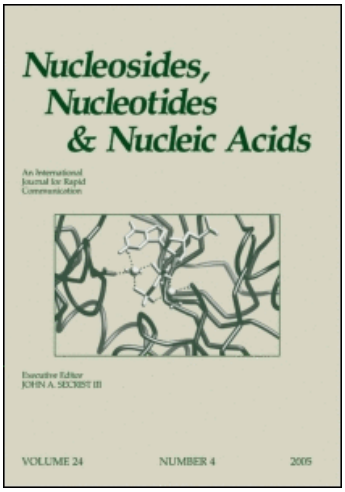

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AN UNEXPECTED NUCLEOPHILIC DISPLACEMENT INVOLVING 6-BROMO-4-CHLORO-5-CYANOPYRROLO[2,3-d]PYRIMIDINE WITH METHANOLIC AMMONIA

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Abstract:

Treatment of 6-bromo-4-chloro-5-cyano-7-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (3) with methanolic ammonia afforded the unexpected 6-amino-4-chloro-5-cyano-7-(2-deoxy-β-D-erythro-pentofuranosyl)-pyrrolo[2,3-d]pyrimidine (4). Hydrogenation of 4 with palladium-charcoal afforded the dehalogenated product 5, an isomer of 2'-deoxytoyocamycin.

Introduction:

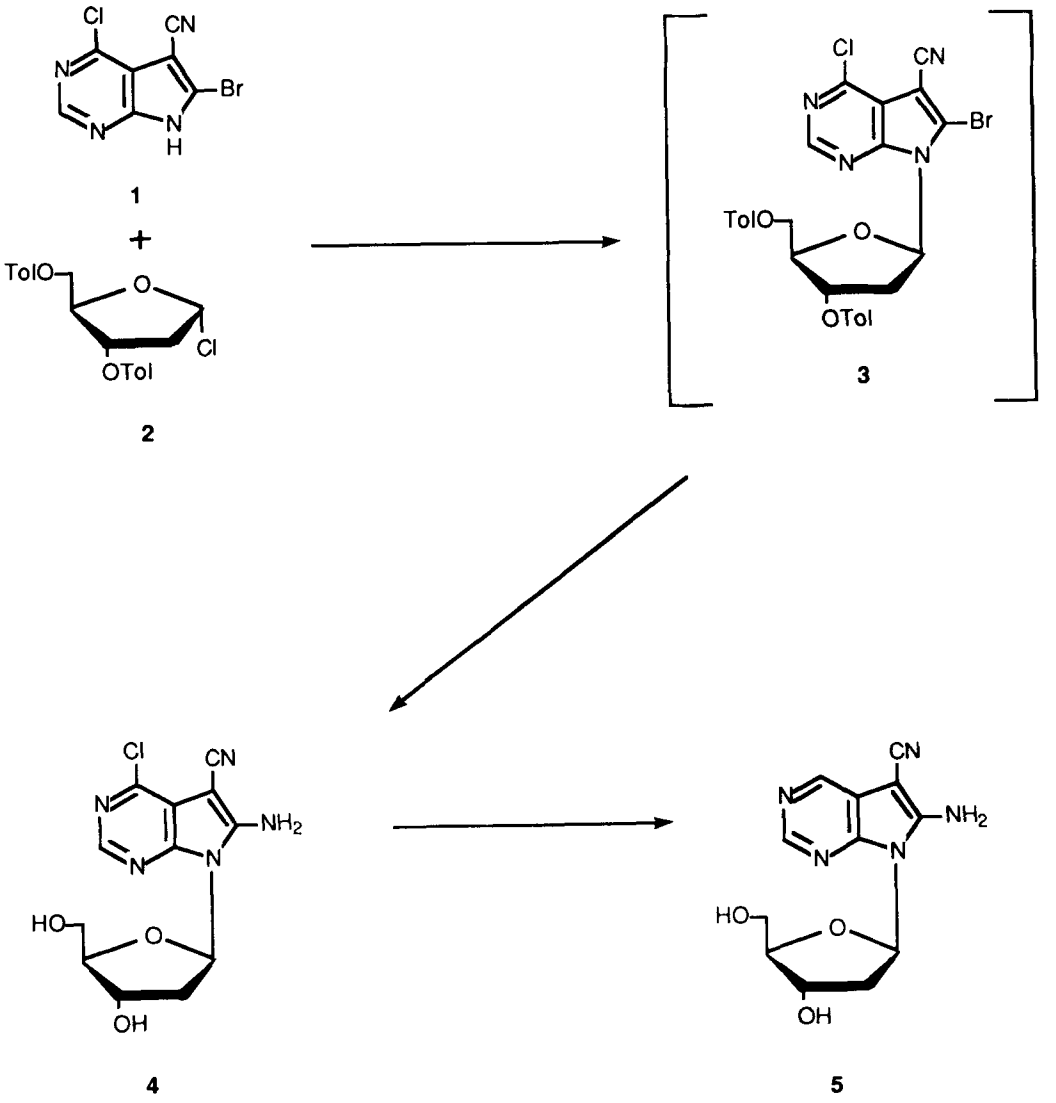
During the past decade, a number of nucleosides possessing tricyclic aglycons have been isolated from naturally occurring sources and prepared by synthetic procedures. Several of these nucleosides have demonstrated the ability to function as biological probes, e.g. ε-adenosine[1], and as chemotherapeutic agents, e.g. 6-amino-4-methyl-8-(β-D-ribofuranosyl)pyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine[2] (TCN) and TCN 5'-phosphate (TCNP). The pyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine nucleoside TCN has shown significant biological activity and the 5'-phosphate derivative (TCNP) is currently in clinical trials (phase-2). In view of the interesting metabolic disposition of TCN and TCNP, we initiated a study designed to synthesize 2'-deoxy TCN and related tricyclic nucleosides in order to study their chemotherapeutic activity and metabolic disposition.

For the synthesis of 2'-deoxy-TCN, we elected to start with the condensation of an appropriately substituted heterocycle, 6-bromo-4-chloro-5-cyanopyrrolo[2,3-d]pyrimidine (1), with the appropriate carbohydrate. This condensation furnished 6-bromo-4-chloro-5-cyano-7-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]-pyrimidine (3). Prior to ring annulation, we elected to remove the blocking groups in order

to provide a more facile isolation of the tricyclic product. Methanolic ammonia treatment of 3, at room temperature, was used to remove the blocking groups from the carbohydrate moiety of 3. However, instead of obtaining the expected 6-bromo-4-chloro-5-cyano-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine, we obtained an unexpected compound. It was subsequently determined that deprotection as well as a displacement of the 6-bromo group with ammonia had taken place. On the basis of spectral data and elemental analysis, the compound was assigned the structure 6-amino-4-chloro-5-cyano-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (4). This site of nucleophilic displacement was very unexpected in view of a previous report[3], in which the treatment of 6-bromo-4-chloro-5-cyano-7-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine[3] with methanolic ammonia at 110°C in a sealed tube resulted in the removal of the protecting groups, and a displacement of the chloro group instead of the bromo group to give 4-amino-6-bromo-5-cyano-7-(β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine. However, our results were similar to a previous report[4] where a different group was residing at N7 of this same heterocycle. Treatment of 3 with methanolic ammonia at 90°C in a sealed reaction vessel also gave only 4 as a major isolable product. A further increase in temperature resulted in major decomposition, including a cleavage of the glycosidic bond.

Molecular mechanics calculation[5] of compound 3, in comparison with the riboside counterpart, does not provide any definite clue to this surprising C6-bromo displacement over the C4-chloro group. However, it is of interest that in the minimum energy conformation of compound 3, the carbon bearing the bromo group of the 2'-deoxyriboside compound is more accessible than the carbon bearing the bromo group of the corresponding riboside compound.

The structures of compound 3 and 4 were firmly established by IR, ^{1}H NMR[6,10] and Mass spectroscopy. The ^{1}H NMR spectrum for compound 4, shows a quartet at δ 6.68 (anomeric proton) with a peak width and shape which are supportive of the β-anomeric configuration[10]. The presence of a chloro group in compound 4 was established



by mass spectroscopy since the molecular ion (M+) for 4 is at 309 and 311, due to the isotopic chlorine. This supports the nucleophilic displacement of a bromo group at C-6 vs chloro at C-4. Compound 4 was hydrogenated in the presence of Pd-charcoal, to obtain[7] compound 5. The UV spectral data for compound 5 is similar to that reported[8] for the corresponding riboside analog of 5. This provides very strong support for the glycosidic linkage assignment as N7. If the glycosidic linkage had been at N1 or N3, the

UV spectra would have been very different and also a nucleophilic displacement of the C-4 chloro would have been much more facile than that observed for the C-6 bromo group in compound 3.

Experimental:

General Procedures. 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 270 MHz with a IBM WP 270 SY spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to the standard chemical shift of the solvent (DMSO-d_6). Ultraviolet spectra were recorded [λ_{max} nm ($\varepsilon \times 10^{-3}$)] on a Hewlett-Packard 0450A spectrophotometer and the infrared spectra were measured on a Perkin Elmer 281 spectrophotometer. Elemental analysis were performed by M-H-W Laboratories, Phoenix, Arizona. Thin layer chromatography (TLC) was on Silica gel 60 F-254 plates (Analtech, Inc.). Mass spectral data were obtained on a Finnigan 4021 mass spectrometer. Detection of components on TLC was made by UV light (254 nm). Rotary evaporations were carried out under reduced pressure with the bath temperature below 35°C unless otherwise specified .

6-Bromo-4-chloro-5-cyano-7-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)-pyrrolo[2,3-d]pyrimidine (3).

6-Bromo-4-chloro-5-cyanopyrrolo[2,3-d]pyrimidine[3] (1, 1.1 g, 4.28 mmole) was dissolved in dry CH_3CN (100 mL). Sodium hydride (60% in oil, 0.19 g, 4.68 mmole) was added to this mixture which was then stirred for 30 minutes at room temperature under nitrogen. 1-Chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose[9] (2, 1.72 g, 4.43 mmole) was added in one portion and the reaction mixture was stirred for an additional 2 hr. The reaction mixture was evaporated to dryness, the residue was suspended in hot ethyl acetate (200 mL) and the mixture was filtered to remove inorganic salts. The filtrate was evaporated, absorbed onto silica gel (10 g), and chromatographed on a column (4 x 30 cm) using silica gel (80 g, 60-200 mesh). Elution of the column with

toluene:ethyl acetate (98:2, v/v) gave the desired nucleoside 3, after evaporation of the solvent, as a foam (1.38 g, crude yield 53.0%); m.p. softens at 70° and melts at 110°C; UV: MeOH, 228 (18.60) 283 (4.53); pH 1, 235 (10.03); pH 11, 219 (27.70) 285 (5.50): ^{1}H NMR (DMSO-d_6): δ 8.58 (s, 1H, C_2-H), 7.8-7.98 (m, 4H, Ar-H), 7.18-7.32 (m, 4H, Ar-H), 6.62 (t, 1H, J = 7.5 Hz; peak width = 15 Hz, $C_{1'}$-H), 6.05 (m, 1H, $C_{3'}$-H) and other sugar protons; Mass: B + 1 (259); S + 1 (353).

6-Amino-4-chloro-5-cyano-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]-pyrimidine (4).

Compound 3 (2.0 g, 3.28 mmole) was combined with methanolic ammonia (80 mL, saturated at 0°C), and the mixture stirred at room temperature in a pressure bottle for 16 hr. The reaction mixture was evaporated to dryness, absorbed onto silica gel (12.0 g) and chromatographed on a column (2 x 60 cm) using silica gel (50 g; 60-200 mesh). Elution of the column with $CHCl_3$:CH_3OH (95:5) gave the desired compound 4. Evaporation of the solvent and crystallization of the residue from EtOH gave 4 (0.4 g, 38.5%); m.p. 212-213°C; UV: EtOH, 235 (17.50) 314 (9.23); pH 1, 234 (14.04) 312 (7.18); pH 11, 221 (28.40) 313 (11.73); Mass (M/e) 309; (B + 1) 194; (S + 1) 117; ^{1}H NMR (DMSO-d_6): δ 8.42 (s, 1H, C_2-H), 8.07 (brs, 2H, D_2O exchangeable, NH_2), 6.68 (q, 1H, J = 5.8, 9.4 Hz; peak width = 15.2 Hz, $C_{1'}$-H), 5.75 (brs, 1H, D_2O-exchangeable, OH), 5.38 (d, 1H, D_2O exchangeable, OH), 4.41 (m, 1H, $C_{3'}$-H), and other sugar protons.

Anal. Calcd. for $C_{12}H_{12}ClN_5O_3 \cdot 1/2\ H_2O$: C, 45.22; H, 4.10; N, 21.97; Cl, 11.12. Found: C, 45.27; H, 4.10; N, 22.12; Cl, 11.21.

6-Amino-5-cyano-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (5).

MgO (0.05 g) and 5% Pd-charcoal (0.07 g) were added to compound 4 (0.05 g; 0.161 mmole) dissolved in EtOH (15 mL) and the mixture was hydrogenated on a Parr apparatus at 15 psi for 4 hr. The mixture was filtered through Celite, the filtrate concentrated in vacuo, and the residue crystallized from abs. EtOH-Et_2O to obtain a white

solid powder (5, 0.036 g, yield 82%); m.p. 192°C; UV: MeOH, 234 (11.53) 280 (4.080) 311 (4.24); pH 1, 239 (17.56) 302 (6.01); pH 11, 218 (28.30) 307 (4.83); ^{1}H NMR (DMSO-d_6): δ 8.58 (s, 1H, C_2-H); 8.52 (s, 1H, C_4-H), 7.91 (brs, 2H, D_2O-exchangeable, NH_2), 6.70 (q, 1H, J = 5.8, 9.4 Hz; peak width = 15.2 Hz, $C_{1'}$-H), 5.77 (t, 1H, D_2O exchangeable, OH), 5.41 (d, 1H, D_2O exchangeable, OH), 4.42 (m, 1H, $C_{3'}$-H) and other sugar protons. Mass (m/e): 275. Anal. Calcd. for $C_{12}H_{13}N_5O_3$: C, 52.36; H, 4.76; N, 25.44. Found: C, 52.18; H, 4.72; N, 25.44.

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