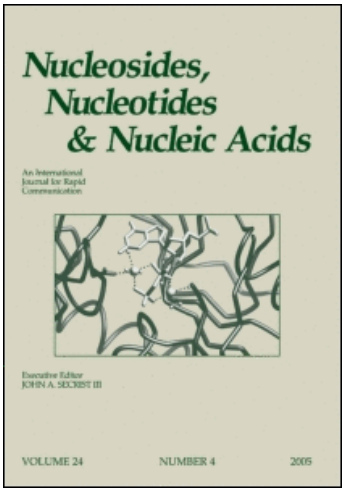

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF (*Z*) AND (*E*) α-ETHENYL ACYCLONUCLEOSIDES

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ABSTRACT

Synthesis of *Z* and *E* ethenyl acyclonucleosides (**6a-e** and **7a-e**) via Michael addition of nucleobases with the diethyl acetylenedicarboxylate is described. The structures of compounds have been confirmed by spectral data. New compounds were found to be inactive against DNA and RNA viruses.

The chemical and biological properties of carbocyclic nucleoside analogues have been the subject of intense research during the past decade.[1–5] A variety of carbocyclic adenosine analogues are assumed to exert their antiviral action through inhibition of S-adenosylhomocysteine hydrolase (AdoHcy, SAH).[6] In fact, a close correlation has been found between the antiviral activity of various carbocyclic and acyclic adenosine analogues and their inhibitory effect on the cell-free SAH hydrolase,[5] and they are not susceptible to degradation *in vitro* by nucleases and phosphorylases. For instance, unsaturated analogues **1–3** (Figure 1) were found to be substrates of adenosine deaminase.[7]

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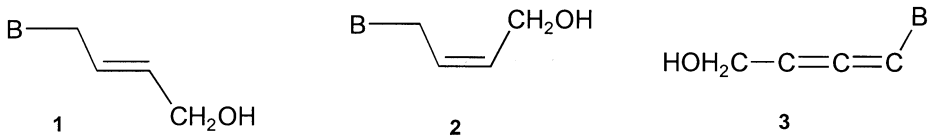
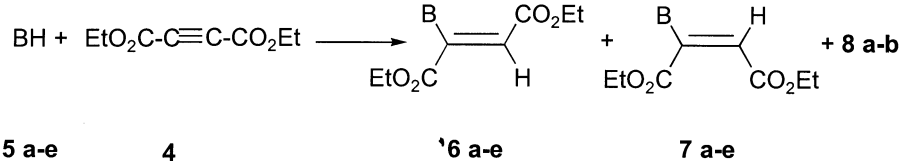


Figure 1.

In view of the above synthetic and biological aspects, and as a part of continuing studies,[8–10] we report here the synthesis of a new group of unsaturated analogues, *trans* and *cis* alkenes **6a-e** and **7a-e** (Scheme 1), respectively. These products are mainly characterised by a nucleobase linked to a double bond. The strategy envisioned to reach this goal involved using a Michael addition, which is one of the most important methods for creating carbon–carbon[11] or nitrogen–carbon[3,12,13] bonds to give functionalized organic compounds. The reaction of NH heterocycles (pyrazole, indazole, triazole . . .) with acetylenic esters having electron withdrawing groups such COOR, CN and SOOR has been studied.[14–16] This type of reaction proceeds initially via nucleophilic addition to an acetylenic bond to form the Michael adduct.

We have applied this strategy to both purine and pyrimidine bases. The nucleobase anions **5a-e** were generated *in situ* by treatment with potassium carbonate in 1,4-dioxane or in DMF and allowed to react with diethyl acetylenedicarboxylate **4** to give, after hydrolytic work up, a mixture of the geometrical isomers **6a-e** and **7a-e** with the N_1, N_3 bisalkylated compounds as side products **8a-b** (Scheme 1).



5 a-e **4** **'6 a-e** **7 a-e**

a: BH = Uracil, b: BH =Thymine, c: BH = Cytosine, d: BH = Adenine, e: BH = N-Ac-Guanine

Scheme 1.

For instance, the reaction of uracil **5a** at room temperature or at 70 °C with **4** led to a mixture of **6a**, **7a** and **8a** (N_1, N_3 bis alkylated) (Table 1). An excess of K_2CO_3 should be avoided because it causes a retro-Michael reaction.

In order to find a method for determining the configuration of the isomers **6a-e** and **7a-e**, the use of NMR spectroscopy appeared to be the most promising. A study of the NMR spectra was made paying close attention to the chemical shifts of the $H_{3'}$ vinylic proton, as well as solvent-induced shifts (Table 2). The proton resonance values of $H_{3'}$ (*Z*) in both solvent ($CDCl_3$ or DMSO:d_6) were considerably higher than the corre-

Table 1. Reaction Conditions for N-alkylation of Purine and Pyrimidine with **4**

Base	Solvent	Time (h)	T °C	Yield %	E %	Z %
Uracil	1,4-dioxane	24	25	65[a]	45	55
		1,5	70	75[b]	15	85
Thymine	1,4-dioxane	18	25	65[a]	70	30
		1	70	75[b]	45	55
Cytosine	DMF	1	25	70	60	40
Adenine	DMF	1	25	65	66	34
NAcGuanine	DMF	1	25	50	50	50

a: bisalkylated N_1N_3 10%, b: bisalkylated N_1N_3 15%.

sponding $H_{3'}$ (*E*). It would be expected that the significant diamagnetic anisotropy of ester carbonyls would lead to a greater deshielding of the vinyl proton.[17–19] In this respect, the spectra are quite similar to those of other unsaturated derivatives of nucleic acid bases which contain a double bond with the heterocyclic moiety.[7]

The difference in the ratio of the maleate-fumarate isomers obtained under a different set of time, solvent and temperature conditions (Table 1), suggests that the maleate adduct (*E*) which is kinetically controlled process isomerizes to the fumarate (*Z*), which is thermodynamically more stable. When the reaction time is shorter (1–3 hours) the isomer *E* is the major product. With longer reaction times (12 hours), the isomer *Z* is becoming the major product. Some experiments were performed to try to understand these results. When the isomer *E* was reacted with potassium carbonate in DMF (Table 3) at room temperature, a mixture of *E* and *Z* was obtained (Scheme 2). The equilibrium ratio *Z*/*E* isomers was determined by ^{1}H NMR after TLC and showed no further changes in isomer composition.

The results (Table 3) appear to be in agreement with some results previously reported.[3,19]

Table 2. Chemical Shift of Vinylic Proton $H_{3'}$ in $CDCl_3$ and DMSO-d_6

	Solvent	Uracil	Thymine	Cytosine	Adenine	NacGuanine
$H_{3'}(Z)$	$CDCl_3$	7.10	7.05	6.85	7.35	8.00
$H_{3'}(Z)$	$CDCl_3$	6.30	6.25	6.15	7.25	7.20
$H_{3'}(Z)$	DMSO-d6	6.95	6.90	6.65	7.20	7.25
$H_{3'}(Z)$	DMSO-d6	6.80	6.65	6.50	7.15	7.15

Biological Activity

Compounds **6a-e** and **7a-e** were evaluated for their activities against human immunodeficiency virus type 1 (HIV-1) (HTLV-III_B/LAI) and HIV-2 ($LAV\text{-}2_{ROD}$) in human T-lymphocyte (CEM) cells, and against herpes simplex virus type 1 (HSV-1) (strain KOS), thymidine kinase-deficient (TK^-) HSV-1 (strain B2006), herpes simplex virus type 2 (HSV-2) (strain G), vaccinia virus and vesicular stomatitis virus in human embryonic skin-muscle (ESM) fibroblasts. In E6SM cells, no toxicity (as assessed by microscopically visible alteration of normal cell morphology) and no antiviral activity were observed at compound concentrations up to 400 μg/ml. Compounds **6a-e**, **7a-e** and **8a-b** proved to be toxic to CEM cells at a 50% cytotoxic concentration (CC_{50}) of 0.8–1 μg/ml. No antiviral activity was observed at concentrations up to 0.8–1 μg/ml (data not shown).

These compounds were subjected to the NCI *in vitro* disease-oriented human cells screening panel assay.[20,21] About 60 cell lines of nine tumor subpanels (I, leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer, V; melonoma, VI; ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer) were incubated with five concentrations (0.01, 0.1, 1.0, 10 and 100 μM) for each compound and were used to create log concentration -% growth inhibition curves. Some of the test compounds (data not shown) showed antineoplastic activity at concentrations less than l00 μM.

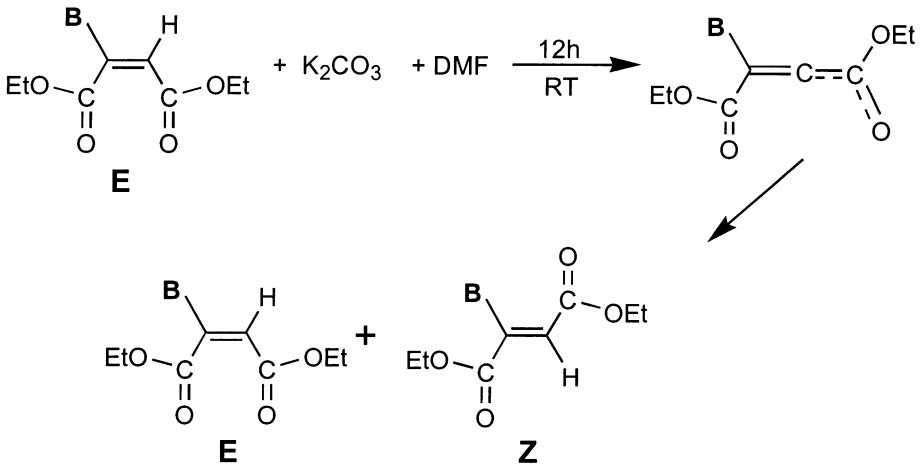
EXPERIMENTAL

All melting points were determined with a Büchi apparatus and are uncorrected. Ultra-Violet spectra were recorded with a CARY 219 spectrophotometer. The ^1H NMR spectra were recorded with a Bruker AC 250 Spectrometer. Chemical shifts are reported in parts per million (δ □ppm)

Table 3. Isomerization of the E Isomers

Compounds	Solvent	Time (h)	T °C	*E* (%)	*Z* (%)
7a	DMF	4	25	10	90
	1,4-dioxane	1	70	20	80
6b, 7b*	DMF	4	25	20	80
	1,4-dioxane	1	70	25	75
7c	DMF	48	25	50	50
7d	DMF	24	25	50	50
7e	DMF	48	25	50	50

*: starting material : mixture E/Z = 70/30.



Scheme 2.

using internal TMS standard. Fast-atom bombardment mass spectra (FAB-MS) were recorded in the positive or negative ion mode on a JEOL DX 300 mass spectrometer. Elemental analyses were determined by the "Service de microanalyse du CNRS, Division de Vernaison, France". Thin layer chromatography (T.L.C) was performed on plates of kieselgel 60 F254 (Merck). Column chromatography was performed on silica gel (0.063–0.2 mm Merck).

GENERAL PROCEDURE

A mixture of nucleobase (4.45 mmol), potassium carbonate (2.22 mmol) in l,4-dioxane or DMF (50 ml) was stirred at room temperature for 15 min. Diethyl acetylenedicarboxylate (4.45 mmol) was then added and the solution was stirred at room temperature for different times (Table 1). The solid was filtered off and the filtrate was evaporated. The residue was chromatographed on a silica gel column.

(*Z*)-Diethyl 2-(Uracil-1-yl)-but-2-enedioate (6a)

mp : 114–116 °C (Ether); Rf : 0.55 (CH_2Cl_2/MeOH:90/10); UV (MeOH) λ_{max} 255 nm ($\varepsilon = 12\,600$); FAB-MS, 283 (M+H); ^{1}H NMR ($CDCl_3$): 9.10 (s, 1H, NH-3); 7.05 (d, 1H, H_6; $J_{6,5} = 7.9$ Hz); 7.05 (s, 1H, $H_{3'}$); 5.80 (d, 1H, H_5, $J_{6,5} = 7.9$ Hz); 4.20 (m, 4H, $CH_3\underline{CH_2}O$); l.30 (m, 6H, $\underline{CH_3}CH_2O$); Anal. Calc. for: $C_{12}H_{14}O_6N_2$: C, 51.06; H, 5.00; N, 9.92; Found; C, 51.10; H, 4.85; N, 9.90.

(*E*)-Diethyl 2-(Uracil-1-yl)-but-2-enedioate (7a)

mp: 135–137 °C (Ether); Rf: 0.54 (CH_2Cl_2/MeOH: 90/10); UV (MeOH) λ_{max} 271.6 nm ($\varepsilon = 11\,000$); FAB-MS, 283 (M+H); ^{1}H NMR ($CDCl_3$): 9.30 (s, 1H, NH-3); 7.30 (d, 1H, H_6; $J_{6,5} = 8.1$ Hz); 6.3 (s, 1H, $H_{3'}$); 5.85 (d, 1H, H_5; $J_{6,5} = 8.1$ Hz); 4.30 (m, 4H, $CH_3\underline{CH_2}O$); 1.30 (m, 6H, $\underline{CH_3}CH_2O$); Anal. Calc. for: $C_{12}H_{14}O_6N_2$; C, 51.06; H, 5.00; N, 9.92; Found; C, 51.12; H, 5.01; N, 9.80.

(*E*, *Z*)-Diethyl 2-(Thymin-1-yl)-but-2-enedioate (6b, 7b)

mp: 128–130 °C (Ether); Rf: 0.57 (CH_2Cl_2/MeOH: 90/10);UV (MeOH) λ_{max} 272 nm ($\varepsilon = 12\,500$); FAB-MS, 297 (M+H) ^{1}H NMR ($CDCl_3$): 9.40 (s, 1H, NH-3, (E, Z)); 7.05 (s, 1H, $H_{3'}$, Z); 7.10 (m, 1H, H_6, E); 6.95 (m, 1H, H_6, Z); 6.25 (s, 1H, $H_{3'}$, E); 4.25 (m, 8H, CH_3CH_2O, (E, Z)); 1.95 (s, 6H, CH_3, (E, Z)); 1.30 (m, 12H, CH_3CH_2O, (E, Z)); Anal. Calc. for: $C_{13}H_{16}O_6N_2$; C, 52.70; H, 5.44, N, 9.45; Found; C, 52.74; H, 5.46; N, 9.51.

(*Z*)-Diethyl 2-(Cytosin-1-yl)-but-2-enedioate (6c)

mp 152–154 °C (Ether); Rf: 0.33 (CH_2Cl_2/MeOH: 90/10); UV (MeOH) λ_{max} 288 nm ($\varepsilon = 12\,400$); FAB-MS, 282 (M+H); ^{1}H NMR ($CDCl_3$): 8.70 (s, 2H, NH2); 7.10 (d, 1H, H_6, $J_{6,5} = 7.4$ Hz); 6.85 (s, 1H, $H_{3'}$); 5.90 (d, 1H, H_5, $J_{6,5} = 7.4$ Hz); 4.25 (m, 4H, $CH_3\underline{CH_2}O$); 1.25 (m, 6H, $\underline{CH_3}CH_2O$); Anal. Calc. for: $C_{12}H_{15}O_5N_3$; C, 51.24; H, 5.37; N, 14.93; Found; C, 51.31; H, 5.40; N, 14.82.

(*E*)-Diethyl 2-(Cytosin-1-yl)-but-2-enedioate (7c)

mp: 165–167 °C (Ether); Rf: 0.30 (CH_2Cl_2/MeOH: 90/10); UV (MeOH) λ_{max} 284 nm ($\varepsilon = 10\,800$); FAB-MS, 282 (M+H); ^{1}H NMR ($CDCl_3$): 8.70 (s, 2H, NH_2); 7.25 (d, 1H, H_6, $J_{6,5} = 7.5$ HZ); 6.15 (s, 1H, $H_{3'}$); 6.00 (d, 1H, H_5, $J_{6,5} = 7.5$ HZ); 4.25 (m, 4H, $CH_3\underline{CH_2}O$); 1.25 (m, 6H, $\underline{CH_3}CH_2O$); Anal. Calc. for: $C_{12}H_{15}O_5N_3$; C, 51.24; H, 5.37; N, 14.93; Found; C, 51.11; H, 5.47, N, 14.83.

(*Z*)-Diethyl 2-(Adenin-9-yl)-but-2-enedioate (6d)

mp: 204–206 °C (Ether); Rf: 0.50 (CH_2Cl_2/MeOH: 90/10); UV (MeOH) λ_{max} 254 nm ($\varepsilon = 38\,400$); FAB-MS, 306 (M+H); ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H, H_8); 7.90 (s, 1H, H_2); 7.35 (s, 1H, $H_{3'}$); 5.65 (s, 2H, NH_2); 4.48 (q, 2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz); 4.28 (q, 2H, $CH_3\underline{CH_2}O$,

J = 7.1 Hz); 1.34 (m, 6H, CH_3CH_2O); Anal. Calc. for: $C_{13}H_{15}O_4N_5$; C, 51.14; H, 4.95; N, 22.94; Found; C, 51.07; H, 4.93; N, 22.91.

(*E*)-Diethyl 2-(Adenin-9-yl)-but-2-enedioate (7d)

mp 140–142 °C (Ether); Rf: 0.47 (CH_2Cl_2/MeOH: 90/10); UV (MeOH) λ_{max} 255 nm ($\varepsilon = 19\,600$); FAB-MS, 306 (M+H); ^{1}H NMR ($CDCl_3$): 8.33 (s, 1H, H_8); 7.90 (s, 1H, H_2); 7.35 (s, 1H, $H_{3'}$); 5.88 (s, 2H, NH_2); 4.36 (q, 2H, CH_3CH_2O, J = 7.1 Hz); 4.07 (q, 2H, CH_3CH_2O, J = 7.1 Hz); 1.32 (t, 3H, CH_3CH_2O; J = 7.1 Hz); 1.08 (t, 3H, CH_3CH_2O; J = 7.1 Hz); Anal. Calc. for: $C_{13}H_{15}O_4N_5$;C, 51.14; H, 4.95; N, 22.94; Found; C, 51.10; H, 4.98; N, 22.92.

(*Z*)-Diethyl 2-(N-Acetylguanin-9-yl)-but-2-enedioate (6e)

mp: 198–200 °C (MeOH); Rf: 0.43 (CH_2Cl_2/MeOH : 90/10); UV (MeOH) λ_{max} 280 nm (ε = 13 700); λ_{max} 251 nm (ε = 23 144); FAB-MS, 364 (M+H); ^{1}H NMR ($CDCl_3$): 12.30 (s, 1H, NH-Ac); 11.15 (s, 1H, NH-1); 8.20 (s, 1H, H_8); 7.80 (s, 1H, $H_{3'}$); 4.20 (m, 4H, CH_3CH_2O); 2.20 (s, 3H, CH_3CO); 1.40 (m, 6H, CH_3CH_2O); Anal. Calc. for: $C_{15}H_{17}O_6N_5$; C, 49.59; H, 4.72; N, 19.28; Found; C, 49.38, H, 4.73; N, 19.11.

(*E*)-Diethyl 2-(N-Acetylguanin-9-yl)-but-2-enedioate (7e)

Rf: 0.41 (CH_2Cl_2/MeOH: 90/10); UV (MeOH) λ_{max} 282 nm (shoulder) λ_{max} 248 (ε = 9200); FAB-MS, 364 (M+H); ^{1}H NMR ($CDCl_3$): 12.30 (s, 1H, NH-Ac); 11.15 (s, 1H, NH-1); 8.00 (s, 1H, H_8); 7.10 (s, 1H, $H_{3'}$); 4.20 (m, 4H, CH_3CH_2O); 2.75 (s, 3H, CH_3CO); 1.25 (m, 6H, CH_3CH_2O); Anal. Calc. for: $C_{15}H_{17}O_6N_5$; C, 49.58; H, 4.71; N, 19.27; Found; C, 49.18, H, 4.70; N, 19.20.

1, 3-Bis(diethylbut-2-enedioate-2-yl)uracil (8a)

Rf: 0.71 (CH_2Cl_2/MeOH: 95/5); UV (MEOH) λ_{max} 262 nm (ε = 9 200); FAB-MS, 453 (M+H); ^{1}H NMR (DMSO-d6): 7,8–8 (m, 1H, H_6); 7–7.15 (m, 2H, $H_{3'}$); 5.95–6.05 (m, 1H, H_5); 4,15 (m, 8H, CH_3CH_2O); 1,3 (m, 12H, CH_3CH_2O); Anal. Calc. for: $C_{20}H_{24}O_{10}N_2$; C, 53.10; H, 5.35; N, 6.19; Found; C, 53.17; H, 5.34; N, 5.97.

1, 3-Bis(diethylbut-2-enedioate-2-yI)thymine (8b)

Rf: 0.77 (CH_2Cl_2/MeOH: 95/5) UV (MeOH) λ_{max} 264 nm (ε = 13 500); FAB-MS, 467 (M+H); $_1$H NMR ($CDCl_3$) : 7.16 and 6.95 (2s, 2H, H_6); 7.02

and 6.30 (2s, 2H, $H_{3'}$); 4.30 (m, 8H, $CH_3\underline{CH_2}O$); 2.00 (s, 3H, CH_3); 1.30 (m, 12H, $\underline{CH_3}CH_2O$); Anal. Calc. for: $C_{21}H_{26}\overline{O_{10}}N_2$;C, 54.05; H, 5.62; N, 6.01; Found; $\overline{C}$, 54.14; H, 5.60; N, 5.97.

ANTIVIRAL ASSAY PROCEDURES

Cytotoxicity measurements were based on either microscopic examination of alteration of normal cell morphology, or inhibition of cell growth. The cell lines used for both the antiviral activity and cytotoxicity assays were CEM cells and human embryonic skin-muscle (E_6SM) fibroblasts. The different compounds were evaluated for their antiviral activity according to well-established procedures.[22,23] The origin of the viruses [human immunodeficiency virus type 1 (HIV-1) (strain HTLV-III_B/LAI), HIV-2 (LAV-2_{ROD}), herpes simplex virus type 1 (HSV-1) (strain KOS), thymidine kinase-deficient (TK^-) HSV-1 (strain B2006), herpes simplex virus type 2 (HSV-2) (strain G), vaccinia virus and vesicular stomatitis virus] has been described previously.[22,23]

ANTITUMOR SCREENING

Compounds **6a-e**, **7a-e** and **8a-e** were subjected to the NCI in vitro screening panel assay as described elswhere.[20,21]

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