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The Homologation of 1-(2,3-Dihydroxypropyl)- into 1-(2,4-Dihydroxybutyl)-thymine

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The homologation of 1-(2,3-dihydroxypropyl)thymine involved the conversion of its 3'-*O*-tosyl derivative II into the corresponding 3'-iodo compound IV, which by nucleophilic displacement with sodium cyanide in DMSO formed 1-(2-hydroxy-3-cyanopropyl) thymine (VIII). 1-(2,3-Dihydroxypropyl)uracil was analogously converted into the corresponding 3'-iodo- III and 3'-cyano- VII propyluracil. The ethanolysis of the 3'-cyano compound VIII to 1-(2--hydroxy-3-ethoxycarbonylpropyl)thymine (X), followed by the reduction with $LiAlH_4$, gave 1-(2,4-dihydroxybutyl)thymine (XIII).

3'-*O*-Acetylthymidylyl(5'→2')-1-(4-*O*-triphenylmethyl-2,4-dihydroxybutyl)thymine was described as possible *N,N*-dicyclohexylpseudourea adduct XIX.

Several naturally occuring aliphatic nucleoside analogs have been investigated at various levels of biochemical criteria. Thus, the investigation of eritadenine[1], isolated as a major component from *Lentinus edodes*[2], was associated with arteriosclerosis and coronary heart diseases[3]. Willardine, a plant non-protein L-amino acid isolated from the seeds of *Acaccia-willardiana, -lemmoni,* and *-millefolia*[4] by unambiguous synthesis[5,6] was established as β-(uracil-1) L-alanine.

9-Ethyl-6-substituted purines were described as potencial anticancer agents[7]. In addition 1-(1,4-dihydroxypent-2-yl)uracil[8], 1-(3,4-dihydroxybutyl)-thymine[9], 1(1,3-dihydroxyprop-2-yl)uracil[10], 1-(2,3-dihydroxypropyl)uracil[11], 1--(2,3-dihydroxypropyl)thymine[12–14], and monohydroxyalkyl analogs[15] were shown to be generally applicable to the synthesis of the corresponding nucleotides, triphosphates[16], and dinucleoside-like phosphates[17,18].

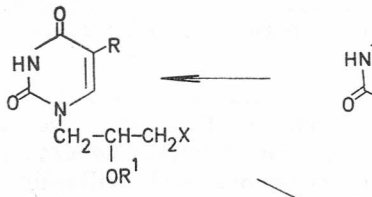
In continuation of our studies on the chemistry of dihydroxyalkyl nucleoside analogs[14] we envisaged the homologation of 1-(2,3-dihydroxypropyl)thymine into the hitherto unknown 1-(2,4-dihydroxybutyl)thymine. This conversion into a sterically less hindered 2,4-dihydroxy compound was also concerned with the possible formation of the dinucleoside-like phosphate and oligonucleotide analogs possessing $2' \rightarrow 4'$ internucleotide linkages.

We have recently reported[14] a new synthesis of 1-(2,3-dihydroxypropyl)--uracil and -thymine and inter alia conversions into the corresponding 1-(3-*O*--*p*-tolylsulphonyl-2,3-dihydroxypropyl) derivatives (I) and (II). The present

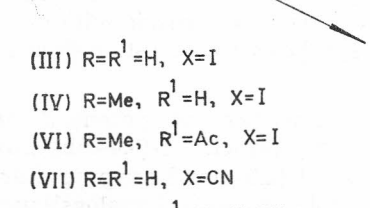
paper deals with the homologation of 1-(2,3-dihydroxypropyl)thymine into its next higher homolog using the 3′-*O*-tosylpropylthymine II as starting material.

To prepare 1-(2-hydroxy-3-iodopropyl)uracil (III) and the corresponding thymine derivative IV, the 3′-*O*-tosylpropyluracil I and 3′-*O*-tosylpropylthymine II was treated with sodium iodide (cf. ref 19), respectively. Analogously 1-(2--*O*-acetyl-3-*O*-*p*-tolylsulphonyl)thymine[14] (V) gave 1-(2-*O*-acetyl-3-iodo-2-hydroxypropyl)thymine (VI). The resonances of 2′-proton in the NMR spectrum of the 2′-*O*-acetyl derivative VI were shifted downfield (at τ 4.77—5.12) disclosing two quartets at τ 5.93 and 6.31 (J = 14.0 Hz) that can be attributed to the geminal 1′-protons, and two quartets centred at τ 6.46 and 6.71 (J = 11.0 Hz) corresponding to the 3′-protons.

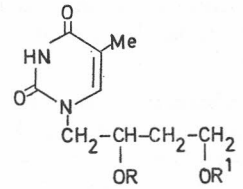
The nucleophilic displacement of the iodo-compounds III and IV in reaction with sodium cyanide proceeded to the corresponding 1-(2-hydroxy-3-cyanopropyl)uracil (VII) and 1-(2-hydroxy-3-cyanopropyl)thymine (VIII) with very high yields due to the ionizing effect of dimethylsulphoxide used as solvent[20,21]. While the IR spectra of the compounds VII and VIII produced the bands at 2273 and 2257 cm^{-1}, which can be attributed to the corresponding cyano groups, the NMR spectra gave rise to the resonances at τ 4.25 (d, J = 5.0 Hz) and at 4.13—4.48 (m), corresponding to 2′-OH. The homologation sequence then involved the ethanolysis of the thus obtained cyano compound VIII in ethanolic hydrochloric acid by the Pinner method[22] to give 1-(2-hydroxy-3-ethoxycarbonylpropyl)thymine (IX), readily acetylated to 1-(2-*O*-acetyl-3-ethoxycarbonyl--2-hydroxypropyl)thymine (X).



(I) R=R^1=H
(II) R=Me, R^1=H
(V) R=Me, R^1=Ac



(III) R=R^1=H, X=I
(IV) R=Me, R^1=H, X=I
(VI) R=Me, R^1=Ac, X=I
(VII) R=R^1=H, X=CN
(VIII) R=Me, R^1=H, X=CN
(IX) R=Me, R^1=H, X=CO_2Et
(X) R=Me, R^1=Ac, X=CO_2Et
(XI) R=Me, R^1=H, X=CH_2NH_2
(XII) R=Me, R^1=Bz, X=CH_2NHBz



(XIII) R=R^1=H
(XIV) R=H, R^1=Trt
(XV) R=Ac, R^1=Trt
(XVI) R=R^1=Ac
(XVII) R=Ac(H), R^1=H(Ac)

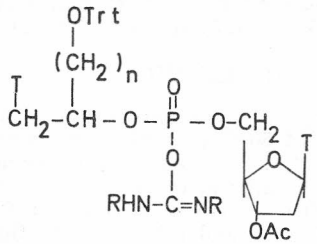
At this stage it seemed highly desirable to have an unambiguous method for the preparation of 1-(2,4-dihydroxybutyl)thymine. An attempt to deaminate[23] 1-(2-hydroxy-4-aminobutyl)thymine (XI), which was prepared from 3′-cyanopropylthymine VIII by Raney nickel hydrogenolysis in saturated me-

thanolic ammonia[24] and characterized as 1-(2-*O*,4-*N*-dibenzoyl-2-hydroxy-4--aminobutyl)thymine (XII), afforded 2′,4′-dihydroxybutylthymine (XIII) in low yields. Our search for a more convenient 2′,4′-diol synthesis showed that the lithium aluminium hydride reduction[25] of 3′-carbethoxypropylthymine IX yielded compound XIII as the major product. It clearly exhibited a doublet at τ 5.19 (J = 6.0 Hz) in the NMR spectrum, assigned to 2′-OH and a triplet at τ 5.65 (J = 5.0 Hz) attributed to 4′-OH.

Both 1-(4-*O*-triphenylmethyl-2,4-dihydroxybutyl)thymine (XIV) and 1-(2--*O*-acetyl-4-*O*-triphenylmethyl-2,4-dihydroxybutyl)thymine (XV) were readily prepared. The NMR spectrum of the latter exhibited, similarly to 2′-*O*-acetylpropylthymine VI, a pronounced downfield shift for 2′-proton at τ 4.49—4.87, and therefore two distinct quartets at τ 5.91 (J = 14.0 Hz) and 6.34 which can be attributed to the geminal 1′-protons. This compound also showed 4′-protons as a triplet centred at τ 6.80 (J = 6.0 Hz). Attempted detritylation of the compound XV in 80% acetic acid or in hydrochloric acid/dioxane gave, to our surprise, two products detected by silica gel TLC [in CH_2Cl_2-MeOH (10 : 1)] at R_F ca. 0.28 and ca. 0.37, presumably as isomeric 1-(2- and 4-*O*-acetyl-2,4-dihidroxybutyl)-thymine (XVII). Unfortunately, no data for direct comparison of thus obtained isomers are available at present, due to a spontaneous transformation of the isomer with higher chromatographic mobility into a crystalline compound showing lower mobility (R_F ca. 0.28). The monoacetyl structures of both isomers were proven by the acetylation of their mixture, which exclusively afforded 1-(2,4-di-*O*-acetyl-2,4-dihydroxybutyl)thymine (XVI), R_F ca. 0.69, identical with an authentic sample, independently prepared from 2′,4′-dihydroxybutylthymine XIII.

The isomerisation of the compound tentatively assigned as 2′-*O*-acetylbutylthymine XVII (R_F ca. 0.37) could be understood by assuming a 6-membered cyclic intermediate and an intramolecular acyl migration, particularly studied in the field of natural nucleosides[26,27] and 5-membered cyclic intermediates of monoacylated 1,2-diol systems[28].

Our earlier reported condensation pattern for the preparation of thymidylyl(5′ → 2′)-1-(2,3-dihydroxypropyl)thymine and *O*-[3′-*O*-acetylthymidylyl--(5′ → 2′)-1-(3-*O*-triphenylmethyl-2,3-dihydroxypropyl)thymine]-*N*,*N*-dicyclohexylpseudourea[14] (XVIII), as the soluble intermediate, was analogously applied to the synthesis of *O*-[3′-*O*-acetylthymidylyl(5′ → 2′)-1-(4-*O*-triphenylmethyl-2,4--dihydroxybutyl)thymine]-*N*,*N*-dicyclohexylpseudourea (XIX), extremely suitable for conventional characterizations. Thus the desired internucleotide linkage formation was successfully performed by action of the pyridinium salt of 3′-*O*-



(XVIII) R=C_6H_{11}, n=1 } Trt=trityl
(XIX) R=C_6H_{11}, n=2 } T=thymine

-acetylthymidine-5′-phosphate[29] on 4′-*O*-trityl-2′,4′-dihydroxybutylthymine XIV in the presence of dicyclohexylcarbodi-imide[30].

EXPERIMENTAL

The same technique and apparatus were used as previously described[31].

1-(2-Hydroxy-3-iodopropyl)uracil (III)

To a solution of 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)uracil (I) (341 mg, 1 mmol) in butan-2-one (45 ml) sodium iodide (700 mg, 4.7 mmol) was added and heated in a nitrogen atmosphere for 2.5 h. A precipitate was then filtered off, the filtrate evaporated to dryness, and chromatographed on a silica gel (16 g) column, preformed by sodium thiosulphate (0.5 g). Methylene chloride-methanol (25 : 1) eluted the product (270 mg, 91%), m. p. 178—179 °C (from methanol), R_F ca. 0.56 [CH_2Cl_2-MeOH (9 : 1)].

Anal. $C_7H_9N_2O_3J$ (296.08) calc'd.: C 28.40; H 3.06; N 9.46; J 42.87%
found: C 28.26; H 3.21; N 9.67; J 42.81%

UV spectrum: λ_{max} 263 nm (log ε 4.19), λ_{min} 228 nm (log ε 3.19). IR spectrum: ν_{max} 3534, 3040, 2849, 1736, and 1695 cm^{-1}. NMR spectrum: τ (in d_6-DMSO) —1.12 br (1 H,s, 3 NH), 2.53 (1 H,d,6-H, $J_{6,5}$ 8.0 Hz), and 4.49 (1 H,d, with secondary splitting, 5-H, $J_{5,6}$ 8.0 Hz).

1-(2-Hydroxy-3-iodopropyl)thymine (IV)

Following the above described procedure 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine (II) (354 mg, 1 mmol) afforded the titled compound (276 mg, 89%), m. p. 175—176 °C (from acetone-*n*-hexane), R_F ca. 0.47 [CH_2Cl_2-MeOH (9 : 1)].

Anal. $C_8H_{11}N_2O_3J$ (310.11) calc'd.: C 30.98; H 3.57; N 9.03; J 40.93%
found: C 30.70; H 3.80; N 8.87; J 40.39%

UV spectrum: λ_{max} 271 nm (log ε 3.95), λ_{min} 236 nm (log ε 3.24). IR spectrum: ν_{max} 3497, 3012, 2817, and 1672 br cm^{-1}. NMR spectrum: τ (in d_6-acetone) 2.53 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), and 8.16 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz).

1-(2-O-Acetyl-3-iodo-2-hydroxypropyl)thymine (VI)

A solution of 1-(2-*O*-acetyl-3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine (V) (120 mg, 0.3 mmol) in butan-2-one (10 ml) was treated with sodium iodide (112.5 mg, 0.75 mmol) and worked up as for compound (III). It yielded 83 mg (78%), m. p. 171—173 °C (from methanol-ether), R_F ca. 0.78 [CH_2Cl_2-MEOH (19 : 1)].

Anal. $C_{10}H_{13}N_2O_4J$ (352.12) calc'd.: C 34.11; H 3.72; N 7.96%
found: C 34.20; H 3.91; N 8.13%

UV spectrum: λ_{max} 268 nm (log ε 3.96), λ_{min} 234 nm (log ε 3.30). IR spectrum: ν_{max} 3175, 3030, 2957, 1739, 1695, and 1667 br cm^{-1}. NMR spectrum: τ (in d_6-DMSO) —1.18 br (1 H,s,3-NH), 2.59 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), 4.77—5.12 (1 H,m,2′-H), 5.93 (1 H,q,1′-H_a, $J_{1'a,b}$ 14.0 Hz, $J_{1'a,2'}$ 4.0 Hz), 6.31 (1 H, q, 1′-H_b, $J_{1'a,b}$ 14.0 Hz, $J_{1'b,2'}$ 8.0 Hz), 6.46 (1 H,q,3′-H_a, $J_{3'a,b}$ 11.0 Hz, $J_{3'a,2'}$ 4.5 Hz), 6.71 (1 H,q, 3′-H_b,, $J_{3'b,a}$ 11.0 Hz, $J_{3'b,2'}$ 7.0 Hz), 8.03 (3 H,s,MeCO), and 8.25 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz).

1-(2-Hydroxy-3-cyanopropyl)uracil (VII)

To a solution of anhydrous sodium cyanide (59 mg, 1.2 mmol) in dimethylsulphoxide (10 ml), heated at 50 °C in a nitrogen atmosphere, 3′-iodopropyluracil III (296 mg, 1 mmol) was added and heated at 70 °C for an additional 1.5 h. The solvent was removed at 80 °C/$5 \cdot 10^{-2}$ mm Hg, the residue dissolved in methanol (10 ml), and chromatographed on a silica gel (15 g) column, preformed by sodium thiosulphate (0.5 g). Methylene chloride-methanol (20 : 1) eluted the product (144 mg, 74%), m. p. 149—150 °C (from methanol), R_F ca. 0.38 [CH_2Cl_2-MeOH (9 : 1)].

Anal. $C_8H_9N_3O_3$ (195.18) calc'd.: C 49.23; H 4.65; N 21.53%
found: C 49.18; H 4.81; N 21.79%

UV spectrum: λ_{max} 262 nm (log ε 4.05), λ_{min} 228 nm (log ε 3.27). IR spectrum: ν_{max} 3571, 3289, 3115, 2273, 1695 br, and 1642 sh cm^{-1}. NMR spectrum: τ (in d_6-DMSO) —1.15 br (1 H,s,3-NH), 2.50 (1 H,d,6-H, $J_{6,5}$ 8.0 Hz), 4.25 (1 H,d,2′-OH, $J_{OH,2'}$ 5.0 Hz), 4.48 (1 H,d, 5-H, $J_{5,6}$ 8.0 Hz), 5.81—6.56 (3 H,m,1′-H_2 and 2′-H), and 7.23—7.41 (2 H, multiplet, 3′-H_2).

1-(2-Hydroxy-3-cyanopropyl)thymine (VIII)

A solution of anhydrous sodium cyanide (1.1 g, 22 mmol) in dimethylsulphoxide (60 ml) was used for the reaction with 1-(2-hydroxy-3-iodopropyl)thymine (IV) (6.1 g, 19.5 mmol) and worked up as for compound VII. The product was isolated in 68.4% yield (2.81 g), m. p. 209—212 °C (from methanol), R_F ca. 0.29 [CH_2Cl_2-MeOH (19 : 1)].

Anal. $C_9H_{11}N_3O_3$ (209.20) calc'd.: C 51.67; H 5.30; N 20.09%
found: C 51.56; H 5.21; N 20.03%

UV spectrum: λ_{max} 269 nm (log ε 3.96), λ_{min} 236 nm (log ε 3.19). IR spectrum: ν_{max} 3484, 3030, 2841, 2257, 1669 br, and 1639 sh cm^{-1}. NMR spectrum: τ (in d_6-DMSO) —1.13 br (1 H,s,3-NH) 2.60 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), 4.13—4.48 (1 H,m,2′-OH), 5.81—6.66 (3 H,m, 1′-H_2 and 2′-H), 7.24—7.41 (2 H,m,3′-H_2), and 8.25 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz).

1-(2-Hydroxy-3-ethoxycarbonylpropyl)thymine (IX)

To anhydrous ethanolic 6 mol dm^{-3} HCl (400 ml) 3′-cyanopropylthymine VIII (2.5 g, 12 mmol) was added and set aside at 4 °C for 16 h, then treated with anhydrous hydrochloric acid by bubbling for 5 h, and then left aside at room temperature for an additional 3 h. The solvent was removed under reduced pressure, the residue redissolved in 90% ethanol (100 ml), evaporated to dryness and then triturated with methylene chloride (150 ml). A precipitate was filtered off and the filtrate concentrated into a small volume (3 ml) to which methylene chloride-*n*-hexane (1 : 1, 12 ml) was added. The product was separated in a 89.5% yield (2.75 g), m. p. 117—119 °C (from methylene chloride-*n*-hexane), R_F ca. 0.46 [CH_2Cl_2-MeOH (19 : 1)].

Anal. $C_{11}H_{16}N_2O_5$ (256.26) calc'd.: C 51.56; H 6.29; N 10.93%
found: C 51.28; H 6.19; N 11.16%

UV spectrum: λ_{max} 271 nm (log ε 3.90), λ_{min} 236 nm (log ε 3.19). IR spectrum: ν_{max} 3448, 3279, 3175, 3040, 2857, 1724, 1701, 1681, 1664, and 1647 sh cm^{-1}. NMR spectrum: τ 0.42 br (1 H,s,3-NH), 2.83 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), 5.84 (2 H,q,CH_2, J_{Et} 7.0 Hz), 7.30—7.62 (2 H,m,3′-H_2), 8.14 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz), and 8.74 (3 H,t,Me, J_{Et} 7.0 Hz).

1-(2-O-Acetyl-3-ethoxycarbonyl-2-hydroxypropyl)thymine (X)

To a solution of 2′-hydroxy-3′-carbethoxypropylthymine IX (52 mg, 0.2 mmol) in anhydrous pyridine (0.5 ml) acetic anhydride (0.2 ml, 2.12 mmol) was added and stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and then the residue was dissolved in chloroform (10 ml). This solution was partitioned with water and the product (55 mg, 92%), m. p. 180—181 °C (from methanol), R_F ca. 0.69 [CH_2Cl_2-MeOH (19 : 1)] separated from the organic layer.

Anal. $C_{13}H_{18}N_2O_6$ (298.29) calc'd.: C 52.34; H 6.08; N 9.39%
found: C 52.22; H 6.34; N 9.57%

UV spectrum: λ_{max} 269 nm (log ε 3.96), λ_{min} 236 (log ε 3.28). IR spectrum: ν_{max} 3215. 3077, 2825, 1739, 1695, and 1653 cm^{-1}. NMR spectrum: τ (in d_6-DMSO) — 1.16 (1 H,s, 3-NH), 2.62 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), 4.47—4.82 (1 H,m,2′-H), 5.83 (2 H,q,CH_2, J_{Et} 7.0 Hz), 7.22—7.47 (2 H,m,3′-H_2), 8.08 (3 H,s,MeCO), 8.25 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz), and 8.84 (3 H,t,Me, J_{Et} 7.0 Hz).

1-(2-Hydroxy-4-aminobutyl)thymine (XI)

To a solution of 3′-cyanopropylthymine VIII (84 mg, 0.4 mmol) in saturated methanolic ammonia (30 ml) a suspension of Raney nickel, W-2 (0.3 ml) in methanol

(3 ml) was added. This suspension was hydrogenated at 1 atm by stirring for 5 h. The catalyst was filtered off, and the filtrate afforded the crude product (87 mg), slightly soluble in organic solvents and water.

1-(2-O,4-N-Dibenzoyl-2-hydroxy-4-aminobutyl)thymine (XII)

To the crude 4′-aminobutylthymine XI (87 mg) anhydrous pyridine (10 ml) and benzoic anhydride (360 mg, 1.6 mmol) were added, and the mixture stirred at room temperature for 16 h. The solvent was removed under reduced presure, and from the residue the product (25 mg) crystallized from methanol. From the mother liquor, evaporated to dryness and chromatographed on a silica gel (2 g) column, an additional amount of the product (12 mg) was isolated by elution with methylene chloride--methanol (25 : 1), m. p. 238—239 °C (from methanol), R_F ca. 0.27 [CH_2Cl_2-MeOH (19 : 1)].

Anal. $C_{23}H_{23}N_3O_5 \cdot CH_3OH$ (453.48) calc'd.: C 63.56; H 6.00; N 9.27%
found: C 63.77; H 6.07; N 9.43%

UV spectrum: λ_{max} 226 and 267 nm (log ε 4.35 and 3.99), λ_{min} 210 and 251 nm (log ε 4.24 and 3.92). IR spectrum: ν_{max} 3425, 3226, 3106, 2874, 1724 sh, 1701, 1645, 1613, 1587, 1546, 762, and 714 cm^{-1}.

1-(2,4-Dihydroxybutyl)thymine (XIII)

(a) To a suspension of lithium aluminium hydride (228 mg, 6 mmol) in anhydrous (freshly distilled over $LiAlH_4$) tetrahydrofurane (30 ml) 2′-hydroxy-3′-carbethoxypropylthymine IX (512 mg, 2 mmol) dissolved in tetrahydrofurane (30 ml) was added dropwise. The suspension was stirred then at room temperature for 16 h, and the excess of $LiAlH_4$ destroyed by adding ethyl acetate (1 ml) and water (1 ml). A precipitate was separated and suspended in tetrahydrofurane (80 ml) and 2 mol dm^{-3} HCl (4.5 ml), to be separated by suction and washed with hot tetrahydrofurane. The combined filtrate and washings were evaporated to dryness. The residue was partitioned between water and chloroform. The water layer evaporated to a crude product (250 mg). Preparative TLC plate [in CH_2Cl_2-MeOH (9 : 1), eluant MeOH] gave the analytical sample, R_F ca. 0.1 [CH_2Cl_2-MeOH (9 : 1)], m. p. 159—161 °C (from methanol--ether).

Anal. $C_9H_{14}N_2O_4$ (214.21) calc'd.: C 50.46; H 6.59; N 13.08%
found: C 50.21; H 6.70; N 13.35%

UV spectrum: λ_{max} 268 nm (log ε 3.83), λ_{min} 232 nm (log ε 2.90). IR spectrum: ν_{max} 3546, 3226, 3077, 2857, and 1681 cm^{-1}. NMR spectrum: τ (in d_6-DMSO) 2.69 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), 5.19 (1 H,d,2′-OH, $J_{OH,2'}$ 6.0 Hz), 5.65 (1 H,t,4′-OH, $J_{OH,4'}$ 5.0 Hz), 6.23—6.62 (5 H,m,1′-H_2, 2′-H, and 4′-H_2) and 8.27 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz).

(b) To a solution of 2′-hydroxy-4′-aminobutylthymine XI (120 mg, 0.56 mmol) in 10% acetic acid (2.5 ml) sodium nitrite (60 mg, 0.87 mmol) in water (1 ml) was added dropwise. The mixture was stirred at room temperature for 30 min and then at 70 °C for 30 min to be evaporated to dryness under reduced pressure. The residue was dissolved in methanol and purified on a preparative TLC [3 time developed in CH_2Cl_2-MeOH (19 : 1), eluant methanol]. The rechromatography afforded the pure product (34 mg, 28%), m. p. 158—161 °C, identical (mixed m. p., IR, and NMR spectra) to that obtained under *(a)*.

1-(4-O-Triphenylmethyl-2,4-dihydroxybutyl)thymine (XIV)

To a solution of 2′,4′-dihydroxybutylthymine XIII (250 mg, 1.17 mmol) in anhydrous pyridine (8 ml) chlorotriphenylmethane[32] (550 mg, 2 mmol) was added and set aside at room temperature for 16 h. The mixture was evaporated to dryness and the residue partitioned between water and chloroform. The organic layer was concentrated to a small volume and chromatographed on a silica gel (12 g) column. Chloroform eluted the product (119 mg, 36.7%), R_F ca. 0.73 [CH_2Cl_2-MeOH (19 : 1)].

Anal. $C_{28}H_{28}N_2O_4$ (456.52) calc'd.: C 73.66; H 6.18; N 6.14%
found: C 73.68; H 6.36; N 6.08%

UV spectrum: λ_{max} 268 nm (log ε 3.88) λ_{min} 241 nm (log ε 3.34. IR spectrum: ν_{max} 3484 br, 3226, 3077, 2950, 1689 br, and 1603 cm^{-1}. NMR spectrum: τ 1.17 br (1 H,s,3-NH), 2.46—2.73 (15 H,m,aromatic), 2.86 (1 H,d,6-H, $J_{Me,6}$ 1.2 Hz), 5.80—5.98 (1 H,m,2′-H), and 8.12 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz).

1-(2-O-Acetyl-4-O-triphenylmethyl-2,4-dihydroxybutyl)thymine (XV)

A solution of 4′-*O*-tritylbutylthymine XIV (133 mg, 0.29 mmol) in anhydrous pyridine (5 ml) acetic anhydride (0.5 ml, 5.3 mmol) was added, set aside at room temperature for 16 h, and then evaporated to dryness. The residue was partitioned between water and chloroform. From the organic layer the titled compound was purified on a preparative TLC plate [two developments in CH_2Cl_2-Et_2O (3 : 1), eluant acetone] (110 mg, 76%), m. p. 204—206 °C (from methylene chloride-ether), R_F ca. 0.88 [CH_2Cl_2-MeOH (19 : 1)].

Anal. $C_{30}H_{30}N_2O_5$ (498.56) calc'd.: C 72.27; H 6.07; N 5.62%
found: C 72.44; H 6.29; N 5.49%

UV spectrum: λ_{max} 266 nm (log ε 3.86), λ_{min} 241 nm (log ε 3.47). IR spectrum: ν_{max} 3185, 3058, 2941, 2899, 1739, 1701, 1672, and 1595 cm^{-1}. NMR spectrum: τ 1.52 br (1 H,s, 3-NH), 2.45—2.76 (15 H,m, aromatic), 3.08 (1 H,d,5-Me, $J_{Me,6}$ 1.2 Hz), 4.49—4.87 (1 H,m, 2′-H), 5.91 (1 H,q,1′-H_a, $J_{1'a,b}$ 14.0 Hz, $J_{1'a,2'}$ 4.5 Hz), 6.34 (1 H,q,1′-H_b, $J_{1'b,a}$ 14.0 Hz, $J_{1'b,2'}$ 7.5 Hz), 6.80 (2 H,t,4′-H_2, $J_{4',3'}$ 6.0 Hz), and 8.13 br (6 H,s,MeCO and 5-Me).

1-(2,4-Di-O-acetyl-2,4-dihydroxybutyl)thymine (XVI)

A solution of crude 2′,4′-dihydroxybutylthymine XIII (64.3 mg, 0.3 mmol) in anhydrous pyridine (5 ml) was treated with acetic anhydride (0.5 ml, 5.3 mmol) and worked up as for compound XV. Preparative TLC [two developments in CH_2Cl_2-MeOH (19 : 1), eluant acetone] and rechromatography [five developments in CH_2Cl_2-MeOH (24 : 1)] gave the title compound (25 mg, 28%), m. p. 122—124 °C (from acetone-ether), R_F ca. 0.69 [CH_2Cl_2-MeOH (19 : 1)].

Anal. $C_{13}H_{18}N_2O_6$ (298.29) calc'd.: C 52.34; H 6.08; N 9.39%
found: C 52.57; H 5.97; N 9.55%

UV spectrum: λ_{max} 267 nm (log ε 3.99), λ_{min} 233 nm (log ε 3.30). IR spectrum: ν_{max} 3155, 3021, 2801, 1739, 1715, and 1672 cm^{-1}. NMR spectrum: τ 3.04 (1 H,d,6-H, $J_{6,Me}$ 1.2 Hz), 4.61—5.00 (1 H,m,2′-H), 5.86 (2 H,t,4′-H_2, $J_{4',3'}$ 6.2 Hz), 5.90 (1 H,q,1′-H_a, $J_{1'a,b}$ 14.5 Hz, $J_{1'a,2'}$ 3.8 Hz), 6.38 (1 H,q,1′-H_b, $J_{1'b,a}$ 14.5 Hz, $J_{1'b,2'}$ 7.5 Hz), 7.98 (3 H,s,MeCO), and 8.10 (3 H,d,5-Me, $J_{Me,6}$ 1.2 Hz).

The Detritylation of 1-(2-O-Acetyl-4-O-trityl-2,4-dihydroxybutyl)thymine (XV)

A solution of 2′-*O*-acetyl-4′-*O*-tritylbutylthymine XV (110 mg, 0.22 mmol) in 80% acetic acid (1 ml) was heated under reflux for 15 min. TLC showed the appearance of two products at R_F ca. 0.28 and ca. 0.37 [CH_2Cl_2-MeOH (19 : 1)]. Trituration with methylene chloride separated a crystalline product (18 mg, 31.9%), R_F ca. 0.28. Preparative TLC of the mother liquor and attempted elution of an oily product (R_F ca. 0.37), followed by a rechromatography, again gave two products (R_F ca. 0.28 and ca. 0.37) which on acetylation, in acetic anhydride and anhydrous pyridine, transformed quantitatively into a product identified as 2′,4′-di-*O*-acetylbutylthymine XVI, R_F ca. 0.69. The crystalline and stabile product (R_F ca. 0.28), tentatively assigned as 1-(4-*O*-acetyl-2,4-dihydroxybutyl)thymine (XVII), was recrystallized from methanol--ether, m. p. 189—191 °C.

Anal. $C_{11}H_{16}N_2O_5$ (256.25) calc'd.: C 51.56; H 6.29%
found: C 51.61; H 6.10%

UV spectrum: λ_{max} 269 nm (log ε 4.00), λ_{min} 244 nm (log ε 3.36). IR spectrum: ν_{max} 3571, 3226, 3077, 2841, 1724, 1681 br, and 1667 cm^{-1}.

O-[3′-O-Acetylthymidylyl(5′ → 2′)-1-(4-O-triphenylmethyl-2,4-dihydroxybutyl)thymine]-N,N,-dicyclohexylpseudourea (XIX)

To a solution of 3′-*O*-acetylthymidine-5′-phosphate[29] as a pyridinium salt (67 mg, 0.15 mmol) in anhydrous pyridine (5 ml) 4′-*O*-trityl-2′,4′-dihydroxybutylthymine XIV (137 mg, 0.3 mmol) and dicyclohexylcarbodi-imide (610 mg, 3 mmol) were added. The mixture was set aside at room temperature for 5 days and then treated with water (3 ml) by stirring during a time interval of 2 h. A precipitate was filtered off, the filtrate evaporated to dryness and the residue partitioned between water and chloroform. The organic layer was concentrated to a small volume and chromatographed on a silica gel (30 g) column. Chloroform-methanol (9 : 1 — 7.5 : 2.5) eluted the product which crystallized from chloroform-*n*-hexane. Yield 35 mg (23.1%) m. p. 191—194 °C [purified on a preparative TLC in CH_2Cl_2-MeOH (8.7 : 1.3), eluant methanol], R_F ca. 0.42 [CH_2Cl_2-MeOH (8.5 : 1.5)].

Anal. $C_{53}H_{65}N_6O_{12}P$ (1009.10) calc'd.: C 63.08; H 6.49%
found: C 62.89; H 6.62%

UV spectrum: λ_{max} 269 nm (log ε 4.22), λ_{min} 244 nm (log ε 3.91). IR spectrum: ν_{max} 3448 br, 3236, 3077, 2857, 1686 br, 763, and 704 cm^{-1}.

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SAŽETAK

Homologizacija 1-(2,3-dihidroksipropil)- u 1-(2,4-dihidroksibutil)-timin

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Homologizacija 1-(2,3-dihidroksipropil)timina polazi od 3′-*O*-tosil-derivata II koji, nakon prevođenja u odgovarajući 3′-jodo-spoj IV nukleofilnom zamjenom s natrijevim cijanidom u DMSO kao otapalu, daje 1-(2-hidroksi-3-cijanopropil)timin (VIII). Analogno tome je 1-(2,3-dihidroksipropil)uracil preveden u 3′-jodo-III i 3′-cijano-VII propiluracil. Etanoliza 3′-cijano spoja VIII do 1-(2-hidroksi-3-etoksikarbonilpropil) timina (X) i njegova naknadna redukcija sa $LiAlH_4$ daje 1-(2,4-dihidroksibutil)timin (XIII).

3′-*O*-Acetiltimidilil(5′→2′)-1-(4-*O*-trifenilmetil-2,4-dihidroksibutil)timin opisan je kao mogući adukt s *N*,*N*-dicikloheksilpseudoureom XIX.

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