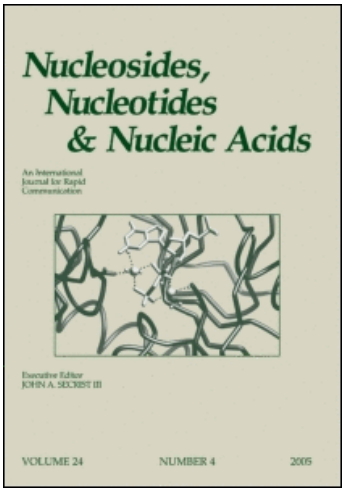

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Cytidlne Nucleosides I: Photochemical Approach for the Synthesis of C-5 Aryl and Heteroaryl Substituted 2'-Deoxycytidine

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CYTIDINE NUCLEOSIDES I: Photochemical Approach for the Synthesis of C-5 Aryl and Heteroaryl Substituted 2'-Deoxycytidine

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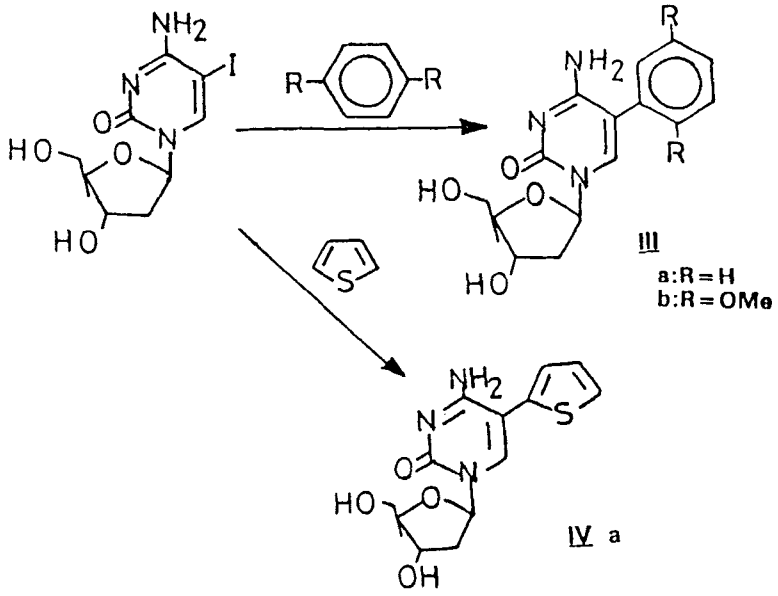
Abstract: Different photochemical approaches for the synthesis of 5-aryl and 5-heteroaryl-2'-deoxycytidines are reported. In one approach the photolytic reaction of 5-iodo-2'-deoxycytidine in the presence of arenes or heteroarenes is described. Alternatively, the photolysis of haloarenes or haloheteroarenes in the presence of 2'-deoxycytidine was utilized.

Over the past two decades several C-5 substituted uracil nucleosides have been synthesized and reported to exhibit significant antiviral activity.[1-3] Being analogues of thymidine they are potential inhibitors of thymidylate synthetase and therefore are potentially important in the clinical control of cancer growth and/or viral infections.[4,5] Two synthetic methods were found to be useful for the direct synthesis of these modified nucleosides: a palladium-catalyzed coupling reaction[2,3] and a photochemical method.[3,6,7]

The activity spectrum of 5-substituted cytosine nucleosides is essentially similar to that of their deaminated counterparts. However, they are considerably less toxic to the uninfected host cells.[8-10] Recent evidence suggests that the activity to toxicity ratio of certain thymidine analogs can be significantly improved upon conversion to the corresponding cytidine derivatives.[11-12]

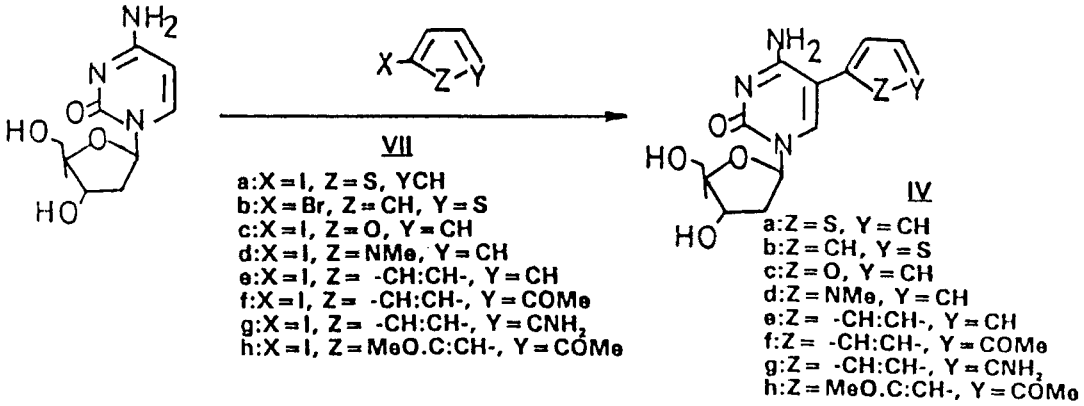
The aim of this paper is to report simple and direct photochemical synthetic approaches to a series of 5-aryl and 5-heteroaryl cytidine nucleosides. The



(SCHEME 1)

trimethylsilyl derivative of 5-iodo-2′-deoxycytidine (I) was prepared by its treatment with hexamethyldisilazane in pyridine at room temperature, and the product II was used without further purification after removal of pyridine in vacuo .5-Phenyl-2′-deoxycytidine IIIa was prepared in 26% yield by photo-irradiating deoxygenated solution of II in benzene at 254 nm in a quartz reaction vessel for 24 hr. Derivatization of 5-iodo-2′-deoxycytidine was a necessity to render it soluble in benzene. Photolysis of II in acetonitrile with a five fold excess of 1,4-dimethoxybenzene afforded 5- (2,5-dimethoxycytidine) IIIb in 37% yield. The higher yield of IIIb may be due to the electron releasing effect of the methoxy groups on the reactivity of the 1,4-dimethoxybenzene ring.

Preparation of C-5 heteroaryl cytidine derivatives IVa,c,d was achieved by the treatment of II with the corresponding heteroarenes. The reaction is regiospecific on the α-position of the heteroatom. Similar regiospecificity had previously been observed in the photo-coupling reactions of heteroarenes.[13,14] Substitutions at different positions of the heteroaryl nucleus were not accessible under these reaction conditions. However, an alternative route for the synthesis



(SCHEME 2)

of these substituted nucleosides is available through the exploitation of the free radical nature of the photolytic reaction of haloarenes (or haloheteroarenes). Therefore, photo-irradiation of deoxygenated solution of the trimethylsilyl derivative of 2'-deoxycytidine VI, in iodobenzene at 254 nm afforded 5-Phenyl-2'-deoxycytidine IVe in 32% yield, identical by NMR, mass spectrum, and high pressure L.C. with IIIa obtained according to the previous method. No trace of the 6-Phenyl isomer could be detected under these conditions.

The regioselectivity of the reaction could be explained by the higher electron density on C-5, compared to the C-6 atom of the cytosine ring, in the ground state of the nucleoside. Therefore, C-5 will be the preferable site for addition of the aryl (or heteroaryl) radical formed by cleavage of the carbon-halogen bond in the photoexcited haloarenes (or heteroarenes). Treatment of VI with 2-iodothiophene (VIIa), 3-bromothiophene (VIIb), 2-iodofuran (VIIc), 2-iodo-1-methyrrole (VIId) afforded 5-(2-thienyl), 5-(3-thienyl), 5-(2-furyl) and 5-(1-methylpyrrole-2-yl)-2'-deoxycytidines IVa-d, respectively. Similarly, 5-(4-anisyl)-2'-deoxycytidine IVf and 5-(4-aminophenyl)-2'-deoxycytidine IVg were available upon the treatment of VI with 4-iodoanisole and 4-iodoaniline, respectively.

Direct irradiation of underivatized 2'-deoxycytidine (V) solubilized in a mixed solvent (25% aqueous acetonitrile) in the presence of haloarenes (or

Table 1: Photochemical reactions of 2'-deoxycytidine and 5-iodo-2'-deoxycytidine with haloaryland heteroaryl compounds.

Reactants	Yield	Compound	M.P. °C	Micro Analysis C H N
IDC(1);Benzene OR DC(2);Iodobenzene	26 22.4	5-phenyl-2'-deoxycytidine IIIa (or IVe)	186	C15 H17 N3 O4 Calc. 59.40 5.61 13.86 Fnd. 58.96 5.32 13.29
IDC; 1,4-dimethoxybenzene OR DC; 2-Chloro-1,4-dimethoxybenzene	37 28	5-(2,5-dimethoxyphenyl)-2'-deoxycytidine IIIb (or IVh)	132	C17 H21 N3 O6 Calc. 56.20 5.79 11.57 Fnd. 55.82 5.28 11.16
IDC; Thiophene OR DC; 2-Iodothophene	32 24	5-(2-Thienyl)-2'-deoxycytidine IVa	164	C13 H15 N3 O4 S Calc. 50.49 4.85 13.59 Fnd. 50.32 5.41 13.32 (S; Calc:10.35 Fnd:10.59)
DC; 3-Bromothiophene	18	5-(3-Thienyl)-2'-deoxycytidine IVb	173-175	C13 H15 N3 O4 S Calc. 50.49 4.85 13.59 Fnd. 50.92 5.21 13.21 (S;Calc:10.35 Fnd:10.68)
DC; 2-Iodofuran	20	5-(2-Furyl)-2'-deoxycytidine IVc	180	C13 H15 N3 O5 Calc. 53.24 5.12 14.33 Fnd. 53.49 5.55 14.00
DC; N-Methyl-2-iodopyrrole	16	5-(1-Methylpyrrol-2-yl)-2'-deoxycytidine IVd	126	C14 H18 N4 O4 Calc. 54.90 5.88 18.30 Fnd. 54.52 5.64 18.78
DC; 4-Iodoanisole	27	5-(4-anisyl)-2'-deoxycytidine IVf	154	C16 H19 N3 O5 Calc. 57.66 5.70 12.61 Fnd. 57.82 5.94 12.18
DC; 4-Iodoaniline	12	5-(4-aminophenyl)-2'-deoxycytidine IVg	197	C15 H18 N4 O4 Calc. 56.60 5.66 17.61 Fnd. 56.21 6.03 17.28

(1) IDC = 5-Iodo-2'-deoxycytidine.
(2) DC = 2'-Deoxycytidine.

haloheteroarenes) under a nitrogen atmosphere afforded the corresponding 5-substituted nucleosides. The yield in this approach was considerably lower than the yield obtained from the previous approach. However, this is compensated for by the simplicity and directness of the approach.

EXPERIMENTAL

IR spectra were measured with a Unicam S.P.2006, and U.V. spectra with a Perkin-Elmer 554 recording spectrophotometer. H-NMR spectra were obtained

Table 2: Spectral data of compounds III and IV.

Compound	Mass Spec. m/e	U.V. in MeOH λ max.(ε)	min.(ε)	^{1}H NMR (CD_3 OD)
IIIa	303(7.mol.ion), 187(100,5ph-cytosine),144(12),143(21), 117(38,deoxyribose).	280 (9200)	250 (8400)	δ8.12(s,1H,C6-H),7.60-7.32(m,5H,aromatic),6.29(t,1H,J = 6.2Hz,Cl'-H).
IIIb	363(28,mol.ion)274(100,heterocyclic base)232(30),231 (28),205(15).	269 (8350)	245 (7600)	δ7.98(s,1H,C6-H),7.08 (s,3H,aromatic),6.23 (t,1H,J = 6.5Hz,Cl'-H).
IVa	309(26,mol.ion),193(100, heterocyclic base),158(12), 117(68,deoxyribose).	274 (13230)	256 (11700)	δ8.24(s,1H,C6-H),7.62-7.48(m,3H,heterocyclic) 6.28(t,1H,J = 6.2Hz,Cl'-H)
IVb	309(18,mol.ion),193(100,base) 159(20),158(17),117(72,sugar)	270 (12400)	254 (10900)	δ8.20(s,1H,C6-H),7.58-7.41(m,3H,heterocyclic) 6.31(t,1H,J = 6.1Hz,Cl'-H)
IVc	293(6,mol.ion),225(32),177 (40-base),176(50),117(100).	268 (11300)	236 (10180)	δ7.98(s,1H,C6-H),7.22-7.06(m,3H,heterocyclic) 6.40(t,1H,J = 6.1Hz,Cl'-H)
IVd	306(10,mol.ion),291(32),225 (28),189(100,heterocyclic base), 117(70,deoxyribose).	277 (11850)	258 (9540)	δ7.36(s,1H,C6-H),7.21 (m,1H,heterocyclic),6.82(m,2H),3.42(s.3H,NCH_3) 6.28(t,1H,J = 6.5Hz,Cl'-H)
IVf	333(32,mol.ion)329(10),302(6), 295(40),216(47,base),195(20), 117(100,deoxyribose).	279 (8970)	248 (7400)	δ8.03(s,1H,C6-H),7.53-7.39(m,4H,aromatic),6.18 (t,1H,Cl'-H,3.46(s.3H, O-CH_3)
IVg	318(6,mol.ion),252(10),240 (16),203(37,heterocyclic base),137(27),117(100, deoxyribose).	249 (8450)	224 (5090)	δ7.93-7.41(m.5H,aromatic C6-H),6.32(t,1H,J6.5Hz, Cl'-H).

on a Varian 56/69 A and Mass spectra on a Varian CH5 mass spectrometer. Unless indicated C, H, N analysis were +0.4% of the calculated values, and were performed at the Micro-analytical Center, Cairo University. Our Rayonet Model RPR 100 photochemical reactor is a product of Southern New England Ultraviolet Co. High pressure L.C. was performed using Partisil PXS 10/25 ODS-2, and preparative Partisil M9-10/50 ODS-2 columns.

5-(2,5-Dimethoxyphenyl)-2'-deoxycytidine IIIb:

Method A: A solution of 5-iodo-2'-deoxycytidine (500 mg, 41 mmol) and hexamethyldisilazine (0.33 g, 2 mmol) in 5 mL of dry pyridine was stirred

overnight at 25°C in an argon atmosphere. After removal of the pyridine in vacuo the residue was dissolved in 100 mL of anhydrous acetonitrile, 1,4-dimethoxybenzene (0.87 g, 6.3 mmol) was added and the solution was deoxygenated by bubbling dry argon gas through the solution. Irradiation at 254 nm for 30 hrs. was done, followed by the addition of 10 mL of 0.1 N hydrochloric acid in 50% methanol-water. The resulting mixture was stirred for 3 hours at 25°C to assure deprotection. After evaporation in vacuo the residue was resolved on silica gel using 7% ethanol in chloroform to give 890 mg of IIIb, 44% yield.

Method B: Using the above procedure a solution of 100 mg of 2'-deoxycytidine (V, 0.4 mmol) and 450 mg of hexamethyldisilazine (2.8 mmol) in 2 mL of pyridine was stirred overnight. The residue after evaporation in vacuo was dissolved in 30 mL of acetonitrile containing 6.4 g of 2-chloro-1,4-dimethoxybenzene (37 mmol) and irradiated for 48 hr. at 254 nm. The product IIIb, identified by HPLC fractionation and the ultraviolet spectrum, was formed in 30% yield.

Method C: 2'-Deoxycytidine (500 mg, 2.19 mmol), and 2-chloro-1,4-dimethoxybenzene (1.7 g, 10 mmol), were dissolved in 100 mL of acetonitrile containing 25% water, the reaction mixture was deoxygenated with argon and irradiated at 254 nm for 48 hours. The solvent was removed under vacuum and the residue resolved on a silica gel column with 10% methanol in chloroform as eluent to give the product in crude dark form containing some deoxycytidine and other impurities. This crude product was then resolved by high pressure liquid chromatography using a Partisil preparative M 9-10/50 ODS-2 column, with 50% aqueous methanol as eluent, to afford IIIb in 22% yield.

REFERENCES

1. P. Danenberg, Biochim, Biophys. Acta. 473, 73 (1977).
2. D. E. Bergstrom, Nucleosides and Nucleotides, 1,1 (1982).
3. C. F. Bigge and M. P. Mertes, J. Org. Chem., 46, 1994 (1981).
4. M. Friedkin, Adv. in Enzymology 38, 235 (1973).

5. C. F. Maley, R. L. Bellisario, D. U. Guarino and F. Maley, J. Biol. Chem., 254, 1288 (1979) and references therein.

6. V. V. Kaminski, A. J. Wexler, R. J. Balchunis and J. S. Swenton, J. Org. Chem., 49, 2738 (1984).

7. I. Saito, H. Ikehara and T. Matsuura, J. Org. Chem., 51, 5148 (1986).

8. H. E. Renis, Cancer Res., 30, 189 (1970).

9. M. A. Jerkofsky, M. J. Dobersen and S. Greer, Ann. N.Y. Acad. Sci., 284, 389 (1977).

10. E. De Clercq and P. F. Torrence, J. Carb. Nucleosides Nucleotides, 5, 187 (1978).

11. E. De Clercq, J. Balzarini, J. Descamps, G. F. Huang, P. F. Torrence, D. E. Bergstrom, A. S. Joanes, P. Serafinowski, G. Verhelst, R. T. Walker, Mol. Pharmacology, 21, 217 (1982).

12. G. F. Huang and P. F. Torrence, J. Carb. Nucleosides Nucleotides, 5, 317 (1978) and references therein.

13. D. W. Allen, D. J. Buckland, B. G. Hutley, A. C. Oades and J. B. Turner, J. Chem. Soc. 621 (1977).

14. M. E. Hassan, An Real Acad. Farmacia 50, 57 (1984).

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