

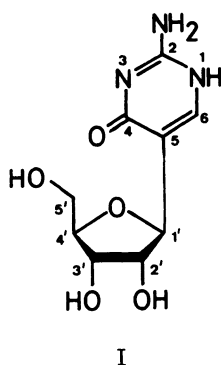
A CONVENIENT ROUTE TO 5'-MODIFIED PSEUDOISOCYTIDINES  
AND 2-THIOPSEUDOURIDINES<sup>1</sup>

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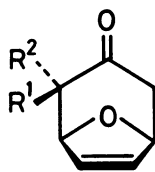
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A stereo- and regiocontrolled synthesis of 5'-alkylated or -arylated pseudoisocytidines and 2-thiopseudouridines is described.

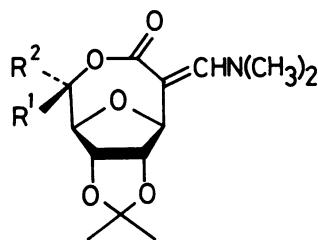
Pseudoisocytidine (I) is a recently developed antileukemic agent that is currently under phase I clinical investigation.<sup>2</sup> Although certain nucleosides possessing a branched chain sugar moiety are known to exhibit unique biological and therapeutic efficacy,<sup>3</sup> to date no report exists 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.<sup>4</sup>



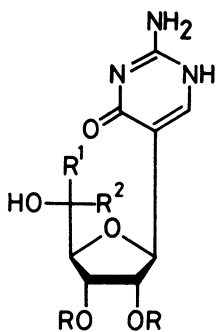
The dimethylaminomethylene lactones, IIIa--d, are obtainable regiospecifically from the corresponding oxabicyclic ketones of type II in three steps as described previously.<sup>1,4</sup> When IIIa was treated with guanidine hydrochloride (8 equiv) in refluxing ethanolic sodium ethoxide (1.7 M) for 5 hr, the isocytosine derivative IVa was obtained in 73% yield, mp 242–243 °C (from methanol).<sup>5</sup> The  $\beta$  configuration of the C-1' appendage was suggested by the Imbach rule; the NMR spectrum showed two singlets due to the isopropylidene methyls at  $\delta$  1.28 and 1.49 ( $\Delta\delta$  = 0.21 ppm).<sup>6</sup> 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).<sup>7</sup> The NMR and UV spectral data were consistent with the assigned structure: NMR (dimethyl sulfoxide-d<sub>6</sub>)  $\delta$  1.14 (s, 2 CH<sub>3</sub>), 3.52 (d, H<sub>4'</sub>), 3.97 (m, H<sub>2'</sub> and H<sub>3'</sub>), 4.49 (d, H<sub>1'</sub>), 4.6–6.4 (br, OH), 7.91



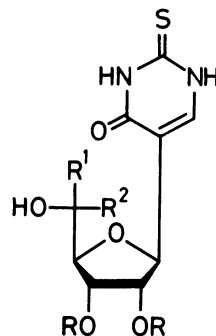
II



III



IV, R-R = C(CH<sub>3</sub>)<sub>2</sub>  
 V, R = H (HCl salt)



VI, R-R = C(CH<sub>3</sub>)<sub>2</sub>  
 VII, R = H

- a: R<sup>1</sup> = R<sup>2</sup> = CH<sub>3</sub>  
 b: R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = H  
 c: R<sup>1</sup> = (CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>; R<sup>2</sup> = H  
 d: R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>; R<sup>2</sup> = H

(s, H<sub>6</sub>), 8.53 (br, NH<sub>2</sub>);  $J_{1',2'} = 5.0$  Hz,  $J_{3',4'} = 4.1$  Hz; UV  $\lambda_{\max}$  (methanol) 223 ( $\epsilon$  9840), 263 nm (7100),  $\lambda_{\max}$  (0.1 N HCl) 221 (12900), 262 nm (10100),  $\lambda_{\max}$  (0.1 N NaOH) 233 (8080), 276 nm (6430). Similarly, the bicyclic compounds, IIIb-d, were converted to the corresponding pseudoisocytidine derivatives (Vb-d)<sup>8</sup> 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.<sup>9</sup> Again only the  $\beta$  stereoisomer was produced; NMR  $\Delta\delta$  value for the isopropylidene methyls was 0.19 ppm.<sup>6</sup> Treatment of VIa with 10% HCl in methanol at 25 °C for 10 min afforded 5',5'-dimethyl-2-thiopseudouridine (VIIa) in quantitative yield.<sup>10</sup> Other derivatives, VIIb–d,<sup>11</sup> 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

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- 2) C. K. Chu, I. Wempfen, 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. Wempfen, and J. J. Fox, *Cancer Res.*, **36**, 1520 (1976).
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- 4) R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, **100**, 2561 (1978).
- 5) NMR (dimethyl sulfoxide- $d_6$ )  $\delta$  1.10 (s,  $\text{CH}_3$ ), 1.28 and 1.49 (s, isopropylidene  $\text{CH}_3$ ), 3.67 (d,  $\text{H}_{4'}$ ), 4.51 (m,  $\text{H}_{2'}$ ), 4.68 (m,  $\text{H}_{1'}$  and  $\text{H}_{3'}$ ), 6.64 (br,  $\text{NH}_2$ ), 7.66 (s,  $\text{H}_6$ ), 11.00 (br, NH);  $J_{3',4'} = 3.0$  Hz. UV  $\lambda_{\text{max}}$  (methanol) 227 ( $\epsilon$  5330), 290 nm (5370),  $\lambda_{\text{max}}$  (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- $d_5$ )  $\delta$  1.58 (d,  $\text{CH}_3$ ), 4.35 (m,  $\text{H}_{4'}$  and  $\text{H}_{5'}$ ), 4.92 (m,  $\text{H}_{3'}$ ), 5.18 (m,  $\text{H}_{1'}$  and  $\text{H}_{2'}$ ), 6.50 (br, NH,  $\text{NH}_2$ , and OH);  $J_{5',\text{CH}_3} = 5.8$  Hz; UV  $\lambda_{\text{max}}$  (methanol) 223 ( $\epsilon$  10500), 265 (7160), 290 nm (3910),  $\lambda_{\text{max}}$  (0.1 N HCl) 221 (8950), 262 nm (6890),  $\lambda_{\text{max}}$  (0.1 N NaOH) 233 (8670), 276 nm (6870). Vc: mp 168–172 °C; NMR (dimethyl sulfoxide- $d_6$ )  $\delta$  0.88 (t,  $\text{CH}_3$ ), 1.1–1.6 (m,  $\text{CH}_2$ ), 3.6 (m,  $\text{H}_{4'}$  and  $\text{H}_{5'}$ ), 4.0 (m,  $\text{H}_{2'}$  and  $\text{H}_{3'}$ ), 4.47 (d,  $\text{H}_{1'}$ ), 7.80 (s,  $\text{H}_6$ ), 8.45 (br,  $\text{NH}_2$ );  $J_{1',2'} = 4.9$  Hz,  $J_{\text{CH}_3,\text{CH}_2} = 6.0$  Hz; UV  $\lambda_{\text{max}}$  (methanol) 224

- ( $\epsilon$  9630), 266 (6220), 290 nm (4180),  $\lambda_{\max}$  (0.1 N HCl) 220 (11800), 262 nm (9070),  $\lambda_{\max}$  (0.1 N NaOH) 233 (7340), 276 nm (5840). Vd: wax; NMR (dimethyl sulfoxide- $d_6$ )  $\delta$  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  $\lambda_{\max}$  (methanol) 225 ( $\epsilon$  12700), 264 (8240), 290 nm (3960),  $\lambda_{\max}$  (0.1 N HCl) 263 nm (10300),  $\lambda_{\max}$  (0.1 N NaOH) 233 (13200), 277 nm (10100).
- 9) Mp 161–162 °C. NMR (acetone- $d_6$ )  $\delta$  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  $\lambda_{\max}$  (methanol) 213 ( $\epsilon$  11100), 276 (13800), 290 nm (13000),  $\lambda_{\max}$  (0.1 N NaOH) 222 (14700), 264 (12000), 285 nm (9490).
- 10) Mp 109–115 °C. NMR (pyridine- $d_5$ )  $\delta$  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  $\lambda_{\max}$  (methanol) 214 ( $\epsilon$  5780), 276 (6660), 292 nm (5990),  $\lambda_{\max}$  (0.1 N HCl) 214 (7560), 274 (8810), 289 nm (8810),  $\lambda_{\max}$  (0.1 N NaOH) 222 (7910), 263 (6670), 284 nm (5020).
- 11) VIIb: wax; NMR (pyridine- $d_5$ )  $\delta$  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  $\lambda_{\max}$  (methanol) 215 ( $\epsilon$  6610), 277 (8350), 291 nm (7590),  $\lambda_{\max}$  (0.1 N HCl) 213 (6080), 280 (4630), 295 nm (5600),  $\lambda_{\max}$  (0.1 N NaOH) 221 (11400), 264 (10200), 285 nm (7730). VIIc: mp 164–170 °C; NMR (pyridine- $d_5$ )  $\delta$  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,  $J_{CH_2,CH_2} = 7.0$  Hz; UV  $\lambda_{\max}$  (methanol) 214 ( $\epsilon$  4310), 276 (5160), 291 nm (4670),  $\lambda_{\max}$  (0.1 N HCl) 215 (7090), 276 (8230), 290 nm (8230),  $\lambda_{\max}$  (0.1 N NaOH) 222 (5300), 264 (4340), 285 nm (3420). VIId: mp 126–130 °C; NMR (dimethyl sulfoxide- $d_6$ )  $\delta$  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  $\lambda_{\max}$  (methanol) 212 ( $\epsilon$  4380), 277 (3620), 290 nm (3240),  $\lambda_{\max}$  (0.1 N HCl) 275 (6900), 290 nm (6440),  $\lambda_{\max}$  (0.1 N NaOH) 264 (6510), 285 nm (5030).

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