Intramolecular Cyclisation Reactions in Aliphatic Thymidine Analogues Series

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The intramolecular cyclisation of 1-(2-hydroxy-3-iodopropyl)thymine (2) by means of silver acetate afforded 2,3-dihydro-3-hydroxy-7-methyl-4*H*,8*H*-pyrimido[2,1-*b*][1,3]oxazin-8-one (3). On the other hand treatment of 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine (7) with sodium methoxide effected transformations yielding 2,3-dihydro-2-hydroxymethyl-6-methyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (8), *via* the intermediary 1-(2,3-epoxypropyl)thymine (6). The 3'-*O*-methylsulphonyl-2,2'- (16) rather than 2'-*O*-methylsulphonyl-2,3'-anhydro-(19) structure was formed when 1-(2,3-dimethylsulphonyloxypropyl)thymine (12) was treated with sodium methoxide in methanol. In addition the mesyl derivative (16) was converted into 2-azidomethyl- (20) and 2-aminomethyl- (21) 2,3-dihydro-6-methyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one.

THE structural and stereochemical features of the 2,3-dihydroxypropyl nucleoside analogues have been related to those of the naturally occurring nucleosides.[1,2] Thus, (*S*)-9-(2,3-dihydroxypropyl)adenine compared with adenosine showed similar affinity towards some ribonucleases.[3] (*S*)-1-(2,3-Dihydroxypropyl)thymine underwent epimerization to give its *R* form *via* a transient bicyclic 2,2'-anhydro-structure,[1] consistent with the 2,3'-anhydro-structure and stereochemical inversions in thymidine series.[4,5]

Bio-transformations of 1-allyl-3,5-diethyl-6-chlorouracil, possessing significant antiviral activities,[6,7] produced 6,8-diethyl-2-hydroxymethyl-tetrahydro-oxazolo[3,2-*c*]-pyrimidine-5,7-(4*H*,6*H*)-dione [6] *via* 1-(2,3-epoxypropyl)- and 1-(2,3-dihydroxypropyl)-derivatives as the intermediates.[8] It is interesting that (*S*)-9-(2,3-dihydroxypropyl)adenine itself could inhibit replication of a number of DNA and RNA viruses at concentrations at which cellular DNA and RNA syntheses were not affected.[9,10]

No precise information has yet been obtained with regard to the intramolecular cyclisation reactions in the aliphatic nucleoside analogues series. The bicyclic 2,2'-anhydro-compounds in monohydroxyalkyl pyrimidine series have been obtained previously from 1-(2-hydroxyethyl)thymine (uracil) and its 2-thio-analogues.[11,12] In evaluating the factors inducing these transformations we have found that the suitably activated derivatives of (*R*,*S*)-1-(2,3-dihydroxypropyl)thymine [13] (1) could afford a number of bicyclic products.

The intramolecular cyclisation of 1-(2-hydroxy-3-iodopropyl)thymine [14] (2) by means of silver acetate [15] in methanol seemed the most appropriate one for the synthesis of the hitherto unknown 2,3-dihydro-3-hydroxy-7-methyl-4*H*,8*H*-pyrimido[2,1-*b*][1,3]oxazin-8-one [2,3'-anhydro-1-(2,3-dihydroxypropyl)thymine], (3). The ^{1}H n.m.r. spectrum of the thus formed bicyclic product (3) revealed multiplets for the secondary hydroxy-group at τ 4.26—4.40 and for 2'- and 3'-H at τ 5.60—5.85. Pertinent to the assignment of 2'-H was the fact that in the spectrum of the 3-benzoyloxy-derivative (4) its signal was shifted downfield to τ 4.30—4.45.

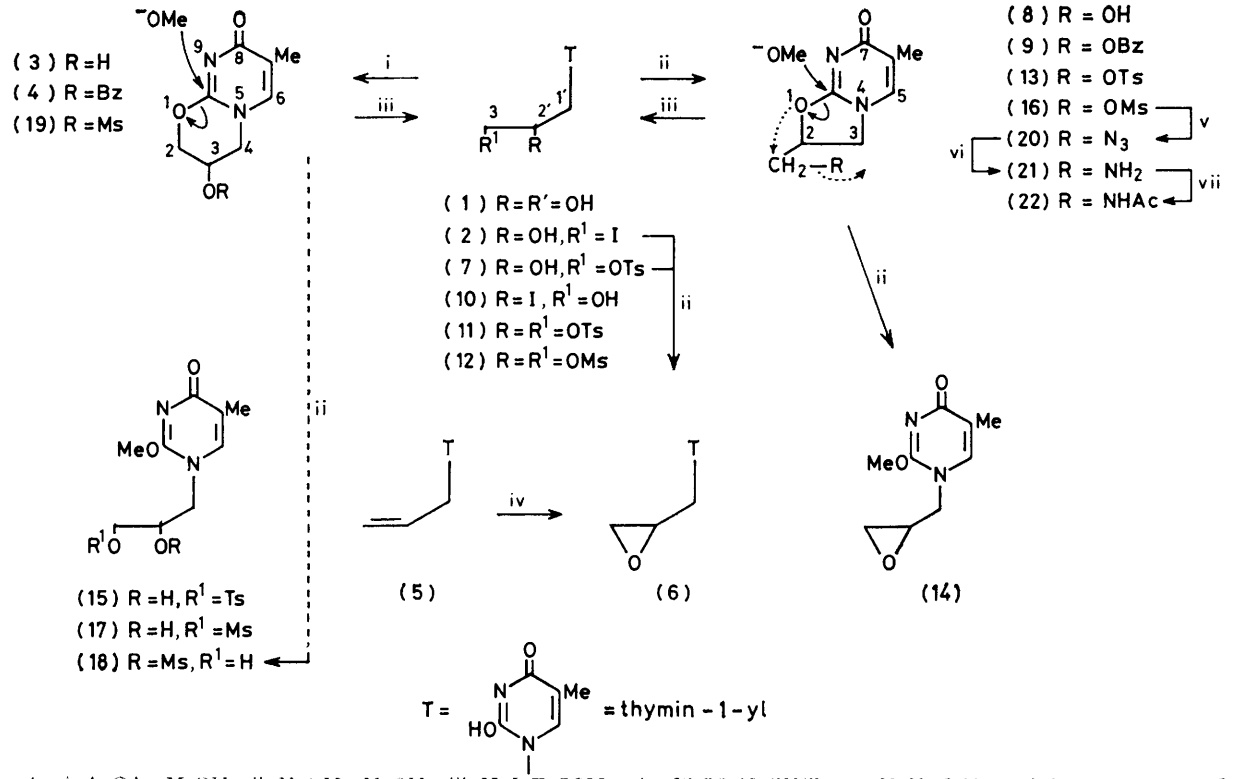
Together with the above reaction to give compound (3) concomitant intramolecular nucleophilic substitution in compound (2) gave rise to 1-(2,3-epoxypropyl)thymine (6) by C(2') alkoxide ion displacement of the neighbouring 3'-iodine. The oxiran (6) was also conveniently prepared in good yield by the action of perbenzoic acid on the allylthymine (5).[13]

The treatment of 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine (7) [13] with sodium methoxide in methanol gave rise to a transformation yielding 2,3-dihydro-2-hydroxymethyl-6-methyl-7*H*-oxazolo[3,2-*a*]-pyrimidin-7-one [2,2'-anhydro-1-(2,3-dihydroxypropyl)-thymine], (8) as the main product. This unexpected 2,2'-cyclisation may be explained by a two-step process, the first step of which facilitated a displacement of the 3'-*O*-tosyl group of the compound (7) by the neighbouring C(2') alkoxide ion participation and the oxiran (6) formation. We showed that the intermediary oxiran (6) could then be transformed to the 2,2'-anhydro-compound (7) by an independent reaction with sodium methoxide in methanol.

The 2,2'-anhydro-compound (8) showed in the ^{1}H n.m.r. spectrum the characteristic triplet centred at τ 4.73 for the primary hydroxy-group, and 3'-H resonances at 6.27—6.42. The 2,2'-anhydro-structure (8) was also characterized as the 3'-*O*-benzoyl derivative (9). The ^{1}H n.m.r. spectrum of the latter caused an expected downfield shift of the 3'-protons to τ 5.31—5.46.

The structures of the above described bicyclic 2,3'- (3) and 2,2'- (8) anhydro-compounds were also assigned on the basis of their reactions with sodium iodide in butan-2-one–acetic acid. These reactions effected the 2,3'- and 2,2'-ring cleavages and the isolation of the already described 3'-iodopropylthymine [14] (2) and 1-(3-hydroxy-2-iodopropyl)thymine (10), respectively. The structure of the latter was proved by the ^{1}H n.m.r. spectral data showing the triplet for the primary hydroxy-group at τ 4.60.

At this point it seemed desirable to evaluate the preferences for the formation of the above described five-membered 2,2'- (8) over six-membered 2,3'- (3) anhydro-structure. We therefore made a systematic search for the products of the intramolecular reactions of 1-(2,3-di-



Reagents: i, AgOAc–MeOH; ii, NaOMe–MeOH; iii, NaI–EtCOMe; iv, $PhCO_3H$–$CHCl_3$; v, NaN_3–DMF; vi, H_2–Pd black–MeOH; vii, $(Ac)_2O$–py

p-tolylsulphonyloxypropyl)thymine [13] (11) and the corresponding 2,3-dimesyloxy-derivative (12) using sodium methoxide in methanol as a condensing agent. Treatment of compound (11) furnished 2,3-dihydro-6-methyl-2-*p*-tolylsulphonyloxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (13) as the main product. It is interesting that besides this intramolecular cyclisation by nucleophilic attack of the C(2) enoxide ion at the C(2′) rather than at the C(3′) position, a concomitant ring opening of compound (13) proceeded to give 1-(2,3-epoxypropyl)-2-*O*-methylthymine (14). The appearance of the latter as a by-product can be explained by invoking a methoxide ion attack at C-2 of the bicyclic compound (13) and the formation of 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)-2-*O*-methylthymine (15) as an intermediate.

We have further extended our investigations of the intramolecular cyclisation reactions of (2,3-dimethylsulphonyloxypropyl)thymine (12). The preferred formation of the five-membered 2,2′-anhydro-structure was evidenced by the isolation of 2,3-dihydro-6-methyl-2-methylsulphonyloxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (16) in 50% yield and by the appearance of 1-(2,3-epoxypropyl)-2-*O*-methylthymine (14) (20%) as a by-product [formed *via* 1-(3-*O*-methylsulphonyl-2,3-dihydroxypropyl)-2-*O*-methylthymine (17) as the intermediate]. However, the isolation of 1-(2-*O*-methylsulphonyl-2,3-dihydroxypropyl)-2-*O*-methylthymine (18) in 16% yield evidenced an intramolecular cyclisation on the dimesyl derivative (12) into the thermodynamically less favoured and insufficiently stable six-membered 2,3′-anhydro-structure (19) as a minor intermediate. The primary hydroxy-group of compound (18) thus obtained gave rise to a multiplet at τ 4.69—4.92, while the 2-OMe and mesyl group exhibited singlets at τ 6.17 and 6.96, respectively.

An attempted iodation of the bicyclic mesyl derivative (16) by the action of sodium iodide in butan-2-one afforded 1-allylthymine (5).[13] It can be concluded from this result that the iodation was followed by displacement of the iodine and concomitant ring opening. On the other hand the mesyl derivative (16) was converted into 2-aminomethyl-2,3-dihydro-6-methyl-7*H*-oxazolo-[3,2-*a*]pyrimidin-7-one (21) *via* 2-azidomethyl-2,3-dihydro-6-methyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (20). The amino-compound (21), which should be suitable for exocyclic elongation in the form of *N*-aminoacyl and peptidyl derivatives, was characterized as the *N*-acetyl compound (22).

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. I.r. spectra were obtained for potassium bromide pellets or liquid films on a Perkin-Elmer 297 spectrophotometer. U.v. spectra were taken for solution in ethanol with a Perkin-Elmer 124 spectrophotometer. ^1H N.m.r. spectra were measured for solutions in dimethyl sulphoxide on a ' JEOL JNM-FX 100 ' FT-NNM spectrometer with tetra-

methylsilane as internal standard unless otherwise stated. The silica gel (Merck HF_{254}, type 60) for t.l.c. and for preparative t.l.c. was activated at 110 °C for 60 min. The products were developed in methylene chloride–methanol (9 : 1) unless otherwise stated and rendered visible by u.v. illumination.

2,3-*Dihydro*-3-*hydroxy*-7-*methyl*-4H,8H-*pyrimido*[2,1-b]-[1,3]*oxazin*-8-*one* (3).—A solution of 1-(2-hydroxy-3-iodopropyl)thymine [14] (2) (620 mg, 2 mmol) in anhydrous methanol (200 ml) was treated with silver acetate [15] (1.6 g, 9.5 mmol) and heated under reflux for 10 min. The precipitate was filtered off and the excess of silver ion removed from the filtrate by precipitation with hydrogen sulphide and filtration through a short Celite column. The filtrate thus obtained was concentrated to a volume from which the product was precipitated (208 mg, 57%), R_F *ca.* 0.07, m.p. 228—230 °C (from methanol) (Found: C, 52.6; H, 5.7; N, 15.4. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.55; N, 15.4%); $\lambda_{max.}$ 235 and 256 nm (log ε 3.98 and 3.92); $\lambda_{min.}$ 220 and 247 nm (log ε 3.83 and 3.90); $\nu_{max.}$ 3 202br, 1 671br, 1 611br, 1 571, 1 546infl., and 1 516br cm^{-1}; τ 2.63 (1 H, d, 6-H; $J_{6,Me}$ 1.2 Hz), 4.26—4.40 (1 H, m, OH), 5.60—5.85 (1 H and 2 H, m, 2-H′ and 3′-H_2), 5.95—6.05 (1 H, m, 1′-H_a), 6.11—6.25 (1 H, m, 1′-H_b), and 8.22 (3 H, d, Me).

The methanolic mother-liquor was evaporated to dryness and subjected to preparative t.l.c. (three developments, recovery with acetone) which on re-chromatography afforded a product, 60 mg (16.5%), R_F *ca.* 0.61 (CH_2Cl_2–MeOH, 19 : 1), m.p. 118—122 °C (from acetone–ether) identified as 1-(2,3-epoxypropyl)thymine (5), identical (mixed m.p., i.r., and ^1H n.m.r. spectra) with that obtained from allylthymine.

3-*Benzoyloxy*-2,3-*dihydro*-7-*methyl*-4H,8H-*pyrimido*-[2,1-b][1,3]*oxazin*-8-*one* (4).—A solution of 2,3′-anhydro-1-(2,3-dihydroxypropyl)thymine (3) (109 mg, 0.6 mmol) in anhydrous pyridine (15 ml) and benzoic anhydride (226 mg, 1 mmol) was heated under reflux for 3 h after which the solvent was azeotropically removed under reduced pressure by means of toluene. The residue was then purified by preparative t.l.c. (CH_2Cl_2–MeOH, 19 : 1; two developments, recovery with acetone); yield 90 mg (52.4%), R_F *ca.* 0.4, m.p. 235 °C (decomp.) (from methanol) (Found: C, 62.75; H, 4.7; N, 9.8. $C_{15}H_{14}N_2O_4$ requires C, 62.95; H, 4.95; N, 9.8%); $\lambda_{max.}$ 233 and 257infl. nm (log ε 4.24 and 3.81); $\lambda_{min.}$ 213.5 nm (log ε 3.86); $\nu_{max.}$ 3 416br, 1 721, 1 700, 1 659, 1 644, 1 613br, 1 601, 1 584, 1 567, 1 547, 747, 730, 712, and 687 cm^{-1}; τ 1.96—2.56 (5 H, m, ArH), 3.61 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), 4.30—4.45 (1 H, m, 2′-H), 5.31—5.50 (2 H, m, 3′-H), 5.63—6.11 (2 H, m, 1′-H), and 8.22 (3 H, d, $J_{Me,6}$ 1.2 Hz, Me).

1-(2,3-*Epoxypropyl*)*thymine* (6).—To a cooled solution of perbenzoic acid (250 mg, 1.8 mmol) in chloroform 1-allylthymine [13] (5) (166.2 mg, 1 mmol) was added and stirred at 0 °C for 3 h. The solvent was then removed under reduced pressure and the residue subjected to preparative t.l.c. It separated the starting 1-allylthymine (60 mg) and 82 mg of the product (82%, based on the transformed 1-allylthymine), R_F *ca.* 0.61 (CH_2Cl_2–MeOH, 19 : 1), m.p. 120—122 °C (from acetone–ether) (Found: C, 52.95; H, 5.85; N, 15.2. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.55; N, 15.4%); $\lambda_{max.}$ 210 and 269 nm (log ε 3.52 and 3.68); $\lambda_{min.}$ 234 nm (log ε 2.74); $\nu_{max.}$ 3 422br, 1 710, 1 686br, and 1 646 cm^{-1}; τ ($CDCl_3$) 0.31br (1 H, s, NH), 2.95 (1 H, d, $J_{6,Me}$ 1.0 Hz, 6-H), 5.63 (1 H, q, $J_{a,b}$ 14.0 Hz and $J_{1'a,2'}$, 1.5 Hz, 1′-H_a), 6.51 (1 H, q, $J_{b,a}$ 14.0 Hz and $J_{1'b,2'}$ 6.0 Hz 1′-H_b), 6.63—6.89 (1 H, m, 2′-H), 7.15 (1 H, q, $J_{a,b}$ 4.4 Hz and $J_{3'a'2'}$, 4.0 Hz, 3′-H_a), 7.42 (1 H, q, $J_{b,a}$ 4.4 Hz and $J_{3'b,2'}$ 2.4 Hz, 3′-H_b), and 8.11 (3 H, d, $J_{Me,6}$ 1.0 Hz, 5-Me).

1-(2-*Hydroxy*-3-*iodopropyl*)*thymine* (2).—Into a suspension of 2,3′-anhydro-1-(2,3-dihydroxypropyl)thymine (3) (9 mg, 0.05 mmol) in butan-2-one (0.5 ml) sodium iodide (7.5 mg, 0.05 mmol) and 3 drops of glacial acetic acid were added. The mixture was heated under reflux for 2 h. The solvent was removed under reduced pressure and the product purified by preparative t.l.c.; it had m.p. 174—176 °C (14 mg, 90%), identical (mixed m.p. and i.r. and ^1H n.m.r. spectra) with that obtained from 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine (7).[12]

2,3-*Dihydro*-2-*hydroxymethyl*-6-*methyl*-7H-*oxazolo*[3,2-a]-*pyrimidin*-7-*one* (8).—A suspension of 1-(3-*O*-*p*-tolylsulphonyl-2,3-dihydroxypropyl)thymine [13] (7) (1.069 g, 3 mmol) in anhydrous methanol (60 ml) was treated with methanolic 0.5 mol dm^{-3} methoxide (6 ml, 3 mmol); the mixture was stirred at room temperature for 30 h and then concentrated to 5 ml. The crystalline product was filtered off (220 mg), additional quantities (134 mg) being obtained from the filtrate after it had been evaporated to dryness and purified by preparative t.l.c. (four developments, recovery with methanol). The overall yield was 354 mg (64.8%), m.p. 202—205 °C (from methanol–ether) (Found: C, 52.9; H, 5.85; N, 15.3. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.55; N, 15.4%); $\lambda_{max.}$ 230 and 261 nm (log ε 3.77 and 3.84); $\lambda_{min.}$ 217 and 242 nm (log ε 3.67 and 3.70); $\nu_{max.}$ 3 181br, 1 669br, 1 645infl., 1 603, 1 577, 1 546, and 1 540 cm^{-1}; τ 2.39 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), 4.73 (1 H, t, $J_{OH.3'}$, 5.6 Hz, 3′-OH), 4.70—5.10 (1 H, m, 2′-H), 5.75 (1 H, q, $J_{1'a,b}$ 9.8 Hz and $J_{1'a,2'}$ 9.4 Hz, 1′-H_a), 6.01 (1 H, q, $J_{1'a,b}$ 9.8 Hz and $J_{1'b,2'}$ 6.6 Hz, 1′-H_b), 6.27—6.42 (2 H, m, 3′-H_2), and 8.22 (3 H, d, $J_{Me,6}$ 1.2 Hz, Me).

2-*Benzoyloxymethyl*-2,3-*dihydro*-6-*methyl*-7H-*oxazolo*-[3,2-a]*pyrimidin*-7-*one* 9).—To a solution of 2,2′-anhydro-1-(2,3-dihydroxypropyl)thymine (8) (75.9 mg, 0.416 mmol) in anhydrous pyridine (15 ml) benzoic anhydride (162.9 mg, 0.72 mmol) was added and heated under reflux for 2.5 h. The solvent was azeotropically removed under reduced pressure by several evaporations in the presence of toluene. The product was purified by preparative t.l.c. (CH_2Cl_2–MeOH, 19 : 1; two developments, recovery with acetone) (37 mg, 31.3%), R_F *ca.* 0.34, m.p. 211—214 °C (from methanol) (Found: C, 62.85; H, 5.2; N, 10.0. $C_{15}H_{14}N_2O_4$ requires C, 62.95; H, 4.95; N, 9.80%); $\lambda_{max.}$ 231 and 260 nm (log ε 4.15 and 3.81); $\lambda_{min.}$ 213 and 250 nm (log ε 3.78 and 3.79); $\nu_{max.}$ 3 416br, 1 711, 1 665br, 1 615br, 1 603, 1 584, 1 551br, 735, 711, and 690; τ 2.06—2.53 (5 H, m, ArH), 2.33 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), 4.45—4.85 (1 H, m, 2′-H), 5.31—5.46 (2 H, m, 3′-H_2), 5.46—5.89 (2 H, m, 1′-H_2), and 8.21 (3 H, d, $J_{Me,6}$ 1.2 Hz, Me).

1-(3-*Hydroxy*-2-*iodopropyl*)*thymine* (10).—A suspension of 2,2′-anhydro-1-(2,3-dihydroxypropyl)thymine (8) (91 mg, 0.5 mmol) in butan-2-one (10 ml) was treated with sodium iodide (100 mg, 0.66 mmol) and glacial acetic acid (0.2 ml) and worked-up as described for the ring opening of compound (3). Acetone recovered the product (87 mg, 56%) from chromatographic plates, R_F *ca.* 0.58, and it was purified by trituration with methylene chloride; it had m.p. 155—157 °C (from acetone–ether) (Found: I, 40.55; N, 9.25. $C_8H_{11}IN_2O_3$ requires I, 40.9; N, 9.05%), $\lambda_{max.}$ 269 nm (log ε 4.04); $\nu_{max.}$ 3432, 1 687, 1 667br, 1 645infl., and 1 595 cm^{-1}; τ −1.32br (1 H, s, NH), 2.51 (1 H, d, $J_{6,Me}$ *ca.* 1.0 Hz, 6-H), 4.6 (1 H, t, $J_{OH,3'}$ *ca.* 5.0 Hz, 3′-OH),

5.47—5.77 (1 H, m, 2'-H), 5.98—6.05 (2 H, m, 3'-H_2), 6.26—6.41 (2 H, m, 1'-H_2), 8.25 (3 H, d, $J_{Me,6}$ *ca.* 1.0 Hz, Me).

1-(2,3-*Dimethylsulphonyloxypropyl*)*thymine* (12).—To a solution of 1-(2,3-dihydroxypropyl)thymine [13] (1) (500 mg, 2.5 mmol) in pyridine (7.5 ml), cooled at 8—10 °C, methanesulphonyl chloride (0.43 ml, 5.7 mmol) was added; the mixture was then set aside for 16 h. Evaporation of the mixture to dryness left a residue which on trituration with methanol afforded a crystalline product (815 mg, 91.5%), R_F *ca.* 0.53, m.p. 194—195 °C (from dioxan–n-hexane) (Found: C, 33.6; H, 4.55; N, 7.6. $C_{10}H_{16}N_2O_8S_2$ requires C, 33.7; H, 4.5; N, 7.85%); $\lambda_{max.}$ 260 nm (log ε 4.06); $\lambda_{min.}$ 234 nm (log ε 3.37); $\nu_{max.}$ 3 460br, 1 704br, 1 669, and 1 654infl. cm^{-1}; τ −1.19br (1 H, s, NH), 2.64 (1 H, d, $J_{6,Me}$ *ca.* 1.0 Hz, 6-H), 4.82—5.10 (1 H, m, 2'-H), 5.52—5.69 (2 H, m, 3'-H_2), 5.89—6.20 (2 H, m, 1'-H_2), 6.76 and 6.83 (each 3 H, 2s, 2Me-Ms), and 8.28 (3 H, d, $J_{Me,6}$ *ca.* 1.0 Hz, 5-Me).

2,3-*Dihydro*-6-*methyl*-2-O-p-*tolylsulphonyloxymethyl*-7H-*oxazolo*[3,2-a]*pyrimidin*-7-*one* (13).—To a suspension of 1-(2,3-di-*p*-tolylsulphonyloxypropyl)thymine [13] (11) (153 mg, 0.3 mmol) in anhydrous methanol (30 ml) methanolic 0.5 mol dm^{-3} sodium methoxide (0.6 ml, 0.3 mmol) was added; the mixture was stirred at room temperature for 20 h and then evaporated to dryness. The residue was triturated with acetone and the precipitate filtered off. The filtrate was evaporated to leave a residue which was chromatographed on preparative plates (CH_2Cl_2–MeOH, 19 : 1; three developments). Besides starting material (most-mobile fraction; 45 mg) the product, R_F *ca.* 0.31, was separated in 35% (25 mg) yield [based on the transformed ditosyl derivative (11)], m.p. 178—180 °C (from methanol) (Found: C, 53.65; H, 4.8; N, 8.45. $C_{15}H_{16}N_2O_5S$ requires C, 53.55; H, 4.8; N, 8.35%); $\lambda_{max.}$ 228 and 260 nm (log ε 4.27 and 3.93); $\lambda_{min.}$ 212 and 244 nm (log ε 4.06 and 3.87); $\nu_{max.}$ 3 440br, 1 666, 1 622br, 1 596, 1 560, 1 551, 760, 731, and 691 cm^{-1}; τ 2.16—2.55 (4 H, m, ArH), 2.39 (1 H, d, $J_{6,Me}$ *ca.* 1.2 Hz, 6-H), 4.55—5.05 (1 H, m, 2'-H), 5.60—5.64 (2 H, m, 3'-H), 5.71 (1 H, q, $J_{a,b}$ 10.3 Hz and $J_{1'a,2'}$ 9.8 Hz, 1'-H_a), 6.10 (1 H, q, $J_{b,a}$ 10.3 Hz and $J_{1'b,2'}$, 6.8 Hz, 1'-H_b), 7.57 (3 H, s, Ts-Me), and 8.23 (3 H, d, $J_{Me,6}$ 1.2 Hz, 5-Me).

The preparative t.l.c. afforded a fraction at R_F *ca.* 0.53, identified as 1-(2,3-epoxypropyl)-2-*O*-methylthymine (14) (65 mg, 16.5%), m.p. 110—113 °C (from methylene chloride–n-hexane) (Found: C, 54.9; H, 6.45; N, 14.05. $C_9H_{12}N_2O_3$ requires C, 55.1; H, 6.15; N, 14.30%); $\lambda_{max.}$ 232 and 255 nm (log ε 3.96 and 4.02); $\lambda_{min.}$ 214 and 239 nm (log ε 3.74 and 3.95); $\nu_{max.}$ 3 450br, 1 667, 1 626, 1 572, and 1 530 cm^{-1}; τ ($CDCl_3$) 2.95 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), 5.72 (1 H, q, $J_{a,b}$ 14.6 Hz and $J_{1'a,2'}$, 2.8 Hz, 1'-H_a), 5.96 (3 H, s, OMe), 6.42 (1 H, q, $J_{b.a}$ 14.6 Hz and $J_{1'b,2}$, 6.3 Hz, 1'-H_b), 6.66—6.90 (1 H, m, 2'-H), 7.12 (1 H, *q*, $J_{a,b}$ 4.4 Hz and $J_{3'a,2'}$, 4.0 Hz, 3'-H_b), 7.44 (1 H, q, $J_{b,a}$ 4.4 Hz and $J_{3'b,2'}$, 2.4 Hz, 3'-H_b), and 8.04 (3 H, d, $J_{Me,6}$ 1.2 Hz, 5-Me).

2,3-*Dihydro*-6-*methyl*-2-*methylsulphonyloxymethyloxazolo*-7H-[3,2-a]*pyrimidin*-7-*one* (16).—(*a*) Into a suspension of 1-(2,3-dimethylsulphonyloxypropyl)thymine (12) (178.2 mg, 0.5 mmol) in anhydrous methanol (125 ml), heated under reflux, methanolic 0.1 mol dm^{-3} sodium methoxide (4.72 ml, 0.5 mmol) was added. The solution was then stirred at room temperature for 2 h and finally evaporated to dryness. The residue was triturated with methylene chloride, filtered off, and then washed with water; yield 65 mg (50%), R_F *ca.* 0.22, m.p. 192—193 °C (from methanol–ether–n-hexane) (Found: C, 41.65; H, 4.7; N, 10.95. $C_9H_{12}N_2O_5S$ requires C, 41.55; H, 4.65; N, 10.75%); $\lambda_{max.}$ 230 and 259 nm (log ε 3.51 and 3.57); $\lambda_{min.}$ 241 (log ε 3.47); $\nu_{max.}$ 3 441br, 1 670, 1 614br, 1 556, and 1 552 cm^{-1}; τ 2.36 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), and 4.50—5.00 (1 H, m, 2'-H), 5.44—5.49 (2 H, m, 3'-H_2), 5.64 (1 H, q, $J_{a,b}$ 10.0 Hz and $J_{1'a,2'}$, 9.5 Hz, 1'-H_a), 6.01 (1 H, q, $J_{b,a}$ 10.0 Hz and $J_{1'b.2'}$, 6.9 Hz, 1'-H_b), 6.75 (3 H, s, Ms-Me), and 8.21 (3 H, d, $J_{Me.6}$ 1.2 Hz, 5-Me).

The methylene chloride solution from the above trituration was evaporated to dryness and subjected to preparative t.l.c. The fraction, R_F *ca.* 0.53, m.p. 110—112 °C, was identified as 1-(2,3-epoxypropyl)-2-*O*-methylthymine (14) (20 mg, 20%) identical (i.r. and ^1H n.m.r. spectra and m.p.) with that obtained from the di-tosyl derivative (11). The fraction, R_F 0.33, was identified as 1-(2-*O*-methylsulphonyl-2,3-dihydroxypropyl)-2-*O*-methylthymine (18) (24 mg, 16.5%), m.p. 100—102 °C (from methylene chloride–n-hexane) (Found: C, 40.55; H, 5.8; N, 9.3. $C_{10}H_{16}N_2O_6S$ requires C, 41.05; H, 5.55; N, 9.6%); $\lambda_{max.}$ 232.5 and 254 nm (log ε 4.10 and 4.19); $\lambda_{min.}$ 237.5 nm (log ε 4.10); $\nu_{max.}$ 3 458, 3 392, 1 763br, 1 570, and 1 528br cm^{-1}; τ 2.67 (1 H, d, $J_{6,Me}$ *ca.* 1.0 Hz, 6-H), 4.68—4.92 (1 H, m, 3'-OH), 5.14—5.55 (1 H, m, 2'-H), 5.98—6.58 (4 H, m, 3'-H_2 and 1'-H_2), 6.17 (3 H, s, 2-OCH_3), 6.96 (3 H, s, Ms-Me), 8.27 (3 H, d, $J_{Me,6}$ *ca.* 1.0 Hz, 5-Me).

(*b*) To a cooled solution of 2,2'-anhydro-1-(2,3-dihydroxypropyl)thymine (8) (55 mg, 0.3 mmol) in pyridine (10 ml) methanesulphonyl chloride (0.07 ml, 0.9 mmol) was added and the mixture then set aside for 7 days. After this time the solvent was removed under reduced pressure and the residue separated by preparative t.l.c. (CH_2Cl_2–MeOH, 94 : 6; 4 developments, recovery with methanol). Besides the starting material (20 mg) the desired product was obtained in 58% (29 mg) yield [based on transformed anhydro-compound (8)], m.p. 192—193 °C (from methanol–ether–n-hexane), identical (mixed m.p. and i.r. and ^1H n.m.r. spectra) with that obtained under (*a*).

Treatment of 2,3-*Dihydro*-2-*methylsulphonyloxymethyl*-7H-*oxazolo*[3,2-a]*pyrimidin*-7-*one* (16) *with Sodium Iodide*.—A solution of 2,2'-anhydro-1-(3-*O*-methylsulphonyl-2,3-dihydroxypropyl)thymine (16) (104 mg, 0.4 mmol) in butan-2-one (18 ml) was treated with sodium iodide (300 mg, 2 mmol) and then heated under reflux for 2 h. The solvent was removed and the residue partitioned between chloroform and a dilute solution of sodium thiosulphate. The organic layer was washed with water, dried, and separated by preparative t.l.c. It afforded a product, R_F *ca.* 0.47 (CH_2Cl_2–MeOH, 19 : 1; two developments, recovery with chloroform), m.p. 111—112 °C, identified as 1-allylthymine (5) (50 mg, 75%), identical (mixed m.p. and i.r. and ^1H n.m.r. spectra) with that obtained by allylation of thymine.[13]

2-*Azidomethyl*-2,3-*dihydro*-6-*methyl*-7H-*oxazolo*[3,2-a]-*pyrimidin*-7-*one* (20).—A suspension of 2,2'-anhydro-1-(3-*O*-mesyl-2,3-dihydroxypropyl)thymine (16) (390 mg, 1.5 mmol) and sodium azide (292 mg, 4.5 mmol) in anhydrous DMF (15 ml) was heated at 90 °C for 1 h according to the method of Sasaki *et al.*[16] The precipitate was filtered off and the filtrate evaporated to dryness. The residue was triturated with chloroform and the product crystallized from methanol (117 mg, 37.6%). An additional quantity of the product separated from the chloroform solution (105 mg, 33.8%) and this was purified by preparative t.l.c. (CH_2Cl_2–MeOH, 93 : 7; two developments); overall yield 222 mg, (71.4%), R_F *ca.* 0.32, m.p. >300 °C (from methanol)

(Found: C, 46.25; H, 4.65; N, 33.9. $C_8H_9N_5O_2$ requires C, 46.35; H, 4.4; N, 33.8%); $\lambda_{max.}$ 231 and 261 nm (log ε 3.86 and 3.93); $\lambda_{min.}$ 242 nm (log ε 3.81); $\nu_{max.}$ 3 437br, 2 143, 2 097, 1 664, 1 611, 1 553, and 1 504 cm^{-1}; τ 2.36 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), 4.77—4.93 (1 H, m, 2′-H), 5.69 (1 H, a, $J_{a,b}$ 10.3 Hz and $J_{1'a,2'}$ 9.0 Hz, 1′-H_a), 6.06 (1 H, q, $J_{b,a}$ 10.3 Hz and $J_{1'b,2'}$ 6.6 Hz, 1′-H_b), 6.18—6.24 (2 H, m, 3′-H_2), 8.21 (3 H, s, $J_{Me,6}$ 1.2 Hz, Me).

2-*Aminomethyl*-2,3-*dihydro*-6-*methyl*-7H-*oxazolo*[3,2-a]-*pyrimidin*-7-*one* (21).—A solution of 2,2′-anhydro-1-(2-hydroxy-3-azidopropyl)thymine (20) (150 mg, 0.67 mmol) in methanol (40 ml) containing Pd-black (70 mg) was stirred in atmosphere of hydrogen (0.34 MPa) for 3 h. The catalyst was then filtered off and the filtrate evaporated to give a hygroscopic oil (110 mg), showing very low chromatographic mobility; τ [$(CD_3)_2SO$] 2.39 (1 H, d, $J_{6,Me}$ 1.2 Hz, 6-H), 4.98—5.23 (1 H, m, 2′-H), 5.77 (1 H, q, $J_{a,b}$ 9.5 Hz and $J_{1'a,2'}$, 9.0 Hz, 1′-H_a), 6.0 (1 H, q, $J_{b,a}$ 9.5 Hz and $J_{1'b,2'}$ 6.8 Hz, 1′-H_b), 6.65br (2 H, s, exchanging in D_2O,NH_2), 7.11—7.17 (2 H, m, 3′-H_2), 8.23 (3 H, d, $J_{Me,6}$ 1.2 Hz, Me).

2-*Acetamidomethyl*-2,3-*dihydro*-6-*methyl*-7H-*oxazolo*-[3,2-a]*pyrimidin*-7-*one* (22).—A solution of 2,2′-anhydro-1-(2-hydroxy-3-aminopropyl)thymine (21) (90 mg, 0.5 mmol) in anhydrous pyridine (4 ml) and acetic anhydride (0.7 ml, 7.4 mmol) was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue separated by preparative t.l.c. (two developments, recovery with methanol) giving the product (74 mg, 66.4%), R_F *ca.* 0.13, m.p. 142—143 °C (from methanol–ether) (Found: C, 53.6; H, 5.8; N, 19.1. $C_{10}H_{13}N_3O_3$ requires C, 53.8; H, 5.85; N, 18.8%); $\lambda_{max.}$ 231 and 260 nm (log ε 3.87 and 3.96); $\lambda_{min.}$ 242 nm (log ε 3.83); $\nu_{max.}$ 3 280, 3 220, 1 687, 1 661, 1 640, 1 617, 1 613, 1 560, and 1 551 cm^{-1}; τ 1.70 (1 H, t, $J_{NH,3'}$, 5.37, exchanging in D_2O, 3′-NH), 2.98 (1 H, d $J_{6,Me}$ 1.2 Hz, 6-H), 4.88—5.13 (1 H m, 2′-H), 5.73 (1 H, q, $J_{a,b}$ 9.8 Hz and $J_{1'a,2'}$, 9.0 Hz, 1′-H_a), 6.11 (1 H, q, $J_{b,a}$ 9.8 Hz and $J_{1'b,2'}$, 7.3 Hz, 1′-H_b), 6.53 (2 H, t, $J_{3',NH\ and\ 3',2'}$ 5.4 Hz, 3′-H_2), 8.17 (3 H, s, Ac), 8.22 (3 H, d, $J_{Me,6}$ 1.2 Hz, 5-Me).

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