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A CONVENIENT ROUTE TO 5'-MODIFIED PSEUDOISOCYTIDINES AND 2-THIOPSEUDOURIDINES[1]

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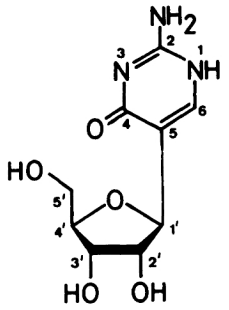
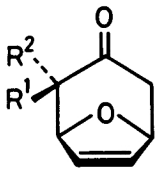
A stereo- and regiocontrolled synthesis of 5'-alkylated or -arylated pseudoisocytidines and 2-thiopseudouridines is described.

Pseudoisocytidine (I) is a recently developed antileukemic agent that is currently under phase I clinical investigation.[2] Although certain nucleosides possessing a branched chain sugar moiety are known to exhibit unique biological and therapeutic efficacy,[3] to date no report exists for structural modification of the ribose skeleton of I. The discovery of this important C-nucleoside has prompted us to synthesize its analogues via the new preparative procedure developed in our laboratories.[4]

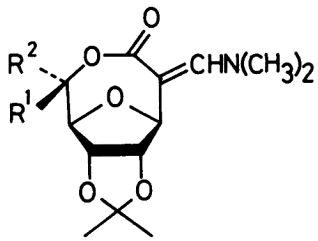


I

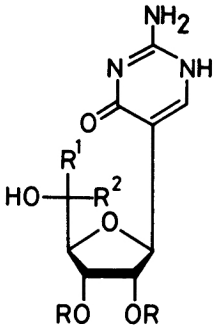
The dimethylaminomethylene lactones, IIIa--d, are obtainable regiospecifically from the corresponding oxabicyclic ketones of type II in three steps as described previously.[1,4] When IIIa was treated with guanidine hydrochloride (8 equiv) in refluxing ethanolic sodium ethoxide (1.7 M) for 5 hr, the isocytosine derivative IVa was obtained in 73% yield, mp 242—243 °C (from methanol).[5] The β configuration of the C-1' appendage was suggested by the Imbach rule; the NMR spectrum showed two singlets due to the isopropylidene methyls at δ 1.28 and 1.49 ($\Delta\delta$ = 0.21 ppm).[6] The glycol protective group was then removed by treating with 10% HCl in methanol at 25 °C for 5 min, leading to 5',5'-dimethylpseudoisocytidine hydrochloride (Va).[7] The NMR and UV spectral data were consistent with the assigned structure: NMR (dimethyl sulfoxide-d_6) δ 1.14 (s, 2 CH_3), 3.52 (d, $H_{4'}$), 3.97 (m, $H_{2'}$ and $H_{3'}$), 4.49 (d, $H_{1'}$), 4.6—6.4 (br, OH), 7.91



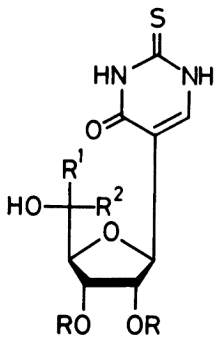
II



III



IV, R--R = $C(CH_3)_2$
V, R = H (HCl salt)



VI, R--R = $C(CH_3)_2$
VII, R = H

a: $R^1 = R^2 = CH_3$
b: $R^1 = CH_3$; $R^2 = H$
c: $R^1 = (CH_2)_4CH_3$; $R^2 = H$
d: $R^1 = C_6H_5$; $R^2 = H$

(s, H_6), 8.53 (br, NH_2); $J_{1',2'}$ = 5.0 Hz, $J_{3',4'}$ = 4.1 Hz; UV λ_{max} (methanol) 223 (ε 9840), 263 nm (7100), λ_{max} (0.1 N HCl) 221 (12900), 262 nm (10100), λ_{max} (0.1 N NaOH) 233 (8080), 276 nm (6430). Similarly, the bicyclic compounds, IIIb—d, were converted to the corresponding pseudoisocytidine derivatives (Vb—d)[8] in a stereocontrolled fashion.

The base catalyzed condensation of III with thiourea furnished the 2-thiopseudouridine derivative VI. For example, when a mixture of IIIa and thiourea (7 equiv) was stirred in 1.1 M sodium ethoxide in ethanol at 80—90 °C for 5 hr, the 2-thiouracil VIa was obtained in 71% yield.[9] Again only the β stereoisomer was produced; NMR $\Delta\delta$ value for the isopropylidene methyls was 0.19 ppm.[6] Treatment of VIa with 10% HCl in methanol at 25 °C for 10 min afforded 5',5'-dimethyl-2-thiopseudouridine (VIIa) in quantitative yield.[10] Other derivatives, VIIb—d,[11] were obtained in a like manner.

The described methodology offers a direct and selective route to a number of pyrimidine C-nucleoside analogues. Unlike conventional approaches using carbohydrate precursors, this method provides an easy way allowing incorporation of alkyl or aryl substituents at the C-5' position.

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REFERENCES AND NOTES

1) C-Nucleoside Synthesis V. Part IV: T. Sato, M. Watanabe, and R. Noyori, Tetrahedron Lett., in press.

2) C. K. Chu, I. Wempen, K. A. Watanabe, and J. J. Fox, J. Org. Chem., 41, 2793 (1976); C. K. Chu, K. A. Watanabe, and J. J. Fox, J. Heterocycl. Chem., 12, 817 (1975); J. H. Burchenal, K. Ciovacco, K. Kalaher, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, Cancer Res., 36, 1520 (1976).

3) E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmermann, and F. W. Holly, J. Am. Chem. Soc., 88, 4524 (1966); H. T. Shigeura and S. D. Sampson, Nature, 215, 419 (1967); S. R. Jenkins, B. Arison, and E. Walton, J. Org. Chem., 33, 2490 (1968); E. Walton, S. R. Jenkins, R. F. Nutt, and F. W. Holly, J. Med. Chem., 12, 306 (1969); H. Grisebach and R. Schmid, Angew. Chem., Int. Ed. Engl., 11, 159 (1972).

4) R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 100, 2561 (1978).

5) NMR (dimethyl sulfoxide-d_6) δ 1.10 (s, CH_3), 1.28 and 1.49 (s, isopropylidene CH_3), 3.67 (d, $H_{4'}$), 4.51 (m, $H_{2'}$), 4.68 (m, $H_{1'}$ and $H_{3'}$), 6.64 (br, NH_2), 7.66 (s, H_6), 11.00 (br, NH); $J_{3',4'}$ = 3.0 Hz. UV λ_{max} (methanol) 227 (ε 5330), 290 nm (5370), λ_{max} (0.1 N NaOH) 233 (7420), 276 nm (5940).

6) J.-L. Imbach, Ann. N.Y. Acad. Sci., 255, 177 (1975).

7) All compounds described herein are racemic. Stable new compounds afforded correct elemental analysis and/or exact mass spectral data.

8) Vb: mp 198--202 °C; NMR (pyridine-d_5) δ 1.58 (d, CH_3), 4.35 (m, $H_{4'}$ and $H_{5'}$), 4.92 (m, $H_{3'}$), 5.18 (m, $H_{1'}$ and $H_{2'}$), 6.50 (br, NH, NH_2, and OH); J_{5',CH_3} = 5.8 Hz; UV λ_{max} (methanol) 223 (ε 10500), 265 (7160), 290 nm (3910), λ_{max} (0.1 N HCl) 221 (8950), 262 nm (6890), λ_{max} (0.1 N NaOH) 233 (8670), 276 nm (6870). Vc: mp 168—172 °C; NMR (dimethyl sulfoxide-d_6) δ 0.88 (t, CH_3), 1.1—1.6 (m, CH_2), 3.6 (m, $H_{4'}$ and $H_{5'}$), 4.0 (m, $H_{2'}$ and $H_{3'}$), 4.47 (d, $H_{1'}$), 7.80 (s, H_6), 8.45 (br, NH_2); $J_{1',2'}$ = 4.9 Hz, J_{CH_3,CH_2} = 6.0 Hz; UV λ_{max} (methanol) 224

(ε 9630), 266 (6220), 290 nm (4180), λ_{max} (0.1 N HCl) 220 (11800), 262 nm (9070), λ_{max} (0.1 N NaOH) 233 (7340), 276 nm (5840). Vd: wax; NMR (dimethyl sulfoxide-d_6) δ 3.98 (m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 4.48 (d, $H_{1'}$), 4.70 (m, $H_{5'}$), 4.4–5.7 (br, OH), 7.35 (m, C_6H_5), 7.61 (s, H_6), 8.57 (br, NH_2); $J_{1',2'}$ = 6.0 Hz; UV λ_{max} (methanol) 225 (ε 12700), 264 (8240), 290 nm (3960), λ_{max} (0.1 N HCl) 263 nm (10300), λ_{max} (0.1 N NaOH) 233 (13200), 277 nm (10100).

9) Mp 161–162 °C. NMR (acetone-d_6) δ 1.20 (s, CH_3), 1.32 and 1.51 (s, isopropylidene CH_3), 3.79 (d, $H_{4'}$), 4.68 (dd, $H_{2'}$), 4.80 (d, $H_{1'}$), 4.82 (dd, $H_{3'}$), 7.71 (s, H_6); $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 4.5 Hz, $J_{3',4'}$ = 3.1 Hz. UV λ_{max} (methanol) 213 (ε 11100), 276 (13800), 290 nm (13000), λ_{max} (0.1 N NaOH) 222 (14700), 264 (12000), 285 nm (9490).

10) Mp 109–115 °C. NMR (pyridine-d_5) δ 1.58 and 1.60 (s, CH_3), 4.34 (d, $H_{4'}$), 4.96 (m, $H_{2'}$ and $H_{3'}$), 5.31 (d, $H_{1'}$), 5.7 (br, NH and OH), 8.19 (s, H_6); $J_{1',2'}$ = 5.0 Hz, $J_{3',4'}$ = 3.8 Hz. UV λ_{max} (methanol) 214 (ε 5780), 276 (6660), 292 nm (5990), λ_{max} (0.1 N HCl) 214 (7560), 274 (8810), 289 nm (8810), λ_{max} (0.1 N NaOH) 222 (7910), 263 (6670), 284 nm (5020).

11) VIIb: wax; NMR (pyridine-d_5) δ 1.51 (d, CH_3), 4.67 (m, $H_{4'}$ and $H_{5'}$), 4.96 (m, $H_{2'}$ and $H_{3'}$), 5.35 (d, $H_{1'}$), 6.0 (br, NH and OH), 8.16 (s, H_6); $J_{1',2'}$ = 5.2 Hz, J_{5',CH_3} = 6.0 Hz; UV λ_{max} (methanol) 215 (ε 6610), 277 (8350), 291 nm (7590), λ_{max} (0.1 N HCl) 213 (6080), 280 (4630), 295 nm (5600), λ_{max} (0.1 N NaOH) 221 (11400), 264 (10200), 285 nm (7730). VIIc: mp 164–170 °C; NMR (pyridine-d_5) δ 0.81 (t, CH_3), 1.0–2.0 (m, CH_2), 4.30 (m, $H_{5'}$), 4.57 (t-like, $H_{4'}$), 5.0 (m, $H_{2'}$ and $H_{3'}$), 5.35 (d, $H_{1'}$), 5.4–6.8 (br, NH and OH), 8.14 (s, H_6); $J_{1',2'}$ = 5.2 Hz, $J_{3',4'}$ = $J_{4',5'}$ = 3.0 Hz, J_{CH_3,CH_2} = 7.0 Hz; UV λ_{max} (methanol) 214 (ε 4310), 276 (5160), 291 nm (4670), λ_{max} (0.1 N HCl) 215 (7090), 276 (8230), 290 nm (8230), λ_{max} (0.1 N NaOH) 222 (5300), 264 (4340), 285 nm (3420). VIId: mp 126–130 °C; NMR (dimethyl sulfoxide-d_6) δ 3.95 (d-like, $H_{4'}$), 4.46 (d, $H_{3'}$), 4.70 (m, $H_{2'}$), 4.90 (m, $H_{1'}$), 5.59 (d, $H_{5'}$), 7.2–7.5 (m, C_6H_5), 7.44 (s, H_6); $J_{2',3'}$ = 7.0 Hz, $J_{4',5'}$ = 3.1 Hz; UV λ_{max} (methanol) 212 (ε 4380), 277 (3620), 290 nm (3240), λ_{max} (0.1 N HCl) 275 (6900), 290 nm (6440), λ_{max} (0.1 N NaOH) 264 (6510), 285 nm (5030).

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