The Synthesis of 5-Amino-*v*-triazolo[4,5-*b*]pyridin-7-one (1-Deaza-8-azaguanine) and 5-Amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-Deaza-8-azaguanosine) (1)

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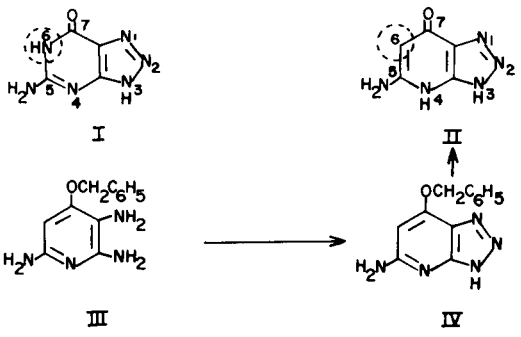
The synthesis of 1-deaza-8-azaguanine has been accomplished *via* a facile route from pyridine precursors. The site of ribosylation and anomeric configuration of 1-deaza-8-azaguanosine and several closely related derivatives was accomplished by cmr and pmr, respectively.

J. Heterocyclic Chem., 13, 1365 (1976).

Sir:

The wide-spectrum of chemotherapeutic activity reported (2-4) for 8-azaguanine (I) prompted a number of synthetic studies whose ultimate design was to provide related heterocycles which might possess similar properties. Of particular interest to us was the synthesis of 5-amino-*v*-triazolo[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanine, II). This unique analog of I lacks the N-6 nitrogen (N-1 if purine nomenclature), a critical requirement for hydrogen bonding of base pairs in the Watson-Crick DNA model. Although a number of 7-substituted *v*-triazolo[4,5-*b*]-pyridine heterocycles (5,6) and nucleosides (7) are known, only a few 5,7-disubstituted *v*-triazolo[4,5-*b*]pyridine heterocycles have been prepared (8). We now wish to report the synthesis of 5-amino-*v*-triazolo[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanine, II) and its nucleoside derivative 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanosine, IX).

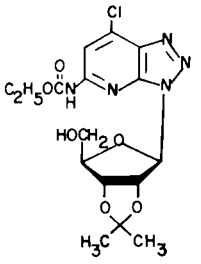
Synthesis of the 8-azaguanine analog was accomplished by a two-step sequence starting with 4-benzyloxy-2,3,6-triaminopyridine dihydrochloride (III) (9). A solution of III, in 1*N* hydrochloric acid at 0°, was treated with one equivalent of sodium nitrite to give 5-amino-7-benzyloxy-*v*-triazolo[4,5-*b*]pyridine (IV, m.p. 194-195°) in 77% yield. Hydrogenolysis of IV with 5% palladium on charcoal in a hydrogen atmosphere (42 psi) for 6 hours afforded a near-quantitative yield of 5-amino-*v*-triazolo-[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanine, II), m.p. slowly darkens above 250°, explodes at 296°; uv (λ max in nm, $\epsilon \times 10^{-3}$); (*p*H 1) 297 (14.7), 264 (7.1); (*p*H 11) 284 (16.5); pmr (DMSO-d_6): δ 5.72 (1, s, H-6).



The second phase of this study involved the synthesis of 1-deaza-8-azaguanosine (IX). Ethyl 7-chloro-*v*-triazolo-[4,5-*b*]pyridine-5-carbamate (10) was silylated with *N,O*-bis-silylacetamide in methylene chloride at room temperature. The excess solvents were removed and the silyl derivative V (foam) was used without further purification. Condensation of this silyl derivative with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (VI) (11) using mercuric cyanide (12) in benzene at reflux for 45 minutes furnished a white, crystalline solid (75% yield) which was homogeneous on tlc. This solid was tentatively assigned (and later confirmed) as ethyl 7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (VIIa, m.p. 164-165°). Subsequent treatment of VIIa with sodium methoxide in a mixture of tetrahydrofuran and methanol at 35° for two hours afforded, ethyl 7-chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]-pyridine-5-carbamate (VIIb) in near-quantitative yield; m.p. 196-197°; uv (λ max in nm, $\epsilon \times 10^{-3}$): (*p*H 1) sh 310 (16.8), 302 (21.0), 274 (11.0), 265 (11.1); (*p*H 11) sh 310 (17.6), 302 (18.7), 274 (9.8), 266 (10.0); pmr (DMSO-d_6): δ 10.85 (1, br s, 5-NH), 8.15 (1, s, H-6), 6.24 (1, d, H-1′, $J_{1',2'}$ = 4.5 Hz), 4.24 (2, 1, 5-CH_2), 1.30 (3, t, 5-CH_3).

The site of ribosylation was established using the well documented (13,14) behavior of carbon ^{13}C chemical shifts for the carbon atoms in positions α and β to a ring nitrogen in nitrogen heterocycles. The ^{13}C nmr signal of the carbon α to the alkyl- or glycosyl-substituted nitrogen moves upfield and that of the β carbon moves downfield relative to the signals exhibited by the unsubstituted heterocycle. A comparison of the ^{13}C nmr spectra of VIIb with that of ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate showed that the carbon atoms C-3a (the α carbon) and C-7a (the β carbon) of VIIb shifted 6.6 ppm upfield and 4.4 ppm downfield, respectively. This is consistent with the expected behavior of bridgehead carbons only if substitution had occurred at N-3. The observed signals for the C-5 and C-6 carbons did not show this behavior and thus excluded the possibility of substitution at N-4 (15).

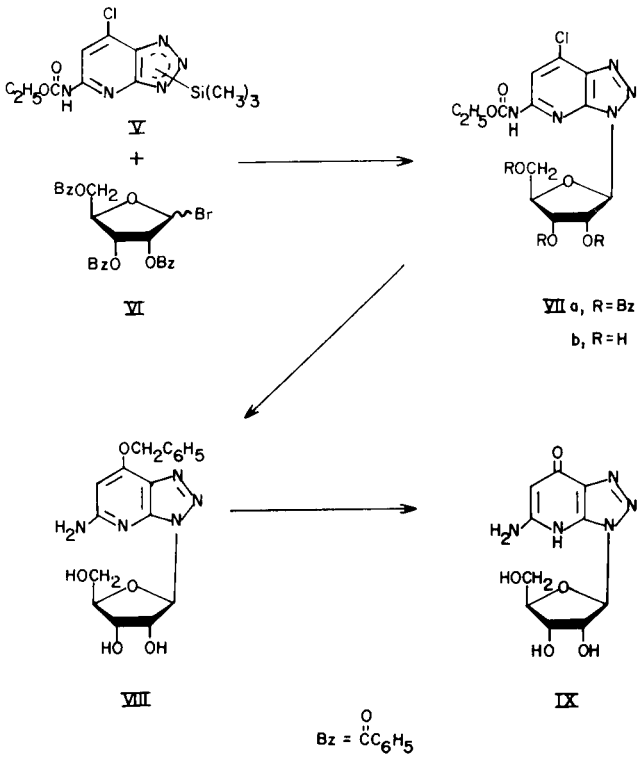
The anomeric configuration was assigned using pmr spectral data obtained on the 2′,3′-*O*-isopropylidene derivative X. The doublet ($J_{1',2'}$ = 4.5 Hz) exhibited by the anomeric proton of VIIb was observed as a singlet in the pmr spectrum of X. This spectral characteristic is generally accepted as proof of β anomeric configuration (16). In addition, the observed difference in the chemical



X

shifts ($\Delta\delta$) of the isopropylidene methyl groups in DMSO-d_6 was δ 0.17, which is consistent with the reported criteria for β-D-ribofuranosyl nucleosides (17).

The compound VIIb was used as the starting nucleoside material for our synthesis of 1-deaza-8-azaguanosine (IX). Heating VIIb with sodium benzylate (10 equivalents) in freshly distilled benzyl alcohol at 80° for 5 hours in a nitrogen atmosphere provided 5-amino-7-benzyloxy-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine (VIII, 72% yield, m.p. 155-156°) (18). Hydrogenolysis of VIII using 5% palladium on charcoal in a hydrogen atmosphere at 42 psi for 3 hours furnished 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanosine, IX) in 83% yield; m.p. 148° (sinters); uv (λ max in nm, $\epsilon \times 10^{-3}$): (*p*H 1) 296 (17.7), 250 (7.9); (*p*H 11) 284 (18.3); (ethanol) 291 (14.7), sh 272 (11.4); pmr (DMSO-d_6): δ 11.27 (1, br s, 4-NH), 6.45 (2, s, NH_2), 6.03 (1, d, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.90 (1, s, H-6) (19).



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(1) This research was supported by research contract NO1-CM-43806 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

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(15) Complete spectral data for this ^{13}C nmr study will be published at a later date. It should be mentioned here that the chemical shift assigments in this study were greatly simplified by the long-range (two-, and three-bond) ^{13}C-H coupling constants observed in the high-resolution spectra obtained for this study.

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(18) Higher temperatures (100-120°) thermally degrade the product to the base, V; at these higher temperatures and after longer reaction times (2-3 days) benzylation of the amino group also occurs; a phenomenon reported in our previous paper; B. L. Cline, R. P. Panzica and L. B. Townsend, *J. Heterocyclic Chem.*, **12**, 603 (1975).

(19) Satisfactory analytical data (C,H,N), pmr and uv spectra were obtained for all new compounds.