The Synthesis of Bicyclic Nucleosides Related to Cytidine; 3-(β-D-Ribofuranosyl)isoguanine (I)

Charles L. Schmidt and Leroy B. Townsend

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

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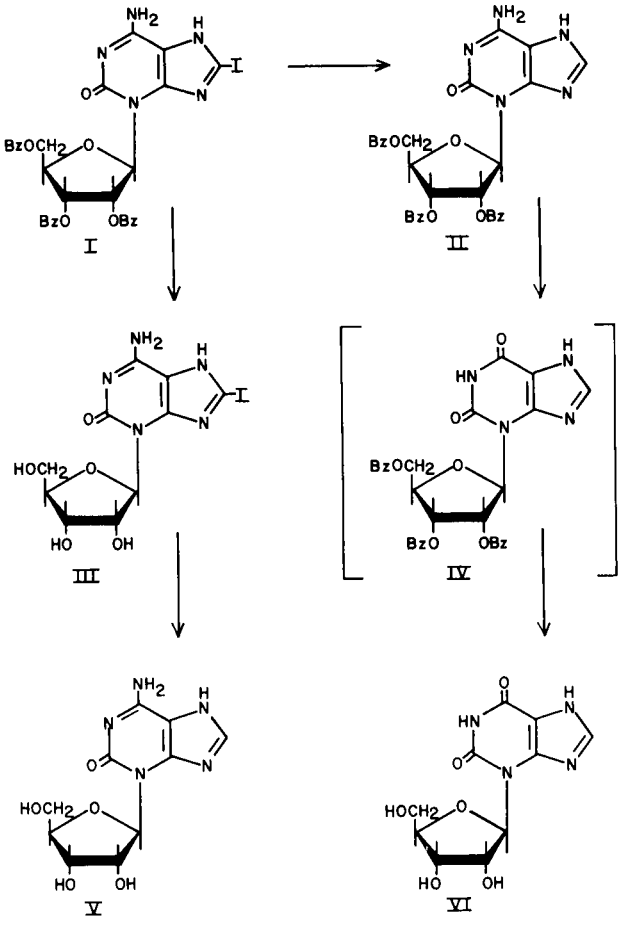
Sir:

Isolation (2) of the naturally occurring 3-glycosylpurine, 3-ribofuranosyl uric acid, from beef blood, and the report of biological activity for 3-ribofuranosyl purines in bacterial (3-4) and viral (5) systems has generated considerable interest in the synthesis of 3-glycosyl purines and other closely related bicyclic [5:6] nucleosides with the carbohydrate moiety attached to a nitrogen atom of the pyrimidine ring (6). It has been postulated (4) that although 3-isoadenosine can be viewed as a pyrimidine type nucleoside, it did not fulfill the pyrimidine requirement for the growth of thymine 15T due to the absence of a 2-keto group which would have furnished a cytidine type nucleoside. Syntheses in this area have generally relied on the use of pyrimidine nucleosides with the appropriate exocyclic groups in a suitable juxtaposition for ring annulation (7-8) or on alkylation reactions which take advantage of specific directing forces in the purine molecule (9-10). These bicyclic nucleosides can be viewed as uridine analogs, and we have recently reported on two novel approaches to the synthesis of these compounds. The first report involved the use of a thiazolo[5,4-*d*]pyrimidine derivative in which a sulfur atom is substituted for the nitrogen atom in the 9-position (11) of purine. This furnished the uridine analog 4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione. The second approach involved the introduction of a bulky substituent into the 8-position of a purine. The steric hindrance to ribosylation at N-9 due to the bulky group at C-8 resulted in a high proportion of substitution at N-3 (12). This latter approach has now been used to achieve the synthesis of 3-(β-D-ribofuranosyl)isoguanine (V), a bicyclic analog of cytidine.

Fusion of 4,5,6-triaminopyrimidin-2-one (13) with thiourea at 180° afforded 8-mercaptoisoguanine which was converted to 8-iodoisoguanine by the reported (14) method. The physical data for this compound differed significantly from those previously reported (14), decomposing above 235° with evolution of iodine vapor, and having a uv spectra with maxima at 295 nm (ε, 1.63 x 10^4) at *p*H 1 and 292.5 (ε, 1.74 x 10^4) at *p*H 11. This prompted us to obtain elemental analysis (15) on this compound which revealed that the compound was a half sulfate salt. Silylation of 8-iodoisoguanine with hexamethyldisilizane and ammonium sulfate followed by reaction with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile gave a good yield of the desired 8-iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoguanine (I). Sodium methoxide in methanol removed the protecting benzoyl groups to furnish 8-iodo-3-(β-D-ribofuranosyl)-isoguanine (III). Treatment of III with 5% palladium on



carbon in water containing ammonium hydroxide under 1 atmosphere of hydrogen gas yielded the title compound 3-(β-D-ribofuranosyl)isoguanine (V). The ultraviolet spectra of this compound, showing maxima at 286 nm (*p*H 1, ε, 1.61 x 10^4) and 288 (*p*H 11, ε, 1.43 x 10^4) agreed closely with that reported for 3-methylisoguanine (16) which supported the assignment of N-3 as the position of attachment for the ribofuranosyl moiety.

Attempts to deaminate V directly to afford the known 3-(β-D-ribofuranosyl)xanthine (VI) (8) which would have established, unequivocally, both the site of ribosylation and the anomeric configuration were unsuccessful. An alternate route was initiated which involved the removal of the iodo group with 5% palladium on carbon in DMF containing triethylamine to give 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoguanine (II). Deamination of II with nitrosyl chloride in DMF and pyridine at 5° gave 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)xanthine (IV). This compound was not isolated, but deblocked directly with sodium methoxide in methanol to give VI. A comparison of the ultraviolet spectra, melting points and optical rotations showed that VI was, indeed, identical to the reported (8) 3-(β-D-ribofuranosyl)xanthine and established structures for the entire series.

This has furnished the 2-keto derivative [3-(β-D-ribofuranosyl)isoguanine, 3-*iso*isoguanosine] of 3-isoadenosine which should now function more effectively as a cytidine derivative rather than an adenosine derivative.

REFERENCES

(1) This research was supported by research grant CA-11147-05 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) H. S. Forrest, D. Hatfield, and J. M. Lagowski, *J. Chem. Soc.*, 963 (1961).

(3) N. J. Leonard and R. A. Laursen, *J. Am. Chem. Soc.*, **85**, 2026 (1963).

(4) K. Gerzon, I. S. Johnson, G. B. Boder, J. C. Cline, P. J. Simpson, C. R. Speth, N. J. Leonard, and R. A. Laursen, *Biochim. Biophys. Acta*, **119**, 445 (1966).

(5) C. G. Tindall, Jr., W. Hutzenlaub, R. K. Robins, and R. L. Tolman, Abstracts, 163 ACS National Meeting, Boston, Mass., April, 1972, MEDI 20.

(6) G. Ritzmann, K. Harzen, and W. Pfleiderer, *Angew. Chem. Intern. Ed. Engl.*, **10**, 932 (1971).

(7) R. Lohrmann, J. M. Lagowski, and H. S. Forrest, *J. Chem. Soc.*, 451 (1964).

(8) D. Lipkin, C. T. Cori, and J. A. Rabi, *J. Heterocyclic Chem.*, **6**, 995 (1969).

(9) N. J. Leonard and R. A. Laursen, *Biochem.*, **4**, 354 (1965).

(10) L. Birkofer, A. Ritter, and H. D. Kuhlthau, *Angew. Chem. Intern. Ed. Engl.*, **2**, 155 (1963).

(11) C. L. Schmidt, W. J. Rusho, and L. B. Townsend, *Chem. Commun.*, 1515 (1971).

(12) C. L. Schmidt and L. B. Townsend, *J. Org. Chem.*, **37**, 2300 (1972).

(13) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948).

(14) R. T. Koda, J. A. Biles, and W. Wolf, *J. Pharm. Sci.*, **57**, 2056 (1968).

(15) Acceptable elemental analyses were obtained for all new compounds reported herein.

(16) G. T. Rogers and T. L. V. Ulbricht, *J. Chem. Soc. (C)*, 2364 (1971).