Tricyclic Nucleosides I. Synthesis of the New Tricyclic Ring System Tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine and Certain Tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine Ribonucleosides

*Karl H. Schram, Steven J. Manning and Leroy B. Townsend**

Division of Medicinal Chemistry, Department of Biopharmaceutical Sciences and Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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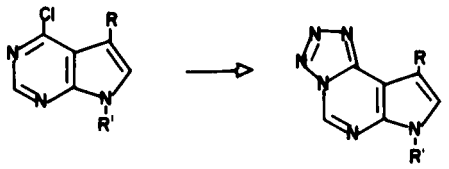
The identification and/or synthesis of fluorescent nucleosides from natural (1) or synthetic (2) sources has prompted several recent investigations (3) directed towards the synthesis of tricyclic nucleosides including reports (4) from our laboratory on the preparation of tricyclic compounds derived from pyrrolopyrimidine nucleosides. We would now like to report on the synthesis of the new tricyclic ring system tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine and some ribonucleoside derivatives of this new tricyclic ring system.

A reaction of 4-chloropyrrolo[2,3-*d*]pyrimidine (**1**) (5) with sodium azide (6) in dimethylformamide (DMF) and gentle heating afforded a product which we assigned the structure tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine (**2**). This structure assignment for the parent ring system was based on pmr and ir spectral evidence and elemental analysis. The pmr spectrum of **2** displayed peaks at δ 9.96 (1H, s, H5), δ 12.6 (1H, broad, H7), δ 7.72 (1H, d, $J_{8,9}$ = 3 Hz, H8) and δ 7.10 (1H, d, $J_{9,8}$ = 3 Hz, H9). The ir spec-

Reaction Scheme



1 R = R' = H
3 R=H, R' = $C_5H_9O_4$
5 R=Cl, R' = $C_5H_9O_4$
7 R=Br, R' = $C_5H_9O_4$
9 R=I, R' = $C_5H_9O_4$

2 R = R' = H
4 R=H, R' = $C_5H_9O_4$
6 R=Cl, R' = $C_5H_9O_4$
8 R=Br, R' = $C_5H_9O_4$
10 R=I, R' = $C_5H_9O_4$

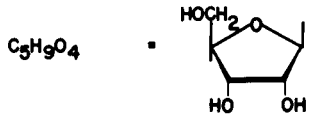


TABLE I

Uv Spectral Data for Certain Tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidines

	λ *p*H 1 max	ε (a)	λ Methanol max	ε	λ *p*H 11 max	ε
Tetrazolo[1,5-*c*]pyrrolo-[2,3-*d*]pyrimidine (**2**)	304 (238) (b)	9.9 9.4	300 (236)	10.5 9.8	300	8.3
7-(β-D-Ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (**4**)	300 (236)	12.6 15.7	300 240	7.5 7.9	300 239	8.9 15.0
9-Chloro-7-(β-D-ribofuranosyl)-tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]-pyrimidine (**6**)	301 (231)	8.0 14.1	301 (230)	7.8 12.4	303 234	5.8 9.8
9-Bromo-7-(β-D-ribofuranosyl)-tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]-pyrimidine (**8**)	302 (233)	9.3 18.2	301 230	8.2 13.7	304 232	4.8 9.8
9-Iodo-7-(β-D-ribofuranosyl)-tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]-pyrimidine (**10**)	303 234	7.9 16.3	305 236	6.7 12.1	305 236	5.0 10.0

(a) ε max x 10^{-3}. (b) Parens ( ) = shoulder.

trum of **2** showed no absorbance band in the 2100 cm^{-1} region which excluded the possibility of a simple nucleophilic displacement of the 4-chloro group to afford the 4-azido derivative (7). Treatment of 4-chloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**3**) (8) with sodium azide in DMF furnished the 7-ribosyl derivative of the new tricyclic ring system 7-(β-D-ribofuranosyl)tetrazolo[1,5-*c*]-pyrrolo[2,3-*d*]pyrimidine (**4**). The pmr spectrum of **4** showed peaks at δ 10.0 (H1, s, H5), δ 8.10 (H1, d, J = 2 Hz, H8), δ 7.25 (H1, d, J = 2 Hz, H9) and δ 6.42 (H1, d, H1′). These downfield chemical shifts of δ 1.4 for H5 and δ 0.07 for H1′, in comparison to H5 and H1′ for **3** (9) would be expected with the formation of an additional aromatic ring. The most significant chemical shift would also be expected for H5 (7). The possibility of a simple nucleophilic displacement of the 4-chloro group to form the 4-azido derivative was again excluded, due to the absence of a band in the 2100 cm^{-1} region of the infrared spectrum (7). The ultraviolet spectrum of **4** (Table I) showed a large bathochromic shift (28 nm) which also indicated the formation of an additional aromatic ring (3c, 4a, 4b). The elemental analyses were also consistent with the assigned structure.

Similar treatment of **5**, **7** and **9** afforded **6**, **8** and **10** with the structure assignments being based on the aforementioned data (ir, uv and pmr spectral data and elemental analysis).

A reinvestigation of the reaction of 6-chloro-9-(β-D-ribofuranosyl)purine with sodium azide in DMF using milder conditions than those used by the initial investigators (11) afforded 7-(β-D-ribofuranosyl)tetrazolo[5,1-*i*]-purine in 37% yield which was identical in all respects to the product obtained from 6-hydrazino-9-(β-D-ribofuranosyl)purine (10).

EXPERIMENTAL

Ultraviolet spectra were obtained on a Beckman DK2 spectrophotometer and infrared spectra were obtained on a Beckman IR-8 using potassium bromide pellets. Pmr spectra were recorded using a Varian A-56/60 spectrometer with tetramethylsilane (TMS) as an internal standard and the chemical shifts are expressed as δ, parts per million, from TMS with DMSO-d_6 as solvent. Thin-layer chromatograms were run on glass plates coated with a 0.25 mm layer of Silic AR-7GF (Mallinckrodt Chem. Co.) using ethyl acetate-1-propanol-water (4:1:2, v/v/v, upper phase) as the solvent system. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine (**2**).

4-Chloropyrrolo[2,3-*d*]pyrimidine (**1**) (5) (4.0 g.), sodium azide (4.0 g.) and dimethylformamide were mixed and heated on a steam bath for 6 hours. The resulting brown solution was filtered while still hot and the filtrate was evaporated to dryness *in vacuo* using a steam bath to give a tan solid. The solid was triturated with methylene chloride (50 ml.), the methylene chloride insoluble material was dissolved in a minimum of boiling ethanol, decolorized using charcoal, filtered and the filtrate allowed to stand at 5° for 12 hours. The resulting crystals were collected by filtration and air dried to yield 3.68 g. (88%) of **2**, m.p. slow dec. above 200°.

Anal. Calcd. for $C_6H_3N_6$: C, 45.00; H, 2.50; N, 52.52. Found: C, 44.78; H, 2.66; N, 52.30.

7-(β-D-Ribofuranosyl)tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine (**4**).

4-Chloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine, (**3**, 500 mg.) (8), sodium azide (500 mg.) and DMF (20 ml.) were mixed and heated on a steam bath for 4 hours. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo* using a steam bath. The residue was dissolved in boiling ethanol (75 ml.), decolorized with charcoal, filtered and the filtrate was allowed to stand at 5° for 12 hours. The crystals which had formed were collected by filtration and air dried to yield 630 mg. (62%) of **4**, m.p. 200° dec.

Anal. Calcd. for $C_{11}H_{12}N_6O_4$: C, 45.20; H, 4.11; N, 28.11. Found: C, 45.20; H, 4.10; N, 28.48.

9-Chloro-7-(β-D-ribofuranosyl)tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]-pyrimidine (**6**).

4,5-Dichloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**5**, 550 mg.) (9), sodium azide (550 mg.) and DMF (10 ml. were mixed and heated on a steam bath for 2.5 hours after which time the reaction mixture was evaporated to dryness *in vacuo* using a steam bath. The residue was dissolved in boiling water (30 ml.) and allowed to stand at 5° for 12 hours. The crystals which had formed were collected by filtration and air dried to give 260 mg. (47%) of **6**, m.p. 182-183°.

Anal. Calcd. for $C_{11}H_{11}ClN_6O_4 \cdot 2H_2O$ (verified by pmr): C, 36.36; H, 4.13; N, 23.14. Found: C, 36.41; H, 4.12; N, 22.81.

9-Bromo-7-(β-D-ribofuranosyl)tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]-pyrimidine (**8**).

4-Chloro-5-bromo-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**7**, 1.0 g.) (9), sodium azide (1.0 g.) and DMF (20 ml.) were mixed, heated on a steam bath for 3 hours and evaporated to dryness *in vacuo*. The residue was dissolved in boiling water (40 ml.), decolorized using charcoal, filtered and the filtrate allowed to stand at 5° for 12 hours. The resulting crystals were collected by filtration and recrystallized a second time from water to yield 520 mg. (54%) of **8**, m.p. 198° dec.

Anal. Calcd. for $C_{11}H_{11}BrN_6O_4$: C, 35.58; H, 2.97; N, 22.64. Found: C, 35.42; H, 3.09; N, 22.68.

9-Iodo-7-(β-D-ribofuranosyl)tetrazolo[1,5-*c*]pyrrolo[2,3-*d*]pyrimidine (**10**).

4-Chloro-5-iodo-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**9**, 1.0 g.) (9), sodium azide (1.0 g.) and DMF (20 ml.) were mixed and heated on a steam bath for 2.5 hours. The reaction mixture was taken to dryness *in vacuo* using a steam bath and the residue was dissolved in a minimum of water and allowed to stand at 5° for 3 hours. The crystals which had formed were collected by filtration and dried *in vacuo* over toluene for 12 hours to yield 510 mg. (71%) of **10**, m.p. 190° dec.

Anal. Calcd. for $C_{11}H_{11}IN_6O_4 \cdot 2H_2O$ (verified by pmr): C, 29.08; H, 3.31; N, 18.50. Found: C, 29.31; H, 3.31; N, 18.39.

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