# Nucleosides. CIX. 2′-Deoxy-ψ-isocytidine, 2′-Deoxy-ψ-uridine, and 2′-Deoxy-1-methyl-ψ-uridine. Isosteres of Deoxycytidine, Deoxyuridine and Thymidine



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2′-Deoxy-ψ-isocytidine (VIIβ), a 2′-deoxy analog of antileukemic ψ-isocytidine and also a *C*-nucleoside analog of deoxycytidine, was synthesized from ψ-uridine by making use of the newly discovered pyrimidine to pyrimidine transformation reaction [*J. Heterocyclic Chem.*, 14, 537 (1977)]. 2′-Deoxy-ψ-uridine (IIβ) and 2′-deoxy-1-methyl-ψ-uridine (V), both *C*-nucleoside analogs of deoxyuridine and thymidine, were also synthesized.

ψ-Uridine was converted into the 2′-chloro analogs (I) which was reduced with tributyltin hydride to give an α,β-mixture of 2′-deoxy-ψ-uridines. The β-isomer (IIβ) was trimethylsilylated and the product (III) treated with methyl iodide to afford the 1-methyl derivative (IV). After hydrolytic removal of the trimethylsilyl groups from IV, the thymidine analog (V) was obtained in good yield.

A crude mixture of II was converted in good yield into an α,β-mixture of 1,3-dimethyl-2′-deoxy-ψ-uridines (VI) by treatment with DMF dimethyl acetal in DMF. Treatment of the β-isomer (VIβ) with guanidine, however, gave the α,β-mixture of 2′-deoxy-ψ-isocytidines (VII). The pure β-isomer (VIIβ) was obtained by thick layer chromatography. The pure α-isomer (VIIα) was obtained when VIα was treated with guanidine.

2′-Deoxy-ψ-isocytidine (VIIβ) and 2′-deoxy-1-methyl-ψ-uridine (V) exhibited inhibitory activity against P815 cells ($ID_{50}$ 1.2 μg./ml. and 4.9 μg./ml., respectively) and the thymidine analog V was found to be active against *Streptococcus faecium* var. *duran*.

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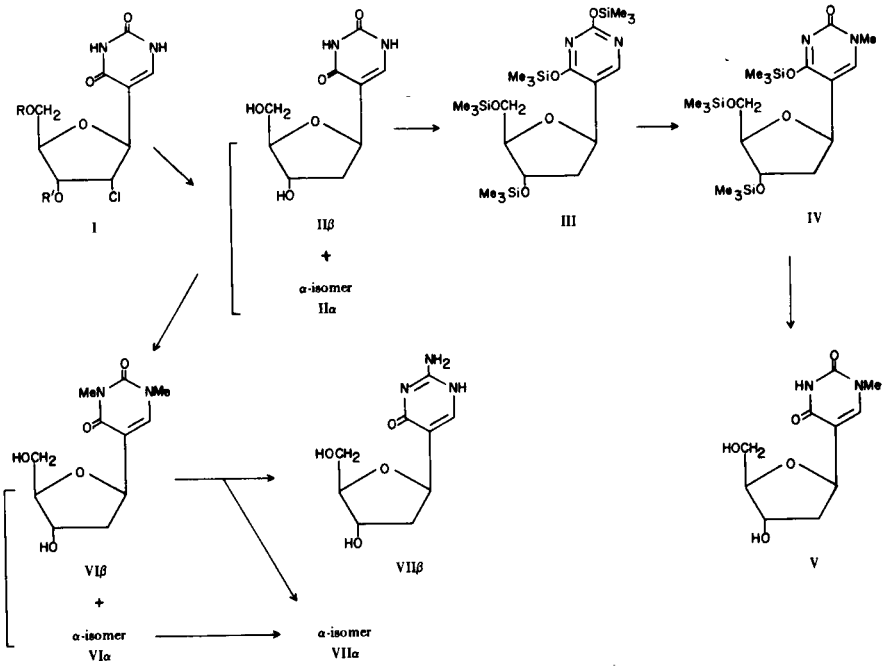
*Sir:*

Pseudoisocytidine (ψ-isocytidine) (1) was found to be active against leukemic cells in culture and also markedly active against transplanted mouse leukemia (2). ψ-Isocytidine is currently undergoing phase I clinical trial at this Center. These findings prompted us to synthesize the 2′-deoxy analog of ψ-isocytidine and related *C*-nucleosides. We report herein the syntheses and some preliminary bio-



logical studies on 2′-deoxy-ψ-uridine, 2′-deoxy-1-methyl-ψ-uridine (an analog of thymidine) and 2′-deoxy-ψ-isocytidine.

ψ-Uridine was treated with α-acetoxyisobutyryl chloride (3) or *O*-acetoxybenzoyl chloride (4) in acetonitrile to afford a mixture of variously protected anhydronucleosides and 2′-chloro-2′-deoxy-ψ-uridines (I) (5). A mixture of crude I, tri-*n*-butyltin hydride (6), and 2,2′-azobis(2-methylpropionitrile) in dimethoxyethane was refluxed whereupon an α,β-mixture (1:1) of 2′-deoxy-ψ-uridine (II) was obtained. These isomers were separated by silica gel column chromatography. The α-isomer (IIα) had m.p. 216-217° (7); nmr (deuterium oxide): δ 1.87-2.00 (m, 2H, H-2′,2″), 3.61 (q, 1H, H-5′, $J_{4',5'}$ = 5.2, $J_{5',5''}$ = 12.5 Hz), 3.82 (q, 1H, H-5″, $J_{4',5''}$ = 3.1, $J_{5',5''}$ = 12.5 Hz), 4.36 (m, 1H, H-3′), 4.66 (q, 1H, H-1′, $J_{1',2'}$ = 2.8, $J_{1',2''} < 0.2$ Hz), 7.58 (s, 1H, H-6). The β-isomer (IIβ) had m.p. 221-223°; nmr (deuterium oxide): δ 2.05-2.19 (m, 2H, H-2′,2″), 3.64 (t, 2H, H-5′,5″), 3.93 (m, 1H, H-4′), 4.18 (m, 1H, H-3′), 4.97 (t, 1H, H-1′, $J_{1',2'} \cong J_{1',2''} \cong 7.4$ Hz), 7.58 (s, 1H, H-6).

Compound IIβ was trimethylsilylated with hexamethyldisilazane in the presence of a catalytic amount of ammonium sulfate (8). The syrupy product IIIβ was treated without purification with methyl iodide in acetonitrile to give intermediate IVβ. After hydrolytic removal of the trimethylsilyl groups, 1-methyl-2′-deoxy-ψ-uridine (V) was obtained, m.p. 158-160°; nmr (deuterium oxide): δ 2.08-2.22 (m, 2H, H-2′,2″), 3.35 (s, 3H, $NCH_3$), 3.55-3.70 (m, 2H, H-5′,5″), 3.96 (m, 1H, H-4′), 4.70 (m, 1H, H-3′), 4.99 (m, 1H, H-1′, $J_{1',2'} \cong J_{1',2''} \cong 7.8$, $J_{1',6} < 0.5$ Hz), 7.69 (d, 1H, H-6, $J_{1',6} < 0.5$ Hz).

A crude mixture of II, when treated with DMF dimethyl acetal, was converted in good yield into an α,β-mixture of 1,3-dimethyl-2′-deoxy-ψ-uridine (VI). These isomers were separated by silica gel column chromatography: The α-isomer (VIα), m.p. 171-172°, nmr (deuterium oxide): δ 1.90-2.00 (m, 2H, H-2′,2″), 3.30 (s, 3H, $NCH_3$), 3.42 (s, 3H, $NCH_3$), 3.69 (q, 1H, H-5′, $J_{4',5'} \cong 12.4$ Hz), 3.91 (q, 1H, H-5″, $J_{4',5''} \cong 3.4$, $J_{5',5''} \cong 12.4$ Hz), 4.39 (m, 2H, H-3′,4′), 4.73 (q, 1H, H-1′, $J_{1',2'} \cong 2.4$, $J_{1',2''} < 0.2$, $J_{1',6} \cong 0.7$ Hz); the β isomer (VIβ), m.p. 136-137°, nmr (deuterium oxide): δ 2.07-2.25 (m, 2H, H-2′,2″), 3.30 (s, 3H, $NCH_3$), 3.42 (s, 3H, $NCH_3$), 3.68 (q, 1H, H-5′, $J_{4',5'} \cong 2.1$, $J_{5',5''} \cong 13.0$ Hz), 3.83 (q, 1H, H-5″, $J_{4',5''} \cong 0.5$, $J_{5',5''} \cong 13.0$ Hz), 4.01 (m, 1H, H-4′), 4.39 (m, 1H, H-3′), 4.99 (q, 1H, H-1′, $J_{1',2'} \cong 6.4$, $J_{1',2''} \cong 9.7$ Hz), 7.13 (s, 1H, H-6).

Treatment of VIβ with guanidine (neat) at 80-90° (9) for 70 minutes afforded, however, a mixture of 2′-deoxy-ψ-isocytidines (quantitative). The β-isomer (VIIβ) was obtained in 16% yield as a pure powder from the upper part of an elongated band on a thick layer plate coated with silica gel $GF_{254}$ (2-propanol-ethyl acetate-water, 2:2:1); nmr (deuterium oxide): δ 2.09-2.20 (m, 2H, H-2′,2″), 3.65 (d, 2H, H-5′,5″), 3.95 (q, 1H, H-4′), 4.34 (m, 1H, H-3′), 4.99 (t, 1H, H-1′, $J_{1',2'} \cong J_{1',2''} \cong 8.0$ Hz), 7.65 (s, 1H, H-6). The tri-acetyl derivative of VIIβ could be crystallized from ethanol, m.p. 194-197°. When VIα was treated with guanidine, only the α-isomer (VIIα) of 2′-deoxy-ψ-isocytidine was obtained (20% yield after purification); nmr (deuterium oxide): δ 1.92-2.13 (m, 2H, H-2′,2″), 3.64 (q, 1H, H-5′, $J_{4',5'} \cong 5.2$, $J_{5',5''} \cong 12.2$ Hz), 3.84 (q, 1H, H-5″, $J_{4',5''} \cong 3.2$, $J_{5',5''} \cong 12.2$ Hz), 4.33-4.48 (m, 2H, H-3′, H-4″), 4.68 (d, 1H, H-1′, spacing 3.4 Hz), 7.68 (s, 1H, H-6). The triacetyl derivative of VIIα had m.p. 254-256°.

The 5′-phosphate of 2′-deoxy-ψ-uridine (IIβ) has been prepared (10) enzymatically from 5-*O*-phosphoryl-2-deoxy-D-*erythro*-pentose and uracil in the presence of an ψ-uridine synthetase obtained from *Agrobacterium tumefaciens*. This *C*-nucleotide was found to be an effective inhibitor of thymidylate synthetase (10). More recently, Bridges, *et al.*, reported (11) the syntheses of both IIα and IIβ *via* condensation of 2,4-di-*t*-butoxy-5-lithiopyrimidine with 3,4-*O*-benzyl-2-deoxy-D-*erythro*-pentose. They (11) confirmed the structure of IIβ by reduction of I (5).

Preliminary studies (12) of the 2′-deoxy-*C*-nucleosides against P815 cells *in vitro* showed a 50% inhibition of growth at 4.9 μg./ml. for V (an isostere of thymidine) and 1.2 μg./ml. for VIIβ (an isostere of 2′-deoxycytidine). All the other compounds reported herein did not show inhibitory activity against P815 cells at 10 μg./ml. It is also interesting to note that an antibacterial and antiviral triazine *N*-nucleoside antibiotic, U-44590, recently isolated from the culture filtrate of *Streptomyces platensis* var. *clarensis* (13) possesses a structure closely related to V. Compound V was also found active against *Streptococcus faecium* var. *duran* (14) by the microbiological disc assay method for antibiotic susceptibility testing (15).

Further biological studies on the 2′-deoxy-*C*-nucleosides, V and VII are in progress.

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