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Anti-Cyclisation Reactions of Enantiomeric 1-(2,3-Dihydroxypropyl)uracil Derivatives

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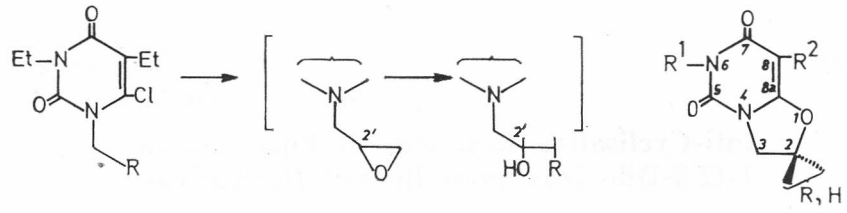
The synthesis and enantiomeric features of 2-hydroxymethyl--tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-diones (*V*) are described. The diazomethane methylation of these bicyclic compounds afforded 2-hydroxymethyl-6-methyl-tetrahydro-oxazolo--[3,2-c]pyrimidine-5,7-(4H,6H)-diones (R)-(*XXII*) and (S)-(*XXII*), respectively. For the synthesis of (R)-V and (S)-V the respective 5-bromo-1-(2,3-dihydroxypropyl)uracil (R)-(*XVII*) and (S)-(*XVII*) were treated with KCN in DMF. The intermediate (R,S)-6-cyano--1-(2,3-dihydroxypropyl)uracil (*XI*) was shown to undergo the anti-cyclisation yielding (R,S)-*V* if heated in DMSO at 40 °C.

The bio-transformations of 1-allyl-6-chloro-3,5-diethyluracil[1] (ACIU, *I*), a drug for the external treatment of viral infections, and 6-chloro-3,5-diethyl--1-propyluracil[2] (*II*) possessing similar activities yielded 6,8-diethyl-2-hydroxymethyl-[3] (*III*) and 6,8-diethyl-2-methyl-[2] (*IV*) tetrahydro-oxazolo[3,2-c]-pyrimidine-5,7-(4H,6H)-dione, respectively, as major metabolites. In order to shed light on these transformations (Scheme 1), consisting of 2',3'-epoxide- [A] and 2',3'-dihydroxypropyl- [B] uracil as intermediates for the formation of metabolite *III* and 2'-hydroxypropyl-uracil [C] as the intermediate for the formation of the metabolite *IV*, our search was directed towards the synthesis and enantiomeric features of the hitherto unknown 2-hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-diones (*V*).

Sulphonylated derivatives of (R,S)-1-(2,3-dihydroxypropyl)-uracil[4] (*VI*) and its thymine analogue[5] (*VII*) underwent the syn-cyclisations to give the respective (R,S)-2-hydroxymethyl-2,3-dihydro- (*VIII*) and (R,S)-2-hydroxymethyl-2,3-dihydro-6-methyl (*IX*)-oxazolo-7H-[3,2-a]pirimidin-7-one (Scheme 2) on a route analogous the natural pyrimidine nucleosides. Attempting also to generalize the anti-cyclisation reactions, applied in uridine series, by a possible enhancement of the preponderantly anti-oriented pentofuranosyl moieties[6–8] and suitably halogenated[9] aglycones, we studied the analogous reaction sequence for the properly activated uracil analogue *VI*.

Reaction sequences for the synthesis of C(6), O-C(5') cyclouridine and C(6), O-C(5') cyclocytidine[10,11] provided reagents and conditions (KCN in DMF at room temperature) for the regioselective anti-cyclisation of (R,S)-5-bromo-

Scheme 1



(I) R = $CH{=}CH_2$
(II) R = CH_2CH_3

[A]

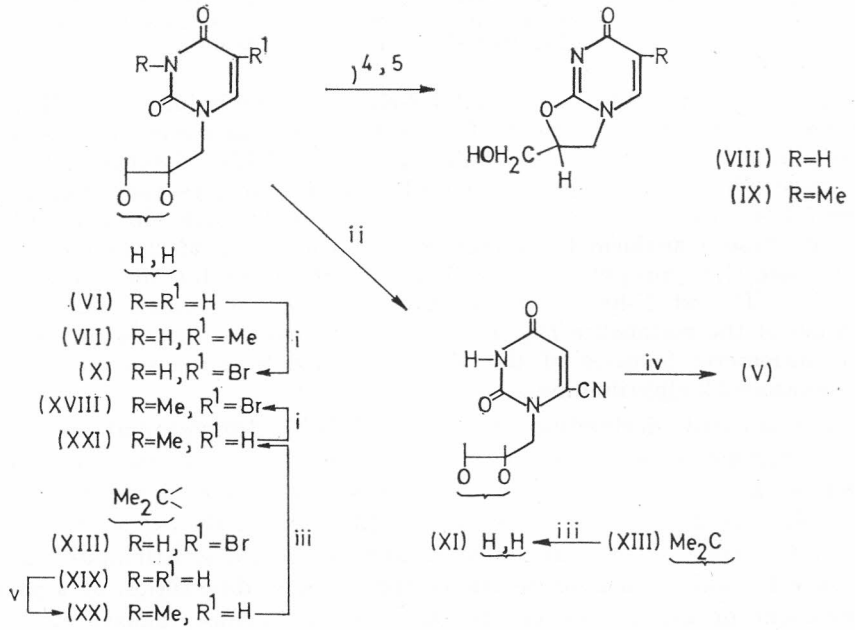
[B] R=OH
[C] R=H

(III) $R=CH_2OH, R^1=R^2=Et$
(IV) $R=CH_3, R^1=R^2=Et$
(V) $R=CH_2OH, R^1=R^2=H$
(XXII) $R=CH_2OH, R^1=Me, R^2=H$

i

Reagent: i, CH_2N_2–Et_2O–MeOH

Scheme 2



(VIII) R=H
(IX) R=Me

H,H
(VI) $R=R^1=H$
(VII) $R=H, R^1=Me$
(X) $R=H, R^1=Br$
(XVIII) $R=Me, R^1=Br$
(XXI) $R=Me, R^1=H$

Me_2C<
(XIII) $R=H, R^1=Br$
(XIX) $R=R^1=H$
(XX) $R=Me, R^1=H$

Reagents: i, Br_2–EtOH–CH_2Cl_2; ii, NaCN–DMF at RT; iii, 80 % AcOH reflux; iv, t-OBuK–DMF or DMSO only at 40°C; v, CH_2N_2–Et_2O–MeOH

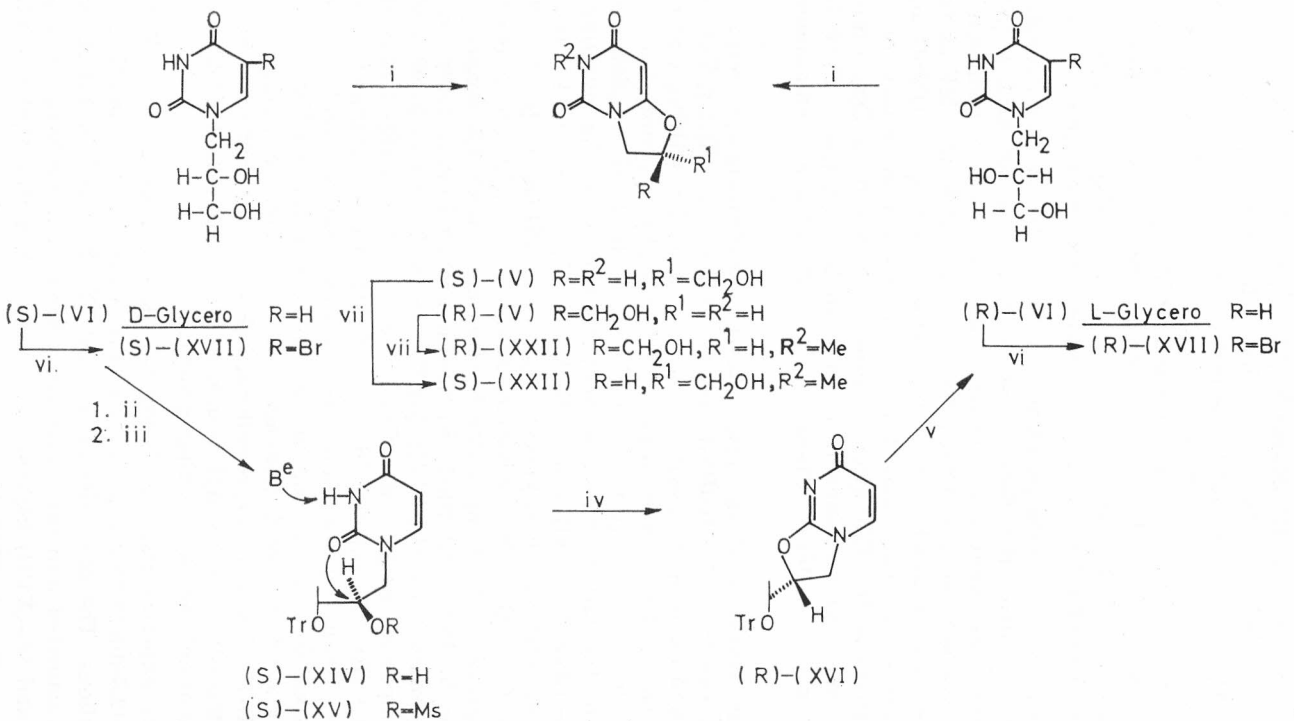
-1-(2,3-dihydroxypropyl)uracil (*X*) into (R,S)-2-hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-dione (*V*). This C(6), O-C(2') cyclisation most probably proceeded via the intermediate (R,S)-6-cyano-1-(2,3-dihydroxypropyl)uracil (*XI*) by a mechanistic approach described for the formation of C(6), O-C(5') cyclocytidine derivative[10,12]. Therefore, (R,S)-6-cyano-1-(2,3-O--isopropylidene-2,3-dihydroxypropyl)uracil (*XII*) (Scheme 2) was prepared by a cyanation (NaCN in DMF at room temperature) reaction of (R,S)-5-bromo-1--(2,3-O-isopropylidene-2,3-dihydroxypropyl)uracil (*XIII*), the latter being prepared from 5-bromouracil and the suitably activated glycerol derivative[13].

The hydrolysis of isopropylidene derivative *XII* in 80 % AcOH at room temperature yielded (R,S)-6-cyano-1-(2,3-dihydroxypropyl)uracil (*XI*) (97%), which indeed underwent anti-cyclisation into the bicyclic compound *V*. This reaction proceeded under standard conditions (*t*-BuOK in DMF at room temperature) but also in much higher yields when dissolved in DMSO and heated at 40 °C. These intramolecular transformations via an attack of the C(2')--hydroxy group at the C(6)-cyano position (possibly by a C(5), C(6)-addition--dehydrobromination mechanism), remains to be elaborated. Work is in progress, particularly on the synthesis of the deuterated and enantiomeric compounds.

For our synthesis of the enantiomeric 2-hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-diones (*V*) (Scheme 3) (S)-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)-uracil[13,14], $[\alpha]_D^{23}$ — 38° (c 2.5, $CHCl_3$), was firstly deblocked in boiling 80% AcOH to give (S)-1-(2,3-dihydroxypropyl)uracil (S)-*VI*), $[\alpha]_D^{25}$ — 76° (c 1, EtOH) (Lit. 15 $[\alpha]_D^{25}$ — 22.3° (c 1, H_2O)) (Scheme 3). The tritylation of the latter and subsequent mesylation of the resulting (S)-1-(2--hydroxy-3-trityloxypropyl)-uracil (S)-(*XIV*), $[\alpha]_D^{23.5}$ — 22° (c 1, EtOH), furnished (S)-1-(2-mesyloxy-3-trityloxypropyl)uracil (S)-(*XV*), $[\alpha]_D^{26}$ — 36° (c 2, EtOH). The C(2'), O—C(2) cyclisation, accompanied with an inversion of the C(2') configuration[14,16] of the latter by treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene in DMF, afforded (R)-2,3-dihydro-2-trityloxymethyl-oxazolo-7H--[3,2-a]-pyrimidin-7-one (R)-(*XVI*), $[\alpha]_D^{20}$ + 16° (c 2, $CHCl_3$) in 96% yield. The bicyclic compound (R)-*XVI* was finally converted into (R)--1-(2,3-dihydroxypropyl)uracil (R)-(*VI*), $[\alpha]_D^{26}$ + 76° (c 1, EtOH), by a treatment with boiling 80% AcOH. Besides detritylation, this transformation involved the stereocontrolled oxazolo ring opening through a possible intermediate C(2)-oxonium ion and C(2)—OC(2') bond cleavage. The enantiomeric purity of the thus obtained (R)-1-(2,3-dihydroxypropyl)uracil (R)-(*VI*) was confirmed by an unambigous synthesis[14] using methyl 5-(uracil-1-yl)-5-deoxy-2,3-O-isopropylidene-β--D-ribofuranoside[17] as the starting material.

Decisive experiments, correlating the (R)- and (S)-configuration of (+)- and (—)-1-(2,3-dihydroxypropyl)uracil (*VI*), were in the conditions effecting anti-cyclisations. The diols (R)-*VI* and (S)-*VI*, dissolved in EtOH, were precedingly brominated into the respective 5-bromo-1-(2,3-dihydroxypropyl)uracil (R)-(*XVII*) and (S)-(*XVII*) (Scheme 3). It is worth noting that the interactions of 5-bromouracil with (R,S)-1-O-*p*-tolylsulphonyl-2,3-O-isopropylidene-glycerol by means of NaH in DMF[13] yielded (R,S)-5-bromo-1-(2,3-O-isopropylidene--oxypropyl)uracil (*XIII*) in higher yields than the interactions of uracil itself. Since the C(6), O—C(2') cyclisations of the enantiomeric bromo-compounds

Scheme 3



Reagents: i, KCN–DMF at RT; ii, TrCl–py; iii, MsCl–py; iv, DBU–DMF; v, 80% AcOH reflux; vi, Br_2–EtOH–CH_2Cl_2; vii, CH_2N_2–Et_2O–MeOH.

(R)-*XVII* and (S)-*XVII* by the respective treatments with KCN in DMF proceeded via a series of transformations in the pyrimidine part of molecules, retentions of configurations at the C(2')-chiral centre should be expected. Therefore, the configurational feature of (R)-2-hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-dione (R)-(*V*), $[\alpha]_D^{26}$ — 13° (c 2, EtOH), obtained from (R)-*XVII*, should correspond to L-glycero enantiomer (Scheme 3) and (S)-2-hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-dione (S)-(*V*), $[\alpha]_D^{23}$ + 12° (c 2, EtOH), being derived from the D-glycero structure[13], to D-glycero enantiomer.

Our study of the stereochemistry related to the bio-transformations of AClU (*I*) and here achived synthesis of the enantiomeric 2-hydroxymethyl--tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-diones (R)-(*V*) and (S)-(*V*) improved the synthetic procedure for the biologically interesting anti-cyclisations. However, all attempted anti-cyclisations of (R,S)-5-bromo-1-(2,3-dihydroxypropyl)-3-methyl-uracil (*XVIII*) (Scheme 2) failed. The N(3)-methylated compound *XVIII* was prepared from (R,S)-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)uracil[4] (*XIX*) in a reaction with ethereal diazomethane, followed by the hydrolysis of the resulting (R,S)-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)--3-methyluracil (*XX*) in boiling 80% AcOH, and bromination of the thus obtained (R,S)-1-(2,3-dihydroxypropyl)-3-methyluracil (*XXI*).

Methylation of the preformed bicyclic compound *V* gave (R,S)-2-hydroxymethyl-6-methyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-dione (*XXII*) (Scheme 1) by treatment with ethereal diazomethane. Similar methylations of (R)- and (S)-2-hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,-6H)-diones (R)-(*V*) and (S)-(*V*) (Scheme 3) afforded 2-hydroxymethyl-6-methyl--tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,-6H)-diones (R)-(*XXII*), $[\alpha]_D^{22.5}$ — — 49.5° (c 1, MeOH) and (S)-(*XXII*), $[\alpha]_D^{23}$ + 49.9° (c 1, MeOH), respectively, in high yields.

EXPERIMENTAL

Melting points, uncorrected, were taken with a Kofler hot-stage apparatus. IR spectra were determined for potassium bromide pellets on a Perkin Elmer 297 spectrophotometer; UV spectra for solutions in 95% EtOH, unless otherwise stated, on a Perkin-Elmer 124 spectrophotometer; ^{1}H-NMR spectra for solutions in DMSO-d_6, unless otherwise stated, on a "JEOL FX90Q" spectrometer operating at 89.55 MHz with tetramethylsilane as internal standard. ^{13}C-NMR spectra were measured for solutions in $CDCl_3$ on a "JEOL FX90Q" spectrometer operating at 22.5 MHz. Multiplicities s, d, t, and q refer to off-resonance decoupled spectra. Optical rotations were measured in 95% EtOH, unless otherwise stated, using a Zeiss-Winkler 179707 apparatus. The silica gel (Merck, HF_{254} type 60) for TLC and preparative TLC was activated at 110 °C for 60 min. The products were developed in ethyl-acetate-isopropanol-water (75 : 16 : 9), and recovered from TLC chromatographic plates with 95% EtOH, unless otherwise stated. The products were rendered visible by UV illumination or iodine vapour.

(R,S)-5-Bromo-1-(2,3-dihydroxypropyl)uracil (X)

To a solution of (R,S)-1-(2,3-dihydroxypropyl)uracil (*VI*) (300 mg, 1.6 mmol) in anhydrous EtOH (75 ml), a solution of bromine (0.17 ml, 3.1 mmol) in CH_2Cl_2 (24 ml) was added dropwise. The solution was then stirred at room temperature for 2 h, the solvent removed under reduced pressure, and the residue recrystallized from MeOH. It yielded 365 mg (81%), m. p. 208—210 °C, R_F ca. 0.71.

Anal. $C_7H_9BrN_2O_4$ (265.08) calc'd.: C 31.71; H 3.42; N 10.57%
found: C 31.85; H 3.56; N 10.73%

UV spectrum: λ_{max} 213 and 282 nm (log ε 3.97 and 4.0), λ_{min} 243 nm (log ε 3.22). IR spectrum: ν_{max} 3312, 3177br, 3040br, 2947, 1707br, 1662br, 1652sh, 1614, 1457, 1417, and 1025 cm^{-1}. ^{1}H-NMR spectrum: δ_H 11.72 br (1H, s, 3-NH), 8.01 (1H, s, 6-H), 5.05 (1H, d, 2'-OH; $J_{OH,2'}$ 4.98 Hz), 4.72 (1H, t, 3'-OH; $J_{OH,3'}$ 5.28 Hz), 4.05—3.14 (5H, m, 1'-H_2, 2'-H, 3'-H_2). ^{13}C-NMR spectrum: δ_C 159.59 (C-4, s), 150.29 (C-2, s), 146.48 (C-6, d), 93.56 (C-5, s), 68.61 (C-2', d), 63.45 (C-3', t), 51.41 (C-1', t).

(R,S)-2-Hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-dione (V)

a) To a solution of (R,S)-1-(2,3-dihydroxypropyl)-5-bromouracil (*X*) (200 mg, 0.75 mmol) in anhydrous DMF (5 ml), dried KCN (54 mg, 0.83 mmol) was added. The mixture was stirred at room temperature for 48 h. The precipitate was then filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in MeOH and filtered through a short alumina (neutral) column. It afforded the product *V* (91 mg, 66%), m. p. 243—244 °C (from MeOH), R_F ca. 0.38.

Anal. $C_7H_8N_2O_4$ (184.17) calc'd.: C 45.65; H 4.39; N 15.21%
found: C 45.82; H 4.60; N 15.47%

UV spectrum: λ_{max} 214sh and 253 nm (log ε 3.36 and 3.83), λ_{min} 227 nm (log ε 3.24). IR spectrum: ν_{max} 3330br, 3030br, 1720br, 1650br, 1480br, 1465sh, 1405, and 780 cm^{-1}. ^{1}H-NMR spectrum: δ_H 10.84br (1H, s, 6-NH), 5.26 (1H, t, 1'-OH; $J_{OH,1'}$ 5.57 Hz), 5.16—4.92 (1H, m, 2-H; obscured by those of 8-H), 4.91 (1H, d, 8-H; $J_{8,6}$ 1.47 Hz), 4.03 (1H, dxd, 3-H_a; $J_{a,b}$ 9.96 and $J_{a,2}$ 8.5 Hz), 3.81 (1H, dxd, 3-H_b; $J_{b,a}$ 9.96 and $J_{b,2}$ 6.45 Hz), 3.79—3.44 (2H, m, 1'-H_2 obscured by those of 3-H_b). ^{13}C-NMR spectrum: δ_C 164.73 (C-7, s), 162.81 (C-5, s), 147.86 (C-8a, s), 82.62 (C-8, d), 74.55 (C-2, d), 61.01 (CH_2OH, t), 43.23 (C-3, t).

b) A solution of (R,S)-6-cyano-1-(2,3-dihydroxypropyl)-uracil (*XI*) (22 mg, 0.104 mmol) in anhydrous DMF (0.3 ml) was treated with freshly prepared t-BuOK [K (10.2 mg) in t-BuOH (1.4 ml)] and stirred at room temperature for 90 min. The mixture was neutralized with 1 mol dm^{-3} HCl, the solvent removed under reduced pressure, and the residue subjected to the preparative TLC. It afforded the product V (7.8 mg, 41%), m. p. 243—244 °C (from MeOH), R_F ca. 0.38, identical (IR and ^{1}H-NMR) to that described in section a).

c) A solution of (R,S)-6-cyano-1(2,3-dihydroxypropyl)-uracil (*XI*) (19.2 mg, 0.09 mmol) in DMSO (2.5 ml) was heated at 40 °C for 73 h. The solvent was then removed under reduced pressure and the residue subjected to the preparative TLC. It gave the product V (11 mg, 67%), m. p. 242—244 °C (from MeOH), R_F 0.38, identical (IR and ^{1}H-NMR spectra) to that obtained in section a).

(R,S)-5-Bromo-(2,3-O-isopropylidene-2,3-dihydroxypropyl)-uracil (XIII)

To a solution of 5-bromouracil (603 mg, 3 mmol) in anhydrous DMF (8 ml), NaH (132 mg) was added. The mixture was stirred at room temperature for 1 h and then treated with 1-O-*p*-tolylsulphonyl-2,3-O-isopropylidene-glycerol (512 mg, 2 mmol). This mixture was stirred at 100 °C for 17 h, cooled and filtered through a Celite column. The filtrate was evaporated to dryness under reduced pressure and the residue triturated with hot $CHCl_3$. The chloroform solution was concentrated to a small volume and subjected to the preparative TLC (developed in ether, recovery with EtOH). It afforded the product XIII in 40.5% yield, m. p. 181—182 °C (from $CHCl_3$), R_F ca. 0.42 (ether).

Anal. $C_{10}H_{13}BrN_2O_4$ (305.14) calc'd.: C 39.36; H 4.29; N 9.18%
found: C 39.57; H 4.20; N 9.09%

UV spectrum: λ_{max} 213 and 283 nm (log ε 3.87 and 3.90), λ_{min} 242 nm (log ε 3.09). IR spectrum: ν_{max} 3420br, 3165br, 3100, 3035br, 2990, 2930, 1715br, 1680sh, 1675br, 1650sh, 1615, 1455sh, 1445, and 1420 cm^{-1}. ^{1}H NMR spectrum (in $CDCl_3$): δ_H 7.68 (1H, s, 6-H), 4.41—4.29 (1H, m, 2'-H), 4.12 (1H, dxd, 3'-H_a; $J_{a,b}$ 8.79 $J_{a,2'}$ 6.15 Hz), 4.06 (1H, dxd, 1'-H_a; $J_{a,b}$ 14.06, $J_{a,2'}$ 2.64 Hz), 3.75 (1H, dxd, 1'-H_b; $J_{b,a}$ 14.06, $J_{b,2'}$ 6.45 Hz), 3.70 (1H, dxd, 3'-H_b; $J_{b,a}$ 8.79, $J_{b,2'}$ 5.86 Hz), 1.44 and 1.35 (each 3H, 2s, $C(Me)_2$). ^{13}C-NMR spectrum: δ_C 159.59 (C-4, s), 150.57 (C-2, s), 145.85 (C-6, d),

108.72 (O—C—O, s), 94.24 (C-5, s), 73.05 (C-2', d), 65.74 (C-3', t), 49.56 (C-1', t), 26.31 and 25.00 (each $(CH_3)_2$—C, 2q).

(R,S)-6-Cyano-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)-uracil (XII)

To a solution of (R,S)-5-bromo-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)-uracil (*XIII*) (140 mg, 0.457 mmol) in anhydrous DMF (1.25 ml), dried NaCN (26.9 mg, 0.549 mmol) was added and stirred at room temperature for 24 h. The mixture was diluted with water (0.28 ml) and then neutralized with 1 mol dm^{-3} HCl (0.14 ml) under nitrogen atmospehere within 2 min. The solvent was removed under reduced pressure and the product *XII* crystallized from $CHCl_3$-*n*-hexane (65 mg, 55%), m. p. 188—189 °C (from $CHCl_3$), R_F ca. 0.35 (CH_2Cl_2—MeOH, 20 : 1).

Anal. $C_{11}H_{13}N_3O_4$ (251.23) calc'd.: C 52.59; H 5.21; N 16.73%
found: C 52.31; H 5.23; N 16.46%

UV spectrum: λ_{max} 203 and 290 nm (log ε 4.01 and 3.99), λ_{min} 235 nm (log ε 3.29). IR spectrum: ν_{max} 3435br, 3165, 3085, 3055, 2995, 2245, 1720sh, 1710br, 1665, 1595, 1465, and 1410 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ_H 9.55 (1H, s, 3-NH), 6.26 (1H, s, 5-H), 4.45—4.23 (1H, m, 2'-H), 4.13 (1H, dxd, 1'-H_a; $J_{a,b}$ 14.40, $J_{a,2'}$ 4.64 Hz) 4.07 (1H, dxd, 3'-H_a; $J_{a,b}$ 8.79, $J_{a,2'}$ 6.35 Hz), 3.79 (1H, dxd, 1'-H_b; $J_{b,a}$ 14.16, $J_{b,2'}$ 8.55 Hz), 3.75 (1H, dxd, 3'-H_b; $J_{b,a}$ 8.79, $J_{b,2'}$ 5.62 Hz), 1.51 and 1.34 (each 3H, 2s, $C(CH_3)_2$). ^{13}C-NMR spectrum ($CDCl_3$): δ_C 169.49 (C-4, s), 159.85 (C-2, s), 129.89 (C-6, s), 111.42 (CN, $^2J_{CH}$), 111.42 (C-5, d), 110.76 (O—C—O, s), 72.80 (C-2', d), 66.58 (C-3', t), 50.58 (C-1', t), 26.21 and 25.09 (each $(CH_3)_2$C, 2q).

(R,S)-6-Cyano-1-(2,3-dihydroxypropyl)uracil (XI)

A solution of (R,S)-6-cyano-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)uracil (*XII*) (30 mg, 0.119 mmol) in 80% AcOH (4 ml) was stirred at room temperature for 20 h. The solvent was removed azeotropically with EtOH under reduced pressure. The residue recrystallized from MeOH yielding the product XI (24 mg, 97%), m. p. 161—162 °C, R_F ca. 0.76.

Anal. $C_8H_9N_3O_4$ (211.18) calc'd.: C 45.50; H 4.30; N 19.90%
found: C 45.28; H 4.28; N 20.18%

UV spectrum: λ_{max} 202 and 293 nm (log ε 3.49 and 3.34), λ_{min} 234 nm (log ε 2.69). IR spectrum: ν_{max} 3400br, 3160br, 3080, 3040br, 2950, 2250, 1737sh, 1710sh, 1708br, 1685sh, 1658sh, 1598, 1470, and 1420 cm^{-1}. ^{1}H-NMR spectrum: δ_H 11.75br (1H, s, 3-NH), 6.53 (1H, s, 5-H), 5.25 (1H, d, 2'-OH; $J_{OH,2'}$ 4.03 Hz), 4.77 br (1H, s, 3'-OH), 4.13—3.16 (5H, m, 1'-H_2, 2'-H, 3'-H_2). ^{13}C-NMR spectrum: δ_C 161.27 (C-4, s), 149.40 (C-2, s), 129.51 (C-6, s), 111.76 (CN, $^2J_{CH}$), 110.40 (C-5, d), 67.74 (C-2', d), 63.37 (C-3', t), 50.77 (C-1', t).

(R)-2,3-Dihydro-trityloxymethyl-7H-oxazolo[3,2-a]pyrimidin-7-one (XVI)

To a solution of (S)-1-(2-mesyloxy-3-trityloxypropyl)-uracil (S)-(XV) (270 mg, 0.533 mmol), prepared from (S)-1-(3-O-trityl-2,3-dihydroxypropyl)uracil according to the procedure described by Holy[14], in DMF (5 ml), 1,8 diazabicyclo[5.4.0]-undecen--7-ene (0.085 ml, 0.57 mmol) was added. The mixture was stirred at room temperature for 15 h. The solvent was then removed under reduced pressure. The preparative TLC (CH_2Cl_2—MeOH, 9 : 1) afforded the product *XVI* (209.8 mg, 96%), m. p. 180—181 °C (from MeOH—$CHCl_3$-*n*-hexane), R_F ca. 0.42 (in CH_2Cl_2—MeOH, 9 : 1), $[\alpha]_D^{20}$ + 16° (c 2, $CHCl_3$), identical to that described earlier[14].

(R)-5-Bromo-1-(2,3-dihydroxypropyl)uracil (R)-(XVII)

A solution of (R)-1-(2,3-dihydroxypropyl)uracil[13,17] (R)-(VI), $[\alpha]_D^{26}$ + 76° (c 1, EtOH), (19 mg, 0.102 mmol) in anhydrous EtOH (5 ml) was treated with bromine (0.011 ml, 0.2 mmol) dissolved in CH_2Cl_2 (1.55 ml) and worked up as described for the preparation of the (R,S)-product (R,S)-*X*. Recrystallization from MeOH yielded R-*XVII* (22.5 mg, 85%), m. p. 208—210 °C, R_F ca. 0.71, $[\alpha]_D^{25}$ + 43.5° (c 2, DMF).

IR and ^{1}H NMR spectra were identical with those described for (R,S)-*X*.

(S)-5-Bromo-1-(2,3-dihydroxypropyl)uracil (S)-(XVII)

(S)-1-(2,3-Dihydroxypropyl)uracil (S)-(*VI*), $[\alpha]_D^{35} - 76°$ (c 1, EtOH) (Lit. 15 $[\alpha]_D^{25} - 22.3°$ (c 1, H_2O)), (116.7 mg, 0.627 mmol), prepared from (S)-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)uracil[13,14] by treatment in boiling 80% AcOH, was dissolved in anhydrous EtOH (28 ml) and treated with a solution of bromine (0.065 ml, 1.19 mmol) in CH_2Cl_2 (9.3 ml) and worked up as already described. Recrystallization from MeOH afforded the (S)-enantiomer *XVII* (129.6 mg, 78%), m. p. 208—210 °C, R_F ca. 0.71, $[\alpha]_D^{25} - 44°$ (c 2, DMF).

IR and ^{1}H-NMR spectra were identical with those recorded for (R,S)-X and the (R)-enantiomer *XVII*.

(R)-2-Hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)-dione (R)-(V)

A solution of (R)-5-bromo-1-(2,3-dihydroxypropyl)uracil (R)-(*XVII*) (24 mg, 0.091 mmol) in anhydrous DMF (1 ml) was treated with dried KCN (6.5 mg, 0.1 mmol) and worked up as described for the preparation of (R,S)-V. Recrystallization from MeOH gave the (R)-enantiomer V (8.3 mg, 60%), m. p. 242—244 °C, R_F ca. 0.38, $[\alpha]_D^{26} - 13°$ (c 2, EtOH).

IR spectrum was identical with that described for (R,S)-V.

(S)-2-Hydroxymethyl-tetrahydro-oxazolo[3,2-c]pyrimidine-5,7-(4H,6H)üdione (S)-(V)

A solution of (S)-5-bromo-1-(2,3-dihydroxypropyl)uracil (S)-(*XVII*) (57.5 mg, 0.22 mmol) in anhydrous DMF (2 ml) was treated with dried KCN (15.5 mg, 0.242 mmol) and worked up as already described. Recrystallization from MEOH afforded the (S)-enantiomer V (24.3 mg, 61%), m. p. 243—244 °C, R_F ca. 0.38, $[\alpha]^{23} + 12°$ (c 2, EtOH).

IR and ^{1}H-NMR spectra were identical with those recorded for (R,S)-V and the (R)-enantiomer *V*.

(R,S)-1-(2,3-O-Isopropylidene-2,3-dihydroxypropyl)-3-methyluracil (XX)

To a cooled (0 °C) and freshly prepared solution of diazomethane [prepared from *N*-nitrosotoluene-4-sulphomethylamide (1.07 g, 5 mmol)] in ether (15 ml), a solution of (R,S)-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)uracil[4] (*XIX*) (594 mg, 2.63 mmol) in anhydrous MeOH (16 ml) was added dropwise. The mixture was than kept at room temperature for 1 h and evaporated to dryness under reduced pressure. The product XX crystallyzed from $CHCl_3$-*n*-hexane (555 mg, 88%), m. p. 114—115 °C (from $CHCl_3$), R_F ca. 0.80.

Anal. $C_{11}H_{16}N_2O_4$ (240.26) calc'd.: C 54.99; H 6.71; N 11.66%
found: C 54.61; H 6.80; N 11.54%

UV spectrum: λ_{max} 210 and 265 nm (log ε 4.09 and 4.17), λ_{min} 233 nm (log ε 3.50). IR spectrum: ν_{max} 3355, 3085, 2985, 2955, 2945, 2910, 1715, 1695, 1695, 1665, 1660, 1630, 1465, 1450, 1440, and 1038 cm^{-1}. ^{1}H-NMR spectrum: δ_H 7.29 (1H, d, 6-H; $J_{6,5}$ 8.06 Hz), 5.74 (1H, d, 5-H; $J_{5,6}$ 8.06 Hz), 4.56—4.28 (1H, m, 2'-H), 4.12 (1H, dxd, 3'-H_a; $J_{a,b}$ 8.55, $J_{a,2'}$ 6.35 Hz), 4.11 (1H, dxd, 1'-H_a; $J_{a,b}$ 14.16, $J_{a,2'}$ 2.69 Hz), 3.68 (1H, dxd, 3'-H_b; $J_{b,a}$ 8.55, $J_{b,2'}$ 6.10 Hz), 3.68 (1H, dxd, 1'-H_b; $J_{b,a}$ 14.16, $J_{b,2'}$ 6.84 Hz), 3.34 (3H, s, N-CH_3), 1.42 and 1.34 (each 3H, 2s, C$(CH_3)_2$). ^{13}C-NMR spectrum: δ_C 162.42 (C-4, s), 151.35 (C-2, s), 144.58 (C-6, d), 108.77 (O—C—O, s), 99.55 (C-5, d), 73.14 (C-2, d), 65.23 (C-3', t), 50.78 (C-1', t), 27.24 (N-CH_3, q), 26.16 and 25.10 (each $(CH_3)_2$C, 2q).

(R,S)-1-(2,3-Dihydroxypropyl)-3-methyluracil (XXI)

A solution of (R,S)-1-(2,3-O-isopropylidene-2,3-dihydroxypropyl)-3-methyluracil (*XX*) (760 mg, 3.17 mmol) in 80% AcOH (250 ml) was stirred at room temperature for 16 h. The solvent was removed azeotropically with EtOH under reduced pressure.

The residue crystallized from EtOH—Et_2O yielding the product *XXI* (552 mg, 87%), m. p. 85—87 °C, R_F ca. 0.41.

Anal. $C_8H_{12}N_2O_4$ (200.2) calc'd.: C 47.99; H 6.04; N 14.00%
found: C 47.79; H 6.35; N 13.64%

UV spectrum: λ_{max} 213 and 264 nm (log ε 3.80 and 3.90), λ_{min} 233 nm (log ε 3.18). IR spectrum: ν_{max} 3470br, 3115, 3095, 2910, 1700br, 1665sh, 1558 1650sh, 1620, 1475sh, 1465, 1460sh, 1450sh, and 1410br cm^{-1}. H^1-NMR spectrum: δ_H 7.26 (1H, d, 6-H); $J_{6,5}$ 8.06 Hz), 5.75 (1H, d, 5-H; $J_{5,6}$ 8.06 Hz), 4.07—3.44 (5H, m, 1'-H_2, 2'-H, 3'-H_2), 3.34 (3H, s, N—CH_3), 2.92 (1H, d, 2'-OH; $J_{OH,2'}$ 4.64 Hz), 2.58 (1H, t, 3'-OH; $J_{OH,3'}$ 6.1 Hz). ^{13}C-NMR spectrum: δ_C 162.61 (C-4, s), 151.21 (C-2, s), 145.12 (C-6, d), 98.92 (C-5, d), 68.81 (C-2', d), 63.54 (C-3', t), 52.19 (C-1', t), 27.09 (CH_3N, q).

(R,S)-5-Bromo-1-(2,3-dihydroxypropyl)-3-methyluracil (XVIII)

To a solution of (R,S)-1-(2,3-dihydroxypropyl)-3-methyluracil (*XXI*) (897 mg, 4.4 mmol) in CH_2Cl_2 (195 ml), bromine (0.45 ml, 8.2 mmol) in CH_2Cl_2 (64 ml) was added dropwise. The mixture was then stirred at room temperature for 20 h and evaporated to dryness under reduced pressure. The residue was crystallized from EtOH, yielding the product *XVIII* (825 mg, 66%), m. p. 180—182 °C (from EtOH), R_F ca. 0.71.

Anal. $C_8H_{11}BrN_2O_4$ (279.11) calc'd.: C 34.42; H 3.97; N 10.04%
found: C 34.46; H 4.21; N 9.84%

UV spectrum: λ_{max} 213 and 282 nm (log ε 3.91 and 3.94), λ_{min} 244 nm (log ε 3.94). IR spectrum: ν_{max} 3520, 3455br, 3335sh, 3055, 2955, 2925, 1690, 1645br, 1460br, 1440, 1430, 1240, and 1020 cm^{-1}. ^{1}H-NMR spectrum: δ_H 8.90 (1H, s, 6-H), 3.22 (3H, s, N—CH_3). ^{13}C-NMR spectrum: δ_C 159.00 (C-4, s), 150.43 (C-2, s), 144.77 (C-6, d), 92.93 (C-5, s), 68.61 (C-2', d), 63.50 (C-3', t), 52.58 (C-1', t), 28.67 (CH_3N, q).

(R,S)-2-Hydroxymethyl-6-methyl-tetrahydro-oxazolo[3,2-c]-pyrimidine-5,7-(4H,6H)-dione (XXII)

To a solution of (R,S)-2-hydroxymethyl derivative (R,S)-*V* (23 mg, 0.12 mmol) in anhydrous MeOH (19 ml), a freshly prepared solution of diazomethane [prepared from N-nitrosotoluene-4-sulphomethylamide (214 mg, 1 mmol)] in ether (3 ml) was added. The mixture was set aside at room temperature for 4 h and then concentrated to a smaller (7 ml) volume. On trituration with *n*-hexane, the crystalline product *XXII* was obtained (19.4 mg, 79%), m. p. 204—205 °C (from MeOH), R_F ca. 0.5.

Anal. $C_8H_{10}N_2O_4$ (198.18) calc'd.: C 48.48; H 5.09; N 14.14%
found: C 48.64; H 5.28; N 14.23%

UV spectrum: λ_{max} 204 and 253 nm (log ε 3.89 and 4.08), λ_{min} 227 nm (log ε 3.51). IR spectrum: ν_{max} 3292br, 3107, 3017, 2937, 1727br, 1687sh, 1652br, 1617, 1592, 1482br, 1460, and 1442br cm^{-1}. ^{1}H NMR spectrum: δ_H 5.27 (1H, t, 1'-OH; $J_{OH,1'}$ 5.57 Hz), 5.18—4.93 (1H, m, 2-H), 5.08 (1H, s, 8-H), 4.10 (1H, dxd, 3-H_a; $J_{a,b}$ 9.96, $J_{a,2}$ 8.50 Hz), 3.84 (1H, dxd, 3-H_b; $J_{b,a}$ 9.96, $J_{b,2}$ 6.45 Hz), 3.86—3.51 (2H, m, 1'-H_2; obscured by those of 3-H_b), 3.22 (3H, s, N-CH_3). ^{13}C-NMR spectrum: δ_C 163.54 (C-7, s) 161.01 (C-5, s), 148.25 (C-8a, s), 82.40 (C-8, d), 74.21 (C-2, d), 60.95 (CH_2OH, t), 44.08 (C-3, t), 26.75 (CH_3—N, q).

(R)-2-Hydroxymethyl-6-methyl-tetrahydro-oxazolo[3,2-c]-pyrimidine-5,7-(4H,6H)-dione (R)-(XXII)

A solution of (R)-2-hydroxymethyl-tetrahydro-oxazolo-[3,2-c]pyrimidine-5,7-(4H,6H)-dione (R)-(*V*) (32.7 mg, 0.178 mmol) in MeOH (17.5 ml) was treated with a freshly prepared solution of diazomethane [prepared from *N*-nitrosotoluene-4-sulphomethylamide (214 mg, 1 mmol)] in Et_2O (3 ml) and worked up as described for the preparation of (R,S)-*XXII*. The preparative TLC afforded the crystalline

product (R)-*XXII* (27.5 mg, 78%), m. p. 203—205 °C (from MeOH), R_F ca. *0.5*, $_x[\alpha]_D^{22.5}$ —49.5° (c 1, MeOH).

IR spectrum was identical with that described for (R,S)-*XXII*.

(S)-2-Hydroxymethyl-6-methyl-tetrahydro-oxazolo[3,2-c]-pyrimidine-5,7-(4H,6H)-dione (S)-(XXII)

A solution of (S)-2-hydroxymethyl-tetrahydroxo-oxazolo-[3,2-c]pyrimidine-5,7-(4H,6H)-dione (S)-(*V*) (45.5 mg, 0.247 mmol) in MeOH (24.2 ml) was treated with a freshly prepared solution of diazomethane [prepared from *N*-nitrosotoluene-4-sulphomethylamide (214 mg, 1 mmol)] in Et_2O (3 ml) as already described. Preparative TLC afforded the product (S)-*XXII* (36.7 mg, 75%), m. p. 204—205 °C (from MeOH), R_F ca. 0.5, $[\alpha]_D^{23}$ +49.5° (c 1, MeOH).

IR spectrum was identical to that recorded for (R,S)-*XXII* and the (S)-enantiomer (S)-*XXII*.

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SAŽETAK

Anti-ciklizacije enantiomernih 1-(2,3-dihidroksipropil)-uracil-derivata

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Opisane su sinteze i enantiomerne značajke 2-hidroksimetil-tetrahidro-oksazolo-[3,2-c]pirimidin-5,7-(4H,6H)-diona(*V*). Metiliranja tih optički aktivnih bicikličkih spojeva s pomoću diazometana daju (R)-2-hidroksimetil-6-metil-tetrahidro-oksazolo[3,2-c]pirimidin-5,7-(4H,6H)-dion (R)-(*XXII*), odnosno njegov (S)-enantiomer (S)-(*XXII*). Priprava bicikličkih enantiomera (R)-V i (S)-V iz odgovarajućih 5-bromo-1-(2,3-dihidroksipropil)uracila (R)-(*XVII*) i (S)-(*XVII*) vrši se u reakciji sa KCN u DMF. Pritom je utvrđeno da ta transformacija slijedi nastajanje (R,S)-6-cijano-1-(2,3-dihidroksipropil)uracila (*XI*) i njegovu anti-ciklizaciju u DMSO pri 40 °C.