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Synthesis of 5'-deoxyuridine 5'-phosphonic acid

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5'-deoxynucleoside 5'-phosphonates which contain a $C^{5'}$-P bond in place of the $C^{5'}$-O-P bond of the naturally occuring nucleotides are of some biochemical interest because of their structural resemblance to nucleotides on the one hand and their possible resistance to the action of the nucleolytic enzymes on the other.

It has already been shown[1] that the reaction of 5'-deoxy-5'-iodo-2',3'-O--isopropylideneuridine (I) with triethyl phosphite yields diethyl 5'-deoxy-2',3'--O-isopropylideneuridine 5'-phosphonate. However, this compound could not be converted to the free phosphonic acid by acid or alkaline hydrolysis[1] x). This difficulty could in principle be overcome by using of phosphites with more readily removable groups. However, most of the protecting groups commonly used in similar situations (2-cyanoethyl, 2-haloethyl, 2,2,2--trichloroethyl or benzyl group) do not react satisfactorily in the Arbuzov reaction.

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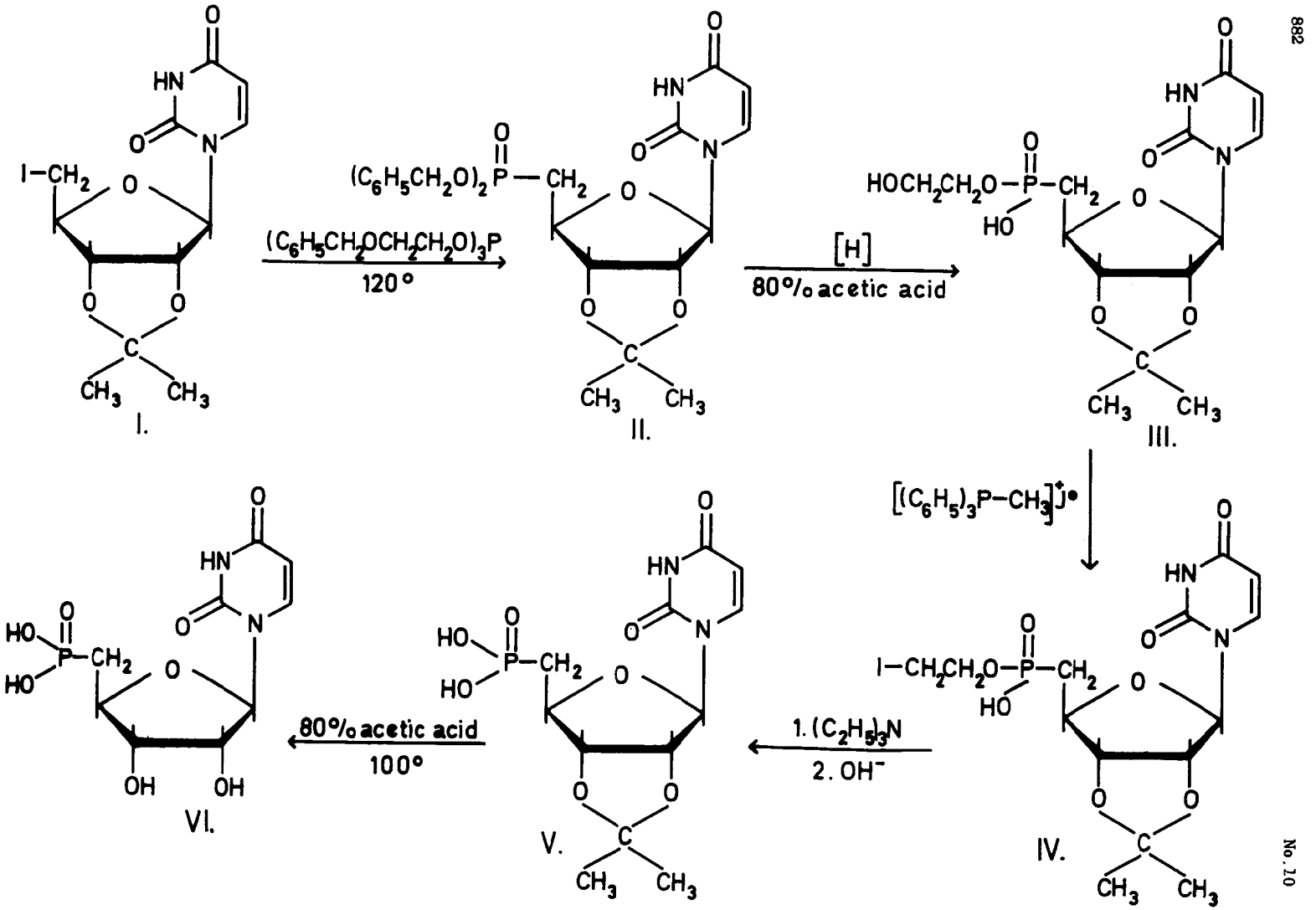
x) During this study a hydrolysis of this derivative with HBr in benzene solution was described in patent literature[2]. However, no details of yields and properties have been given.


I.
II.
III.
IV.
V.
VI.
$(C_6H_5CH_2O)_2P-CH_2$
$(C_6H_5CH_2OCH_2CH_2O)_3P$
120°
[H]
80% acetic acid
$[(C_6H_5)_3P-CH_3]^+I^-$
1. $(C_2H_5)_3N$
2. OH^-
80% acetic acid
100°

This problem was solved by using tri(2-benzyloxyethyl) phosphite[x]) which on reaction with I yielded the phosphonic acid diester II. Removal of the O-benzyl groups by catalytic hydrogenation over a Pd/C catalyst (5% Pd) in 80% acetic acid afforded 2-hydroxyethyl 2',3'-O-isopropylidene-5'-deoxyuridine 5'-phosphonate (III) in 40% overall yield (R_F : A, 0.60, E_{Up} = 0.54)[xx]). The structure of III was established by elemental analysis and n.m.r. spectra; it is resistant to 1N-NaOH at 50° or to the crude snake venom (Vipera russellii). Reaction of III with triphenyl-methyl-phosphonium iodide in dimethylformamide (DMF)[3] led to the 2-iodoethyl ester IV (R_F : A, 0.60), which by treatment with triethylamine in DMF followed by hydrolysis with dilute ammonia yielded 5'-deoxy-2',3'-O-isopropylideneuridine 5'-phosphonate (V) (R_F : A, 0.27, E_{Up}= =0.92). Clevage of the isopropylidene group with 80% acetic acid (100°C, 2 hours) gave 5'-deoxyuridine 5'-phosphonic acid (VI) in 38% yield: $C_{19}H_{13}N_2O_8P$, (308,2) calculated: 35.07% C, 4.25% H, 9.09% N, 10.07% P; found 34.49% C, 4.84% H, 8.83% N, 9.54% P. R_F : A, 0.08 (Up 0.14), B, 0.25 (Up 0.20), E_{Up}=0.95. From potentiometric titration, pK_1=3.72 and pK_2=7.16. UV spectra (pH 2): λ_{max}=260 nm (ε_{260}=10.2 x 10^3), A_{250}/A_{260}=0.76, A_{280}/A_{260}=0.39, A_{290}/A_{260}=0.04.

The phosphonic acid VI is completely stable to crude snake venom (V.russellii), to bovine intestinal alkaline phosphatase or to E.coli alkaline phosphatase under the conditions usually employed.

By the same synthetic approach, other derivatives of the same type should be accessible. Further studies on the chemical and biochemical aspects of this problem are in progress.

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x) Prepared by the reaction of 2-benzyloxyethanol with phosphorus trichloride in the presence of dimethylaniline in ligroin solution.

xx) R_F on Whatman No 1 paper in (A) 2-propanol - conc. aqueous ammonia - - water (7:1:2), (B)1-butanol - acetic acid - water (5:2:3) E_{Up} : relative mobility referred to uridylic acid on paper electrophoresis in 0.05 M Na_2HPO_4 pH 7.5, 40 V/cm, 1 hour.

Literature

1. Bannister B., Kagan F., J.Am.Chem.Soc. 82, 3363 (1960).
2. Myers T.C., US. 3, 238, 191 (cf. Chem.Abstr. 64, 15972 (1966)).
3. Verheyden J.P.H., Moffatt J.G., J.Am.Chem.Soc. 86, 2093 (1964).