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Synthesis and Intramolecular Rearrangement of Enantiomeric Amino-alcohols in the Aliphatic Thymidine Analogues Series

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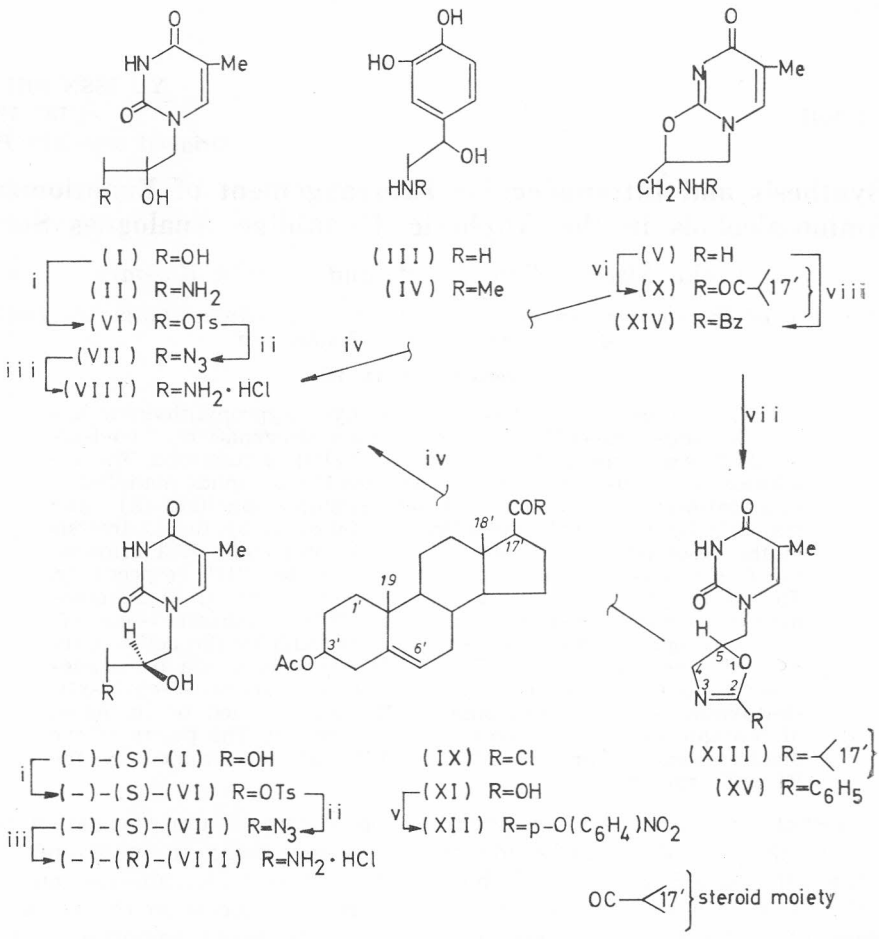
The synthesis of (-)-1-(-3-amino-2-hydroxypropyl)thymine hydrochloride[(-)-(R)-(VIII)] by a catalytic hydrogenation of (-)-1-(3--azido-2-hydroxypropyl)thymine[(-)-(S)-(VII)] is described. The resolution of (2R)- and (2S)-(3β-acetoxy-Δ⁵-etienamidomethyl)-2,3--dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one[(2R)-(X) and (2S)-(X)] by fractional crystallization, followed by the hydrolysis of the resolved stereoisomers in 25% isopropanolic HCl afforded the (+) and (—) amino-alcohol hydrochlorides VIII, respectively. The diastereoisomers X were prepared from (R,S)-2-aminomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (V) and *p*-nitrophenyl 3β-acetoxy-Δ⁵-etienate (XII) by the active ester method. The conversion of X into VIII proceeded via intramolecular formation of (5R)- and (5S)-2-(3β-acetoandrost-5-en-17-yl)--5-(thymin-1-ylmethyl)oxazoline (XIII), accompanied by inversion of configuration at the asymmetric C(2) centre. The purity of the diastereoisomeric products X and XIII was determined by the ^{1}H-NMR spectra.

Recently we described the synthesis and intramolecular cyclization reactions of dihydroxyalkyl nucleoside analogues containing thymine and uracil as the aglycones[1–3]. In view of the biological recognition abilities and antiviral activities in the aliphatic nucleoside series[4–8], access to the chiral analogues of 1-(2,3-dihydroxypropyl)thymine[1] (I) appeared important. In this report we describe the synthesis and enantiomeric features of the hitherto unknown 1-(3-amino-2-hydroxypropyl)thymine (II) (Scheme 1). Amino-alcohol II possesses almost all structural features of norepinephrine (noradrenaline) (III) and epinephrine (adrenaline IV), as well as of several adrenergic and cardiovascular drugs.[9] It should be noted that these versatile compounds are compatible with (R,S)-2-aminomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]--pyrimidin-7-one (V), which we recently described[3] and to which the 2,2'-anhydro structure of the amino-alcohol II could be assigned.

We also showed that (R,S)-1-(2,3-dihydroxypropyl)thymine (I) afforded (R,S)-1-(2-hydroxy-3-tosyloxypropyl)thymine[1] (VI) by selective tosylation. We now report the displacement of the 3'-tosyloxy group of VI with NaN_3 in DMF. Catalytic (Pd-black) hydrogenation of the resulting (R,S)-1-(3-azido-2--hydroxypropyl)thymine (VII) in 25% isopropanolic HCl yielded the desired (R,S)-1-(3-amino-2-hydroxypropyl)thymine hydrochloride (VIII) (Scheme 1).

* Taken in part from the Ph. D. thesis, University of Zagreb, 1984.

Scheme 1.



Reagents: i, TsCl–pyridine; ii, NaN_3–DMF, heat; iii, H_2–Pd black–MeOH; iv, 3 mol dm^{-3} HCl–25% Me_2CHOH, heat; v, p-$NO_2C_6H_4OH$–EtOAc–DCCI; vi, XII–DMF, heat; vii, p-$NO_2C_6H_4OH$–DMF, heat; viii, Bz_2O–pyridine

For the synthesis of the enantiomeric 1-(3-amino-2-hydroxypropyl)thymine (II) (—)-(S)-1-(2,3-dihydroxypropyl)thymine[7,10] [(S)-(I)], possessing the D-glycero structure, was chosen as the starting material. Since the selective tosylation of the glycol[(S)-I] was followed by displacement by azide and then catalytic hydrogenation, the resulting 1-(3-amino-2-hydroxypropyl)thymine hydrochloride [(R)-(VIII)], $[\alpha]_D^{24} -24^\circ$ (c 3, H_2O) should possess the R absolute configuration, corresponding to the D-glycero structure.

Confronted with a number of spontaneous intramolecular transformations of the vicinal amino-alcohol(II) we reasoned that the already described (R,S)-2-aminomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]-pyrimidin-7-ones[3] (V), having intramolecularly protected C(2') and C(2) functional groups, could be

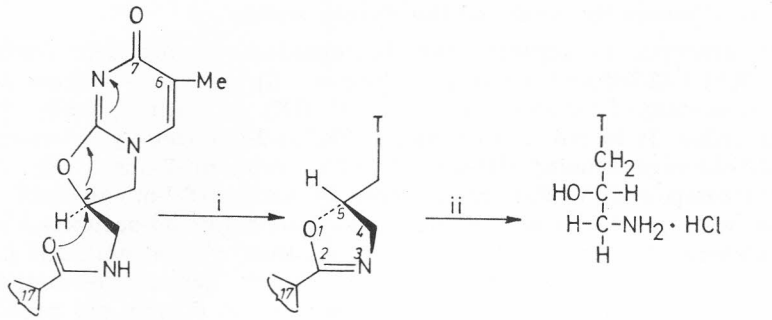
conveniently used for studies of the stereochemistry and resolution of the respective enantiomers by means of the steroid acids.

All our attempts to separate the diastereoisomeric products from the reaction of (R,S)-1-(2,3-dihydroxypropyl)-thymine[1] (I) or its 2,2'-anhydro structure with 3β-acetoxy-Δ^5-etienoyl chloride[11-13] (IX) or with optically active amino acids failed. It forced us to prepare (2R,2S)-2-(3β-acetoxy-Δ^5-etienamidomethyl)-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (X) from aminomethyl compound[3] V. For this purpose 3β-acetoxy-Δ^5-etienic acid[11] (XI) was reacted with *p*-nitrophenol, affording *p*-nitrophenyl 3β-acetoxy-Δ^5-etienate (XII) (Scheme 1). The bicyclic amine V was then reacted with XII giving a stable diastereoisomeric mixture of (2R,2S)-(X) by the active ester method[14,15] and two by-products, indicating transformations of X during the prolonged acylation procedure. Since diastereoisomers (2R)-X and (2S)-X thus formed showed very similar chromatographic mobilities, we took advantage of their different solubilities. Thus the resolution of (2R)- and (2S)-2-(3β-acetoxy-Δ^5-etienamidomethyl)-2,3-dihydro-6-methyl-7H-oxazolo [3,2-a] pyrimidin-7-one (2R)-(X) and (2S)-(X) was carried out by fractional crystallization using MeOH as solvent. This afforded stereoisomer (X) which exhibited $[\alpha]_D^{23}$ — 49° (c 2, $CHCl_3$). The filtrate was then concentrated to a crystalline fraction which was separated, and the mother liquor evaporated to give a product which, on recrystallization from CH_2Cl_2-*n*-hexane, yielded diastereoisomer X, $[\alpha]_D^{26}$ — — 91.5° (c 2, $CHCl_3$). (For more details see Experimental). Due to solubility problems, the hydrolysis of the diastereoisomer X, $[\alpha]_D^{23}$ — 49°, was conveniently achieved in 25% isopropanolic HCl. The thus obtained 1-(3-amino-2-hydroxypropyl)thymine hydrochloride, $[\alpha]_D^{20}$ — 31° (c 3, H_2O), was identical (IR spectrum and nearly identical optical rotation) with that obtained from the (—)-(S)-azido compound [(S)-VII] of known (D-glycero) absolute configuration. This finding also established 2-etienamidomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (X), $[\alpha]_D^{23}$ — 49° as (2S)-diastereoisomer with L-configuration at the C(2) centre (vide infra).

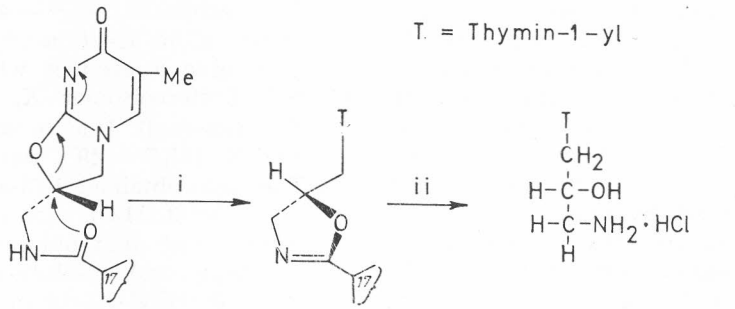
^{1}H NMR shifts of the etienamidomethyl compounds (2S)-(X) and (2R)-(X) have proven to be useful parameters for determining their optical purity. The C(18'), C(19'), and C(6) methyl groups as well as (C(2)-CH_2N showed resonances whose chemical shifts differed by 0.1, 0.03, 0.05, and 0.08 ppm, respectively. The resonances of the (C3) geminal protons were assigned to an unresolved multiplet at 3.56—3.91 ppm for the (2S)-diastereoisomer and to two multiplets around 3.99—4.13 and 3.46—3.63 ppm for the (2R)-diastereoisomer. In contrast to the ^{1}H-NMR spectrum of (2S)-X, which exhibited the resonances of NH as a triplet centred at 6.84 ppm (J_{NH,CH_2} 5.6 Hz), NH of (2R)-X was shifted downfield to 7.12—7.20 ppm. It was also noted that the C(17') proton of (2S)-X was shifted and obscured by those of the steroid protons in comparison with that of (2R)-X which appeared as a triplet centred at 2.64 ppm ($J_{16',17'}$ 8.3 Hz).

In rationalizing the stereochemical outcome of the above conversion of the etienamidomethyl compound X, $[\alpha]_D^{23}$ — 49° into amino-alcohol hydrochloride VIII, $[\alpha]_D^{20}$ — 31°, concomitant formation of (5R,5S)-2-(3β-acetoandrost-5-en-17-yl)-5-(thymin-1-ylmethyl)oxazoline (XIII) during the acylations of aminomethyl compound V (with the active ester XII) must be taken into

Scheme 2.



T = Thymin-1-yl



Reagents: i, p-$NO_2C_6H_4OH$–DMF, heat; ii, 3 mol dm^{-3} HCl–25% Me_2CHOH

consideration (Scheme 2). These concomitant transformations of the etienamidomethyl compound (2R,2S)-X in DMF at 90 °C were enhanced by *p*-nitrophenol liberated during acylation with the active ester XII. For a better understanding of this transformation *p*-nitrophenol was added to a solution of (2R,2S)-etienamidomethyl compound X in DMF and heated at 90 °C. From this reaction (5R,5S)-oxazoline XIII was isolated in a much shorter period of time than in the absence of *p*-nitrophenol.

In a similar manner, we succeeded in transforming etienamidomethyl--oxazolo[3,2-a]pyrimidin-7-one (2S)-X and (2R)-X into 2-(3β-acetoxyandrost-5--en-17-yl)-5-(thymin-1-ylmethyl)oxazoline [(5R)—(XIII)], $[\alpha]_D^{21}$ — 103°, and [(5S)-(XIII)], $[\alpha]_D^{21}$ + 9°, respectively (Scheme 2). These stereospecific transformations proceeded by an intramolecular nucleophilic attack of the carbonyl oxygen of the etienamido group at the C(2) position with concomitant inversion of the configuration, followed by cleavage of the C(2')-O bond[16]. This

allowed the conclusion that the L-configuration of (2S)-X was inverted to the D-configuration in (5R)-XIII, and the D-configuration of (2R)-X to the L-configuration in (5S)-XIII.

The ^{1}H-NMR spectra of oxazolines (5R)-XIII and (5S)-XIII clearly showed thymin-1-yl HN(3) resonances centred at 8.93 and 8.99 ppm, respectively. The disappearance of the CONH protons of the (2S)-X or (2R)-X can be explained by the rearrangement of the structures. The appearance of the C(18') methyl group at 0.72 and 0.68 ppm in the respective oxazolines (5R)-XIII and (5S)-XIII proved to be advantageous for observation of the diastereoisomeric purity of the products.

Further information on the stereochemical transformations of X into VIII was obtained by the observation that oxazoline (5R)-XIII hydrolyzed stereospecifically in 25% isopropanolic HCl to yield (R)-1-(3-amino-2-hydroxypropyl)thymine hydrochloride [(R)-(VIII)], $[\alpha]_D^{25} - 27^\circ$ (c 1.5, H_2O) (Scheme 2) in agreement with the previously reported oxazoline ring-opening under acidic conditions[17,18]. In a similar enantioselective ring opening of the steroid oxazoline, (5S)-XIII afforded (S)-1-(3-amino-2-hydroxypropyl)thymine hydrochloride [(S)-(VIII)], $[\alpha]_D^{25} + 27.8^\circ$ (c 3, H_2O).

Based on the above conversion of the etienamidomethyl compounds X into oxazolines XIII, (R,S)-2-benzamidomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (XIV) (Scheme 1) was transformed into 2-phenyl-5-(thymin-1-ylmethyl)oxazoline (XV). The latter was then hydrolyzed into (R,S)-1-(3-amino-2-hydroxypropyl)thymine, hydrochloride (VIII) by being heated in 25% isopropanolic HCl. This reaction sequence completed and confirmed the structural correlations between the amidomethyl-oxazolo[3,2-a]-pyrimidin-7-ones, oxazolines and amino-alcohols.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. IR spectra were obtained for potassium bromide pellets on a Perkin-Elmer 297 spectrophotometer. UV spectra were taken for solution in EtOH with a Perkin-Elmer 124 spectrophotometer. ^{1}H and ^{13}C spectra were measured for solutions in $CDCl_3$ on JEOL FX 90Q and —JEOL FX 100 spectrometers with tetramethylsilane as internal standard, unless otherwise stated. Chemical shifts are given in δ values and spin coupling constants J in Hz. Ms were recorded with a KRATOS LS 25 spectrometer. Optical rotations were measured using a Zeiss-Winkel 179707 apparatus. The silica gel (Merck HF_{254}, type 60) for preparative TLC was activated at 110 °C for 60 min. The products were rendered visible by UV illumination.

(R,S)-1-(3-Azido-2-hydroxypropyl)thymine (VII)

A solution of 1-(2-hydroxy-3-tosyloxypropyl)thymine[1] (VI) (354 mg, 1 mmol) in dry DMF (10 ml) was treated with NaN_3 (195 mg, 3 mmol) and heated at 90 °C for 2 h. The solvent was removed under reduced pressure and the residue triturated with acetone. The solid residue was filtered off and the filtrate evaporated to dryness. The residue was crystallized from MeOH to give the product VII (143 mg). From the mother liquor, evaporated to dryness and purified by preparative TLC (CH_2Cl_2—MeOH, 19 : 1, recovery with acetone), an additional amount of the product VII (35 mg) was isolated (overall 178 mg, 79%), R_F ca. 0.47 (CH_2C_2—MeOH, 9 : 1), m.p. 148—150 °C (from MeOH).

Anal. $C_8H_{11}N_5O_3$ (225.21) calc'd.: C 42.66; H 4.92; N 31.10%
found: C 42.66; H 5.09; N 30.86%

UV spectrum: $\lambda_{max.}$ 217 and 270 nm (log ε 3.88 and 3.95), $\lambda_{min.}$ 237 nm (log ε 3.53). IR spectrum: $\nu_{max.}$ 3363br, 3148br, 3023, 2928, 2833, 2193, 2138, 2113, 1678br, 1647, 1615, and 1517 cm^{-1}. ^{1}H-NMR spectrum (in DMSO-d_6, at 80 °C): 10.93br (1H, s, NH), 7.34 (1H, d, 6-H; $J_{6,Me-5}$ 1.2), 5.31 (1H, d, 2′-OH; $J_{OH,2'}$ 5.6), 3.94—3.83 (1H, m, 2′-H), 3.88 (1H, dxd, 1-H_a; $J_{a,b}$ 13.5, $J_{a,2'}$ 4.1), 3.50 (1H, dxd, 1-H_b; $J_{b,a}$ 13.5, $J_{b'2}$ 7.6), 3.28—3.21 (2H, m, 3-H), 1.76 (3H, d, 5-Me; $J_{Me-5,6}$ 1.2).

(R,S)-1-(3-Amino-2-hydroxypropyl)thymine Hydrochloride (VIII)

a) To a solution of (R,S)-1-(3-azido-2-hydroxypropyl)-thymine (VII) (67 mg, 0.3 mmol) in MeOH (20 ml), Pd-black (20 mg) was added. The suspension was stirred under H_2 (0.34 MPa) at room temperature for 3 h. The catalyst was filtered off and the filtrate evaporated to a small volume (2—3 ml) and adjusted to pH 6.0 by 1 mol dm^{-3} HCl. The solution was evaporated to dryness and the residue triturated with EtOH to the solid product VIII (3 mg, 75%), R_F ca. 0.26 (MeOH—NH_4OH, 96 : 4), m. p. 256—259 ° (from 90% EtOH).

Anal. $C_8H_{14}ClN_3O_3$ (235.67) calc'd.: C 40.77; H 5.99; N 17.83%
found: C 40.85; H 6.15; N 17.93%

UV spectrum: λ_{max} 210 and 268 nm (log ε 4.02 and 4.06), λ_{min} 235 nm (log ε 3.33). IR spectrum: ν_{max} 3420br, 3320, 3270, 3045sh, 2955br, 2870br, 1702, 1655br, 1633sh, and 1605 cm^{-1}. ^{1}H-NMR spectrum (in D_2O): 7.3 (1H, d, 6-H; $J_{6,Me-5}$ 1.2), 4.27—3.97 (1H, m, 2′-H), 3.97 (1H, dxd, 1′-H_a; $J_{a,b}$ 14.2, $J_{a,2'}$ 3.9), 3.68 (1H, dxd, 1′-H_b; $J_{b,a}$ 14.2, $J_{b,2'}$ 8.1), 3.22 (1H, dxd, 3′-H_a; $J_{a,b}$ 13.2, $J_{a,2'}$ 3.4), 2.94 (1H, dxd, 3′-H_b; $J_{b,a}$ 13.2, $J_{b,2'}$ 9.3), 1.84 (3H, d, 5-Me; $J_{Me-5,6}$ 1.2).

b) A solution of (2R,2S)-2-(3β-acetoxy-Δ^5-etienamidomethyl)-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (X) (vide infra) (52.63 mg, 0.1 mmol) in 3 mol dm^{-3} HCl in 25% isopropanol (2 ml) was heated under reflux for 5 h. The mixture was then cooled to room temperature, the precipitate filtered off, and the filtrate coevaporated several times with EtOH. The thus obtained residue was triturated with acetone to give the product VIII (16 mg, 67.9%), m. p. 255—259 °C (from 90% EtOH), identical (^{1}H-NMR and IR spectra) with that obtained under a).

c) A solution of (R,S)-2-phenyl-5-(thymin-1-ylmethyl)oxazoline (XV) (vide infra) (85.5 mg, 0.3 mmol) in 3 mol dm^{-3} HCl in 25% isopropanol (3 ml) was heated under reflux for 20 h. The solution was partitioned with ether and acidic water-layer, concentrated to a small volume under reduced pressure and then to a residue which was coevaporated several times with EtOH. The residue was triturated with EtOH to give the product VIII (52 mg, 73.5%), R_F ca. 0.26 (MeOH—NH_4OH, 96 : 4), m. p. 256—259 °C (from 90% EtOH), identical (IR and ^{1}H-NMR spectra) with that obtained under a).

(S)-1-(2-Hydroxy-3-tosyloxypropyl)thymine (S)-(VI)

To a solution of (S)-1-(2,3-dihydroxypropyl)thymine[7] [(S)-(I)], $[\alpha]_D^{23}$ — 53.1° (c 1, H_2O), [Lit.[7]: $[\alpha]_D^{25}$ — 54.3° (c 1, H_2O)], (200 mg, 1 mmol) in dry pyridine (7 ml) tosylchloride (267 mg, 1.4 mmol) was added and the solution stirred at room temperature for 16 h. The solvent was then removed azeotropically with toluene under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was concentrated to a small volume and subjected to preparative TLC (CH_2Cl_2—MeOH, 19 : 1, recovery with acetone). This afforded the product (S)-VI (171 mg, 48.25%), R_F ca. 0.50 (CH_2Cl_2—MeOH, 9 : 1), $[\alpha]_D^{22}$ — 35° (c 3,95% EtOH). IR and ^{1}H-NMR spectra were identical with that of (R,S)-1-(2-hydroxy-3-tosyloxypropyl)thymine[1]. Preparative TLC afforded also (S)-1-(2,3-ditosyloxypropyl)thymine (48 mg, 9.4%) as the by-product, R_F ca. 0.72 (CH_2Cl_2—MeOH, 9 : 1). IR spectra and R_F values were identical with those of the corresponding (R,S)-compound[1].

(S)-1-(3-Azido-2-hydroxypropyl)thymine (S)-(VII)

A solution of (S)-1-(2-hydroxy-3-tosyloxypropyl)thymine [(S)-(VI)] (165 mg, 0.46 mmol) in DMF (5 ml) was treated with NaN_3 (90 mg, 1.38 mmol), heated at 90 °C for 2 h, and worked up as for (R,S)-azido compound VII. It yielded 70 mg of

the product (S)-VII (67.5%), R_F 0.47 (CH_2Cl_2—MeOH, 9 : 1), crystallized from CH_2Cl_2, $[\alpha]_D^{25}$ — 70° (c 3, 95% EtOH). IR spectra and R_F values were identical with those of (R,S)-azido compound VII.

(—)-(R)-1-(3-Amino-2-hydroxypropyl)thymine Hydrochloride (—)-(R)-(VIII)

a) To a solution of (—)-(S)-1-(3-azido-2-hydroxypropyl)-thymine (S)-(VII) (55 mg, 0.24 mmol) in MeOH (20 ml) Pd-black (20 g) was added. The suspension was stirred under H_2 (0.34 MPa) at room temperature for 3 h and worked up as for (R,S)-compound VIII (under a). This afforded the product (—)-(R)-VIII (37 mg, 65.4%), R_F ca. 0.26 (MeOH—NH_4OH, 96 : 4), m. p. 256—259 °C (from 90% MeOH), $[\alpha]_D^{24}$ — 24° (c 3, H_2O).

Anal. $C_8H_{14}ClN_3O_3$ (235.67) calc'd.: C 40.77; H 5.99; N 17.83%
found: C 40.93; H 6.13; N 17.91%

IR spectrum was identical with that of the (R,S)-compound VIII.

b) A solution of (5R)-2-(3β-acetoxyandrost-5-en-17-yl)-5-(thymin-1-ylmethyl)--oxazoline (R)-(XIII) (vide infra) (52.63 mg, 0.1 mmol) in 3 mol dm^{-3} HCl in 25% isopropanol (8 ml) was heated under reflux for 5 h and worked up as described for (R,S)-VIII (under b). It afforded the product (—)-(R)-VIII (14 mg, 60%), m. p. 257—259 °C (from 90% EtOH), $[\alpha]_D^{24.5}$ — 27° (c 1.5, H_2O), identical (IR spectrum) with that described under a).

(+)-(S)-1-(3-Amino-2-hydroxypropyl)thymine Hydrochloride (+)-(S)-(VIII)

A solution of (5S)-2-(3β-acetoxyandrost-5-en-17-yl)-5-(thymin-1-ylmethyl)oxazoline [(S)-(XIII)] (vide infra) (26.5 mg, 0.05 mmol) in 3 mol dm^{-3} HCl in 25% isopropanol (4 ml) under the conditions and work up as described for the enantiomer (R)-VIII afforded the product (+)-(S)-VIII (8 mg, 67%), on recrystallization from 90% EtOH, $[\alpha]_D^{25}$ + 27.8° (c 3, H_2O). The IR spectrum and chromatographic mobility were identical with those of the enantiomer (R)-VIII.

p-*Nitrophenyl 3β-acetoxy-*Δ^5*-etienate (XII)*

To a solution of 3β-acetoxy-Δ^5-etienic acid[12] (XI) (180 mg, 0.5 mmol) in ethyl-acetate (5 ml), *p*-nitrophenol (85 mg, 0.6 mmol) and DCC (103 mg, 0.5 mmol) were added. The suspension was stirred at room temperature for 16 h and then for 1 h after addition of CH_2Cl_2 (2 ml). The precipitate was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue crystallized from EtOH as the product XII (163 mg, 67.8%), m. p. 228—229 °C, R_F ca. 0.9 (from $CHCl_3$).

Anal. $C_{28}H_{35}NO_6$ (481.57) calc'd.: C 69.89; H 7.33; N 2.98%
found: C 70.12; H 7.21; N 3.19%

UV spectrum: λ_{max} 217inf. and 270 nm (log ε 3.89 and 3.98), λ_{min} 233 nm (log ε 3.41). IR spectrum: ν_{max} 3112, 3085, 2975, 2960, 2932, 2882, 2857, 2832, 1760, 1727, 1612, 1588, and 737 cm^{-1}. ^{1}H-NMR spectrum: 8.26 (2H, d, o-NO_2-ph; $J_{o,m}$ 9.3), 7.27 (2H, d, m-NO_2-ph; $J_{m,o}$ 9.3), 5.42—5.37 (1H, m, 6-H), 4.7—4.45 (1H, m, 3-H), 2.66 (1H, t, 17-H; $J_{17.16}$ 9.0), 2.38—2.29 (2H, m, 4-H_2), 2.03 (3H, s, Ac), 1.05 (3H, s, 19-Me), 0.83 (3H, s, 18-Me).

Diastereoisomeric Amides from the Acylation of (R,S)-2-Amino-methyl--2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (V) with p-*Nitrophenyl 3β-acetoxy-*Δ^5*-etienate (XII)*

To a solution of (R,S)-2-aminomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]--pyrimidin-7-one[3] (V) (210 mg, 1.14 mmol) in dry DMF (6 ml), *p*-nitrophenyl-etienate XII (604 mg, 1.25 mmol) was added. The mixture was heated at 90 °C for 3 h and then evaporated to dryness under reduced pressure. The residue was triturated with CH_2Cl_2. From the CH_2Cl_2 solution a crystalline product (27 mg) was isolated, R_F ca. 0.4 (MeOH) which remained to be identified. The CH_2Cl_2 solution was then partitioned with water and the organic layer dried, concentrated to a small volume, and subjected to preparative TLC (CH_2Cl_2-MeOH, 19 : 1), recovery with acetone).

Besides the starting material *p*-nitrophenyl etienate XII (193 mg), R_F ca. 0.9, two products with R_F ca. 0.28 and 0.34 were isolated. The product with R_F ca. 0.28 was identified as a mixture of (2R)- and (2S)-2-(3β-acetoxy-△⁵-etienamidomethyl)-2,3--dihydro-6-methyl-7H-oxazolo[3,2-a]pyrimidin-7-one (X) (298 mg, 50%). Fractional crystallization of the mixture from MeOH (15 ml) afforded diastereoisomer (2S)-X (54 mg, 18.2%) (based on the isolated (2R)- and (2S)-mixture), m. p. 195—197 °C, R_F ca. 0.72 (CH_2Cl_2—MeOH, 92.5 : 7.5 (A), MeOH—NH_4OH, 96 : 4 (B); A—B, 1 : 1), m. p. 197—199 °C (from MeOH), $[\alpha]_D^{23}$ — 49° (c 2, $CHCl_3$).

Anal. $C_{30}H_{41}N_3O_5$ (523.63) calc'd.: C 68.81; H 7.89; N 8.02%
found: C 69.14; H 8.22; N 8.15%

MS (*m/z*): 523.5 (M^+), 508.5 (M—CH_3), 463.5 (M—AcO), 448.5 (M—AcO, CH_3). UV spectrum: λ_{max}, 229 and 260 nm (log ε 3.84 and 3.92), λ_{min} 243 nm (log ε 3.78). IR spectrum: ν_{max} 3277br, 3047, 2972, 2959, 2914, 2897, 1731, 1670, 1641, 1622sh, 1552, and 1537 cm^{-1}. ^{1}H-NMR spectrum: 7.06 (1H, s, 5-H; $J_{5,Me-6}$ 1.0), 6.84 (1H, t, NHCO, J_{NH,CH_2} 5.9), 5.39—5.35 (1H, m, 6′-H), 5.17—5.07 (1H, m, 2-H), 4.7—4.45 (1H, m, 3′-H), 4.22—4.1 (2H, m, 2-CH_2), 3.91—3.56 (2H, m, 3-H_2), 2.35—2.28 (2H, m, 4′-H_2), 2.03 (3H, s, Ac), 1.92br (3H, s, 6-Me), 1.01 (3H, s, 19′-Me), 0.67 (3H, s, 18′-Me).

From the above obtained methanolic mother liquor, concentrated to ca. 10 ml volume, a mixture of (2R)- and (2S)-diastereoisomer X precipitated (130 mg, 43.8%) in a ratio 1 : 1 (evidenced by ^{1}H-NMR data), and separated by suction. Concentration of the thus obtained mother liquor, to ca. 1.5 ml volume, afforded (2R)-diastereoisomer (43 mg, 14.9%) as 90% pure product. It was purified by recrystallization from CH_2Cl_2-*n*-hexane, R_F ca. 0.79 (CH_2Cl_2—MeOH, 92.5 : 7.5 (A); MeOH—NH_4OH, 96 : 4 (B); A : B, 1 : 1) and then from acetone to give the product (2R)-X, m. p. 147—149 °C, $[\alpha]_D^{26}$ — 91.5° (c 2, $CHCl_3$).

Anal. $C_{30}H_{41}N_3O_5 \cdot H_2O$ (541.66) calc'd.: C 66.52; H 8.00; N 7.76%
found: C 66.29; H 8.11; N 7.73%

MS (*m/z*): 523.5 (M^+), 508.5 (M—CH_3), 463.5 (M—AcO), 448.5 (M—AcO, CH_3). UV spectrum: λ_{max} 228 and 262 nm (log ε 3.98 and 4.00), λ_{min} 243 nm (log ε 3.87). IR spectrum: ν_{max} 3450br, 3280br, 3065, 2970, 2950, 2907, 2875, 1732, 1667, 1643, 1610, 1553sh, and 1537 cm^{-1}. ^{1}H-NMR spectrum: 7.04 (1H, d, 5-H; $J_{5,Me-6}$ 1.0), 7.3—7.12 (1H, m, NHCO), 5.43—5.38 (1H, m, 6′-H), 5.23—5.06 (1H, m, 2-H), 4.7—4.45 (1H, m, 3′-H), 4.22—4.14 (2H, m, 2-CH_2), 4.13—3.99 (1H, m, 3-H_a), 3.63—3.46 (1H, m, 3-H_b), 2.64 (1H, t, 17′-H; $J_{17',16'}$ 8.3), 2.35—2.29 (2H, m, 4′-H_2), 2.03 (3H, s, Ac), 1.97 (3H, d, 6-Me; $J_{Me-6,5}$ 1.0), 0.98 (3H, s, 19′-Me), 0.57 (3H, s, 18′-Me).

(5R,5S)-2-(3β-Acetoxyandrost-5-en-17-yl)-5-(thymin-1-ylmethyl)--oxazoline (XIII)

The product XIII with R_F ca. 0.34, separated by the above described preparative TLC (66 mg, 11%), was triturated with acetone. The solid residue was recrystallized from CH_2Cl_2-*n*-hexane, m. p. 177—179 °C.

Anal. $C_{30}H_{41}N_3O_5$ (523.63) calc'd.: C 68.81; H 7.89; N 8.02%
found: C 68.87; H 7.94; N 7.92%

UV spectrum: λ_{max} 269 nm (log ε 4.02), λ_{min} 235 nm (log ε 3.67). IR spectrum: ν_{max} 3453br, 3187br, 3058br, 2970, 2947, 2908, 2853, 1730, 1701, 1685br, 1664sh, 1652, 1642, and 1632 cm^{-1}.

(5R)-2-(3β-Acetoxyandrost-5-en-17-yl)-5-(thymin-1-ylmethyl)--oxazoline (5R)-(XIII)

A solution of (2S)-2-etienamidomethyl-oxazolo[3,2-a]pyrimidin-7-one (2S)-X (105 mg, 0.2 mmol) in dry DMF (4 ml) was treated with *p*-nitrophenol (28 mg, 0.2 mmol) and stirred at 90 °C for 5 h and then at 100 °C for 2 h. The solvent was removed under reduced pressure and the residue subjected to preparative TLC (CH_2Cl_2—MeOH, 96 : 4; recovery with acetone). This afforded the product (5R)-

-(XIII) (84 mg, 80%), R_F ca. 0.36 (CH_2Cl_2—MeOH, 92.5 : 7.5), m. p. 164—166 °C (from Me_2CO), $[\alpha]_D^{26} - 103°$ (c 1, $CHCl_3$).

Anal. $C_{30}H_{41}N_3O_5$ (523.63) calc'd.: C 68.81; H 7.89; N 8.02%
found: C 68.69; H 7.75; N 8.05%

MS (*m/z*): 523.5 (M^+), 463 (M—AcO), 448.5 (M—AcO, CH_3). UV spectrum: λ_{max} 269 nm (log ε 3.98), λ_{min} 235 nm (log ε 3.59). IR spectrum: ν_{max} 3184br, 3024br, 2964sh, 2941, 2897sh, 2847, 1724sh, 1706sh, 1684, and 1519 cm^{-1}. ^{1}H-NMR spectrum: 8.93br (1H, s, NH), 7.06 (1H, d, 6-H; $J_{6,Me-5}$ 1.2), 5.41—5.36 (1H, m, 6'-H), 4.9—4.45 (2H, m, 5-H and 3'-H), 4.16 (1H, dxd, 5-CH_a; $J_{a,b}$ 14.6 and $J_{a,5}$ 2.9), 3.52 (1H, dxd, 5-CH_b; $J_{b,a}$ 14.6 and $J_{b,5}$ 8.5) 4.16—3.39 (2H, m, 4-H_2), 2.37—2.28 (2H, m, 4'-H_2), 2.04 (3H, s, Ac), 1.92 (3H, d, 5-Me; $J_{Me-5,6}$ 1.2), 1.03 (3H, s, 19'-Me), 0.72 (3H, s, 18'-Me).

(5S)-2-(3β-Acetoxyandrost-5-en-17-yl)-5-(thymin-1-ylmethyl)--oxazoline Hydrate (5S)-(XIII)

A solution of (2R)-2-etienamidomethyl-oxazolo [3,2-a] pyrimidin-7-one (2R)-X (65 mg, 0.124 mmol) in dry DMF (2.5 ml) was treated with *p*-nitrophenol (17 mg, 0.12 mmol) and stirred at 90 °C for 5 h and then at 100 °C for 2 h. The mixture was worked up as described for the diastereoisomer (5R)-XIII. It afforded the product (5S)-XIII (52 mg, 80%), R_F ca. 0.36, m. p. 165—167 °C (from acetone-ether), $\alpha]_D^{21} + 9°$ (c 3, $CHCl_3$). The sample recrystallized as the hydrate.

Anal. $C_{30}H_{41}N_3O_5 \cdot H_2O$ (541.66) calc'd.: C 66.52; H 8.00; N 7.76%
found: C 66.29; H 7.94; N 7.68%

MS (*m/z*): 523.5 (M^+), 463 (M—AcO), 448.5 (M—AcO, CH_3). UV spectrum: λ_{max} 269 nm (log ε 4.00), λ_{min} 235 nm (log ε 3.59). IR spectrum: ν_{max} 3171br, 3051br, 2961sh, 2939, 2871, 2851, 1723, 1698, 1681, and 1636sh cm^{-1}. ^{1}H-NMR spectrum: 8.99br (1H, s, NH), 7.05 (1H, d, 6-H; $J_{6,Me-5}$ 1.2) 5.41—5.36 (1H, m, 6'-H), 4.9—4.45 (2H, m, 5-H and 3'-H), 4.12 (1H, dxd, 5-CH_a; $J_{a,b}$ 14.6 and $J_{a,5}$ 2.9), 3.56 (1H, dxd, 5-CH_b; $J_{b,a}$ 14.6 and $J_{b,5}$ 8.5) 4.11—3.44 (2H, m, 4-H_2), 2.37—2.29 (2H, m, 4'-H_2), 2.04 (3H, s, Ac), 1.92 (3H, d, 5-Me; $J_{Me-5,6}$ 1.2), 1.02 (3H, s, 19'-Me), 0.68 (3H, s, 18'-Me).

(R,S)-2-(Benzamidomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]--pirimidin-7-one (XIV)

A solution of (2R)-2-etienamidomethyl-oxazolo [3,2-a] pyrimidin-7-one (2R)-X midin-7-one[3] (V) (90 mg, 0.05 mmol) in dry pyridine (4 ml) was treated with benzoic anhydride (141 mg, 0.825 mmol) and stirred at room temperature for 1 h. The solvent was removed azeotropically with benzene under reduced pressure. The residue was triturated with ether to give the product XIV (122 mg, 85%), R_F ca. 0.38 (CH_2Cl_2—MeOH, 9 : 1), m. p. 171—173 °C (from MeOH).

Anal. $C_{15}H_{15}N_3O_3$ (285.29) calc'd.: C 63.15; H 5.30; N 14.73%
found: C 63.28; H 5.22; N 14.91%

MS (*m/z*): 285.2 (M^+), 180 (M—Bz), 164 (M—Bz, Me). UV spectrum: λ_{max} 229 nm (log ε 3.97), λ_{infl} 261 nm (log ε 3.68), λ_{min} 215 nm (log ε 3.77). IR spectrum: ν_{max} 3234br, 3094, 3054, 2970, 2916, 1737, 1717, 1664, 1651, 1608, 1539sh, 1534, 780, and 704br cm^{-1}. ^{1}H-NMR spectrum (in DMSO-d_6): 8.86 (1H, t, NH; J_{NH,CH_2} 5.6), 7.87—7.77 (2H, m, ph-m), 7.62 (1H, d, 5-H; $J_{5,Me-6}$ 1.0), 7.52—7.44 (3H, m, ph-o, p), 5.23—5.00 (1H, m, 2-H), 4.34 (1H, dxd, 3-H_a; $J_{a,b}$ 10.2, $J_{a,2}$ 8.5), 4.02 (1H, dxd, 3-H_b; $J_{b,a}$ 10.2, $J_{b,2}$ 7.1), 3.69 (2H, dxd, C(2)—C—H_2; $J_{CH_2,NH}$ 5.6 $J_{CH_2,2}$ 5.6), 1.76 (3H, dxd, 6-Me; $J_{Me-6,5}$ 1.0).

(R,S)-2-Phenyl-5-(thymin-1-ylmethyl)oxazoline (XV)

To a solution of 2-benzamidomethyl-2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]--pyrimidin-7-one (XIV) (480 mg, 1.68 mmol) in dry DMF (23 ml) *p*-nitrophenol (234 mg, 1.68 mmol) was added and the mixture heated at 90 °C for 67 h. The mixture was evaporated to dryness under reduced pressure and the residue subjected to preparative TLC (CH_2Cl_2—MeOH, 94 : 6; recovery with acetone). Besides the star--

ting compound (25 mg), the product XV (391 mg, 81.5%) separated; it had R_F ca. 0.51 (CH_2Cl_2—MeOH, 9 : 1), m. p. 148—151 °C (from CH_2Cl_2).

Anal. $C_{15}H_{15}N_3O_3$ (285.29) calc'd.: C 63.15; H 5.30; N 14.73%
found: C 62.92; H 5.15; N 14.91%

UV spectrum: λ_{inlf} 220 nm (log ε 4.16), λ_{max} 252 nm (log ε 4.14), λ_{min} 233 nm (log ε 4.10). IR spectrum: ν_{max} 3595br, 3375br, 3160br, 3060, 3020br, 2975, 2935, 2835, 1695br, 1660br, 1650sh, 1577, 781, and 693 cm^{-1}. ^{1}H-NMR spectrum: 9.23br (1H, s, NH), 7.95—7.86 (2H, m, ph-m), 7.48—7.31 (3H, m, ph-o, p), 7.05 (1H, d, 6-H; $J_{6,Me-5}$ 1.0), 5.16—4.89 (1H, m, 5_{ox}-H), 4.27 (1H, dxd, 4_{ox}-H_a; $J_{a,b}$ 8.8, $J_{a,5_{ox}}$ 5.9), 4.10 (1H, dxd, 4_{ox}-H_b; $J_{b,a}$ 8.8, $J_{b,2'}$ 5.6), 3.81 (1H, dxd, 1′-H_a; $J_{a,b}$ 14.6, $J_{a,5_{ox}}$ 6.8), 3.65 (1H, dxd, 1′-H_b; $J_{b,a}$ 14.6, $J_{b,2'}$ 8.1), 1.85 (3H, d, 5-Me; $J_{Me-5,6}$ 1.0) (ox = oxazoline ring).

REFERENCES

1. V. Škarić, D. Erben, Z. Raza, and D. Škarić, *Croat. Chem. Acta* **52** (1979) 281.
2. V. Škarić and M. Jokić, *Croat. Chem. Acta.* **56** (1983) 125.
3. V. Škarić, Z. Raza, and D. Škarić, *J. Chem. Soc. Perkin I* (1982) 223.
4. E. De Clercq, J. Descamps, P. De Somer, and A. Holý, *Science* **200** (1978) 563.
5. E. De Clercq and A. Holý, *J. Med. Chem.* **22** (1979) 510.
6. A. Holý, *Pharmazie* **348** (1979) 290.
7. A. Holý, *Collect. Czech. Chem. Commun.* **40** (1975) 187.
8. P. Fischer, R. Kaul, S. Erhardt, and B. Hempel, *Tetrahedron Lett.* **41** (1975) 3521.
9. W. O. Foye, *Principles of Medical Chemistry,* Lea and Febinger — Philadelphia, Henry Kimpton Publishers — London.
10. G. S. Ghangas and T. P. Fondy, *Biochemistry* **10** (1971) 3204.
11. T. J. Katz and R. B. Woodward, *Tetrahedron* **5** (1959) 70.
12. C. Djerassi and J. Staunton, *J. Amer. Chem. Soc.* **83** (1961) 736.
13. D. M. Feigl and R. A. Mosher, *J. Org. Chem.* **33** (1968) 4242.
14. M. Bodansky and V. D. Vigneaud, *J. Amer. Chem. Soc.* **81** (1959) 5688.
15. H. Schwarz and K. Arezawa, *J. Amer. Chem. Soc.* **81** (1959) 5691.
16. R. J. Ferrier and P. M. Collins, *Monosacharide Chemistry,* Penguin Books, 1972.
17. G. E. McCasland and D. A. Smith, *J. Amer. Chem. Soc.* **72** (1950) 2190.
18. A. I. Mayers, G. Knaus, K. Kamata, and M. E. Ford, *J. Amer. Chem. Soc.* **98** (1976) 567.

POVZETEK

Sinteze in intramolekularne premestitve enantiomernih aminoalkoholov v vrsti alifatskih analogov timidinov

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Opisana je sinteza (-)-1-(3-amino-2-hidroksipropil)timin hidroklorida iz (-)-1-(3-azido-2-hidroksipropil)timina s katalitskim hidrogeniranjem. Po ločitvi (2R)- in (2S)-(3β-acetoksi-△^{5}-etienamidometil)-2,3-dihidro-6-metil-7H-oksazolo (3,2-a)pirimidin-7-ona s frakcionirano kristalizacijo in hidrolizi obeh stereoizomerov dobimo hidrokloride (+) in (—) aminoalkoholov. Oba omenjena diastereoizomera dobimo iz (R,S)-2-aminometil-2,3-dihidro-6-metil-7H-oksazolo(3,2-a)-pirimidin-7-ona in p-nitrofenil 3β-acetoksi-△^{5}-etienata po metodi aktiviranih estrov. Pretvorba omenjenih oksazolopirimidinov v ustrezne aminoalkohole poteka preko vmesnega oksazolina, kar spremlja inverzija konfiguracije na kiralnem C_2 centru. Čistoto diastereoizomernih produktov smo ugotovili s pomočjo ^{1}H NMR spektrov.