Tetrahedron Letters No. 13, pp 1185 - 1188, 1975. Pergamon Press. Printed in Great Britain.

A NOVEL PURINE NUCLEOSIDE SYNTHESIS 9-β-D-ARABINOFURANOSYL-ADENINE

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(Received in USA 10 December 1974; received in UK for publication 25 February 1975)

This communication deals with a simple and novel approach to the stereospecific total synthesis of a wide range of modified purine nucleosides of possible interest as anti-viral or anti-tumor agents. In view of the simplicity of the operations involved, this method may have considerable practical utility. In particular, it provides an efficient route for the synthesis of the important naturally occurring anti-viral agent, 9-β-D-arabinofuranosyl adenine (ara A) (VIII), which has shown[1-4] significant activity against herpes simplex and vacinia viruses in cell cultures and in experimental animals. Ara-A has earlier been synthesized either by the modification of preformed nucleosides[5] or by nucleoside synthesis with arabinose or its derivatives.[6]

For the synthesis of ara-A (VIII), the arabinofurano-thionoxazolidine (I), which was prepared in good yield by a modification of the procedure of Bromund and Herbst[7] was chosen as the starting material. Treatment of the thionoxazolidine (I) with sodium hydride in dry DMF, followed by the addition of an equivalent amount of mercuric bromide gave a solution, which is believed to contain the bromo-mercury derivative (II). This solution was treated with 4-amino-6-chloro-5-nitropyrimidine (III). The reaction mixture was freed of inorganic salts by extraction and precipitation methods, and the condensation product (IV) was isolated as a colorless foam, after column chromatography over silica gel in 30% yield. This compound showed UV absorption in methanol at 215, 245 and 327 nm. Compound (IV) proved to be a rather unstable material and apparently underwent extensive decomposition during the isolation procedure, thereby accounting for the low isolated yield. Exclusion of mercuric bromide in the above reaction lead mainly to the unwanted S-alkylated product (V). Catalytic hydrogenation of the condensation product (IV) over 10% Pd/C, followed by isolation by chromatography over silica gel yielded the diamino-pyrimidinyl-thionoxazolidine (VI) as a colorless foam in 46% yield. Elemental analysis calculated for $C_{10}H_{13}N_5O_4 \cdot 1/2\ H_2O$ C, 38.95, H, 4.58, N, 22.72, S, 10.40. Found C, 39.05, H, 4.68, N, 22.46, S, 10.07. UV (H_2O), λ_{max} (pH 8 and 12) 245.5 (18, 900) and 297 nm (8, 600), (pH 1) 240 (15, 900) and 310 nm (10, 100). IR γ_{max} (KBr), 3200 to 3450, 1635 and 1580 cm^{-1}, MS, m/e, 299 ($M^{\ddagger}$), 281 (M-H_2O) and 265 (M-H_2S), $[\alpha]_D^{25} = -181^{\circ}$ (1% solution in MeOH). The NMR spectrum is

in agreement with the structure. Paper chromatography* R_f (A) 0.64, R_f (B) 0.49, R_f(C) 0.7, and R_f (D) 0.35. The reduction of the nitro-thione (IV) could also be accomplished by employing aluminum amalgam.

In view of the instability of the nitro-thione (IV) to hydrolytic conditions, it was found to be of advantage to reduce it to the amino-thione (VI) without prior chromatographic purification. When an aqueous solution of the crude reduced product (VI) at pH 6 was heated at 85°, in an atmosphere of N_2, it was smoothly converted into the known[5b, 8] 8-mercapto-ara-adenosine (VII), isolated as white needles in an overall yield of 47% from the thionoxazolidine (I). m.p. 154° (foams), UV (H_2O), λ_{max} (pH 2.2) 221 (12,800), 240 (12,600), 300 (Sh.), 307 nm (22,650), (pH 6.8) 220 (Sh.), 235 (15,950), 298 (23,400) and 305 nm (23,900), (pH 11.5) 228 (19,900) and 297 nm (17,700), IR γ_{max} (KBr), 3100 to 3450, 1660 cm^{-1}, MS, m/e $M^{\bullet}$ not observed, 281 ($M-H_2O$), 265 ($M-H_2S$), 167 [(B + 1)] peak, $[\alpha]_D^{25}$ + 13.4° (0.5% solution in MeOH). Paper chromatography R_f(A) 0.36, R_f (B) 0.42, R_f (C) 0.52.

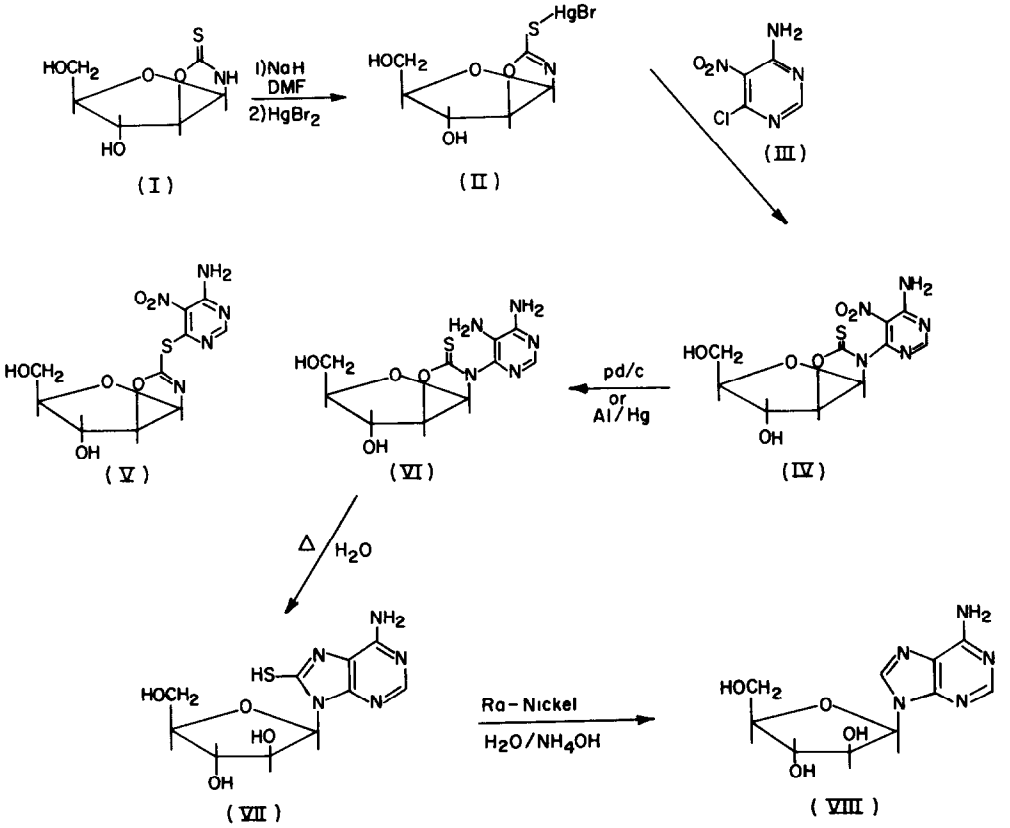
Desulfurization of 8-mercapto-ara-adenosine (VII) to ara-A (VIII) was achieved either in about 46% yield by treatment with hydrogen peroxide in aqueous methanol in the presence of hydrochloric acid following the procedure of Ikehara[5b], or more efficiently by heating at 90° with Raney Nickel in aqueous ammonia. By the latter method ara-A (VIII) was obtained as white needles in 83% yield, m.p. 255-56°, UV (H_2O), λ_{max} (pH 2.2) 257 nm (14,900), (pH 6.8) 259.5 nm (14,900), (pH 11.6) 259.5 nm (14,900), IR γ_{max} (KBr), 3475, 3300, 3195 and 1630 cm^{-1}, $[\alpha]_D^{40}$ + 12° (0.25% solution in water). Authentic ara-A[9] showed $[\alpha]_D^{40}$ + 9.9° (0.25% solution in water). Paper chromatography R_f(A) 0.48, R_f (C) 0.80, R_f (D) 0.09, R_f (relative to adenosine) (B) 0.98, paper electrophoresis 0.05M borate buffer, pH 6.8, 3000 V for 1.5 hr -1.1, under identical conditions adenosine has R + 4.8. By essentially following the steps described above, but without isolating or purifying any of the intermediate compounds, the arabinofurano-thionoxazolidine (I) could be converted into ara-adenosine (VIII) in an overall yield of 39%.

By suitable modifications of the substituents in the chloronitropyrimidine derivative and by employing thiocyanic acid adducts of other sugars, it should be possible to extend the scope of this approach for the synthesis of other promising purine nucleoside analogs. Our efforts are currently directed towards this goal.

Acknowledgements

I wish to thank the National Institute of Health for the award of a grant (CA 12960), Mrs. E. McLendon for able technical assistance and Dr. L. E. Orgel for helpful discussions.

* System A, 1-PrOH, NH_4OH, H_2O (7 1·2), System B, n-BuOH, 5N AcOH (2 1), System C, 95% C_2H_5OH 1N NH_4OAc (7 3), pH 7.5, System D, n-BuOH saturated with water.


HOCH2
HO
NH
S
1)NaH
DMF
2)HgBr2
HgBr
OH
(I)
(II)
NH2
O2N
Cl
(III)
(IV)
(V)
(VI)
pd/c
or
Al/Hg
Δ
H2O
HS
(VII)
Ra-Nickel
H2O/NH4OH
(VIII)

References

(1) Parke, Davis and Company, Belgian Pat. 671, 557 (1967).

(2) F. M. Schabel, Jr., J. A. Montgomery, "Purines and Pyrimidines, International Encyclopedia Pharmacology Therapy", Pergamon Press, Oxford, 1972.

(3) F. A. Miller, G. J. Dixon, J. Ehrlich, B. J. Sloan and I. W. McLean, Jr., Antimicrob. Ag. Chemother., 136 (1968).

(4) B J Sloan, F. A. Miller, I. W. McLean, Jr., and H. E. Machamer, ibid., 161 (1968).

(5) (a) E. J. Reist, A. Benitz, L. Goodman, B. R. Baker, and W. W. Lee, J. Org. Chem., 27, 3274 (1962).
(b) M Ikehara and Y. Ogiso, Tetrahedron, 28, 3695 (1972).

(6) (a) C P J. Glaudemans and H. G. Fletcher, Jr., J. Org. Chem., 29, 3286 (1964).
(b) G Lunzmann and G. Schramm, Biochim. Biophys. Acta, 169, 263 (1968).

(7) W. H. Bromund and R. M. Herbst, J. Org. Chem., 10, 267 (1945).

(8) E. J. Reist, D. F. Calkins, L. V. Fisher and L. Goodman, J. Org. Chem., 33, 1600 (1968).

(9) A commercial sample of ara-A purchased from Terra-Marine Bioresearch was recrystallized from methanol before use.