Cytidine nucleosides
II. Photochemical synthesis of 5-alkylcytidine nucleosides

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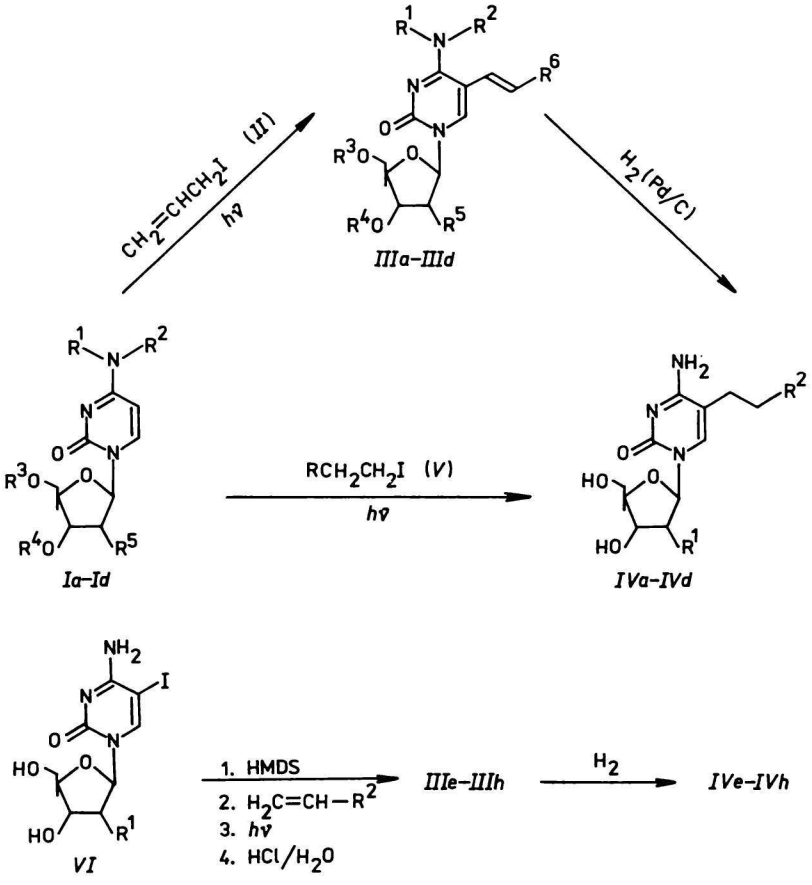
5-Alkylcytidine nucleosides were synthesized *via* a photocoupling reaction. 5-Propylcytidine and 5-propyl-2′-deoxycytidine have been prepared through the reduction of 5-(3-propenyl)cytidine and its 2′-deoxy derivative, which in turn were prepared by photoirradiation of cytidine or 2′-deoxycytidine in the presence of 3-iodopropene. 5-(2-Hydroxyethyl)cytidine and its derivatives were obtained from the reaction of cytidine or 2′-deoxycytidine with 2-iodoethanol. Trimethylsilyl derivatives of 5-iodocytidine and 5-iodo--2′-deoxycytidine, when treated with methyl acrylate, or acrylonitrile and the reaction product in each case subjected to catalytic hydrogenation, afforded 5-[2-(methoxycarbonyl)ethyl]cytidine and its 2′-deoxycytidine analogue, and the corresponding 5-(2-cyanoethyl)nucleosides, respectively.

5-Substituted pyrimidine nucleosides are potential inhibitors of thymidilate synthetase, which is the sole source of the essential DNA precursor thymidilic acid [1—4]. Therefore several approaches for the synthesis of the 5-alkyl-substituted uracil nucleosides have been reported in the last few years. Two main synthetic approaches are widely used: A palladium-catalyzed coupling reaction of alkenes with 5-chloromercury or 5-iodouridine derivatives [5—8] and a second approach utilizing a photochemical reaction as the key step [9, 10].

5-Substituted cytosine nucleosides while exhibiting essentially the same chemotherapeutic activity as their deaminated counterparts, are less toxic to the uninfected host cells [11, 12]. Since the only synthesis of 5-alkyl-substituted cytidine nucleosides has been reported through a palladium-catalyzed coupling reaction [2], we have sought a different synthetic route to these biologically and clinically important nucleosides.

Photoirradiation of cytidine (*Ia*), 2′-deoxycytidine (*Ib*) or their trimethylsilyl derivatives *Ic* and *Id* in the presence of 3-iodopropene at $\lambda = 254$ nm affords the corresponding nucleosides *IIIa*—*IIId* (Scheme 1). Hydrolytic removal of the trimethylsilyl protecting groups in *IIIc* and *IIId* gave *IIIa* and *IIIb*. The reaction of *Ic* and *Id* was carried out in anhydrous acetonitrile, while 25 % aqueous acetonitrile was used as a solvent for the reaction of *Ia* and *Ib*. The use of such solvent system eliminates the need for prior nucleoside derivation and hydrolytic removal of the protecting groups. The structure of compounds *IIIa* and *IIIb*



For *I*

	a	*b*	*c*	*d*
R^1–R^4:	H	H	Me_3Si	Me_3Si
R^5:	OH	H	H	$OSiMe_3$

For *III*

	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
R^1–R^4:	H	H	Me_3Si	Me_3Si	H	H	H	H
R^5:	OH	H	$OSiMe_3$	H	OH	H	OH	H
R^6:	Me	Me	Me	Me	CN	CN	COOMe	COOMe

For *IV*

	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
R^1:	OH	H	OH	H	OH	H	OH	H
R^2:	CH_3	CH_3	OH	OH	CN	CN	COOMe	COOMe

For *V*

	a	*b*	*c*
R:	OH	CH_3	H

For *VI*

	a	*b*
R^1:	OH	H

Scheme 1

was established using ^{1}H NMR, IR, and mass spectroscopy and compared to standards prepared according to the known method [2] by HPLC on Partisil PXS 10/25 ODS-II using methanol—water as the solvent. Catalytic hydrogenation of *IIIa* and *IIIb* afforded the corresponding 5-propylcytidine (*IVa*) and 5-propyl-2′-deoxycytidine (*IVb*) [2]. Similarly, photoirradiation of *Ia* or *Ib* in the presence of 2-iodoethanol (*Va*) affords the corresponding 5-(2-hydroxyethyl)cytidine (*IVc*) and 5-(2-hydroxyethyl)-2′-deoxycytidine (*IVd*), respectively.

Attempts to extend this reaction to the attachment of simple unsubstituted alkyl groups at C-5 of the cytosine ring have been met with little success. Photoirradiation of cytidine or its trimethylsilyl derivative in the presence of 1-iodopropane (*Vb*) or other alkyl halides (as iodoethane or iodomethane) afforded only starting material.

In a different approach we observed that photoirradiation of the trimethylsilyl derivative of 5-iodocytidine (*VIa*) or 5-iodo-2′-deoxycytidine (*VIb*), in the presence of methyl acrylate at $\lambda = 254$ nm, affords methyl 3-(5-cytidinyl)propenoate (*IIIg*), or methyl 3-(2′-deoxy-5-cytidinyl)propenoate (*IIIh*), after removal of the trimethylsilyl protecting groups. The reaction product in each case was directly subjected to catalytic hydrogenation to afford 5-[2-(methoxycarbonyl)ethyl]cytidine (*IVg*) and its 2′-deoxycytidine analogue (*IVh*).

The same approach was utilized for the photocoupling of acrylonitrile with 5-iodocytidine or 5-iodo-2′-deoxycytidine, 5-(2-cyanoethenyl)cytidine (*IIIe*) and its 2′-deoxycytidine analogue (*IIIf*) were obtained. The products in each case were similarly subjected to catalytic hydrogenation to afford the corresponding nucleosides *IVe* and *IVf*.

Experimental

IR spectra were measured with a Unicam SP 2006, and UV spectra with a Perkin—Elmer 554 recording spectrophotometer. ^{1}H NMR spectra were obtained on a Varian 56/69 A and mass spectra on a Varian CH5 mass spectrometer. The determined mass fractions of C, H, N (Microanalytical Centre, Cairo University) differed maximally by ± 0.4 % from the calculated values. HPLC was performed using Partisil PXS 10/25 ODS-II, and preparative Partisil M9-10/50 ODS-2 columns.

5-(3-Propenyl)cytidine (IIIa)

Method A. Cytidine *Ia* (500 mg; 2.05 mmol) and 3-iodopropene (10 cm^3) in 25 % aqueous acetonitrile (100 cm^3) were deoxygenated and irradiated in a quartz reaction vessel at $\lambda = 254$ nm in a Rayonet photochemical reactor (Model RPR 100, Southern New England Ultraviolet Co.) for 24 h.

The solution was concentrated under reduced pressure and the residue subjected

to silica gel column chromatography using 10 % methanol in chloroform as eluent to give *IIIa* in an impure form. The crude product was then resolved by HPLC using a Partisil preparative column, with 50 % aqueous methanol solution as eluent to afford *IIIa* in 42 % yield as white crystals. M.p. = 176 °C (decomp.) (Ref. [2] gives m.p. = = 176—176.5 °C).

Method B. Ia (500 mg; 2.05 mmol) and hexamethyldisilazane (650 mg; 4.30 mmol), in 5 cm^3 of anhydrous pyridine were stirred under argon at room temperature overnight. The pyridine and the excess hexamethyldisilazane were removed *in vacuo* at ambient temperature. The cytidine trimethylsilyl derivative *Ic* was dissolved in 600 cm^3 of anhydrous acetonitrile, treated with 3-iodopropene (10 cm^3) deoxygenated and irradiated at $\lambda = 254$ nm for 24 h. The solution was concentrated under vacuum. The residue was then hydrolyzed with 10 cm^3 H_2O, and after evaporation it was worked up as described in method *A* to afford *IIIa* in 46 % yield.

5-Propylcytidine (IVa)

The nucleoside *IIIa* (200 mg; 0.706 mmol) in 100 cm^3 of methyl alcohol was treated with 10 % Pd/C (50 mg) and stirred under 165 kPa of hydrogen for 10 h. The catalyst was removed by filtration and the solvent was removed under reduced pressure. The white solid residue was recrystallized from CH_3CN (181 mg, 90 % yield). M.p. = 179—182 °C (Ref. [2] gives m.p. = 178—182 °C, charring).

5-(3-Propenyl)-2′-deoxycytidine (IIIb) and 5-propyl-2′-deoxycytidine (IVb)

2′-Deoxycytidine *Ib* (500 mg; 2.2 mmol) was photoirradiated in the presence of 3-iodopropene (10 cm^3) according to the above described procedure to afford *IIIb* as white crystals. M.p. = 180 °C (Ref. [2] gives m.p. = 180 °C (decomp.)).

Catalytic hydrogenation of *IIIb* (200 mg; 0.749 mmol) as described above afforded *IVb* as white crystals (185 mg, 90 % yield). M.p. = 184 °C (Ref. [2] gives m.p. = = 182.5—184 °C (decomp.)).

5-(2-Hydroxyethyl)cytidine (IVc)

Cytidine *Ia* (500 mg; 2.05 mmol) and 2-iodoethanol (10 cm^3) in 25 % aqueous acetonitrile (100 cm^3) were deoxygenated and irradiated at $\lambda = 254$ nm for 24 h. Work-up as above afforded *IVc* in 32 % yield. For $C_{11}H_{17}N_3O$ w_i(calc.): 45.99 % C, 5.92 % H, 14.63 % N; w_i(found): 46.23 % C, 6.18 % H, 14.96 % N. Mass spectrum, m/z (I_r/%): 287 (12, M^+), 154 (100, hydroxyethylcytosine), 242 (21), 211 (28), 154 (36), 143 (13), 133 (58, ribose). ^{1}H NMR spectrum (D_2O), δ: 2.24 (t, 2H, $J = 3.2$ Hz, CH_2CH_2OH), 3.08 (m, 2H, CH_2OH), 3.62—4.2 (m, 4H), 5.92 (narrow m, 1H, H-1′), 7.62 (s, 1H, H-6).

5-(2-Hydroxyethyl)-2′-deoxycytidine (IVd)

This compound was obtained as described for the previous synthesis, from *Ib* or *Id*, in 28 % yield (method *A*), resp. 33 % yield (method *B*). Mass spectrum, m/z (I_r/%): 271 (18, M^+), 187 (21), 154 (100, heterocyclic base), 127 (32), 117 (48, 2-deoxyribose).

Reaction of cytidines with alkyl halides

Ia (500 mg; 2.05 mmol) or *Ib* (500 mg; 2.19 mmol), and 1-iodopropane (iodoethane or iodomethane; 10 cm^3) were dissolved in 25 % aqueous acetonitrile (100 cm^3), deoxygenated and irradiated at $\lambda = 254$ nm for 24 h. After removal of the solvent and work-up as described above, only starting cytidines were obtained.

Reaction of cytidine with allyl chloride

Ia (500 mg; 2.05 mmol) and allyl chloride (10 cm^3, 123 mmol) were dissolved in 25 % aqueous acetonitrile (100 cm^3), deoxygenated and irradiated at $\lambda = 254$ nm for 24 h. After removal of the solvent and work-up as above only brown polymerized material was obtained.

Methyl 3-(2′-deoxy-5-cytidinyl)propenoate (IIIh) and 5-[2-(methoxycarbonyl)ethyl]-2′-deoxycytidine (IVh)

5-Iodo-2′-deoxycytidine *VIb* (500 mg; 1.24 mmol) and hexamethyldisilazane (650 mg; 4.03 mmol) in 5 cm^3 of anhydrous pyridine were stirred at room temperature under argon overnight and the solvent evaporated under vacuum. The trimethylsilyl derivative, dissolved in 60 cm^3 of anhydrous acetonitrile, was treated with methyl acrylate (10 cm^3), deoxygenated and irradiated at $\lambda = 254$ nm for 24 h. Removal of the solvent and work-up as described above afforded *IIIh* in 24 % yield. Mass spectrum, m/z (I_r/%): 300 (12, M^+), 310 (15), 282 (24), 254 (38), 194 (32, heterocyclic base), 117 (100, 2-deoxyribose). The prepared nucleoside *IIIh* in 100 cm^3 of methyl alcohol was treated with 50 mg of Pd/C and stirred under 165 kPa of hydrogen for 10 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed over silica gel using 10 % ethanol in chloroform as eluent to give *IVh* in 72 % yield. ^{1}H NMR spectrum (D_2O), δ: 2.60 (m, 4H, CH_2CH_2COOMe), 3.62 (s, 3H, OCH_3), 5.82 (d, 1H, $J = 3.2$ Hz, H-1′), 7.68 (s, 1H, H-6). For $C_{13}H_{19}N_3O_6$ MeOH w_i(calc.): 48.70 % C, 6.67 % H, 12.17 % N; w_i(found): 49.09 % C, 7.02 % H, 12.42 % N.

Methyl 3-(5-cytidinyl)propenoate (IIIg) and 5-[2-(methoxycarbonyl)ethyl]cytidine (IVg)

This reaction was carried out as described for the previous compound starting with 5-iodocytidine (*VIa*). Nucleoside *IIIg* was obtained in 22 % yield. Catalytic hydrogena-

tion performed as in the previous synthesis gave *IVg* in 79 % yield. ^{1}H NMR spectrum (D_2O), δ: 2.73 (m, 4H, CH_2CH_2COOMe), 3.54 (s, 3H, OCH_3), 6.18 (t, 1H, $J = 6.4$ Hz, H-1′), 7.89 (s, 1H, H-6). For $C_{13}H_{19}N_3O_7$ w_i(calc.): 47.42 % C, 5.78 % H, 12.77 % N; w_i(found): 47.74 % C, 5.95 % H, 12.94 % N.

5-(2-Cyanoethenyl)cytidine (IIIe) and 5-(2-cyanoethyl)cytidine (IVe)

VIa (500 mg; 1.35 mmol) was treated with hexamethyldisilazane as described above. The trimethylsilyl derivative thus obtained was dissolved in 60 cm^3 of anhydrous acetonitrile, treated with acrylonitrile (6 cm^3), deoxygenated and irradiated at $\lambda = 254$ nm for 24 h. Removal of the solvent and work-up as described above gave *IIIe* in 18 % yield. Mass spectrum, m/z (I_r/%): 294 (9, M^+), 253 (18), 161 (32, heterocyclic base), 133 (100, ribose). The nucleoside *IIIe* (500 mg; 1.7 mmol) was dissolved in methanol (100 cm^3), treated with 50 mg of 10 % Pd/C and stirred under 165 kPa of hydrogen for 10 h. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel using 10 % methanol in chloroform as eluent to give *IVe* in 76 % yield. ^{1}H NMR spectrum (D_2O), δ: 2.72 (m, 4H, CH_2CH_2CN), 5.78 (d, 1H, $J = 3.2$ Hz, H-1′), 7.18 (s, 1H, H-6). For $C_{12}H_{16}N_4O_5$ w_i(calc.): 48.65 % C, 5.41 % H, 18.92 % N; w_i(found): 49.97 % C, 5.63 % H, 18.74 % N.

5-(2-Cyanoethenyl)-2′-deoxycytidine (IIIf) and 5-(cyanoethyl)-2′-deoxycytidine (IVf)

This reaction was performed as described for the previous synthesis starting from *VIb*. Nucleoside *IIIf* was obtained in 20 % yield and was subjected to catalytic hydrogenation following the same procedure as above to afford *IVf* in 82 % yield. ^{1}H NMR spectrum (D_2O), δ: 262 (t, 2H, CH_2CN), 3.0 (t, 2H, CH_2CH_2CN), 7.2 (s, 1H, C-6—H). For $C_{12}H_{16}N_4O_4$ MeOH w_i(calc.): 50.00 % C, 6.41 % H, 17.95 % N; w_i(found): 50.21 % C, 6.72 % H, 18.13 % N.

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