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Aliphatic Thymidine and Deoxyuridine Analogs

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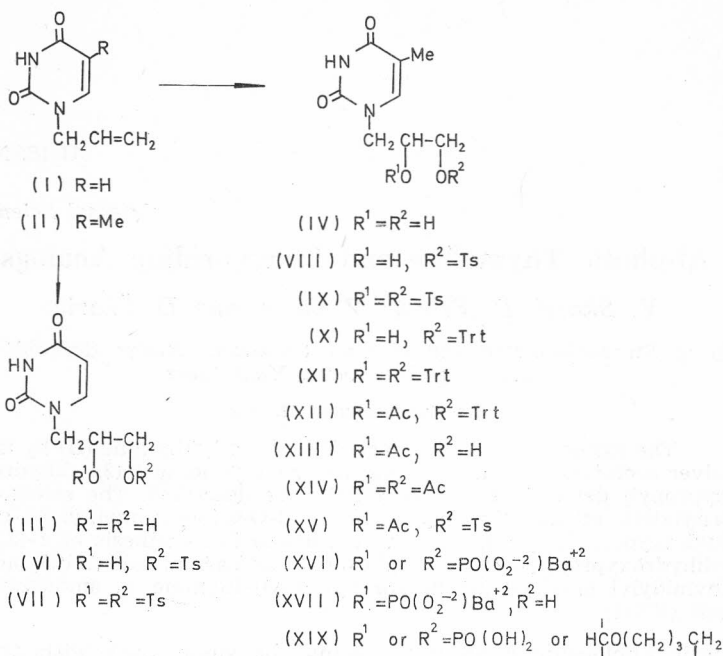
The oxidation of 1-allyluracil (I) and 1-allylthymine (II) by the silver acetate-iodine method into the corresponding 1-(2,3-dihydroxypropyl) derivatives (III) and (IV) was described. The selective tritylation of the glycol (IV) into 1-(3-O-triphenylmethyl-2,3-dihydroxypropyl)thymine (X) made feasible the synthesis of 1-(2,3-dihydroxypropyl)thymine-2'-phosphate as barium salt (XVII) and thymidylyl (5'→2')-1-(2,3-dihydroxypropyl)-thymine as ammonium salt (XXII).

Aliphatic nucleoside analogs replacing the sugar part with an aliphatic diol or triol might be of biological and chemotherapeutical interest¹⁻³. Thus, phenylalanine esters of the aliphatic adenosine analog exhibited a pronounced »pyromycin-like« activity⁴, while eritadenine (lentinacin), isolated from a species of Japanese mushroom (*Lentinus edodes*), proved to be a highly hypocholesterolaemic substance⁵. The structures of these compounds and their stereochemical similarities to naturally occurring nucleosides stimulated our search toward the synthesis and chemistry of thymidine and deoxyuridine analogs bearing the dihydroxypropyl residue in place of the deoxyribose moiety.

It has been recently reported that 1-(2,3-dihydroxypropyl)uracil (III) and the corresponding thymine (IV) can be prepared by condensation of the suitably protected uracil⁶ and thymine⁷ with glycidol. The Hilbert-Johnson reaction⁸ has also been applied for the preparation of 1-allylthymine (II) which, upon oxidation⁹ with sodium chlorate and OsO₄, afforded dihydroxypropyl derivative (IV). The condensation of 3-O-*p*-tolylsulphonyl-1,2-O-isopropylidene-*D*-glycerine with 5-methyl-4-methoxypyrimidine-2-one afforded *D*-glycero-enantiomer of compound (IV), as the configurational analog of natural thymidine¹⁰⁻¹².

The present paper deals with a new preparation of non-glycosidic thymidine analog (IV) and its derivatives, relevant to the synthesis of the corresponding dinucleoside-like phosphates. We first showed that 2,4-di-*O*-trimethylsilylthymine^{13,14} could be conveniently used in a catalytic reaction with allyl bromide to give 1-allylthymine (II), the latter being converted into 1-(2,3-dihydroxypropyl) thymine (IV) in high yields by selective oxidation with iodine, silver

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acetate, and wet acetic acid¹⁵. Our studies revealed additionally that 1-allyl-uracil (I) and 1-allylthymine (II) could be superiorly prepared from the corresponding silyl derivatives, at room temperature even in the absence of silver perchlorate, when acetonitrile¹⁶ was used as solvent. According to Levene and Tipson¹⁷ the glycol (IV) was readily converted into 1-(2,3-O-isopropylidene-2,3-dihydroxypropyl) thymine (V).

NMR spectra of 1-allyl derivatives (I) and (II) revealed the 3'-geminal protons as the multiplets at τ 4.55—4.97 and the 1'-protons as the doublets with secondary splittings at τ 5.65 and 5.68, respectively. However, glycol (III) clearly showed the triplet for 3'-OH at τ 5.37 and the doublet with secondary splitting for 1'-protons at τ 6.61, the latter being analogously shifted at τ 6.65 in the spectrum of compound (IV).

The much higher reactivity of the primary hydroxylic group of dihydroxypropyl-uracil (III) and -thymine (IV) made possible specific preparations of 1-(3-O-*p*-tolylsulphonyl-2,3-dihydroxypropyl) uracil (VI) and the corresponding derivative of thymine (VIII). The 1-(2,3-di-O-*p*-tolylsulphonyl-2,3-dihydroxypropyl) uracil (VII) and the corresponding di-tosyl derivative of thymine (IX) were obtained only as minor products. Similarly, treatment of dihydroxypropyl-thymine (IV) with chlorotriphenylmethane¹⁸ yielded 1-(3-O-triphenylmethyl-2,3-dihydroxypropyl) thymine (X) in 72% yield and di-2',3'-O-trityl derivative (XI) as a by-product. This is in contrast with the non-specific acetylation of glycol (IV) which afforded 1-(2,3-di-O-acetyl-2,3-dihydroxypropyl) thymine (XIV), conveniently used in the recovery of slightly soluble glycol (IV) after having been hydrolysed in methanolic ammonia (vide infra).

The mono-tosyl and -trityl derivatives (VIII) and (X) were successfully acetylated to give 1-(2-O-acetyl-3-O-*p*-tolylsulphonyl-2,3-dihydroxypropyl) thy-

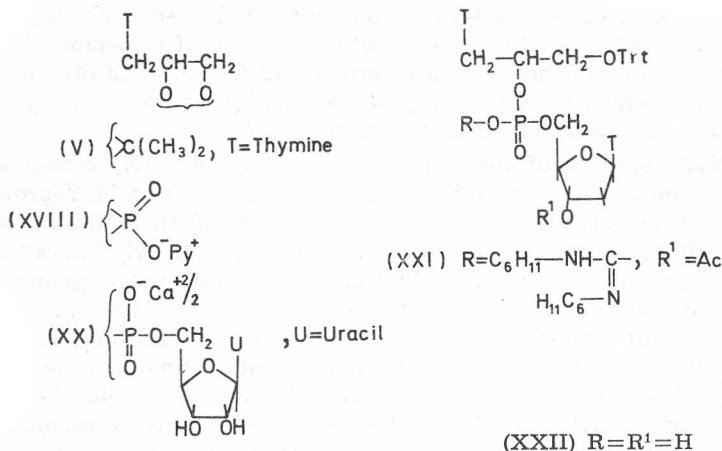
mine (XV) and 1-(2-*O*-acetyl-3-*O*-triphenylmethyl-2,3-dihydroxypropyl) thymine (XII), respectively, while the selective removal of acid-labile trityl group from the latter in 80% acetic acid afforded 1-(2-*O*-acetyl-2,3-dihydroxypropyl) thymine (XIII) which most probably isomerized by well known acyl migration of monoacyl derivatives of 1,2-diol systems¹⁹⁻²¹.

The NMR spectra of tosyl derivatives (VII) and (IX) reveal a marked influence of the 2'-*O*-*p*-tolylsulphonyl group on the position of 2'-proton signal. This signal is more shifted downfield (τ 4.83—5.30, m) than those (τ 5.77—6.74, m) of 2',3'-dihydroxypropyl derivatives (III), (IV), and (X) having a free 2'-hydroxylic group. In contrast with this observation, the 3'-geminal protons of the trityl derivatives (X—XII) showed resonances which were pronounced and more shifted upfield (τ 6.65—7.17) than those (τ 5.72 and 5.75) in the spectra of 3'-*O*-tosyl derivatives (VII) and (IX). It is interesting to note that the 1'-geminal protons of 2',3'-di-*O*-tosyl- (IX), 2'-*O*-acetyl-3'-*O*-tosyl- (XV), 2'-*O*-acetyl-3'-*O*-trityl- (XII), and 2',3'-di-*O*-acetyl- (XIV) derivatives, most probably restricted in rotations in aliphatic parts of molecules, exhibited two quartets at τ 5.82—6.05 and 6.22—6.40 ($J = 14.0$ — 14.5 Hz). The trityl- (XII) and acetyl- (XIV) derivatives showed also two quartets at τ 6.65 (5.73) and 6.86 (5.96) [$J = 11.0$ (12.0) Hz] corresponding to the geminal 3'-protons.

For an unambiguous synthesis of 1-(2,3-dihydroxypropyl)thymine-2'-phosphate (XVII), 3'-*O*-tritylpropyl-thymine (X) was phosphorylated by a standardized solution of β -cyanoethyl phosphate²² in the presence of dicyclohexylcarbodi-imide²³. The selective removal of β -cyanoethyl group by mild alkaline treatment with lithium hydroxide, followed by the detritylation on a Dowex 50 (H⁺) ion exchange resin column, afforded the desired product (XVII) which was stored as barium salt.

Dihydroxypropyl thymine (IV) was then examined in phosphorylation reaction with β -cyanoethyl phosphate. The 1-(2,3-dihydroxypropyl) thymine-2'(3')-phosphate, barium salt (XVI) isolated from this reaction as a mixture of 2'- and 3'-phosphomonoesters was easily converted into a cyclic product, which proved to be mainly the racemic 1-(2,3-dihydroxypropyl) thymine-2',3'-cyclophosphate (XVIII) partially reopened by means of the pancreatic ribonuclease. It is worth noting that the mixture of isomeric phosphates (XVI) afforded 1-[3(2)-*O*-tetrahydropyran-2-yl-2,3-dihydroxypropyl] thymine-2'(3')-phosphate which in the condensation (DCCI) reaction with 2',3'-*O*-ethoxymethylideneuridine²⁴, followed by deprotection in 20% acetic acid, yielded uridylyl-[5'→2'(3')] -1-(2,3-dihydroxypropyl) thymine, as calcium salt (XX). This product showed electrophoretic mobility at 0.2 (mmV⁻¹, h⁻¹ cm) and its NMR spectrum exhibited two doublets with secondary splittings at τ 2.05 (6-H) and 4.0 (5-H) of uracil, as well as two doublets at τ 2.42 (6-H) and 8.09 (5-Me) of thymine, consistent with the proposed structure.

The afore-described method for internucleotide linkage formation was successfully applied in the reaction of the piridinium salt of 3'-*O*-acetyl-thymidine-5'-phosphate^{25,26} with 3'-*O*-tritylpropylthymine (X) in the presence of dicyclohexylcarbodi-imide. Thus, *O*-[3'-*O*-acetylthymidylyl(5'→2')-1-(3-*O*-triphenylmethyl-2,3-dihydroxypropyl) thymine]-*N,N*-dicyclohexylpseudourea (XXI), as a possible intermediate, was isolated and readily deprotected by 80% acetic acid into thymidylyl(5'→2')-1-(2,3-dihydroxypropyl)thymine, isolated as ammonium salt (XXII). The intermediate (XXI) having masked the anionic site by



pseudourea residue was soluble in organic solvents and suitable for conventional characterizations.

In a preliminary reaction a sample of dinucleoside-like analog (XXII) was treated with Russell's viper venom (phosphodiesterase) and hydrolysed into 1-(2,3-dihydroxypropyl)thymine and thymidine, as evidenced by paper chromatography.

EXPERIMENTAL

The same techniques and apparatus were used as described previously²⁷. In addition, optical rotation was measured using a Zeiss-Winkel 179707 apparatus.

1-Allyluracil (I)

A solution of uracil (1.12 g, 10 mmol) in a mixture of hexamethyldisilasane (4 ml) and anhydrous dimethylformamide (0.4 ml) was heated at 150 °C for 15 h and then cooled. To this cooled solution allyl bromide (2 ml, 22 mmol), dissolved in acetonitrile (20 ml), was added, set aside for 4 days, and evaporated to dryness under reduced pressure. The oily residue was dissolved in ethanol (20 ml), neutralised with 1 mol dm⁻³ methanolic KOH, and evaporated to dryness. The residue was then triturated with chloroform and filtered off. The filtrate was partitioned with water and the organic layer evaporated to a crystalline product (1.3 g, 85%), m. p. 108–109 °C (from EtOAc), R_F ca. 0.70 [CH_2Cl_2 –MeOH (9 : 1)].

Anal. $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$ (152.15) calc'd.: C 55.25; H 5.30; N 18.41%
 found: C 55.05; H 5.62; N 18.55%

UV spectrum: λ_{max} 266 nm (lg ϵ 3.94), λ_{min} 232 nm (lg ϵ 3.08). IR spectrum: 3448, 3135, 3030, 2809, 1709, 1684br, and 1642 cm⁻¹ NMR spectrum: τ – 0.08br (1 H, s, 3-NH), 2.82 (1 H, d, 6-H; $J_{6,5} = 8.0$ Hz), 2.74–4.40 (1 H, m, 2'-H), 4.29 (1 H, d, 5-H; $J_{5,6} = 8.0$ Hz), 4.55–4.97 (2 H, m, 3'-H₂) and 5.65 (2 H, d, with secondary splitting, 1'-H₂; $J_{1',2'} = 5.5$ Hz).

1-Allylthymine (II)

(a) To a solution of 2,4-di-*O*-trimethylsilylthymine^{13,14} (10.85 g, 40 mmol) in anhydrous benzene (40 ml) a suspension of silver perchlorate (8.5 g, 41 mmol) in anhydrous benzene (40 ml) and then freshly distilled allyl bromide (7 ml, 80 mmol) were added. The mixture was stirred in a dry box at room temperature for 16 h. The precipitate was separated by filtration, while the filtrate and methanolic KOH washings were evaporated to dryness. The residue was triturated with ethanol (100 ml), heated to reflux and filtered off. The filtrate was then evaporated to

dryness and chromatographed on a silica gel (20 g) column. The ether eluate (250 ml) separated the product (5.6 g, 80%), m. p. 111—112 °C (from EtOAc-*n*-hexane), R_F ca. 0.76 [CH_2Cl_2 —MeOH (9 : 1)].

Anal. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ (166.18) calc'd.: C 57.82; H 6.07; N 16.86%
found: C 57.89; H 6.35; N 17.23%

UV spectrum: λ_{max} 271 nm ($\lg \epsilon$ 3.99), λ_{min} 236 nm ($\lg \epsilon$ 3.11). IR spectrum: ν_{max} 3448, 3165, 3030, 2825, 1681br, 1647, and 1631 cm^{-1} . NMR spectrum: τ 0.41 br (1 H, s, 3-NH), 3.04 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 3.84—4.40 (1 H, m, 2'-H), 4.57—4.97 (2-H, m, 3'-H₂), 5.68 (2 H, d, with secondary splitting, 1'-H₂; $J_{1',2'} = 5.5$ Hz), and 8.09 (3 H, d, 5-Me; $J_{\text{Me},6} = 1.2$ Hz).

(b) A solution of thymine (50.4 g, 0.4 mmol) in hexamethyldisilane (260 ml) and dimethylformamide (20 ml) was heated and then treated with allyl bromide (80 ml, 0.95 mmol) in acetonitrile (700 ml) at room temperature for 14 days. It was worked up as described for compound (I). Yield 62 g (93%), m. p. 111—112 °C, identical (mixed m. p., IR, NMR spectra) to that obtained under (a).

1-(2,3-Dihydroxypropyl)uracil (III)

A suspension of 1-allyluracil (I) (305 mg, 2 mmol) and silver acetate (751 mg, 4.5 mmol) in glacial acetic acid (10 ml) was stirred and treated portionwise with iodine¹⁵ (531 mg, 2.1 mmol) during a time interval of 30 min. The suspension was then diluted with 99% acetic acid (5 ml), heated at 95 °C for 4 h, cooled, and treated with sodium chloride (0.5 g). The precipitate was filtered off and the filtrate evaporated to dryness. The residue was dissolved in anhydrous ethanol and neutralized with 1% methanolic KOH. This solution was treated with KOH (550 mg) in methanol (20 ml), flushed with nitrogen, and set aside at room temperature for 16 h to be neutralized with 2 mol dm^{-3} hydrochloric acid. The precipitate was filtered off and the filtrate evaporated to dryness. The residue was chromatographed on a silica gel (46 g) column. Methylene chloride—methanol (10 : 1) eluted the product (134 mg, 37%), m. p. 142—143 °C from MeOH), R_F ca. 0.18 [CH_2Cl_2 —MeOH (9 : 1)].

UV spectrum: λ_{max} 267 nm ($\lg \epsilon$ 3.95), λ_{min} 233 nm ($\lg \epsilon$ 3.29). IR spectrum: ν_{max} 3509 br, 3067, 2857, 1698 sh, 1678, and 1621 cm^{-1} . NMR spectrum: τ (d_6 -DMSO) — 1.08 br (1 H, s, 3-NH), 2.50 (1 H, d, 6-H; $J_{6,5} = 8.0$ Hz), 4.50 (1 H, d, 5-H; $J_{5,6} = 8.0$ Hz), 5.88—6.52 (3 H, m, 2'-H and 3'-H₂), and 6.61 (2 H, d, with secondary splitting, 1'-H₂; $J_{1',2'} = 4.5$ Hz).

1-(2,3-Dihydroxypropyl)thymine (IV)

(a) A suspension of 1-allylthymine (II) (4.98 g, 30 mmol) and silver acetate (11.27 g, 68 mmol) in glacial acetic acid (150 ml) was treated with iodine (7.95 g, 32 mmol) and worked up as described for compound (III). Silica gel (240 g) column chromatography and elution with methylene chloride—methanol (9 : 1, 5.5 l) separated the product (3.2 g, 53%), m. p. 144—145 °C (from MeOH-Et₂O-*n*-hexane), R_F ca. 0.2 [CH_2Cl_2 —MeOH (9 : 1)].

Anal. $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2$ (200.19) calc'd.: C 47.99; H 6.04; N 13.99%
found: C 47.77; H 6.28; N 14.25%

UV spectrum: λ_{max} 271 nm ($\lg \epsilon$ 4.01), λ_{min} 236 nm ($\lg \epsilon$ 3.26) IR spectrum: ν_{max} 3322 br, 3986, 2959, 2865, 2770, 1706, 1681 br, 1637, and 1520 cm^{-1} . NMR spectrum: τ (d_6 -DMSO) — 1.3—0.83 (1 H, m, 3-NH), 2.63 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 5.91—6.52 (3 H, m, 2'-H and 3'-H₂), 6.65 (1 H, d with secondary splitting, 1'-H; $J_{1',2'} = 4.5$ Hz) and 8.25 (3 H, d, 5-Me; $J_{\text{Me},6} = 1.2$ Hz).

(b) 1-Allylthymine (II) (15 g, 90 mmol) was converted into the title compound as described for compound (III) and isolated as crude material. This product was dried and then treated with acetic anhydride (100 ml) in anhydrous pyridine (170 ml) at room temperature for 16 h. It was evaporated to dryness, and the residue partitioned between water and chloroform. From the organic layer a product was separated (18.56 g, 72.5%) and identified as 1-(2,3-di-O-acetyl-2,3-dihydroxypropyl)thymine (XIV, vide infra). The product thus obtained (3.85 g) was treated with a solution of

saturated methanolic ammonia (100 ml) at room temperature for 16 h. The solvent was removed under diminished pressure and the residue triturated with chloroform. The crystalline product separated 2.57 g (95%), identical (mixed m. p., IR, NMR spectra) to that obtained under (a).

1-(2,3-O-Isopropylidene-2,3-dihydroxypropyl)thymine (V)

To a solution of 1-(2,3-dihydroxypropyl)thymine (IV) (175 mg, 0.95 mmol) in acetone (6 ml) anhydrous sulphuric acid (0.005 ml) and CuSO_4 (0.36 mg, 2.2 mmol) were added and stirred at 37 °C for 48 h. The precipitate was filtered off and the filtrate treated with $\text{Ca}(\text{OH})_2$ (180 mg, 2 mmol) by stirring for 1 h. The precipitate was removed by suction and the filtrate evaporated to dryness. The residue was dissolved in methylene chloride and chromatographed on a silica gel (8 g) column. Methylene chloride—methanol (150 : 1) eluted the product (150 mg, 79%), m. p. 159—160 °C (CH_2Cl_2 -*n*-hexane), R_F ca. 0.57 [CH_2Cl_2 -MeOH (9 : 1)], methylene chloride—methanol (9 : 1) eluted starting material (15 mg), R_F ca. 0.2.

Anal. $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4$ (240.25) calc'd.: C 54.99; H 6.71; N 11.66%
found: C 55.09; H 6.91; N 11.76%

UV spectrum: λ_{max} 269 nm (lg ϵ 3.92), λ_{min} 235 nm (lg ϵ 3.19). IR spectrum: ν_{max} 3356, 3077, 2950, 1681, 1664, 1639, 1520, and 1066 cm^{-1} . NMR spectrum: τ 0.26 br (1 H, s, 3-NH), 2.86 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 5.51—6.53 (5 H, m, 1'- H_2 , 2'-H, and 3'- H_2), and 8.09 (3 H, d, 5-Me; $J_{\text{Me},6} = 1.2$ Hz).

1-(3-O-*p*-Tolylsulphonyl-2,3-dihydroxypropyl)uracil (VI)

To a solution of 1-(2,3-dihydroxypropyl)uracil (III) (364 mg, 2 mmol) in anhydrous pyridine (25 ml) toluene-*p*-sulphonylchloride (586 mg, 3 mmol) was added, stirred at room temperature for 18 h and then evaporated to dryness. The residue was partitioned between water and chloroform and the organic layer evaporated to dryness. Chromatography on a silica gel (30 g) column and elution with methylene chloride—methanol (25 : 1) afforded a fraction identified as 1-(2,3-di-*O-p*-tolylsulphonyl-2,3-dihydroxypropyl)uracil (VII) (218 mg, 22%), m. p. 184—186 °C (from MeOH), R_F ca. 0.67 [CH_2Cl_2 -MeOH (9 : 1)].

Anal. $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_8\text{S}_2$ (494.53) calc'd.: C 51.00; H 4.48; N 5.67; S 12.96%
found: C 50.88; H 4.71; N 5.42; S 13.06%

UV spectrum: λ_{max} 225, 261, and 272 nm (lg ϵ 4.26, 3.85, and 3.71), λ_{min} 208 and 242 nm (lg ϵ 4.10 and 3.57). IR spectrum: ν_{max} 3559, 3236, 3125, 1706, 1695, 1667, 1608, and 763 cm^{-1} . NMR spectrum: τ (d_6 -DMSO) — 0.9 br (1 H, s, 3-NH), 2.63 (1 H, d, 6-H; $J_{6,5} = 8.0$ Hz), 4.6 (1 H, d with secondary splitting, 5-H; $J_{5,6} = 8.0$ Hz), 4.92—5.30 (1 H, m, 2'-H), 5.77 (2 H, d, 3'- H_2 ; $J_{3',2'} = 3.5$ Hz), 6.12 (2 H, d, 1'- H_2 ; $J_{1',2'} = 5.5$ Hz), 7.55 and 7.59 (each 3 H, 2 s, 2 PhMe).

Methylene chloride—methanol (10 : 1) eluted the product (345 mg, 51%), m. p. 119—120 °C (from Me_2CO - Et_2O), R_F ca. 0.42.

Anal. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_6\text{S}$ (340.36) calc'd.: C 49.40; H 4.74; N 8.23; S 9.42%
found: C 49.10; H 4.70; N 8.45; S 9.53%

UV spectrum: λ_{max} 218 and 262 nm (lg ϵ 3.66 and 4.04), λ_{min} 237 nm (lg ϵ 3.63). IR spectrum: ν_{max} 3425, 3205, 3049, 1709, 1689 br, 1595, and 768 cm^{-1} . NMR spectrum: τ (d_6 -DMSO) — 1.17 br (1 H, s, 3-NH), 2.56 (1 H, d with secondary splitting, 6-H; $J_{6,5} = 8.0$ Hz), 4.52 (1 H, d with secondary splitting, 5-H; $J_{5,6} = 8.0$ Hz), 5.49—6.66 (5 H, m, 1'- H_2 , 2'-H, and 3'- H_2), and 7.57 (3 H, s, PhMe).

1-(3-O-*p*-Tolylsulphonyl-2,3-dihydroxypropyl)thymine (VIII)

A solution of 1-(2,3-dihydroxypropyl)thymine (IV) (300 mg, 1.5 mmol) in anhydrous pyridine (20 ml) was treated with toluene-*p*-sulphonylchloride (420 mg, 2.15 mmol) and worked up as for the uracil derivative (VI). Chromatography on a silica gel (15 g) column and elution with methylene chloride—methanol (25 : 1)

afforded a fraction identified as 1-(2,3-di-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine (IX) (123 mg, 12%), m. p. 161—162 °C (from CH₂Cl₂-*n*-hexane), *R*_F ca. 0.72 [CH₂Cl₂-MeOH (9 : 1)].

Anal. C₂₂H₂₄N₂O₈S₂ (508.55) calc'd.: C 52.12; H 4.79; N 5.19; S 12.67%
found: C 51.95; H 4.74; N 5.51; S 12.61%

UV spectrum: λ_{\max} 225, 267, and 272 nm (lg ϵ 4.65, 4.16, and 4.11), λ_{\min} 245 nm (lg ϵ 3.81). IR spectrum: ν_{\max} 3559, 3205, 3040, 2941, 1698, 1675, 1653, 1603, 763, and 758 cm⁻¹. NMR spectrum: τ 1.10 br (1 H, s, 3-NH), 3.16 (1 H, d, 6-H; *J*_{6,Me} = 1.0 Hz), 4.85—5.21 (1 H, m, 2'-H), 5.72 (2 H, d, 3'-H₂; *J*_{3',2'} = 3.5 Hz), 5.85 (1 H, q, 1'-H_a; *J*_{1'a,b} = 14.5 Hz), 6.40 (1 H, q, 1'-H_b; *J*_{1'b,a} = 14.5 Hz, *J*_{1'b,2'} = 9.0 Hz), 7.53 and 7.57 (each 3 H, 2 s, 2 PhMe), and 8.69 (3 H, d, 5-Me, *J*_{Me,6} = 1.0 Hz) in DMSO-*d*₆.

Elution with methylene chloride—methanol (10 : 1) afforded the product (402 mg, 75%), m. p. 159—160 °C (from CH₂Cl₂-*n*-hexane), *R*_F ca. 0.5.

Anal. C₁₅H₁₈N₂O₆S (354.37) calc'd.: C 50.32; H 5.68; N 7.81; S 9.03%
found: C 50.83; H 5.22; N 7.90; S 9.05%

UV spectrum: λ_{\max} 220 and 268 nm (lg ϵ 4.20 and 4.00), λ_{\min} 241 nm (lg ϵ 3.45). IR spectrum: ν_{\max} 3268, 3125, 2994, 2890, 1692, 1672, and 763 cm⁻¹. NMR spectrum: τ (*d*₆-DMSO) — 1.16 (1 H, s, 3-NH), 2.66 (1 H, d, 6-H; *J*_{6,Me} = 1.0 Hz), 5.49—6.66 (6 H, m, 1'-H₂, 2'-H, 3'-H₂, and 2'-OH), 7.57 (3 H, s, PhMe), and 8.27 (3 H, d, 5-Me; *J*_{Me,6} = 1.0 Hz).

1-(3-*O*-Triphenylmethyl-2,3-dihydroxypropyl)thymine (X)

To a solution of 1-(2,3-dihydroxypropyl)thymine (IV) (1 g, 5 mmol) in anhydrous pyridine (30 ml) chlorotriphenylmethane (1.6 g, 5.75 mmol) was added, set aside for 18 h, and then heated at 100 °C for 3 h. The mixture was evaporated to dryness and the residue chromatographed on a silica gel (25 g) column. Chloroform eluted a fraction identified as 1-(2,3-di-*O*-triphenylmethyl-2,3-dihydroxypropyl)thymine (XI) (155 mg, 5%), m. p. 218—220 °C (from CH₂Cl₂-*n*-hexane), *R*_F ca. 0.57 [CHCl₃-Et₂O (3 : 1)].

Anal. C₄₆H₄₀N₂O₄ (684.80) calc'd.: C 80.67; H 5.89; N 4.09%
found: C 80.15; H 6.11; N 3.82%

UV spectrum: λ_{\max} 270 nm (lg ϵ 3.96), λ_{\min} 247 nm (lg ϵ 3.61). IR spectrum: ν_{\max} 3472, 3215, 1695 br, 1590, 763, 749, and 706 cm⁻¹. NMR spectrum: τ 1.53 br (1 H, s, 3-NH), 3.07 (1 H, d, 6-H; *J*_{6,Me} = 1.2 Hz), 5.97—6.57 (3 H, m, 1'-H₂ and 2'-H), 6.98—7.17 (2 H, m, 3'-H₂), and 8.37 (3 H, d, 5-Me; *J*_{Me,6} = 1.2 Hz).

Further elution with chloroform afforded the product (1.59 mg, 72%), m. p. 172—173 °C (from CH₂Cl₂-*n*-hexane), *R*_F ca. 0.17.

Anal. C₂₇H₂₆N₂O₄ (442.49) calc'd.: C 73.28; H 5.92; N 6.33%
found: C 73.40; H 6.07; N 6.36%

UV spectrum: λ_{\max} 270 nm (lg ϵ 3.96), λ_{\min} 243 nm (lg ϵ 3.55). IR spectrum: ν_{\max} 3448, 3195, 3040, 2915, 1692, 1664, 1653, 761, 747, and 702 cm⁻¹. NMR spectrum: τ 0.59 (1 H, s, 3-NH), 2.96 (1 H, d, 6-H; *J*_{6,Me} = 1.0 Hz), 5.77—6.74 (4 H, m, 1'-H₂, 2'-H, and 2'-OH), 6.81 (2 H, d, 3'-H₂; *J*_{3',2'} = 5.0 Hz), 8.21 (3 H, d, 5-Me; *J*_{Me,6} = 1.0 Hz).

1-(2-*O*-Acetyl-3-*O*-triphenylmethyl-2,3-dihydroxypropyl)thymine (XII)

To a solution of 3'-*O*-tritylpropylthymine (X) (2 g, 4.55 mmol) in anhydrous pyridine (12 ml) acetic anhydride (5 ml, 47.5 mmol) was added, set aside at room temperature for 30 h, and then evaporated to dryness. The residue was chromatographed on a silica gel (50 g) column, and methylene chloride—methanol (25 : 1) eluted the product (2 g, 97%), m. p. 168—169 °C (from CHCl₃-*n*-hexane), *R*_F ca. 0.3 [CHCl₃-Et₂O (3 : 1)].

Anal. C₂₉H₂₈N₂O₅ (484.53) calc'd.: C 71.88; H 5.83; N 5.78%
found: C 71.70; H 5.88; N 5.88%

UV spectrum: λ_{\max} 270 nm ($\lg \epsilon$ 3.06), λ_{\min} 243 nm ($\lg \epsilon$ 3.91). IR spectrum: ν_{\max} 3185, 3012, 2833, 1739, 1701, 1658, 1590, 1590, 764, 750, and 701 cm^{-1} . NMR spectrum: τ 1.14 br (1 H, s, 3-NH), 3.02 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 4.64—4.97 (1 H, m, 2'-H), 5.82 (1 H, q, 1'-H_a; $J_{1'a,b} = 14.0$ Hz; $J_{1'a,2'} = 5.0$ Hz), 6.22 (1 H, q, 1'-H_b; $J_{1'b,a} = 14.0$ Hz; $J_{1'b,2'} = 7.0$ Hz), 6.65 (1 H, q, 3'-H_a; $J_{3'a,b} = 11.0$ Hz; $J_{3'a,2'} = 4.5$ Hz), 6.86 (1 H, q, 3'-H_b; $J_{3'b,a} = 4.5$ Hz), 7.96 (3 H, s, COMe), and 8.21 (3 H, d, 5-Me; $J_{\text{Me},6} = 1.2$ Hz).

1-(2-O-Acetyl-2,3-dihydroxypropyl)thymine (XIII)

A solution of 2'-O-acetyl-3'-O tritylpropylthymine (XII) (1.6 g, 3.3 mmol) in 80% acetic acid (8 ml) was heated under reflux for 10 min, and a precipitate filtered off. The filtrate, which was evaporated to dryness, on trituration with chloroform afforded the crystalline product (700 mg, 87.5%), m. p. 145—146 °C (from anhydrous EtOH), R_F ca. 0.35 [CH_2Cl_2 -MeOH (9 : 1)].

Anal. $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_5$ (242.23) calc'd.: C 49.58; H 5.83; N 11.57%
found: C 49.48; H 5.88; N 11.72%

UV spectrum: λ_{\max} 269 nm ($\lg \epsilon$ 3.90), λ_{\min} 236 nm ($\lg \epsilon$ 2.90). IR spectrum: ν_{\max} 3521, 3356, 1736, 1701, 1664, and 1639 cm^{-1} . NMR spectrum: τ (with CD_3OD) 2.59 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 5.68—6.39 (unresolved multiplets), 7.94 (3 H, s, COCH_3), and 8.13 (3 H, d, 5- CH_3 ; $J_{\text{Me},6} = 1.2$ Hz).

1-(2,3-Di-O-acetyl-2,3-dihydroxypropyl)thymine (XIV)

To a solution of 1-(2,3-dihydroxypropyl)thymine (IV) (200 mg, 1 mmol) in anhydrous pyridine (10 ml) acetic anhydride (1 ml, 10.6 mmol) was added. The mixture was set aside at room temperature for 18 h, evaporated to dryness, and the residue partitioned between water and chloroform. From the organic layer the crystalline product was separated by evaporation and trituration with methylene chloride (256 mg, 90%), m. p. 189—190 °C (from MeOH), R_F ca. 0.69 [CH_2Cl_2 -MeOH (19 : 1)].

Anal. $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_6$ (248.27) calc'd.: C 50.70; H 5.67; N 9.86%
found: C 50.86; H 5.47; N 9.68%

UV spectrum: λ_{\max} 208 and 268 nm ($\lg \epsilon$ 4.06 and 4.03), λ_{\min} 236 nm ($\lg \epsilon$ 3.45). IR spectrum: ν_{\max} 3534, 3226, 3077, 2857, 1739, 1706, and 1695 cm^{-1} . NMR spectrum: τ (d_6 -DMSO) — 1.18 (1 H, s, 3-NH), 2.57 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 4.57—4.94 (1 H, m, 2'-H), 5.73 (1 H, q, 3'-H_a; $J_{3'a,b} = 12.0$ Hz, $J_{3'a,2'} = 4.0$ Hz), 5.96 (1 H, q, 3'-H_b; $J_{3'b,a} = 12.0$ Hz; $J_{3'b,2'} = 5.5$ Hz), 5.98 (1 H, q, 1'-H_a; $J_{1'a,b} = 14.5$ Hz; $J_{1'a,2'} = 4.5$ Hz), 6.29 (1 H, q, 1'-H_b; $J_{1'b,a} = 14.5$ Hz; $J_{1'b,2'} = 7.0$ Hz), 7.99 and 8.05 (each 3 H, 2 s, 2 COMe), and 8.27 (3 H, d, 5-Me; $J_{\text{Me},6} = 1.2$ Hz).

1-(2-O-Acetyl-3-O-p-tolylsulphonyl-2,3-dihydroxypropyl)thymine (XV)

A solution of 3'-O-tosylpropylthymine (VIII) (177 mg, 0.5 mmol) in anhydrous pyridine (2 ml) was treated with acetic anhydride (1 ml, 10.6 mmol) and set aside at room temperature for 18 h. The mixture was evaporated to dryness and the residue partitioned between water and chloroform. From the organic layer the crystalline product separated (130 mg, 66%), m. p. 146—147 °C (from MeOH), R_F ca. 0.81 [CH_2Cl_2 -MeOH (19 : 1)].

Anal. $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_7\text{S}$ (396.41) calc'd.: C 51.50; H 5.09; N 7.05; S 8.09%
found: C 51.38; H 5.30; N 7.17; S 8.16%

UV spectrum: λ_{\max} 223, 267, and 273 nm ($\lg \epsilon$ 4.28, 4.07, and 4.04), λ_{\min} 206 and 241 nm ($\lg \epsilon$ 4.17 and 3.61). IR spectrum: ν_{\max} 3215, 3096, 2865, 1745, 1698, 1653, 1600, and 761 cm^{-1} . NMR spectrum: τ (d_6 -DMSO) — 1.16 (1 H, s, 3-NH), 2.64 (1 H, d, 6-H; $J_{6,\text{Me}} = 1.2$ Hz), 4.62—4.97 (1 H, m, 2'-H), 5.57—6.06 (2 H, m, 3'-H₂) 6.05 (1 H, q, 1'-H_a; $J_{1'a,b} = 14.0$ Hz, $J_{1'a,2} = 4.5$ Hz), 6.33 (1 H, q, 1'-H_b; $J_{1'b,a} = 14.0$ Hz, $J_{1'b,2} = 7.0$ Hz), 7.58 (3 H, s, PhMe), 8.11 (3 H, s, COMe), and 8.29 (3 H, d, 5-Me; $J_{\text{Me},6} = 1.2$ Hz).

1-(2,3-Dihydroxypropyl)thymine-2'(3')-phosphate, Barium Salt (XVI)

To a solution of 1-(2,3-dihydroxypropyl)thymine (IV) (500 mg, 2.5 mmol) in pyridine a standardized pyridine solution of β -cyanoethylphosphate²² (5 ml, 5 mmol) was added and then evaporated to dryness. The dried residue, redissolved in anhydrous pyridine (30 ml), was treated with dicyclohexylcarbodi-imide (2 g, 10.3 mmol) and set aside at room temperature for 3 days. To this mixture water (1 ml) was added and after 1 h it was evaporated to an oily residue. To this residue 0.5 mol dm⁻³ LiOH (60 ml) was added and heated at 100 °C for 1 h. The precipitate was filtered off, the filtrate was passed through a Dowex 50 (H⁺) (60 ml) ion exchange resin column, and then the column washed with water. The acidic effluent was neutralized with 0.05 mol dm⁻³ barium hydroxide solution to pH = 7.5. The solution was then concentrated to a small volume (20 ml) and the precipitate removed with centrifugation. From the clear supernatant the product was separated upon addition of two volumes of ethanol. The centrifugation and washings of the precipitate with 50% ethanol and then with anhydrous ethanol and ether yielded 900 mg (72%) of crude material. For analysis the product was redissolved in water, centrifuged, precipitated with ethanol, and dried at 100 °C/10⁻⁴ mm Hg.*

Anal. C₈H₁₁N₂O₇BaP · 3 H₂O (470.57) calc'd.: C 20.46; H 3.65; N 5.96; P 6.59%
found: C 20.59; H 2.90; N 6.08; P 6.87%

UV spectrum: λ_{\max} 271 nm (lg ϵ 3.09), λ_{\min} 237 nm (lg ϵ 2.50). NMR spectrum: τ (D₂O-CF₃COOD) 2.44 (1 H, d, 6-H; $J_{6,Me} = 1.0$ Hz), 5.88–6.29 (unresolved multiplets), 7.47 (1 H, t, 3'-OH; $J_{3'-OH,3'} = 6.5$ Hz), and 8.08 (3 H, d, 5-Me; $J_{Me,6} = 1.0$ Hz).

1-(2,3-Dihydroxypropyl)thymine-2'-phosphate, Barium Salt (XVII)

A solution of (3-O-tritylpropyl)thymine (X) (1 g, 2.26 mmol) in pyridine (30 ml) was treated with the standardized solution of β -cyanoethyl phosphate²² (6 ml) and dicyclohexylcarbodi-imide (3.8 g, 1.84 mmol). The mixture was worked up as described for compound (XVI). Yield 810 mg (70%). Electrophoresis of the product on thin layer cellulose by using 0.05 mol dm⁻³ Na₂HPO₄ buffer solution at 400 V cm⁻¹, 30 mA, for 60 min duration, revealed one major product at 0.62, consistent with the mobility of compound (XVI).

1-(2,3-Dihydroxypropyl)thymine-2',3'-cyclophosphate, Pyridinium Salt (XVIII)

A solution of 2'(3')-phosphate propylthymine as barium salt (XVI) (180 mg, 0.45 mmol) in water was passed through a Dowex 50 (H⁺) (30 ml) ion exchange resin column and then the column washed with water. The effluent was concentrated to a small volume (5 ml) at 35 °C/20 mm Hg, treated with 2 mol dm⁻³ NH₄OH (3 ml), and evaporated to dryness. To the residue, dissolved in 2 mol dm⁻³ NH₄OH (1.3 ml) and dimethylformamide (1.5 ml), dicyclohexylcarbodi-imide (200 mg, 0.98 mmol) in *t*-butanol (1.5 ml) was added and mixture was heated at 110 °C for 3 h. After evaporation to dryness and trituration with water (1.5 ml) and ether (3 ml) the precipitate was filtered off and washed with water. The filtrate and washings afforded an oily residue by evaporation under reduced pressure. It was dissolved in 20% pyridine (3 ml) and passed through a Dowex 50 (pyridinium form, 10 ml) ion exchange resin column. The pyridine effluent (20 ml) was concentrated and then lyophilized to an amorphous product (82 mg, 63%). Electrophoresis of the product on thin layer cellulose by using 0.05 mol dm⁻³ Na₂HPO₄ buffer solution at 400 V cm⁻¹, 30 mA, and for 50 min duration, revealed the mobility at 0.83.

A sample (50 mg) was redissolved in water (2 ml) with traces of triethylamine and NH₄OH (pH = 7.5 to 8). To this solution ribonuclease (10 mg) (5x cryst. from bovine pancreas, A grade »CalBiochem«) was added, incubated at 30 °C for 2 days and then chromatographed on a DEAE-cellulose (HCO₃) (40 ml) column. Linear gradient elution with water — 0.15 mol dm⁻³ triethylammonium bicarbonate (200 ml : 200 ml) gave first the starting material (18 mg) and then a fraction (6 mg) showing the electrophoretic mobility consistent with the monophosphate (XVI).

* 1 mm Hg \approx 133.322 Pa

1-[3(2)-O-Tetrahydropyran-2-yl-2,3-dihydroxypropyl]-thymine-2'(3')-phosphate (XIX)

To a suspension of the barium salt of 2'(3')-phosphate propylthymine (XVI) (623 mg, 1.5 mmol) in dimethylformamide (10 ml) dihydropyran (5 ml) was added. To this cooled suspension (at -20°C) 3 mol dm^{-3} HCl in dioxane (1.35 ml, 5 mmol) was added portionwise and then set aside at room temperature. The electrophoretic mobility of the starting material (at 0.62) disappeared after 18 h. The mixture was then again cooled at -20°C , treated with triethylamine (1 ml), and poured into ether (100 ml). The precipitate was separated by centrifugation, dissolved in water (8 ml), and passed through a Dowex 50 (pyridinium form) ion exchange resin column. The 50% pyridine effluent (100 ml) was evaporated to an amorphous product.

Uridyl[5'→2'(3')]-1-(2,3-dihydroxypropyl)thymine, Calcium Salt (XX)

To crude 2'(3')-phosphate propylthymine (see XIX) (ca. 1.5 mmol) 2',3'-O-ethoxy-methylidene uridine²⁴ (640 mg, 2.1 mmol) dissolved in pyridine (20 ml) was added. The mixture was evaporated to dryness, dissolved again in anhydrous pyridine (30 ml), and treated with dicyclohexylcarbodi-imide (2 g, 10.3 mmol) at room temperature for 3 days. A precipitate was filtered off and the filtrate evaporated to an oily residue which was chromatographed on a silica gel (15 g) column. Methylene chloride—methanol (2:1) eluted an oil (586 mg), the homogeneity of which was evidenced by its electrophoretic mobility.

The thus obtained oil was dissolved in 20% acetic acid (10 ml) and heated at 55°C for 45 min. The mixture was cooled, lyophilized, dissolved in water, and lyophilized again. To the residue triethylammonium bicarbonate to neutral reaction was added and then passed through a DEAE-cellulose (HCO_3^-) (160 ml) column. Linear gradient elution with water— 0.15 mol dm^{-3} triethylammonium bicarbonate (1:1) afforded the product after having been evaporated to dryness and precipitated with 5% ethanolic CaCl_2 (20 ml) in acetone (100 ml). The precipitate was centrifuged, washed with acetone and ether, and then dried to an amorphous powder (242 mg, 31%) showing the electrophoretic mobility at 0.2. NMR spectrum: τ 2.05 (1 H, d with secondary splitting, 6-H of uracil; $J_{6,5} = 8.5\text{ Hz}$), 2.42 (1 H, s with secondary splitting, 6-H of thymine), 4.00 (1 H, d with secondary splitting, 5-H of uracil; $J_{5,6} = 8.5\text{ Hz}$), 8.09 (3 H, s, Me) (in D_2O).

O-[3'-O-Acetylthymidyl(5'→2')]-1-(3-O-triphenylmethyl-2,3-dihydroxypropyl)thymine]-N,N-dicyclohexylpseudourea (XXI)

The anhydrous pyridinium salt of 3'-O-acetylthymidine-5'-phosphate²⁸ (160 mg, 0.36 mmol), prepared by the method of Yoshikawa et al.^{25,26}, was dissolved in anhydrous pyridine (10 ml) and treated with 3-O-tritylpropylthymine (X) (354 mg, 0.8 mmol) in the presence of dicyclohexylcarbodi-imide (824 mg, 4 mmol). The mixture was set aside at room temperature for 5 days and then treated with water (2 ml) and stirred for 2 h. The precipitate was filtered off and the filtrate evaporated to dryness. The residue was partitioned between water and chloroform. From the organic layer an oily product separated which was chromatographed in methylene chloride on a silica gel (40 g) column. Methylene chloride—methanol (9:1 to 7.5:2.5) eluted the product (94 mg, 26.2%), m. p. $203\text{--}205^{\circ}\text{C}$ (from CHCl_3 - n -hexane), $[\alpha]_D^{23} = -6.43^{\circ}$ (c 0.7, CHCl_3), R_F ca. 0.42 [CH_2Cl_2 -MeOH (8.5:1.5)].

Anal. $\text{C}_{52}\text{H}_{63}\text{N}_6\text{O}_{12}\text{P}$ (995.05) calc'd.: C 62.76; H 6.38; P 3.11%
found: C 62.91; H 6.20; P 3.43%

UV spectrum: λ_{max} 268 nm ($\lg \epsilon$ 4.08), λ_{min} 242 nm ($\lg \epsilon$ 3.91). IR spectrum: ν_{max} 3509 br, 3226, 3077, 2941, 1701 sh, 1695 br, 1664 sh, and 1550 cm^{-1} .

Thymidyl(5'→2')-1-(2,3-dihydroxypropyl)thymine, Ammonium Salt (XXII)

A solution of the protected thymidyl(5'→2')-thymine (XXI) (60 mg, 0.06 mmol) in 80% acetic acid (4 ml) was heated under reflux for 30 min. The mixture was then diluted with water (20 ml) and partitioned with ether. The water layer was evaporat-

ed to dryness and separated by ascending preparative paper (66 cm long) chromatography (Whatman E-17) in *iso*-propanol-conc. NH_4OH —water (7:1:2). Diluted ammonia (1:50) eluted a fraction at R_F ca. 0.186 as the ammonium salt of the product (18 mg, 70%). The fraction at R_F ca. 0.045 and 0.65 were identified as thymidine-5'-phosphate and 1-(2,3-dihydroxypropyl)thymine (IV), respectively. UV spectrum (H_2O): λ_{max} 212 sh and 268 nm ($\lg \epsilon$ 4.04 and 4.23), λ_{min} 233 nm ($\lg \epsilon$ 3.70). IR spectrum: ν_{max} 3400 br, 3200 sh, 1703, 1690 br, and 1565 cm^{-1} .

A sample (1 mg) in 0.1 mol dm^{-3} tris buffer solution (0.1 ml) was treated with phosphodiesterase (1 mg in 0.1 ml H_2O) (CalBiochem) from Russell's viper venom (*Crotalus adamanteus*). The solution was incubated at 37 °C for 4 h. TLC and paper chromatography evidenced the appearances of 1-(2,3-dihydroxypropyl)thymine (IV) and thymidine.

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SAŽETAK**Alifatski analogoni timidina i deoksiuridina***V. Škarić, D. Erben, Z. Raza i Đ. Škarić*

Opisana je jod-acetat oksidacija 1-aliluracila (I) i 1-aliltimina (II), koji su priredeni silil metodom. Tako dobiveni 1-(2,3-dihidroksipropil) derivati uracila (III) i timina (IV) podliježu selektivnom tritiliranju, pa je priredjen 1-(3-O-trifenilmetil-2,3-dihidroksipropil)timin (X). Time je otvorena mogućnost jednoznačne sinteze barijeve soli 1-(2,3-dihidroksipropil)timin-2'-fosfata (XVII), a isto tako i amonijske soli timidilil (5'→2')-1-(2,3-dihidroksipropil)timina (XXII).

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