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A SYNTHESIS OF 3-DEAZATHYMIDINE

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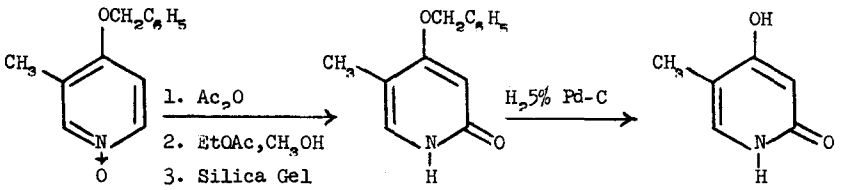
The synthesis of aza analogs of the pyrimidine nucleosides has received considerable attention (1-3) and has resulted in the biologically active and therapeutically useful compounds, 5-azacytidine and 6-azauridine. Efforts directed toward the synthesis of the



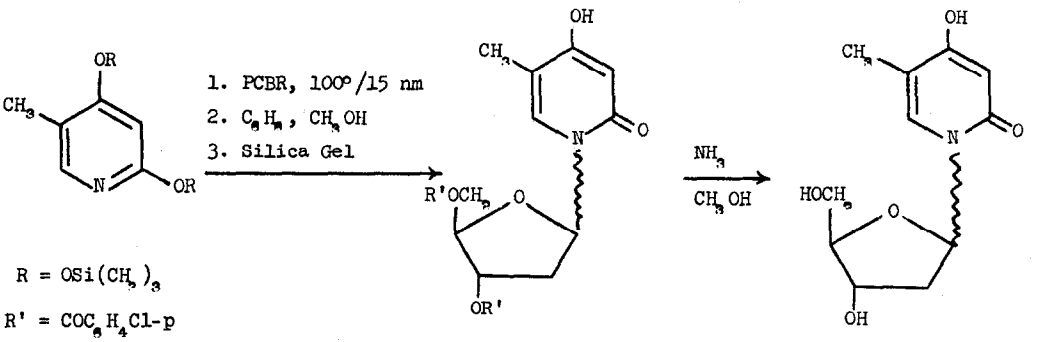
I II III

deazapyrimidine nucleosides have only recently been reported (4-6). Four 3-deazapyrimidine (pyridine) analogs of the common pyrimidine nucleosides of RNA and DNA are possible and of these, only 3-deazathymidine has not been reported (7). We now wish to communicate syntheses of 4-hydroxy-5-methyl-1-(2-deoxy-β-D-ribofuranosyl)-2-pyridone (3-deazathymidine) and its corresponding base, 4-hydroxy-5-methyl-2-pyridone (3-deazathymine).

Anhydrous 4-benzyloxy-3-picoline-N-oxide (8), I, was subject to rearrangement in refluxing acetic anhydride followed by methanolysis of the intermediate alpha acetates. Elution chromatography of the crude reaction mixture furnished 4-benzyloxy-5-methyl-2-pyridone, II (14%). mp 148-150°, $\lambda_{max}^{CH_3OH}$ 283 nm (log e, 3.67), nmr (DMSO-d_6) δ1.92 (3H, s, $-CH_3$), 5.10 (2H, s, $-CH_2-$), 5.83 (1H, s, 3-H), 7.12 (1H, s, 6-H), 7.43 (5H, s, aromatic H's). $C_{13}H_{13}NO_2$ (215.24), calculated, 72.54% C, 6.09% H, 6.51% N; found, 72.32% C, 6.07% H, 6.42% N, along with the isomeric 4-benzyloxy-3-methyl-2-pyridone. Hydrogenation (13) of II produced 4-hydroxy-5-methyl-2-pyridone (3-deazathymine), III, 12% overall from I. mp 330° (DSC), $\lambda_{max}^{CH_3OH}$ 278 nm (log e, 3.68), nmr (DMSO-d_6) δ1.85 (3H, d, $J < 1.0$ Hz, $-CH_3$), 5.62 (1H, s, 3-H), 7.05 (1H,

broad s, 6-H). $C_6H_7NO_2$ (125.12), calculated, 57.59% C, 5.64% H, 11.20% N; found, 57.67% C, 5.70% H, 11.20% N.

3-Deazathymine was refluxed overnight with hexamethyldisilazane and the reaction mixture distilled to yield IV, 2,4-bistrimethylsilyloxy-5-methylpyridine (95%), bp 68-70°/0.35 mm, as



R = $OSi(CH_3)_3$

R' = COC_6H_4Cl-p

IV Va, Vb VIa, VIb

a clear viscous oil. The bistrimethylsilyloxypyridine was immediately fused with 2-deoxy-3,5-di-O-(p-chlorobenzoyl)-α-D-ribofuranosyl chloride (9) (PCBR) for one hour at 100° in vacuo. The fusion mixture was dissolved in benzene and treated with methanol overnight to remove the 4-trimethylsilyloxy group of the blocked nucleosides. The resulting crude mixture of anomers was then separated by elution chromatography on silica gel to furnish the pure β blocked nucleoside, Vb (20.0%). mp 205-207°, 225-227° (recrystallized from acetone-methanol), $\lambda_{max}^{CH_3OH}$ 282 nm (log e, 3.67), $\alpha_D^{25°}$ -7° (c, 0.5, CH_3OH), nmr (DMSO-d_6) δ1.72 (3H, s, $-CH_3$), 5.67 (1H, s, 3-H), 6.57 (1H, "t", J_{app} 7.0 Hz, H_1'), 7.35 (1H, s, 6-H), $C_{25}H_{21}O_7Cl_2N$ (518.35), calculated, 57.92% C, 4.08% H, 2.70% N; found, 57.64% C, 4.05% H, 2.60% N and the pure alpha isomer Va (33.6%). mp 157-159° (recrystallized from acetone-methanol), $\lambda_{max}^{CH_3OH}$ 282 nm (log e, 3.75), $\alpha_D^{25°}$ -59° (c, 0.5 CH_3OH), nmr (DMSO-d_6) δ1.90 (3H, s, $-CH_3$) and 6.40 (1H, "q", J_{app} 5.0 and 2.0 Hz, H_1'), found, 57.58% C, 4.13% H, 2.56% N.

The beta isomer Vb was deblocked by treatment with methanol saturated with ammonia at 0° for four days in a steel bomb. Removal of the solvent in vacuo and repeated trituration with anhydrous ether gave 4-hydroxy-5-methyl-1-(2-deoxy-β-D-ribofuranosyl)-2-pyridone (3-deazathymidine), VIb, in 88.5% yield, mp 212-214° (recrystallized from methanol-ether), $\lambda_{max}^{CH_3OH}$ 288 nm (log e, 3.65), $\alpha_D^{25°}$ +6.35° (c, 0.1, CH_3OH), $[\theta]_{286nm}^{24°}$ +5549, nmr (DMSO-d_6) δ1.90 (3H, s, $-CH_3$), 5.63 (1H, s, pyridine 3-H), 6.40 (1H, "t", J_{app} 7.0 Hz, H_1'), 7.60 (1H, s, pyridine 6-H). $C_{11}H_{15}NO_5$ (241.24), calculated, 54.76% C, 6.27% H, 5.81% N; found, 54.52% C, 6.44% H, 5.71% N. Similar deblocking of Va followed by chromatographic purification of the

crude product furnished 4-hydroxy-5-methyl-1-(2-deoxy-α-D-ribofuranosyl)-2-pyridone, VIa, in 26% yield, mp 200-202°, $\lambda_{max}^{CH_3OH}$ 286 nm (log e, 3.56), $\alpha_D^{25°}$ -17° (c, 0.1, CH_3OH), $[\alpha]_{286nm}^{24°}$ -8202, nmr (DMSO-d_6) δ1.88 (3H, s, $-CH_3$), 5.60 (1H, s, pyridine 3-H), 6.25 (1H, "q", J_{app} 7.5 and 3.5 Hz, H_1'), 7.57 (1H, s, pyridine 6-H), found, 54.53% C, 6.28% H, 5.69% N.

The anomeric pairs Va, Vb and VIa, VIb exhibit the expected bandwidth and multiplicity differences of the anomeric proton (H_1') pmr signal for alpha and beta nucleosides (10-12). The beta isomers show a pseudo triplet with J_{app} 7Hz and a 15 Hz bandwidth while the alpha isomers show a pseudo quartet and a 10-12 Hz bandwidth. Corroborative evidence for the stereochemical assignments is provided by circular dichroism data. The positive and negative Cotton effects shown by VIb and VIa respectively is analogous to that reported for the anomeric pair of N-1-(2-deoxy-D-ribofuranosyl)-2-pyridones (6, 14). Both pairs of isomers of V and VI failed to obey Hudson's isorotational rule (15). The failure of other N-1-2-deoxy-D-ribofuranoside 2-pyridone derivatives to follow Hudson's rule has also been noted (5, 10).

REFERENCES

1. A. Piskala and F. Sorm, Collect. Czech. Chem. Commun., 29, 2060 (1964).
2. M. Prystas and F. Sorm, Collect. Czech. Chem. Commun., 27, 1578 (1962).
3. J. Gut, "Aza Analogs of Pyrimidine and Purine Bases of Nucleic Acids", in "Advances in Heterocyclic Chemistry", Vol. 1, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, N. Y., 1962, p. 189.
4. M. J. Robins and B. L. Currie, Chem. Commun., 1547 (1968).
5. B. L. Currie, R. K. Robins, and M. J. Robins, J. Heterocycl. Chem., 7, 323 (1970).
6. M. P. Mertes, J. Med. Chem., 13, 149 (1970).
7. Attention is called to a synthesis of 3-deazathymidine that has been published since the present work was submitted by S. Nesnow, T. Miyazaki, T. Khwaja, R. B. Meyer, Jr., and C. Heidelberger, J. Med. Chem., 16, 524 (1973).
8. A. R. Katritzky, J. Chem. Soc., 2404 (1956).
9. M. P. Kotlick, C. Szantay, and T. J. Bardos, J. Org. Chem., 34, 3806 (1969).
10. P. Nuhn, A. Zschunke, D. Heller, and G. Wagner, Tetrahedron, 25, 2139 (1969).
11. C. D. Jardetzky, J. Amer. Chem. Soc., 83, 2919 (1961).
12. M. J. Robins and R. K. Robins, J. Amer. Chem. Soc., 87, 4934 (1965).
13. Gratitude is expressed to the Hydrogenation Department of Searle Laboratories headed by Mr. William M. Selby for carrying out the debenzylation of II and the deblocking of Va

and Vb.

14. U. Seguin and C. Tamm, Helv. Chim. Acta, 55, 1196 (1972).

15. C. S. Hudson, J. Amer. Chem. Soc., 31, 66 (1909).