

The Synthesis of 1-Deazaguanosine (I)

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Received March 24, 1975

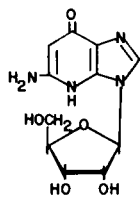
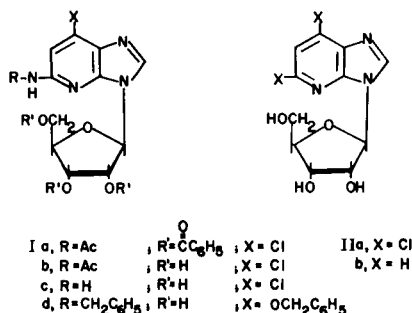
Sir:

The reported chemotherapeutic activity (2) of certain 3-deazapyrimidine nucleosides, *e.g.*, 3-deazauridine, has prompted us to investigate the synthesis of purine nucleoside analogues possessing the 3-deazapyrimidine moiety. We now wish to report the synthesis of 5-amino-3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-one (1-deazaguanosine, III).

5-Acetamido-7-chloroimidazo[4,5-*b*]pyridine (3) was silylated at reflux temperature in hexamethyldisilazane containing a catalytic amount of ammonium sulfate to give a foam that was used without further purification. Condensation of this silyl derivative with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (4) was accomplished using mercuric cyanide (5) in benzene at reflux temperature for 45 minutes to afford an 80% yield of a white crystalline solid. This solid was tentatively assigned the structure 5-acetamido-7-chloro-3-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine (Ia) (6). Confirmation of this structural assignment was accomplished by the following synthetic sequence. Treatment of Ia with sodium methoxide in methanol at 35° for 15 minutes effected a complete removal of the *O*-benzoyl protecting

groups to afford 5-acetamido-7-chloro-3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine (Ib) in quantitative yield. Removal of the *N*-acetyl group of Ib required treatment of Ib with 1 *N* potassium hydroxide in ethanol at reflux temperature for 2 hours to give a 90% yield of Ic. The addition of solid sodium nitrite (1.1 equivalents) to a cold solution of Ic in concentrated hydrochloric acid containing a catalytic amount of cuprous chloride furnished a 50% yield of 5,7-dichloro-3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine (IIa). Dehalogenation of IIa was accomplished using 10% palladium on charcoal in a hydrogen atmosphere at 42 psi to give a near quantitative yield of a nucleoside which was found to be identical to 3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine (IIb) (7). This established the anomeric configuration and site of ribosylation for all nucleosides reported in this investigation since the anomeric configuration (8) and site of glycosylation (9) of IIb have already been firmly established. Additional corroboration of the β configuration was furnished by pmr spectral data for the 2',3'-*O*-isopropylidene derivative of Ib which was prepared by standard procedures. The observed difference in the chemical shifts ($\Delta\delta$) in DMSO-*d*₆ of the isopropylidene methyl groups was δ 0.23 which was consistent with the criteria established for β -D-ribofuranosyl nucleosides (10). On the basis of these data, *vide supra*, the site of ribosylation and anomeric configuration of all nucleosides in this study were established as N-3 and β .

The synthesis of 1-deazaguanosine was accomplished by a two-step sequence starting with Ib. This nucleoside was heated with sodium benzyolate (5 equivalents) in freshly distilled benzyl alcohol at 110° for 48 hours to provide 5-benzylamino-7-benzyloxy-3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine (Id, 40% yield) (11, 12); [pmr in DMSO-*d*₆: δ 4.63 (s, 2, C₆H₅CH₂NH); 5.50 (s, 2, C₆H₅CH₂O); 6.03 (d, 1, H1', J_{1',2'} = 6 Hz); 6.28 (s, 1, H6); 7.55 (2 m, 10, C₆H₅CH₂O, C₆H₅CH₂NH); 8.21 (s, 1, H2)]. Hydrogenolysis of Id using 10% palladium on charcoal in a hydrogen atmosphere at atmospheric pressure for 4 days furnished the desired 5-amino-3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-one (1-deazaguanosine, III) in 85% yield, m.p. 138° dec.; uv: (ϵ x



III

10^{-3}) λ max (pH 1), 297 nm (13.5), 250 nm (7.1), 244 nm (7.4); λ max (pH 11) sh 272 nm (13.8), 264 nm (16.4); pmr (DMSO- d_6): δ 5.86 (s, 1, H6), δ 8.02 (s, 1, H2), δ 5.83 (d, 1, H1', $J_{1',2'} = 6$ Hz), (13).

Acknowledgement

The authors would like to thank Mrs. Suzanne Mason for the uv, ir and pmr spectra.

REFERENCES

- (1) This research was supported by research contract NOI-CM-43806 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.
- (2) A. Bloch, G. Dutschman, B. L. Currie, R. K. Robins and M. J. Robins, *J. Med. Chem.*, **16**, 294 (1972) and references cited therein.
- (3) Prepared by a route similar to that described by J. E. Schelling and C. A. Salemink, *Rec. Trav. Chim.*, **93**, 160 (1974).
- (4) H. Zimmer, A. Koine and H. Ninz, *Chem. Ber.*, **93**, 2705 (1960).
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- (6) The synthesis of a similar derivative 7-chloro-5-formamido-3-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine, has been reported (P. Jain and N. Anand, *Indian J. Chem.*, **6**, 616 (1968), however, neither the site of ribosylation nor the anomeric configuration were rigorously established.
- (7) The physicochemical data of this compound were identical to that reported for 3-(β -D-ribofuranosyl)imidazo[4,5-*b*]pyridine reported by Y. Mizuno, *et al.*, see references 8 and 9.
- (8) Y. Mizuno, M. Ikehara, T. Itoh and K. Saito, *Chem. Pharm. Bull. (Tokyo)*, **11**, 265 (1963).
- (9) Y. Mizuno, M. Ikehara, T. Itoh and K. Saito, *J. Org. Chem.*, **28**, 1837 (1963).
- (10) J.-L. Imbach, J.-L. Barascut, B. L. Kam, B. Rayner, C. Tamby and C. Tapiero, *J. Heterocyclic Chem.*, **10**, 1069 (1973).
- (11) *N*-Benzylation under these conditions, although unexpected, has been observed previously in 2-aminopyridines and 2-aminopyrimidines [I. Hirao and M. Hoyoshi, *Yakugaku Zasshi*, **74**, 853 (1954)] and more recently in the synthesis of certain guanine derivatives (C. R. Frihart and N. J. Leonard, *J. Am. Chem. Soc.*, **95**, 7174 (1973).
- (12) An additional 30% of the yield was accounted for by the isolation of 5-benzylamino-7-benzylxyimidazo[4,5-*b*]pyridine, probably resulting from thermal degradation of the desired nucleoside.
- (13) Satisfactory analytical data (C, H, N), pmr and uv spectra were obtained for all compounds.