; H, 5.79; N, 5.03. Found: C, 69.36; H, 5.96; N, 4.86.

1-(2-Deoxy-β-D-*erythro*pentofuranosyl)-4-methoxy-1*H*-indol-3-ylacetonitrile (**7a**).

To a solution of **6a** (2.15 g, 4 mmoles) in dry methanol (200 ml) was added sodium methoxide until a *p*H of about 12 (by indicator paper) was attained. The mixture was stirred overnight at room temperature, then filtered and evaporated to dryness under reduced pressure. The residue was adsorbed on silica gel and subjected to silica gel flash column chromatography using chloroform-acetone (2:1, v/v) to give **7a** which was crystallized from dioxane to give a colorless crystalline solid (1.05 g, 87%), mp 114-115°; uv λ max (*p*H 1, 7, 11): 264 nm (ε 5100), 283 (4800), 293 (5700); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.47 (s, 1H, C_2H), 7.14 (m, 2H, C_5H, C_6H), 6.65 (d, J = 7.53 Hz, 1H, C_7H), 6.32 ("t", 1H, C_1·H), 4.05 (s, 2H, CH_2), 3.88 (s, 1H, OCH_3), and other sugar protons.

Anal. Calcd. for $C_{16}H_{18}N_2O_4 \cdot 0.25H_2O$: C, 62.63; H, 6.07; N, 9.12. Found: C, 62.97; H, 6.13; N, 8.89.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**6b**).

Glycosylation of 1*H*-indol-3-ylacetonitrile (**4b**, 1.56 g, 10 mmoles) [16] in dry acetonitrile (150 ml) was accomplished by the same procedure as described for **6a** using sodium hydride (0.48 g, 12 mmoles, 60% in oil), and the α-chloro-deoxysugar, **5**, (4.66 g, 12 mmoles). The residual oil was purified by silica gel flash column chromatography using hexane-ethyl acetate (4:1, v/v) to give a colorless foam (3.5 g, 70%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.02-7.12 (m, 13H, aromatics), 6.61 ("t", 1H, C_1·H), 4.01 (s, 1H, CH_2), and other sugar protons.

Anal. Calcd. for $C_{37}H_{28}N_2O_5$: C, 73.21; H, 5.55; N, 5.50. Found: C, 72.98; H, 5.59; N, 5.29.

1-(2-Deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetonitrile (**7b**).

The title compound was prepared by the method described for **7a** starting with **6b** (2.54 g, 5 mmoles). Purification of the residue by silica gel flash column chromatography using chloroform-acetone (1:1, v/v) gave **7b** as a colorless solid. Recrystallization from dioxane gave colorless needles (1.0 g, 75%), mp 113-115°; uv λ max (*p*H 1, 7, 11): 267 nm (ε 8,800); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.62-7.10 (m, 4H, $C_{4,5,6,7}$Hs), 7.59 (s, 1H, C_2H), 6.38 ("t", 1H, C_1·H), and other sugar protons.

Anal. Calcd. for $C_{15}H_{16}N_2O_3 \cdot 0.25H_2O$: C, 65.09; H, 6.00; N, 10.12. Found: C, 65.15; H, 6.09; N, 10.30.

1-(2-Deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indol-3-ylacetamide (**8**).

Compound **7b** (0.59 g, 1.80 mmoles), ethanol (4 ml) and hydrogen peroxide (0.6 g, 7.0 mmoles, 30%) were mixed and cooled to 5°. Aqueous sodium hydroxide (0.2 ml, 6.3 *N*) was added dropwise and the mixture was heated at 50° for 6 hours, evaporated to dryness and the residue was purified by flash silica gel column chromatography using methylene chloride-methanol (5:1, v/v) to provide **8** (0.3 g, 56%) as a colorless solid, mp 137-139°; uv λ max (*p*H 1, 7, 11): 269 nm (ε 6,500); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.56 and 6.89 (2s, 2H, NH_2, exchangeable), 7.54-7.02 (m, 4H, $C_{4,5,6,7}$H), 7.41 (s, 1H, C_2H), 6.35 ("t", 1H, C_1·H), and other sugar protons.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.95; H, 6.18; N, 9.39.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indole (**10a**).

This compound was prepared in the same manner as described for **6a** using indole (3.5 g, 30 mmoles), dry acetonitrile (300 ml), sodium hydride (1.44 g, 36 mmoles) and the chlorosugar **5** (14.1 g, 36 mmoles) [13]. The residue was purified by flash chromatography on silica gel using toluene-ethyl acetate (6:1) to give **10a** as a colorless syrup (9.9 g, 70%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.02-7.06 (m, 13H, aromatics), 6.62 ("t", 1H, C_1·H), and other sugar protons.

Anal. Calcd. for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.88. Found: C, 74.50; H, 5.97; N, 2.77.

1-(2-Deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**11a**).

Compound **10a** (4.7 g, 10 mmoles) in methanol (150 ml) was deprotected with sodium methoxide exactly as described for the preparation of **7a**. The residue was purified by flash chromatography on silica using chloroform-methanol (9:1, v/v) furnishing **11a** (2.0 g, 85%) as a colorless solid, mp 101-103°; uv λ max (*p*H 1, 7, 11): 266 nm (ε 5,800); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.03 (t, 1H, C_6H), 8.01-7.27 (m, 5H, aromatics), 6.68 (d, J = 3.03 Hz, 1H, C_3H), 4.69 ("t", 1H, C_1·H), and other sugar protons.

Anal. Calcd. for $C_{13}H_{15}NO_3 \cdot 0.5H_2O$: C, 64.46; H, 6.61; N, 5.78. Found: C, 64.49; H, 6.76; N, 5.40.

1-(2-Deoxy-3,5,-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indole-4-carbonitrile (**10b**).

Glycosylation of 1*H*-indole-4-carbonitrile (**9b**, 2.84 g, 20 mmoles) [16] in dry acetonitrile (300 ml) was accomplished according to the procedure for **6a** using sodium hydride (0.96 g, 24 mmoles, 60% suspension) and the α-chlorosugar **5** (9.4 g, 24 mmoles). The residue was purified by flash column chromatography using toluene-ethyl acetate (10:1, v/v) to give **10b** (7.8 g, 79%) as a colorless solid, mp 155-156°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 6.73 ("t", 1H, C_1·H), and other aromatic and sugar protons.

Anal. Calcd. for $C_{30}H_{26}N_2O_5$: C, 72.87; H, 5.26; N, 5.67. Found: C, 72.95; H, 5.35; N, 5.57.

1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-4-carbonitrile (**11b**).

Deprotection of **10b** (5.0 g, 10 mmoles) in methanol-dioxane (150 ml, 1:1) using sodium methoxide as in the procedure for the preparation of **7a** followed by purification of the crude product by silica gel flash chromatography with chloroform-methanol (9:1, v/v) provided **11b** (2.0 g, 78%) as colorless crystals, mp 112-113°; uv λ max (*p*H 1, 7, 11): 304 nm (ε 12,250); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.02 (m, 2H, C_2H, C_5H), 7.58 (d, J = 7.35 Hz, 1H, C_7H), 7.31 (t, 1H, C_6H), 6.66 (d, J = 3.24 Hz, 1H, C_3H), 6.48 ("t", 1H, C_1·H), and other sugar protons.

Anal. Calcd. for $C_{14}H_{14}N_2O_3 \cdot 0.25H_2O$: C, 64.00; H, 5.37; N, 10.06. Found: C, 64.20; H, 5.55; N, 9.96.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-4-nitro-1*H*-indole (**10c**).

The glycosylation of 4-Nitro-1*H*-indole (**9c**, 1.0 g, 6 mmoles) [17] was performed in the same manner as described for **6a** using 100 ml dry acetonitrile, sodium hydride (0.272 g, 6.8 mmoles, 60% suspension) and **5** (2.79 g, 7.2 mmoles). The reaction mixture was worked up as usual and the crude product was crystallized from benzene-cyclohexane (1:2, v/v) to give a pale yellow crystalline solid (2.6 g, 82%), mp 140-141°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 6.73 ("t", 1H, C_1·H), and other aromatic and sugar protons.

Anal. Calcd. for $C_{29}H_{26}N_2O_7$: C, 67.70; H, 5.06; N, 5.45. Found: C, 67.43; H, 5.18; N, 5.41.

1-(2-Deoxy-β-D-*erythro*pentofuranosyl)-4-nitro-1*H*-indole (**11c**).

Compound **10c** (1.54 g, 3 mmoles) in dry methanol (50 ml) was deprotected as described for **7a** and the residue was purified by flash silica gel column chromatography using chloroform-methanol (7:1, v/v) to furnish **11c** as a yellow solid (0.8 g, 96%), mp 103-104°; uv λ max (*p*H 1, 7, 11): 240 nm (ε 11,100), 379 (6,700); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.17 (d, J = 7.90 Hz, 1H, C_5H), 8.09 (d, J = 7.90 Hz, 1H, C_7H), 8.03 (d, J = 3.30 Hz, 1H, C_2H), 7.37 (t, 1H, C_6H), 7.10 (d, J = 3.30 Hz, 1H, C_3H), 6.51 ("t", 1H, C_1·H), and other sugar protons.

Anal. Calcd. $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.04; N, 10.07. Found: C, 55.90; H, 5.21; N, 9.86.

4-Amino-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole (**16**).

(1,3,7-Trideaza-2'-deoxyadenosine).

To a solution of **11c** (0.56 g, 2 mmoles) in ethanol (30 ml, 95%) was added palladium on carbon (100 mg, 5%) and the mixture was hydrogenated at 20 psi at room temperature for 6 hours. The reaction mixture was filtered through celite and the filtrate was evaporated to dryness. The residue was purified on a flash silica gel column using chloroform-methanol (8:1, v/v) as eluent to give **16** (0.37 g, 74%) as an off-white crystalline solid, mp 183-185°; uv λ max (*p*H 1): 275 nm (ε 10,100); uv λ max (*p*H 7, 11): 269 nm (ε 12,400), 292 (9,300); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.30 (d, J = 3.30 Hz, 1H, C_2H), 6.63 (t, 1H, C_6H), 6.70 (d, J = 7.82 Hz, 1H, C_7H), 6.58 (d, J = 3.30 Hz, 1H, C_3H), 6.21 ("t", 1H, $C_1'H$), 6.19 (d, J = 7.82 Hz, 1H, C_5H), and other sugar protons.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49; N, 11.28. Found: C, 63.11; H, 6.22; N, 11.45.

4-Chloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carboxamide (**10d**).

Glycosylation of 4-chloro-1*H*-indole-2-carboxamide (**9d**, 1.95 g, 10 mmoles) [19] was accomplished as described for **6a** using acetonitrile (200 ml), sodium hydride (0.42 g, 11 mmoles; 60% in oil) and **5** (4.7 g, 12 mmoles). The reaction mixture was worked up in the usual manner and the crude product was crystallized from ethanol to give **10d** as colorless needles (3.35 g, 60%), mp 104-105°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.26 and 7.65 (2s, 2H, NH_2), exchangeable), 7.93-7.10 (m, 11H, aromatics), 7.21 (s, 1H, C_3H), 6.77 ("t", 1H, $C_1'H$), and other sugar protons.

Anal. Calcd. for $C_{30}H_{27}ClN_2O_6$: C, 65.87; H, 4.94; N, 5.12; Cl, 6.49. Found: C, 65.73; H, 4.79; N, 4.95; Cl, 6.63.

4-Chloro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carboxamide (**11d**).

Compound **10d** (1.6 g, 3 mmoles) was treated with sodium methoxide exactly as described for the preparation of **11c** and the resulting crude material was purified by silica gel flash column chromatography using chloroform-methanol (9:1, v/v) to obtain **11d** (0.72 g, 77%) as colorless crystals, mp 170°; uv λ max (*p*H 1, 7, 11): 280 nm (ε 14,600); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.20 and 7.61 (2s, 2H, NH_2, exchangeable), 7.92 (m, 1H, C_6H), 7.18 (m, 2H, C_5H and C_7H), 7.14 (s, 1H, C_3H), 7.07 ("t", 1H, $C_1'H$), and other sugar protons.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_3$: C, 54.11; H, 4.86; N, 9.02; Cl, 11.43. Found: C, 53.83; H, 4.90; N, 8.80; Cl, 11.61.

4-Chloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carbonitrile (**10e**).

A solution of 4-chloro-1*H*-indole-2-carbonitrile (**9e**, 1.76 g, 10 mmoles) [19] was gylcosylated using dry acetonitrile (150 ml), sodium hydride (0.4 g, 11 mmoles, 60% in oil), and **5** (4.76 g, 12 mmoles) as described for the preparation of **6a**. The residue, after the usual workup, was subjected to silica gel flash column chromatography using hexane-ethyl acetate (5:1, v/v) and the solid obtained was crystallized from cyclohexane to give **10e** (3.0 g, 57%) as a colorless crystalline solid, mp 101-102°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.67 (s, 1H, C_3H), 6.71 ("t", 1H, $C_1'H$), and other aromatic and sugar protons.

Anal. Calcd. for $C_{30}H_{25}ClN_2O_5$: C, 68.12; H, 4.73; N, 5.30; Cl, 6.72. Found: C, 68.02; H, 4.71; N, 5.26; Cl, 6.83.

4-Chloro-1-(2-deoxy-β-D-*erythro*pentofuranosyl)-1*H*-indole-2-carbonitrile (**11e**).

Deprotection of **10e** (1.6 g, 3 mmoles) was achieved as described for the preparation of **7a** and the residue, after workup, was adsorbed on silica gel and purified by flash column techniques using chloroform-methanol (9:1, v/v). Compound **11e** was obtained as colorless needles after recrystallization from dioxane-ethanol (1:1, v/v) (0.67 g, 75%), mp 107-108°; uv λ max (*p*H 1, 7, 11): 278 nm (ε 14,600); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.88 (d, J = 7.98 Hz, 1H, C_7H), 7.60 (s, 1H, C_3H), 7.39 (t, 1H, C_6H), 7.30 (d, J = 7.98 Hz, 1H, C_5H), 6.48 ("t", 1H, $C_1'H$), and other sugar protons.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_3$: C, 57.43; H, 4.44; N, 9.57; Cl, 12.14. Found: C, 57.24; H, 4.39; N, 9.40; Cl, 12.18.

2-(2,6-Dinitrophenyl)ethanol (**13**).

A mixture of 2,6-dinitrotoluene (**12**) (9.1 g, 50 mmoles) and paraformaldehyde (1.5 g, 50 mmoles) in dry dimethyl sulfoxide (25 ml) was stirred in an argon atmosphere. Potassium *t*-butoxide (0.9 g, 8 mmoles) in *t*-butyl alcohol (10 ml) was added to the mixture which then acquired a deep reddish-brown color. After a reaction time of 5 minutes at room temperature the solution was heated at 70-75° for 10 minutes. After neutralization with hydrochloroic acid, the solution was diluted with water (150 ml). Sodium chloride was added until saturation and the mixture extracted with ethyl acetate (3 x 250 ml) and the organic layer was washed with sodium chloride solution and dried over sodium sulfate. The solvent was removed under reduced pressure and the residual oil was crystallized from hexanes to give 2-(2,6-dinitrophenyl)ethanol as pale yellow needles (8.3 g, 77%), mp 69°; ^{1}H nmr (deuteriochloroform): δ 8.05-7.96 (m, 2H, C_3H and C_5H), 7.60 (t, 1H, C_4H), 3.96 (t, 2H, C_1H_2), 3.12 (t, 2H, C_2H_2), 1.92 (s, 1H, OH, exchangeable).

Anal. Calcd. for $C_8H_8N_2O_5$: C, 45.28; H, 3.77; N, 13.21. Found: C, 45.20; H, 3.95; N, 13.32.

1-(2-Chloroethyl)-2,6-dinitrobenzene (**14**).

Thionylchloride (6 ml) was added dropwise while stirring to a solution of **13** (2.12 g, 10 mmoles) in dry pyridine (40 ml) previously cooled to −10°. The temperature was allowed to rise to room temperature, kept at this temperature for one hour and then heated at 80° for 15 minutes. The solution was cooled and cautiously poured into crushed ice while stirring. The solid which separated was collected by filtration, washed with water until acid-free and air dried. Crystallization from hexanes furnished **14** as colorless plates (1.7 g, 74%), mp 69°; ^{1}H nmr (deuteriochloroform): δ 8.16-8.06 (m, 2H, C_3H and C_5H), 7.76 (t, 1H, C_4H), 3.90 (t, 2H, C_1H_2), 3.50 (t, 2H, C_2H_2).

Anal. Calcd. for $C_8H_7ClN_2O_4$: C, 41.65; H, 3.04; N, 12.05; Cl, 15.40. Found: C, 41.80; H, 3.01; N, 12.07; Cl, 15.42.

4-Nitro-2,3-dihydro-1*H*-indole (**15**).

To a solution of **14** (2.3 g, 10 mmoles) in ethanol (20 ml) was added concentrated hydrochloric acid (0.5 ml) and the solution was brought to boiling. Iron filings (1.7 g) were added in 4 equal portions at 5 minute intervals and the mixture was heated under reflux for 2 hours. The reaction mixture was filtered while hot and the inorganic material washed with ethanol. The combined washings and filtrate were evaporated to give a brownish residue which was purified by silica gel column chromatography using hexane-ethyl acetate (1:1, v/v) to provide **15** as a light brownish-yellow solid (1.2 g, 73%), mp 185-186°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.54; H, 4.88; N, 17.07. Found: C, 58.53; H, 4.95; N, 16.86.

4-Nitro-1*H*-indole (**9c**).

Method A:

A solution of **15** (0.82 g, 5 mmoles) in dry toluene (15 ml) was heated to reflux. Palladium on carbon (100 mg, 10%) was added and the mixture was refluxed for 12 hours. The mixture was filtered through a celite pad and the filtrate was evaporated to dryness under reduced pressure to give **9c** as a yellow solid (0.55 g, 70%), mp 205-207°.

Method B:

A solution of **15** (1.6 g, 10 mmoles) in dry xylene (100 ml) was treated with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 2.27 g, 10 mmoles) and heated under reflux for 2 hours. The solution was cooled and the precipitated hydroquinone was filtered off. The filtrate was evaporated to dryness to give **9c** as a yellow solid (0.80 g, 50%), mp

205-207° (lit [23] 205-206°). Product **9c** prepared by both methods A and B exhibited physicochemical properties identical to those reported for **9c** prepared by the Fischer Indole Synthesis [23].

REFERENCES AND NOTES

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