Synthesis of Pyridazine Nucleosides Related to the Naturally Occurring Nucleosides Cytidine and Uridine

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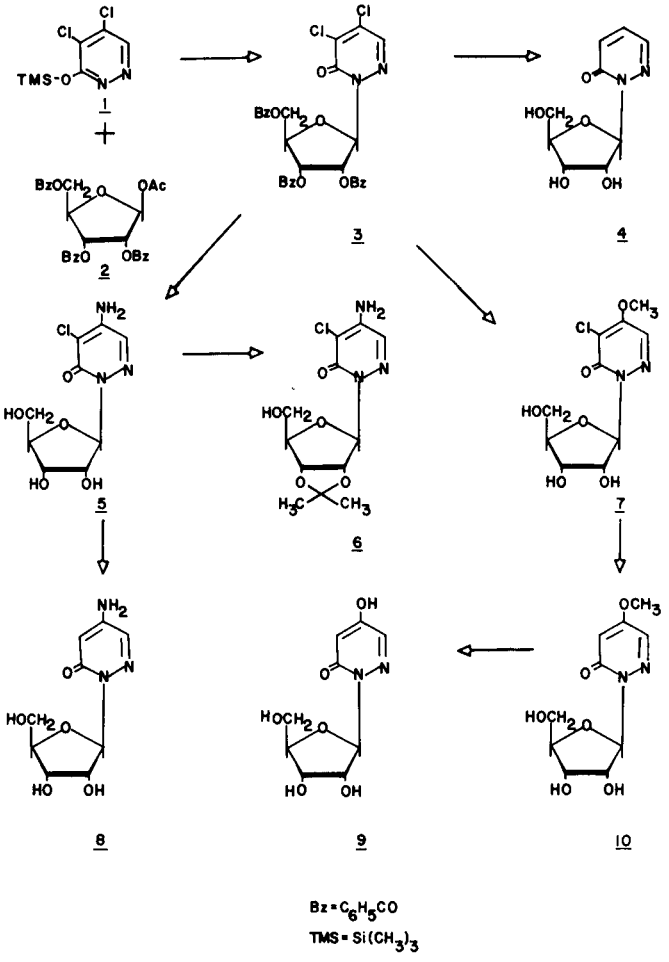
Sir:

In view of the interesting biological and chemotherapeutic activity of the 6-aza (1,2) and 3-deaza- (3,4) analogs of certain pyrimidines and pyrimidine nucleosides, we have initiated research designed to afford nucleosides (pyridazine) (5,6) which incorporate both of the above structural modifications. We now wish to report on the synthesis of pyridazine nucleosides corresponding to the naturally occurring nucleosides cytidine and uridine.

Silylation of 4,5-dichloropyridazin-6-one (6) was accomplished using hexamethyldisilazane with a catalytic amount of ammonium sulfate. The silyl derivative (**1**) was then condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) by the Lewis acid catalyzed silyl procedure (7,8) to furnish a 55% yield of nucleoside material which was assigned the structure 4,5-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**3**), (m.p. 166-167°) (9) on the basis of subsequent studies (*vide infra*). Treatment of **3** with liquid ammonia at 100° effected a removal of the benzoyl groups with a concomitant nucleophilic displacement of the 4-chloro group to yield (74%) 4-amino-5-chloro-1-(β-D-ribofuranosyl)pyridazin-6-one (**5**), (m.p. 243-244°). Treatment of **5** with hydrogen (40 psi), in the presence of a 10% palladium-carbon catalyst, afforded a 60% yield of 4-amino-1-(β-D-ribofuranosyl)-pyridazin-6-one (**8**, 6-aza-3-deazacytidine), m.p. 228°; $[\alpha]_D^{27}$ = - 134° (C = 1, DMF); uv λ max (*p*H 1): 275 (6560), 295 (4460) nm; (methanol): 277 (5780), 302 sh (3100) nm; (*p*H 11): 275 (5900), 295 sh (3930) nm; pmr: (10), δ 7.60 ($J_{3,5}$ = 2.5 Hz, d, H3); δ 5.60 ($J_{5,3}$ = 2.5 Hz, d, H5); δ 6.62 (bs, 4-NH_2); δ 6.19 ($J_{1',2'}$ = 4 Hz, d, H1'), and the characteristic pattern of peaks usually observed (11) for the remaining protons of a ribofuranose moiety. The ultraviolet spectral data for **8** was essentially identical to the uv spectral data previously reported (12) for 4-amino-1-methylpyridazin-6-one. This established the actual site of ribosylation as N1 which left only the assignment of anomeric configuration unresolved.

Dehalogenation and a removal of the benzoyl blocking groups from **3** furnished a nucleoside which was identical in every respect to the reported (13) 1-(β-D-ribofuranosyl)-pyridazin-6-one (**4**). However, we elected to obtain additional data for the substantiation of the anomeric configuration since these authors based the assignment of β configuration for **4** solely on the "*trans rule*" (14). The isopropylidene derivative, 4-amino-5-chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyridazin-6-one (**6**), (m.p. 175°) was prepared by treatment of **5** with dry acetone and a catalytic amount of perchloric acid. The pmr spectrum of **6** in dimethylsulfoxide d_6 exhibited a doublet ($J_{H_1',H_2'}$ = 1 Hz) at δ 6.36 for the anomeric proton and



two singlets for the methyl groups of the acetonide moiety at δ 1.33 and δ 1.52 (Δδ = 0.19 ppm). The small coupling constant for the anomeric proton (11,15) and the Δδ value (16) established the anomeric configuration of **6** and the anomeric configuration of all nucleosides reported in this investigation as β. This unequivocal structure proof for **8** as 4-amino-1-(β-D-ribofuranosyl)pyridazin-6-one (6-aza-3-deazacytidine) prompted us to synthesize the corresponding uridine analog (6-aza-3-deazauridine).

Treatment of **3** with methanolic sodium methoxide at room temperature resulted in a removal of the benzoyl groups and a simultaneous displacement of the 4-chloro group to furnish a 79% yield of 5-chloro-4-methoxy-1-(β-D-ribofuranosyl)pyridazin-6-one (**7**), (m.p. 161-163°). Dehalogenation of **7** with hydrogen and 10% palladium-carbon in methanol gave a 57% yield of 4-methoxy-1-(β-D-ribofuranosyl)pyridazin-6-one (**10**), (m.p. 143-144°). Hydrolysis of **10** with aqueous potassium hydroxide provided a 68% yield of 4-hydroxy-1-(β-D-ribofuranosyl)-pyridazin-6-one (**9**, 6-aza-3-deazauridine); m.p. 185°; $[\alpha]_D^{27}$ = -133° (C = 1, methanol); uv λ max (*p*H 1): 249 (4630), 273 sh (3470) nm; (methanol): 252 (4130), 275 sh (3720) nm; (*p*H 11): 267.5 (6200), 288 sh (4400) nm; pmr: δ 7.82 ($J_{3,5}$ = 2.5 Hz, d, H3); δ 6.10 ($J_{5,3}$ = 2.5 Hz, d, H5); δ 6.22 ($J_{1',2'}$ = 3.5 Hz, d, H1') and the characteristic pattern of peaks expected (11) for a ribofuranose moiety. The addition of deuterium oxide and sodium peroxide (to accelerate exchange) effected a disappearance of the peak at δ 6.10 and a collapse of the doublet at δ 7.82 to a singlet in the pmr spectrum. This provided strong evidence for a dynamic enol ⟷ keto tautomerism similar to that previously noted for 3-deazauridine (17). A comparison of the ultraviolet spectral data for compounds **7**, **9** and **10** with the ultraviolet spectral data of authentic samples of the corresponding methylated analogs (18) provided additional confirmation that the actual site of ribosylation for these nucleosides was N1.

This investigation has provided the 6-aza-3-deaza derivatives of the naturally occurring pyrimidine nucleosides uridine and cytidine. Additional chemical transformations of this novel group of pyrimidine nucleoside analogs along with an evaluation of their biochemical properties are currently under investigation in our laboratory.

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(9) All new compounds were analyzed for C, H and N and the results were within ± 0.4 % of the theoretical values. Ultraviolet spectra were obtained from a Beckman Acta C-III spectrophotometer. Pmr spectra were recorded on a Varian A-56/60 spectrometer in DMSO-d_6 and DMSO-d_6/deuterium oxide solution with DSS as an internal standard. Optical rotations were obtained from a Perkin-Elmer 141 polarimeter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

(10) For pmr data; s = singlet, d = doublet, bs = broad singlet

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