Synthesis and Physico-chemical Properties of Dioxolane Nucleoside Analogues

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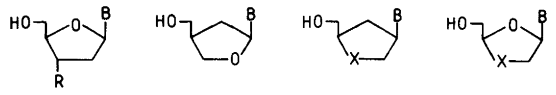
Four novel nucleoside analogues, *viz.* the *cis* and *trans* isomers of 4-hydroxymethyl-2-(uracil-1-ylmethyl)-1,3-dioxolane and 2-(adenin-9-ylmethyl)-4-hydroxymethyl-1,3-dioxolane, have been prepared. Alkylation of the sodium salts of uracil and adenine with 4-benzoyloxymethyl-2-bromomethyl-1,3-dioxolane, separation of the resulting *cis* and *trans* isomers by adsorption and reversed-phase chromatography, and deprotection with methanolic ammonia yielded the desired analogues of 2′,3′-dideoxyribonucleosides. The structures of the products were verified by NMR spectroscopy, and the kinetics of their acid-catalyzed hydrolysis were studied.

Nucleoside analogues are currently the most potent agents active against HIV. However, the drugs approved for clinical use, *viz.* 3′-azido-3′-deoxythymidine (**1**) and 2′,3′-dideoxyinosine (**2**),[1,2] still suffer from several disadvantages, such as toxicity, the appearance of resistant virus strains,[3] and hydrolytic instability of the *N*-glycosidic bond.[4,5] Recent observations have suggested that some alternative modifications of the pentofuranosyl moiety of nucleosides are compatible with anti-HIV activity. For example, several nucleobase derivatives of tetrahydrofuran (**3**,**4**),[6–8] tetrahydrothiophene (**5**),[9] 1,3-dioxolane (**6**),[10–12] and 1,3-oxothiolane (**7**)[12] have recently been prepared, and some of them, e.g. **7**, have been shown to inhibit HIV appreciably. As well as the *cis* isomers (nucleobase relative to the hydroxymethyl group), mimicking the structure of nucleosides, the *trans* compounds also exhibit antiviral activity.[13] Accordingly, preparation of novel nucleoside analogues related to **3**–**7** appeared worthwhile. We now report on the synthesis and physico-chemical properties of the *cis* and *trans* isomers of 4-hydroxymethyl-2-(uracil-1-ylmethyl)-1,3-dioxolane (**13**,**14**) and 2-(adenin-9-ylmethyl)-4-hydroxymethyl-1,3-dioxolane (**15**,**16**).

Results and discussion

Synthetic procedure. The approach depicted in Scheme 1 was used to obtain the desired analogues, **13**–**16**, of 2′,3′-dideoxyribonucleosides. Acid-catalyzed transacetalization of bromoacetaldehyde diethylacetal with 1-*O*-benzoylglycerol,[14] with concomitant removal of ethanol by continuous distillation, gave racemic 4-benzoyloxymethyl-2-bromomethyl-1,3-dioxolane (**8**) in a 79 % yield, the ratio of the *cis* and *trans* isomers being 3:2 according to ^{1}H NMR spectroscopy. Alkylation of the sodium salt of uracil with **8** gave N^1-alkylated and N^1,N^3-bis-alkylated bases as main products.[15] With the sodium salt of adenine the alkylation took place at N^3 and N^9.[16] Separation of the regio isomers on silica gel yielded diastereomeric mixtures of **9**/**10** (23 %) and **11**/**12** (44 %). The mobility of the *cis* and *trans* isomers was very similar on silica gel, but they could be easily separated by reversed-phase chromatography. On a Bondesil C18 column (100 g), good separation was achieved on a gram scale, using a mixture of water and acetonitrile (3:1, v/v) as the eluant. Debenzoylation in methanolic ammonia gave the nucleoside analogues, **13**–**16**.

Spectroscopic characterization. The structure, including configuration of the compounds prepared, was verified with the aid of ^{1}H NMR spectroscopy. Moreover, ^{13}C NMR spectra of compounds **9** and **10** were recorded. Owing to the proton diastereotopy of the three different methylene groups [C(2′)H_2, C(4′)H_2, C(5)H_2], the ^{1}H NMR spectra of compounds **9**–**16** are rather complicated (Tables 1 and 2). All these groups have unequal geminal coupling constants. The C(5)H_2 protons exhibit a typical value of $J_{5a,5b} = -8.5$,[17] and may hence be assigned.



1 R = N_3, B = Thy
2 R = H, B = Hyp
3
4 X = O **6** X = O, B = Thy, Cyt
5 X = S **7** X = S, B = Cyt

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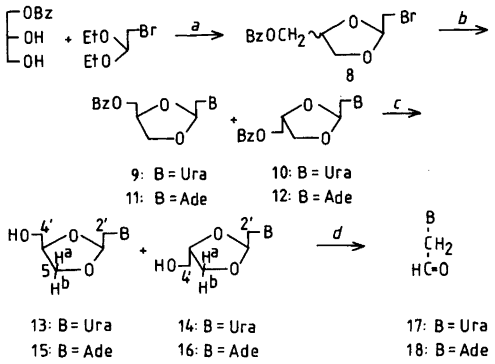


Scheme 1. a, p-TsOH, heating to 150 °C with concomitant distillation of ethanol; *b*, uracil or adenine, NaH, DMF, 110 °C, 10 h; *c*, NH_3–MeOH, 20 °C, 5 days; *d*, H^+.

The C(4′)H_2 group, in turn, can be identified by comparing the chemical shifts obtained with the benzoylated compounds, **9–12**, and their deblocked counterparts, **13–16**; the benzoyl group shifts the adjacent methylene protons downfield by approximately 1 ppm. The geminal constant of this group is smaller than that of the C(2′)H_2 group. The configurational assignment can tentatively be made on the basis of the location of the H-2 triplet. It is known that in 2,4-substituted-1,3-dioxolanes, H-2 of the *cis* isomer resonates at a higher field than that of the *trans* isomer.[17,18] Furthermore, the vicinal coupling constants, $J_{4,5a}$ and $J_{4,5b}$, of the *trans* isomer are approximately equal, whereas with the *cis* isomer $J_{4,5a} < J_{4,5b}$.[17]

The 2-CH_2 protons were unambiguously assigned by NOE difference spectroscopy (Table 3). Saturation of H-2 exerted a rather strong NOE on the neighboring protons, H-2a′ and H-2b′ (total effect > 4 %). The *cis* oriented H-5b was also markedly influenced (1.5–2.1 %), while the effect on the *trans* oriented H-5a remained zero. The latter effect was used to differentiate the C-5 protons. In the 2-CH_2 and 4-CH_2 groups the lowfield proton is marked by symbol a.

The assignment of the *cis/trans* configuration was also verified by NOE measurements. Consistent with the *trans* configuration of compounds **10** and **12**, no NOE on the H-4 resonance occurred upon irradiation of H-2. By contrast, the *cis* isomer, **9**, exhibited an NOE of 2.1 %. The corresponding effects of nucleosides range from 1.6 to 2.1 %.[19] With **11** only the total effect on H-4, H-2a′ and H-2b′ could be measured, owing to severe overlapping of these resonances. Saturation of H-2 also resulted in a weak NOE on H-4a′ and H-4b′ of the *trans* compounds, but not on the corresponding resonances of the *cis* isomers.

The deprotected nucleoside analogues, **13–16**, were UV spectroscopically almost identical with their parent nucleosides, uridine and adenosine. The ^{1}H NMR spectra of **13–16** showed the same features as described above for **9–12**. Their solid-state structures were determined by X-ray crystallography, and will be published later.

Hydrolysis. 1,3-Dioxolanes have been shown to undergo hydrolysis in aqueous acid by a rapid initial protonation of one of the ring-oxygens, followed by a rate-limiting formation of an acyclic oxocarbenium ion via ring-opening between C2 and the protonated oxygen (Scheme 2).[20,21] All subsequents steps, leading to the formation of an acyclic hemiacetal and its breakdown to final products, are fast. Consistent with this mechanism, hydrolysis of the uracil dioxolanes, **13** and **14**, gave, in aqueous hydrogen chloride at elevated temperature, one UV-absorbing product, which by chromatographic comparison with an authentic sample[22] was identified as uracil-1-ylacetaldehyde (**17**). Similarly, the adenine dioxolanes, **15** and **16**, were hydrolyzed to a single UV-absorbing product, although considerably less readily than **13** and **14**. Since the electronegativity of a hydroxymethyl group is almost equal to that of a hydrogen atom, it appears clear that the basicities of the two ring-oxygens are comparable, and the reactions proceeding by protonation of either O-1 or O-3 are of comparable importance. Table 4 summarizes the first-order rate constants determined at $[H^+]$ = 1.00 mol dm^{-3}, and the enthalpies and entropies of activation. The higher hydrolytic stability of the adenine derivatives, **15** and **16**, compared with the uracil derivatives, **13** and **14**, is expected on the basis of the mechanism depicted in Scheme 2. Electron withdrawal by a polar substituent at C2 lowers the basicity of the ring-oxygens and destabilizes the oxocarbenium ion developing in the rate-limiting stage. Accordingly, the effect on both the pre-equilibrium and rate-limiting stage is rate-retard-

Table 1. ^{1}H NMR chemical shifts for the dioxolane nucleoside analogues prepared.[a]

Compd.	Dioxolane moiety								Base moiety		
	H-2	H-2a′	H-2b′	H-4	H-4a′	H-4b′	H-5a	H-5b			
9[b]	5.09	3.92	3.92	4.42	4.33	4.29	3.90	3.98[c]	7.20	5.55	8.78
10[b]	5.23	3.99	3.84	4.42	4.36	4.35	4.15	3.78[c]	7.20	5.63	8.66
11[d]	5.19	4.39	4.37	4.38	4.07	3.96	3.73	3.93[c]	8.18	7.85	
12[d]	5.36	4.40	4.32	4.25	4.30	4.30	3.94	3.72[c]	8.23	7.87	
13[e]	5.02	3.87	3.87	4.04	3.37	3.23	3.51	3.78	7.41	5.58	
14[e]	5.16	3.86	3.80	4.06	3.50	3.41	3.91	3.53	7.43	5.61	
15[e]	5.15	4.27	4.27	3.98	3.00	2.83	3.23	3.72	7.95	7.89	
16[e]	5.24	4.18	4.18	3.74	3.42	3.35	3.60	3.44	7.89	7.85	

[a]As ppm from external TMS at 300 K. [b]In $CDCl_3$. [c]Benzoyl group: d 8.03, t 7.60, t 7.46. [d]In a mixture of $CDCl_3$ and CD_3OD. [e]In D_2O.

Table 2. Vicinal $^1H,^1H$-coupling constants for the dioxolane nucleoside analogues prepared.[a]

Compd.	$J_{2,2a'}$	$J_{2,2b'}$	$J_{2a',2b'}$	$J_{4,4a'}$	$J_{4,4b'}$	$J_{4a,4b'}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$
9	3.6	3.6		4.4	5.7	−11.7	5.0	6.9	−8.5
10	3.3	3.6	−14.5	4.2	5.6	−12.0	6.5	6.4	−8.5
11	3.0	3.0	−14.8	4.6	6.0	−11.6	4.8	6.8	−8.5
12	2.9	3.1	−14.7	4.1	5.6	−11.7	6.4	6.3	−8.5
13	2.7	2.7		3.9	5.9	−12.0	5.9	7.1	−8.5
14	3.0	3.0	−14.7	3.7	5.6	−12.2	6.8	7.0	−8.5
15	2.4	2.4		4.6	6.1	−11.9	5.5	6.8	−8.5
16	2.4	2.4		3.7	5.8	−12.2	6.7	6.7	−8.5

[a]Given in Hz. For the experimental conditions see the footnotes to Table 1.

ing, resulting in a marked deceleration. Since the adenine ring undergoes protonation at N1 under the experimental conditions (pK_a 3.6 at 298.2 K, I = 0.1 mol dm^{-3}), while uracil remains uncharged,[23] the rate-retarding effect of adenin-9-ylmethyl group is greater than that of the uracil-1-ylmethyl group. With both adenine and uracil derivatives, the *cis* isomer is hydrolyzed twice as rapidly as the *trans* compound. The entropies of activation are only slightly negative, consistent with the suggested unimolecular nature of the rate-limiting stage. Comparison of the first-order rate constants listed in Table 4 with those reported previously[4,5] for hydrolysis of various sugar-modified nucleosides reveals that the 2-(uracil-1-ylmethyl)dioxolanes are hydrolyzed approximatley as rapidly as 3′-deoxythymidine, and hence one order of magnitude faster than thymidine. Compared with 2′-deoxyadenosine, the stability is 10^4 times higher.

Experimental

General methods. Melting points (uncorrected) were determined with a TP (USSR) instrument. Silica gel L (40–100 μm, Czechoslovakia) was used for adsorption chromatography. TLC separations were carried out on Silufol UV_{254} (Czechoslovakia), using the following eluants (compositions expressed as v/v): (system A) chloroform, (B) chloroform–ethanol 95:5, (C) chloroform–ethanol 9:1, and (D) ethyl acetate–toluene–ethanol 10:1:1. Preparative reversed-phase chromatography was performed on Bondesil C18 (40 μm, Analytichem International). HPLC analyses were carried out on an Octadecyl = Si100 column of Serva (4.5 × 250 mm, 5 μm), using a mixture of acetonitrile and aqueous sodium acetate (0.1 mol dm^{-3}) as the eluant. The acetonitrile content (v/v) was either 5 % (system E) or 30 % (system F), and the flow rate was 1 cm^3 min^{-1}.

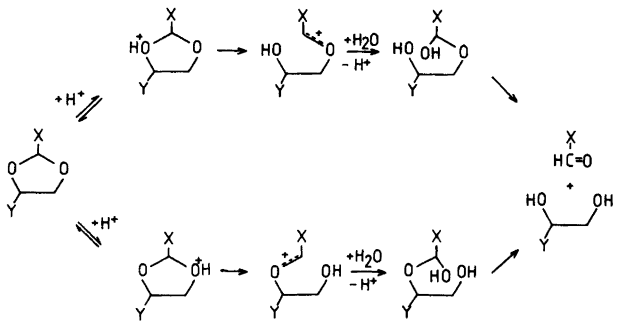
^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer at 300 K. Chemical shifts were measured relative to solvent signals. The signals were assigned by the double resonance technique. The NOE measurements in $CDCl_3$, or in a mixture of $CDCl_3$ and CD_3OD, were carried out under identical spectral and processing conditions by applying an NOEDIFF pulse sequence of the Bruker software package UXNMR (release version 911101) for steady-state NOE measurements. For compounds **9–12**, the values of the chemical shifts and coupling constants were calculated by means of a DAISY program. UV spectra were recorded on a Specord spectrometer.

Table 3. NOE data (%) of benzoylated dioxolane nucleoside analogues, **9–12**, upon irradiation of H-2 at 300 K.

Compd.	H-4	H-2a′	H-2b′	H-4a′	H-4b′	H-5a	H-5b
9	2.1	− Σ 4.1	−	[a]	[a]	[a]	1.9
10	[a]	2.6	2.3	−	Σ 1.0	− [a]	1.6
11	−	Σ 8.1	−	0	0	0	2.1
12	[a]	−	Σ 6.2	−	−	Σ 1.1 −	0 1.9

[a]The enhancement of intensity < 0.5 %.

(±)-cis/trans-*4-Benzoyloxymethyl-2-bromomethyl-1,3-dioxolane* (**8**). A mixture of 1-*O*-benzoylglycerol[14] (10 g, 51 mmol), bromoacetaldehyde diethylacetal (7.7 cm^3, 51 mmol) and *p*-toluenesulfonic acid (0.2 g) was gently heated with continuous distillation of ethanol until the temperature of the reaction mixture reached 150 °C (2 h). The cooled solution was diluted with chloroform (150 cm^3), washed successively with saturated aqueous sodium hydrogencarbonate (20 cm^3) and water (2 × 30 cm^3), dried with Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (50 g), using a mixture of chloroform and hexane (1:1 v/v) as the eluant. The pooled fractions were evaporated to a syrup. Yield 12.2 g (79 %). R_F 0.73 (A). ^1H NMR ($CDCl_3$): δ 7.28–8.07 (5 H, Bz, m), 5.30 (0.4 H, *trans* H-2, t, $J_{2,2'}$ 3.5 Hz), 5.15



Scheme 2.

Table 4. First-order rate constants and the enthalpies and entropies of activation for the acid-catalyzed hydrolysis of dioxolane nucleoside analogues **13–16** in aqueous hydrogen chloride (1.00 mol dm^{-3}).

Comp.	T/K	$k/10^{-5}$ s^{-1}	$\Delta H^{\ominus}$/kJ mol^{-1} [a]	$\Delta S^{\ominus}$/J K^{-1} mol^{-1} [a]
13	363.2	74.9(12)	102(5)	−24(14)
	353.2	30.4(6)		
	343.2	9.84(9)		
14	363.2	37.8(8)	104(5)	−27(15)
	353.2	15.2(2)		
	343.2	4.86(7)		
15	363.2	8.90(15)	102(4)	−43(11)
	353.2	3.57(9)		
	343.2	1.19(3)		
16	363.2	4.54(6)	112(2)	−22(5)
	353.2	1.60(1)		
	343.2	0.497(6)		

[a] At 333.2 K.

(0.6 H, *cis H-2*, *t*, $J_{2,2}$, 3.5 Hz), 3.77–4.59 (5 H, H-4, H-4a′, H-4b′, H-5a, H-5b, m), 3.41 (1.2 H, *cis* H-2a′, H-2b′, d), 3.39 (0.8 H, *trans* H-2a′, H-2b′, d).

(±)-cis- *and* trans-*4-benzoyloxymethyl-2-(uracyl-1-ylmethyl)-1,3-dioxolanes* (**9** *and* **10**). To a suspension of dry uracil (1.12 g, 10 mmol) in dry DMF (30 cm^3) was added sodium hydride (0.5 g, 12.5 mmol, 60 % in oil) and the mixture was stirred for 1 h at 20 °C. The mixture was heated to 110 °C, and a solution of **8** (3.01 g, 10 mmol) in DMF (10 cm^3) was added in several portions over 10 h. The mixture was cooled to 30 °C, filtered and the combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was dissolved in chloroform (150 cm^3), the organic layer was washed with water (2 × 30 cm^3), dried with Na_2SO_4, filtered, evaporated to dryness, and chromatographed on silica gel (70 g). Elution with chloroform (A) gave **8** and the N^1,N^3-bis-alkylated uracil (0.25 g, 5 %). Further elution with system B gave a mixture of **9** and **10**. Yield 0.75 g (23 %). R_F 0.30 (B). The ratio of *cis*/*trans* isomers was 3:2 according to ^{1}H NMR spectroscopy.

The diastereomeric mixture obtained was dissolved in DMF (1.5 cm^3), and water was added until the material began to precipitate (0.75 cm^3). The mixture was applied to a column of Bondesil C18 (100 g) and eluted with a mixture of acetonitrile and water (1:3 v/v). Fractions containing the *cis* isomer (**9**) were combined and evaporated to dryness *in vacuo*. The residue was dissolved in chloroform (50 cm^3), washed with water (10 cm^3), dried with Na_2SO_4, filtered and evaporated to dryness, and the residue was crystallized from ethanol. Yield 0.33 g (10 %). M.p. 133–135 °C. R_F 0.78 (C), 0.46 (D). t_R(HPLC) 8.6 min (F). ^{13}C NMR ($CDCl_3$): carbons of the benzoyl group δ 166.1 (C=O), 150.7 (C-1), 133.4 (C-4, *J* 162.3 Hz, 8.3 Hz), 129.6 (C-3, C-5, *J* 162.3 Hz, 6.9 Hz), 128.5 (C-2, C-6, *J* 162.3 Hz, 6.9 Hz); carbons of the uracil base δ 163.1 (C=O), 163.0 (C=O), 145.4 (C-6, *J* 182 Hz), 101.8 (C-5, *J* 177.6 Hz); carbons of the dioxolane moiety δ 101.4 (C-2, *J* 170.6 Hz), 74.3 (C-4, *J* 151.2 Hz), 67.2 (C-5, *J* 150.5 Hz), 64.3 (C-4′, *J* 148.4 Hz), 49.3 (C-2′, *J* 142.8 Hz). The ^{1}H NMR data are given in Tables 1 and 2.

The combined fractions of the *trans* isomer contained 0.22 g (7 %) of **10**. M.p. 128–130 °C. R_F 0.78 (C), 0.46 (D). t_R(HPLC) 11.1 min (F). ^{13}C NMR ($CDCl_3$): carbons of the benzoyl group δ 166.2 (C=O), 150.8 (C-1), 133.8 (C-4, *J* 161.2 Hz, 7.8 Hz), 129.7 (C-3, C-5, *J* 163.0 Hz, 7.6 Hz), 128.5 (C-2, C-6, *J* 162.3 Hz, 7.6 Hz); carbons of the uracil base δ 163.3 (C=O), 163.2 (C=O), 145.3 (C-6, *J* 181 Hz), 101.9 (C-5, *J* 176.9 Hz); carbons of the dioxolane moiety δ 101.2 (C-2, *J* 171.5 Hz), 74.3 (C-4, *J* 152.6 Hz), 67.3 (C-5, *J* 151.9 Hz), 64.0 (C-4′, *J* 148.4 Hz), 48.8 (C-2′, *J* 142.2 Hz). The ^{1}H NMR data are given in Tables 1 and 2.

(±)-cis- *and* trans-*2-(adenin-9-ylmethyl)-4-benzoyloxymethyl-1,3-dioxolanes* (**11** *and* **12**). These were prepared analogously by alkylation of the sodium salt of adenine (10 mmol) with **8** (10 mmol) in DMF (40 cm^3). The products were separated on silica gel (system C) to give a mixture of **11** and **12**. Yield 1.55 g (44 %). R_F 0.59 (C). The ratio of the *cis*/*trans* isomers was 3:2 according to ^{1}H NMR spectroscopy. Further elution with the same solvent system gave the corresponding mixture of N^3-isomers. Yield 0.25 g (7 %). R_F 0.40 (C). The mixture of **11** and **12** was separated on Bondesil as described above. The *cis* isomer (**11**) was obtained in 18 % yield. M.p. 191–192 °C. R_F 0.59 (C), 0.16 (D). t_R(HPLC) 7.0 min (F). The yield of the *trans* isomer (**12**) was 10 %. M.p. 173–174 °C. R_F 0.59 (C), 0.16 (D). t_R(HPLC) 11.0 min (F). The ^{1}H NMR data of both isomers are given in Tables 1 and 2.

Debenzoylation. A solution of **9–12** (1 mmol) in methanolic ammonia (5 mol dm^{-3}, 10 cm^3) was stored for 3 days at 20 °C and then concentrated to dryness *in vacuo*. The residue was partitioned between water (10 cm^3) and chloroform (10 cm^3), and the organic layer was washed with water (10 cm^3). The combined aqueous solutions were washed with chloroform (5 cm^3), concentrated to dryness, and the residue was recrystallized from ethanol. The following products were obtained (for the ^{1}H NMR data see Tables 1 and 2).

(±)-cis-*4-Hydroxymethyl-2-(uracil-1-ylmethyl)-1,3-dioxolane* (**13**). Yield 88 %. M.p. 143–145 °C. R_F 0.28 (C). t_R(HPLC) 6.2 min (E). UV [water (log ε)]: λ_{max} 264 nm (3.86; pH 1–7), 264 nm (3.71; pH 12). MS [IP 70 eV; *m*/*z* (% rel. int.)]: 228 (7, *M*), 224 (10), 197 (8), 138 (3), 126 (4), 116 (3), 103 (100), 82 (12), 57 (67), 47 (18), 45 (11), 43 (7). Found *M* 228.18, calc. for $C_9H_{12}N_2O_5$ 228.20.

(±)-trans-*4-Hydroxymethyl-2-(uracil-1-ylmethyl)-1,3-dioxolane* (**14**). Yield 68 %. M.p. 149–151 °C. R_F 0.28 (C). t_R(HPLC) 6.2 min (E). UV [water (log ε)]: λ_{max} 265 nm (3.91; pH 1–7), 264 nm (3.77; pH 12). MS [IP 70 eV; *m*/*z*

(% rel. int.)]: 228 (6, *M*), 224 (10), 197 (7), 138 (3), 126 (3), 116 (3), 103 (100), 82 (13), 57 (66), 47 (18), 45 (12), 43 (7). Found *M* 228.18, calc. for $C_9H_{12}N_2O_5$ 228.20.

(±)-cis-*2-(Adenin-9-ylmethyl)-4-hydroxymethyl-1,3-dioxolane* (**15**). Yield 70%. M.p. 189–191°C. R_F 0.15 (C). t_R(HPLC) 16.9 min (E). UV [water (log ε)]: λ_{max} 260 nm (4.17; pH 7–12), 258 nm (4.16; pH 2). MS [IP 70 eV; *m/z* (% rel. int.)]: 251 (12, *M*), 220 (8), 178 (27), 161 (3), 149 (62), 136 (15), 116 (32), 103 (83), 94 (3), 79 (5), 67 (7), 57 (100), 47 (23), 45 (13), 43 (12). Found *M* 251.17, calc. for $C_{10}H_{13}N_5O_3$ 251.25.

(±)-trans-*2-(Adenin-9-ylmethyl)-4-hydroxymethyl-1,3-dioxolane* (**16**). Yield 76%. M.p. 187–188°C. R_F 0.14 (C). t_R(HPLC) 16.9 min (E). UV [water (log ε)]: λ_{max} 260 nm (4.14; pH 7–12), 258 nm (4.13; pH 2). MS [IP 70 eV; *m/z* (% rel. int.)]: 251 (8, *M*), 220 (8), 178 (15), 161 (3), 116 (27), 103 (80), 94 (3), 79 (4), 67 (6), 57 (100), 47 (23), 45 (13), 43 (11). Found *M* 251.17, calc. for $C_{10}H_{13}N_5O_3$ 251.25.

Uracil-1-ylacetaldehyde (**17**) was prepared according to the literature.[22]

Kinetic measurements. The progress of the acid-catalyzed hydrolysis of **13–16** was followed by the HPLC technique described previously.[24] The initial substrate concentration was 5×10^{-4} mol dm^{-3}. Chromatographic separations were carried out on a Spherisorb ODS column (4.5 × 250 mm, 5 μm), using a mixture of acetate buffer (pH 4.3) and acetonitrile (9:1 v/v) as the eluant. The retention times of the starting materials varied from 4 to 6 min, and those of the products from 2.5 to 3.5 min, when the flow-rate was 1.0 cm^3 min^{-1}).

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References

1. Mitsuya, H. and Broder, S. *Proc. Natl. Acad. Sci. USA 83* (1986) 1911.
2. Yarchoan, R., Mitsuya, H., Thomas, R. V., Pluda, J. M., Hartman, N. R., Perno, C.-F., Marczyk, K. S., Allain, J. P., Johns, D. G. and Broder, S. *Science 245* (1989) 412.
3. Larder, B. A., Darby, G. and Richman, D. D. *Science 245* (1989) 1731.
4. York, J. L. *J. Org. Chem. 46* (1981) 2171.
5. Oivanen, M., Viinamäki, T., Zavgorodny, S., Polianski, M., Azhayev, A., Van Aerschot, A., Herdewijn, P. and Lönnberg, H. *Collect. Czech. Chem. Commun. 55* (1990) 17.
6. Bamford, M. J., Humber, D. C. and Storer, R. *Tetrahedron Lett. 32* (1991) 271.
7. Huryn, D. M., Sluboski, B. C., Tam, S. Y., Todaro, L. J. and Weigele, M. *Tetrahedron Lett. 30* (1989) 6259.
8. Tam, S., Holman, M., Huryn, D. M. and Cislo, A. *Nucleosides Nucleotides 10* (1991) 245.
9. Jones, M. F., Noble, S. A., Robertson, C. A. and Storer, R. *Tetrahedron Lett. 32* (1991) 247.
10. Norbeck, D. W., Spanton, S., Broder, S. and Mitsuya, H. *Tetrahedron Lett. 30* (1989) 6263.
11. Chu, C. K., Ahn, S. K., Kim, H. O., Beach, J. W., Alves, A. J., Jeong, L. S., Islam, Q., Van Roey, P. and Schinazi, R. F. *Tetrahedron Lett. 32* (1991) 3791.
12. Belleau, B., Dixit, D., Nguyen-Ba, N. and Kraus, J. L. *Abstract Papers, V Int. Conf. on AIDS, Montreal,* International Development Res. Centre, Ottawa, Ontario 1989; T.C.O.1.
13. Wainberg, M. A., Stern, M., Martel, R., Belleau, B. and Soudeyns, H. *Abstract Papers, V Int. Conf. on AIDS, Montreal,* International Development Res. Centre, Ottawa, Ontario 1989; M.C.P.63.
14. Ogilvie, K. K., Hanna, H. R. and Proba, Z. *Nucleosides Nucleotides 5* (1986) 169.
15. Mikhailov, S. N., Kolobushkina, L. I., Kritzyn, A. M., Padyukova, N. Ch. and Florentiev, V. L. *Izv. Akad. Nauk SSSR Ser. Khim.* (1974) 2582.
16. Holy, A. *Collect. Czech. Chem. Commun. 43* (1978) 3103.
17. Willy, W. E., Binsch, G. and Eliel, E. L. *J. Am. Chem. Soc. 92* (1970) 5394.
18. Wedmid, Y. and Baumann, W. J. *J. Org. Chem. 42* (1977) 3624.
19. Rosemeyer, H., Toth, G. and Seela, F. *Nucleosides Nucleotides 8* (1989) 587.
20. Salomaa, P. and Kankaanperä, A. *Acta Chem. Scand. 15* (1961) 871.
21. Kankaanperä, A. *Ann. Univ. Turkuensis, Ser. A 95* (1966) 1.
22. Martinez, A. P. and Lee, W. W. *J. Org. Chem. 30* (1978) 317.
23. Lönnberg, H. In: Burger, K., Ed., *Biocoordination Chemistry: Coordination Equilibria in Biologically Active Systems,* Ellis Horwood, London 1990, Chap. 8.
24. Oivanen, M., Lönnberg, H., Zhou, X.-X. and Chattopadhyaya, J. *Tetrahedron 43* (1987) 1133.

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