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PHOTOCHEMICAL SYNTHESIS OF DEUTERIUM LABELLED 4-N-SUBSTITUTED CYTOSINES

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Summary

The efficient photochemical method for the preparation of 4-N-(1-deuterio-alkyl)cytosines using as precursors 4-N-(1-carboxy-alkyl)cytosines is described.

Key words: 4-N-(1-deuterio-alkyl)cytosines, photodecarboxylation.

Cytosine derivatives have received considerable attention due to antiviral and anticancer properties of the corresponding nucleosides[1,2]. Among the large number of known cytosine analogs, 4-N-substituted derivatives are of interest as naturally occurring constituents of t-RNA[3]. We have recently reported that 4-N-(1-carboxy-alkyl)cytosines undergo remarkably efficient photochemical decarboxylation to give the proper 4-N-substituted cytosines[4].

The present paper describes photochemical synthesis of 4-N-(1-deuterio-alkyl)cytosines. Ultraviolet irradiation with wavelengths longer than 290 nm in deuterium oxide-acetone (1:1, v/v) solution of compounds 1a-f [4,5] and methanol-d-acetone (3:7, v/v) solution of 1g[5] resulted in formation of photoproducts 2a-g containing a deuterium at the position formerly occupied by the carboxyl.

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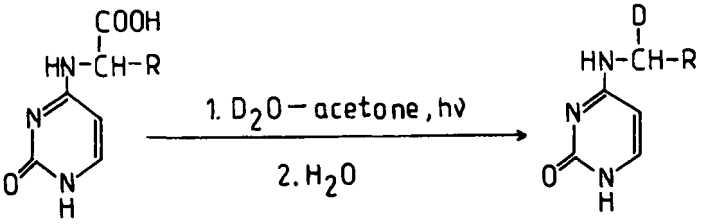
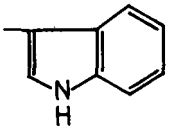


		Yield (%)
1a, R=H	2a	85
1b, R=CH_3	2b	79
1c, R=$CH(CH_3)CH_3$	2c	70
1d, R=CH_2OH	2d	45
1e, R=CH_2COOH	2e	61
1f, R=CH_2Ph	2f	67
1g, R=CH_2 	2g	66

The irradiation of 4-N-(1-carboxy-2-hydroxyethyl)cytosine 1d has to be carefully controled by tlc chromatography because initially produced 2d under prolonged irradiation undergoes futher photochemical reaction to give 4-N-methylcytosine. However it was possible to obtain 2d in 45% yield. In case of photolysis of 4-N-(1,2-dicarboxy-ethyl)cytosine 1e only carboxyl group at the 1 position is decarboxylated and 4-N-(1-deuterio-2-carboxy-ethyl)-cytosine 2e is photochemically stable.

Thus the photodecarboxylation of 4-N-(1-carboxy-alkyl)-cytosines in the presence of deuterium oxide offers an experimentally simple method to prepare 4-N-(1-deuterio-alkyl)-cytosines of high isotopic purity in good yield. The isotopic purity of obtained compounds 2a-g as determined by NMR spectroscopy was higher than 97%.

In conclusion, we have developed a highly efficient method for the synthesis of the specifically deuterated 4-N-substituted cytosines. The utility of the procedure was demonstrated by the synthesis of seven 4-N-(1-deuterio-alkyl)cytosines.

EXPERIMENTAL

Elemental analyses were made on an Elemental Analyser Perkin-Elmer 240. ^{1}H- and ^{13}C-NMR spectra were determined on a Jeol FX 90 Q (90 MHz) and in case of 2g on a Varian (300 MHz) spectrometer. Mass spectra were made on a Jeol JMS-D-100 mass spectrometer. Irradiations at λ>290 nm were carried out with a 400 W high pressure mercury lamp with a cylindrical Pyrex light filter 1.5 mm thick.

Compounds 1a-g were prepared according to the literature method[5].

Synthesis of 4-N-(1-deuterio-alkyl)cytosines 2a-g

Dry 1 (250 mg) was dissolved in deuterium oxide and the solution was evaporated to dryness in vacuum. Then the residue was dissolved in deuterium oxide-acetone (1:1, 100 ml) and irradiated under dry nitrogen atmosphere for 15-50 min, until TLC showed disappearance of 1. After irradiation the solution was evaporated, dissolved in water and again evaporated to dryness. The residue was subjected to chromatography on a silica gel column which eluted with chloroform-methanol 7:3 (v/v) gave 2. Recrystallization from water-ethanol afforded analytically pure samples of the products.

In case of 1g instead of deuterium oxide methanol-d was used due to poor solubility of 1g in deterium oxide.

2a:

^{1}H-NMR (DMSO-d_6) δ 2.74 (d, 2H, $-CDH_2$), 5.68 (d, 1H, C^5-H), 7.30 (d, 1H, C^6-H), 7.78 (t, 1H, N^4-H), 10.40 (br s, 1H, N^1-H).

^{13}C-NMR (DMSO-d_6) δ 26.39 (t, $-CDH_2$), 93.41 (C^5), 140.98 (C^6), 156.96 (C^2), 164.98 (C^4).

MS, m/z (rel. int.) 126 (100), 110 (11), 96 (15), 82 (21).

2b:

^{1}H-NMR (DMSO-d_6) δ 1.08 (d, 3H, CH_3), 2.97-3.24 (m, 1H, CDH), 5.64

(d, 1H, C^5-H), 7.27 (d, 1H, C^6-H), 7.72 (d, 1H, N^4-H), 10.33 (br s, 1H, N^1-H).

^{13}C-NMR (DMSO-d_6) δ 14.09 (CH_3), 34.08 (t, CDH), 93,79 (C^5), 141.14 (C^6), 157.39 (C^2), 164.43 (C^4).

MS, m/z (rel. int.) 140 (100), 125 (50), 111 (50), 95 (27).

2c:

^{1}H-NMR (DMSO-d_6) δ 0.88 (d, 6H, CH_3), 1.61-1.99 (m, 1H, CH), 3.04 (m, 1H, CDH), 5.66 (d, 1H, C^5-H), 7.26 (d, 1H, C^6-H), 7.62 (d, 1H, N^4-H), 10.31 (br s, 1H, N^1-H).

^{13}C-NMR (DMSO-d_6) δ 20.05 (two CH_3), 27.36 (CH), 46.70 (t, CDH), 93.46 (C^5), 141.09 (C^6), 156.85 (C^2), 164 76 (C^4).

MS, m/z (rel. int.) 168 (34), 153 (14), 125 (100), 111 (45).

2d:

^{1}H-NMR (DMSO-d_6) δ 3.36 (m, 1H, CDH), 3.53 (d, 2H, CH_2), 4.34 (br s 1H, OH), 5.77 (d, 1H, C^5-H), 7.35 (d, 1H, C^6-H), 7.89 (d 1H, N^4-H), 10.50 (br s, 1H, N^1-H).

^{13}C-NMR (DMSO-d_6) δ 42.23 (t, CDH), 59.55 (CH_2), 93.79 (C^5), 141.25 (C^6), 157.23 (C^2), 164.76 (C^4).

MS, m/z (rel. int.) 156 (3), 138 (95), 137 (100), 126 (10), 125 (22), 112 (55), 111 (45).

2e:

^{1}H-NMR (DMSO-d_6) δ 2.46 (d, 2H, CH_2), 3.37 (m, 1H, CDH), 5.60 (d, 1H, C^5-H), 7.25 (d, 1H, C^6-H), 7.64 (br s, 1H, N^4-H), 10.24 (br s, 1H, N^1-H).

^{13}C-NMR (DMSO-d_6) δ 33.32 (CH_2), 35.49 (t, CDH), 93.13 (C^5), 141.30 (C^6), 156.48 (C^2), 164.49 (C^4), 172.73 (C=O).

MS, m/z (rel. int.) 166 (9), 138 (5), 137 (5), 125 (3), 111 (38), 73 (100).

2f:

^{1}H-NMR (DMSO-d_6) δ 2.83 (d, 2H, CH_2), 3.53 (m, 1H, CDH), 5.75 (d, 1H, C^5-H), 7.25-7.53 (m, 6H, C^6-H and C_6H_5), 7.99 (br s, 1H, N^4-H), 10.31 (br s, 1H, N^1-H).

^{13}C-NMR (DMSO-d_6) δ 34.46 (CH_2), CDH signals are covered by DMSO-d_6, 93.68 (C^5), 125.97 (C_6H_5), 128.11 (C_6H_5), 128.52 (C_6H_5), 139.35 (C_6H_5), 141.14 (C^6), 157.01 (C^2), 164.43 (C^4).

MS, m/z (rel. int.) 216 (4), 125 (15), 112 (14), 105 (49), 91 (100).

2g:

^{1}H-NMR (CD_3-OD) δ 3.02 (d, 2H, CH_2), 3.67 (m, 1H, CDH), 5.73 (d, 1H, C^5-H), 6.98 (dd, 1H, $C^{5'}$-H), 7.03-7.17 (m, 2H, $C^{2'}$-H and $C^{6'}$-H), 7.27 (d, 1H, $C^{7'}$-H), 7.32 (d, 1H, $C^{4'}$-H), 7.55 (d, 1H, C^6-H).

^{13}C-NMR (CD_3OD) δ 28.50 (CH_2), 44.85 (t, CDH), 99.23 (C^5), 115.02 ($C^{7'}$), 116.02 ($C^{8'}$), 122.10 ($C^{6'}$), 122.95 ($C^{4'}$),125.05 ($C^{5'}$), 126.23 ($C^{2'}$), 131.60 ($C^{9'}$), 140.92 ($C^{10'}$), 144.69 (C^6), 163.41 (C^2), 169.41 (C^4).

MS, m/z (rel. int.) 255 (1), 145 (9), 144 (16), 130 (48), 126 (70), 111 (100).

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