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A SYNTHESIS OF 2′-DEOXY-L-URIDINE

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In connection with investigations on enantiomers of natural nucleoside and nucleotide derivatives[1-3] it was necessary to develop a synthetic method for the preparation of 2′-deoxy-L-nucleosides as an approach to the enantiomers of the DNA type. Recently, two synthetic procedures have been described[4,5] both of them consisting in a nucleoside condensation of a protected 2′-deoxy-L-ribose derivative with the heterocyclic base. In this communication, different tactics of the synthesis are described which make the pyrimidine 2′-deoxy-L-ribonucleosides accessible on the basis of a facile procedure for the preparation of 2′-deoxy-L-uridine.

With the use of the procedure of SANCHEZ and ORGEL[6], L-arabinose was converted to the 2-amino-1,2-oxazoline derivative I by treatment with aqueous cyanamide. On refluxing I with methyl propiolate in 50% ethanol* for 4-5 h, 2,2′-anhydro-(1-β-L-arabinofuranosyl)uracil II was obtained in 70-75% yield; $[\alpha]_D^{20}$ + 32.0 (c=0.5, water). $C_9H_{10}N_2O_5$ (226.2) calculated 47.78% C, 4.45% H, 12.38% N; found 47.69% C, 4.67% H, 12.53% N. This compound was transformed to its 3′,5′-di-O-benzoyl derivative III by treatment with 10% excess of benzoyl cyanide[7] in dimethylformamide as solvent (30 min at room temperature) in the presence of a catalytic amount of tri-n-butylamine. The crystalline material (yield 70-80%) obtained directly from the reaction mixture was essentially homogeneous; m.p. 257-258 °C, $[\alpha]_D^{20}$ + 48.3 (c=0.5, dimethylformamide). $C_{23}H_{18}N_2O_7$ (434.4) calculated 63.59% C, 4.17% H, 6.45% N; found

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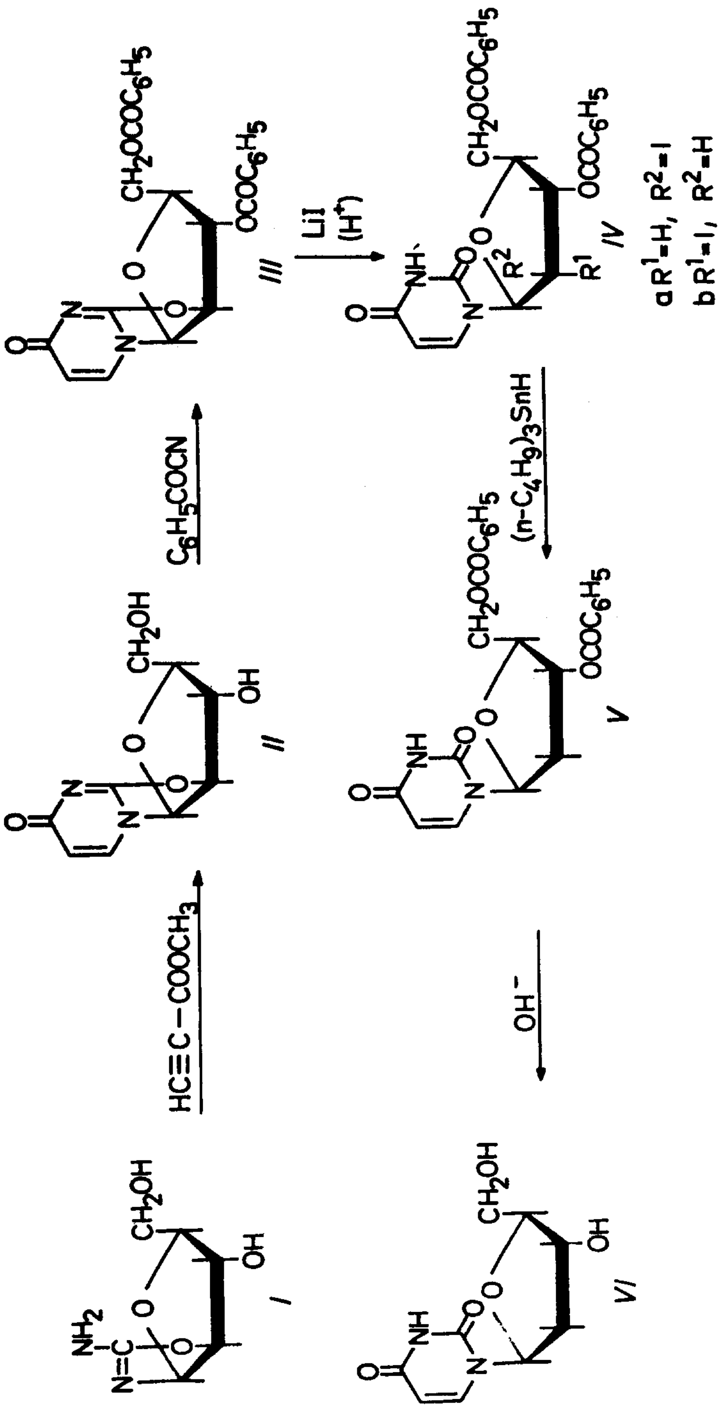
* The conditions described for the reaction with methyl propiolate in the original paper[6] do not afford satisfactory results.


HC≡C−COOCH3
C6H5COCN
LiI
(H+)
(n-C4H9)3SnH
OH−
I
II
III
IV
V
VI
a R1=H, R2=I
b R1=I, R2=H

63.39% C, 4.42% H, 6.27% N. D-Enantiomer: m.p. 262°C, $[\alpha]_D^{20}$ -46.5 (c=0.5, dimethylformamide).

Compound III was converted into the 2′-deoxy-2′-iodo derivative IV on heating at 100°C for 1 hour with a 5-fold molar excess of fused lithium iodide in dimethylformamide in the presence of a 2-fold molar excess of pyridine perchlorate. After removal of the solvent in vacuo, the residue was taken into chloroform, the inorganic salts removed by washing with water, and the chloroform layer filtered through silica gel column (20-fold amount on that of III), and the column washed with chloroform. The mixture of IVa and IVb (2:1) crystallized from the concentrate on trituration with ethanol. Yield, 40-50% (another crop can be obtained on purifying the mother liquor on a loose layer of silica gel in 5% ethanol in chloroform). M.p. 178°C. $C_{23}H_{19}IN_2O_7$ (562.3) calculated 49.12% C, 3.40% H, 22.56% I, 4.98% N; found 48.92% C, 3.52% H, 22.90% I, 5.12% N. On eluting the column with 10% ethanol in chloroform, there was obtained in 30-40% yield a mixture of 3′,5′-di-O--benzoyl derivatives of L-uridine and 1-(β-L-arabinofuranosyl)uracil (ratio 1:2) from which the latter crystallized in a pure form: m.p. 185°C (ethanol), $[\alpha]_D^{25}$ -6,8 (c=0.5, dimethylformamide). $C_{23}H_{20}N_2O_8$ (454.2) calculated 61.06% C, 4.45% H, 6.19% N; found 60.95% C, 4.39% H, 6.07% N.

Upon the action of tri-n-butyltin hydride[8] on IV (2-fold excess of the reagent in benzene solution, and 2,2′-azo-bis(isobutyronitrile) (50 mg), 20 min at reflux temperature) followed by chromatography of the whole mixture on a loose layer of silica gel (30% ethyl acetate in benzene; IV, R_F = 0.50, V, R_F = 0.20), compound V was isolated in 60-70% yield. M.p. 218-219°C (ethanol); $[\alpha]_D^{25}$ + 11.2 (c=0.5, dimethylformamide). $C_{23}H_{20}N_2O_7$ (436.4) calculated 63.29% C, 4.62% H, 6.42% N; found 63.52% C, 5.08% H, 6.37% N. D-Enantiomer: m.p. 225-226°C (ethanol), $[\alpha]_D^{25}$ -17.3 (c=0.5, dimethylformamide).

2′-Deoxy-L-uridine (VI) was obtained from V by methanolysis catalyzed with sodium methoxide at room temperature. Yield 90%, m.p. 158°C (ethanol). Paper--chromatographic properties of VI were identical with those of 2′-deoxyuridine in all systems examined. ORD-spectrum (c=0.025, water): $[\Phi]_{283}$ -2270, $[\Phi]_{275}$ 0, $[\Phi]_{253}$ +9200.

Compounds V and VI can be used as starting materials for the syntheses of 2′-deoxy-L-thymidine and 2′-deoxy-L-cytidine. The procedures will be described in detail in the full paper.

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