# The Synthesis of 4-Hydroxylamino-7(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (7-deaza-HAPR) (1)

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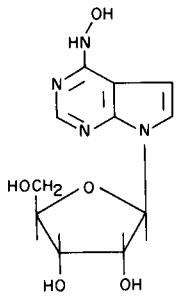
*Sir:*

The purine nucleoside, 6-hydroxylamino-9-β-D-ribofuranosylpurine (HAPR), (2,3) has demonstrated significant inhibition of various mouse leukemias (2,4,5) and the growth of a *Streptococcus faecalis* test system (5). Subsequent pharmacological studies in dogs and monkeys with HAPR established (5) a definite degree of toxicity as revealed by the occurrence of methemoglobinemia. It has been postulated (6) that this condition may be caused by the hydroxylamine formed by the *in vivo* dehydroxylamination (7) of HAPR by an adenosine deaminase.

Tubercidin (7-deazaadenosine) has demonstrated (8) a complete resistance toward deamination by adenosine deaminase and cleavage by adenosine phosphorylase. This has prompted the synthesis of 4-hydroxylamino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (I), by treatment of 4-chloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (9) with hydroxylamine. Compound I should be resistant to dehydroxylamination by adenosine deaminase.




I

## EXPERIMENTAL

4-Hydroxylamino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (10) (I).

Five g. of 4-chloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (9) and 2.5 g. of hydroxylamine (11) were dissolved in 250 ml. of 2-propanol and the solution heated at reflux temperature for 24 hours. The volume was reduced to a thin slurry and the solid collected by filtration. This procedure was repeated two more times. The solid which had been collected was dissolved in the minimum amount of boiling methanol and ethyl acetate slowly added to the cloud point. The solution was then allowed to stand at room temperature (12) for from 4 to 15 days until crystallization appeared complete. The above procedure was repeated utilizing the filtrate to furnish an additional quantity (0.5 g.) of I, and a total yield (13) of 2.0 g. (41%), m.p. 184-185° dec.; λ max (*p*H 1) 273 (ε, 14,700), 229 mμ (ε, 18,200).

*Anal.* Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 47.11; H, 5.10; N, 19.80.

An alternate procedure using a 2-propanol/hydroxylamine solution prepared from 2-propanol, hydroxylamine hydrochloride and potassium hydroxide has furnished the hydrochloride of I, m.p. 205-207° dec.

*Anal.* Calcd. for $C_{11}H_{14}N_4O_5 \cdot HCl$: C, 41.40; H, 4.74; N, 17.55. Found: C, 41.58; H, 5.07; N, 17.26.

Acknowledgment.

The authors wish to thank Mr. A. F. Lewis and staff for the preparation of certain intermediates.

## REFERENCES

(1) Supported by Research Contract No. PH 43-65-1041 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) A. Giner-Sorolla, L. Medrek and A. Bendich, *J. Med. Chem.*, 9, 143 (1966).

(3) P. K. Chang, *J. Med. Chem.*, 8, 884 (1965).

(4) J. H. Burchenal, M. Dollinger, J. Butterbaugh, D. Stoll and A. Giner-Sorolla, *Biochem. Pharmacol.*, 16, 423 (1967).

(5) A. Bloch, E. Mihich, C. A. Nichol, R. K. Robins and R. H. Whistler, *Proc. Amer. Assoc. Cancer Res.*, 7, 7 (1966).

(6) A. Giner-Sorolla, S. A. O'Byrant, C. Nanos, M. R. Dollinger, A. Bendich and J. H. Burchenal, *J. Med. Chem.*, 11, 521 (1968).

(7) Dehydroxylamination of HAPR by ox heart deaminase has been reported: M. Rockwell and M. H. Maquire, *Mol. Pharmacol.*, 2, 57 (1966).

(8) A. Bloch, R. J. Leonard and C. A. Nichol, *Biochim. Biophys. Acta*, 138, 10 (1967).

(9) J. F. Gerster, B. Carpenter, R. K. Robins and L. B. Townsend, *J. Med. Chem.*, 10, 326 (1967).

(10) Melting points were observed on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet absorption spectra were obtained with a Cary recording spectrophotometer, model 14. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Missouri.

(11) C. D. Hurd, *Inorg. Syn.*, 1, 87 (1939).

(12) The rate of evaporation was adjusted periodically to prevent the product from separating as an oil.

(13) The yield may be improved by repeating the evaporation procedure on the residue from the filtrate.

Received September 30, 1968 Salt Lake City 84112