Nucleosides CIII. Anhydropyrimidine-*C*-Nucleosides. Synthesis of 4,2′-Anhydro-5-(β-D-arabinofuranosyl)- and 5-(β-D-Arabinofuranosyl)pyrimidine *C*-Nucleosides

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4,2′-Anhydro-5-(β-D-arabinofuranosyl)isocytosine and 4,2′-anhydro-5-(β-D-arabinofuranosyl)-uracil were synthesized. Treatment of ψ-isocytidine with either α-acetoxyisobutyryl chloride or salicyloyl chloride in acetonitrile afforded the acylated anhydronucleoside. Deacylation of the product with methanol-hydrogen chloride afforded 4,2′-anhydro-5-(β-D-arabinofuranosyl)isocytosine hydrochloride in crystalline form. Analogous reaction of ψ-uridine with the acyl chloride reagents, however, always gave a mixture of the acylated anhydronucleoside and 2′-chloro-2′-deoxy-ψ-uridine. Treatment of these products either singly or as a mixture with sodium methoxide in methanol afforded 4,2′-anhydro-5-(β-D-arabinofuranosyl)uracil in crystalline form in good yield.

5-(β-D-Arabinofuranosyl)isocytosine was obtained upon treatment of the corresponding 4,2′-anhydronucleoside with 10% sodium hydroxide under reflux for 30 minutes. Treatment of the anhydro uracil nucleoside with a small amount of Dowex 50(H^+) in water at 50° gave 5-(β-D-arabinofuranosyl)uracil.

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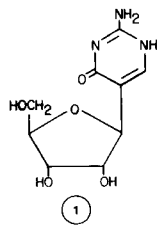
Sir:

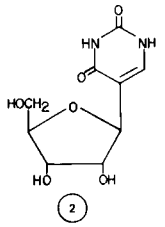
Interest in the chemistry of *C*-nucleosides has been increased by the recent isolation of several *C*-nucleoside antibiotics from the culture filtrates of various *Streptomycetes* (2,3). The recent finding (4) that ψ-isocytidine [5-(β-D-ribofuranosyl)isocytosine] (**1**), a *C*-nucleoside synthesized in our laboratory (5), showed significant antileukemic activities especially against mouse leukemias resistant to ara-C [1-(β-D-arabinofuranosyl)-cytosine] warranted further chemical investigation into this area.

We have achieved synthesis of a new class of anhydro-*C*-nucleosides from ψ-isocytidine (**1**) and ψ-uridine (**2**). Such anhydronucleosides are versatile intermediates for chemical modifications of both the aglycon and sugar moieties of *C*-nucleosides. We also report in this Communication the syntheses of arabinofuranosyl *C*-nucleosides of potential biological importance from the corresponding anhydro *C*-nucleosides.

Treatment of ψ-isocytidine (**1**) with α-acetoxyisobutyryl chloride (6) in acetonitrile under reflux for 2 hours gave the 4,2′-anhydronucleoside **3** (R = 2,5,5-trimethyldioxolanon-2-yl) in 75% yield as colorless crystals (7), m.p. 195-197°. Similar treatment of **1** with salicyloyl chloride (8) afforded the 3′,5′-di-*O*-acetyl derivative **3**, (R = Ac), m.p. 195-200° in 75% yield. Deacylation of **3** with methanol-hydrogen chloride at room temperature afforded 4,2′-anhydro-5-(β-D-arabinofuranosyl)isocytosine hydrochloride (**4**) in crystalline form in high yield, m.p. >275°; uv: λ max (*p*H 1) 277 nm, λ max (*p*H 7-14) 285 nm.

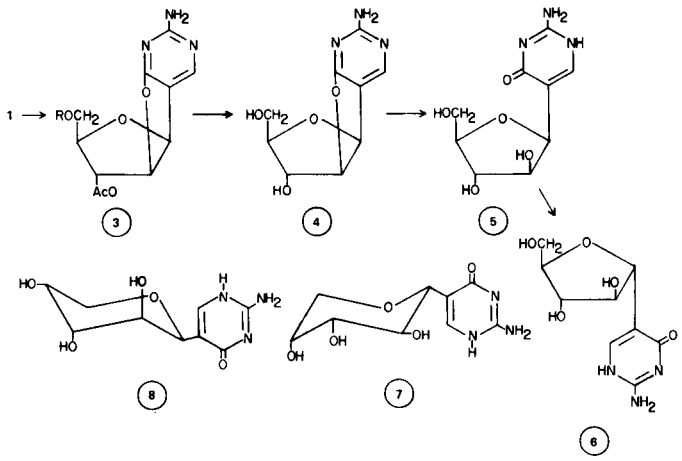


(1)



(2)

Assignment of structure **4** to the product was made on the basis of elemental analyses as well as uv and pmr studies. Uv spectral behavior of the product resembles that of 2-amino-4-methoxypyrimidine (9). The pmr



spectrum of **4** showed a downfield shift of the H-2′ signal (δ = 5.51) from that of ψ-isocytidine (**1**) (δ = 4.20) indicating that an electron withdrawing group is substituted at the 2′ position. Further proof of the anhydro structure **4** was obtained by conversion of **4** into 5-(β-D-arabinofuranosyl)isocytosine (**5**).

The 4,2′-anhydro linkage of **4** was found to be much more stable to base than that of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (10), and stringent conditions (10% sodium hydroxide under reflux for 30 minutes) were required to obtain **5** which was isolated as colorless crystals in 85% yield, m.p. $>270°$; uv: λ max (*p*H 7) 290 nm; λ max (*p*H 1) 261 nm; λ max (*p*H 14) 278 nm.

Compound **5** underwent epimerization at *C*-1′ in dilute acid solution (11). The pmr studies of the solution showed the initial formation of 5-(α-D-arabinofuranosyl)-isocytosine (**6**) (δ = 7.74, H-6 doublet, δ = 4.72, H-1′ quartet) and at equilibrium the major component was the α-pyranosyl derivative **7** (δ = 7.84, H-6 singlet, δ = 4.23, H-1′ doublet, $J_{1',2'}$ = 9.5 Hz) together with small amounts of **5**, **6** and the β-pyranosyl nucleoside **8** (δ = 7.56, H-6, δ = 4.78, H-1′ singlet). 5-(α-D-Arabinofuranosyl)-isocytosine (**6**) was also prepared by a total synthesis (12) from 2,3,5-tri-*O*-benzyl-D-arabinose.

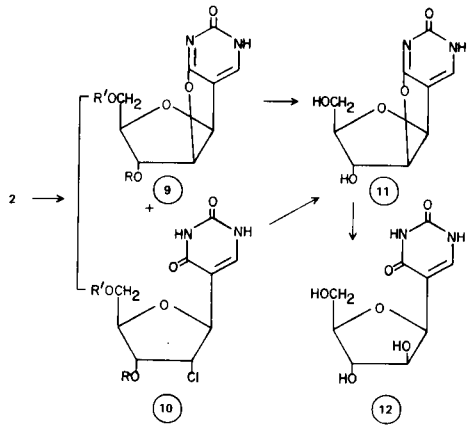
Reaction of ψ-uridine (**2**) with α-acetoxyisobutyryl chloride proceeded rather differently from that with ψ-isocytidine (**1**). Even under carefully controlled conditions, a mixture of several variously protected anhydronucleosides (**9**) and 2′-chloro-2′-deoxy-ψ-uridines (**10**) was obtained. The following *C*-nucleosides were isolated from the mixture by fractional crystallization: **9** [R = Ac, R′ = 2,5,5-trimethyldioxolanon-2-yl, m.p. 170° (browning), 178-179° dec.], **9** [R = Ac, R′ = H, m.p. 207-210° dec.], and **10** [R = Ac, R′ = H, m.p. 204-206° dec.]. The **9**:**10** ratio in the product is dependent upon the reaction condition. Short reaction (*e.g.*, 1 hour) afforded anhydronucleosides **9** as the major products whereas longer treatment (*e.g.*, 24 hours) gave mainly the chloro derivative **10**.

Treatment of **9** (R = Ac, R′ = 2,5,5-trimethyldioxolanon-2-yl) with 0.5 *M* sodium methoxide afforded 4,2′-anhydro-5-(β-D-arabinofuranosyl)uracil (**11**), m.p. 225-227°, uv: λ max (*p*H 1-7) 275 nm; λ max (*p*H 14)

Table I

Chemical Shifts and Coupling Constants

Compound	H1′	H2′	H3′	H4′	H5′,5″	H6
4 (deuterium oxide)	δ = 5.76 d $J_{1',2'}$ = 6 Hz	5.51 q $J_{2',3'}$ = 2.1	4.48 q $J_{3',4'}$ = 3.4	4.09 sextet $J_{4',5'}$ = 3.4 $J_{4',5''}$ = 5.4	3.66 octet $J_{5'5''}$ = 12.5	8.26 s
5 (deuterium oxide)	5.02 q $J_{1',2'}$ = 3.7	4.32 q $J_{2',3'}$ = 1.5	4.11 q	3.97 quintet	3.77 m	7.69 d $J_{1',6}$ = 1.5
6 (deuterium oxide)	4.67 $J_{1',2'}$ = 6.1	4.35 deformed t	4.10 d $J_{3',4'}$ = 3.4	4.10 d	3.76 m	7.69
10 (R = acetyl, R′ = H) (DMSO-d_6)	5.16	4.68	4.54	4.21	3.67	8.08
11 (deuterium oxide)	5.67 d $J_{1',2'}$ = 6.1	5.39 q $J_{2',3'}$ = 2.1	4.43 q $J_{3',4'}$ = 3.4	4.05 sextet $J_{4',5'}$ = 3.6 $J_{4',5''}$ = 5.8	3.62 octet	8.05 s
12 (deuterium oxide)	5.01 d $J_{1',2'}$ = 3.6	4.27 q	4.09 deformed t	3.95 quintet	3.77 m	7.59



285 nm. The pmr spectrum of **11** was almost identical with that of 4,2′-anhydro-5-(β-D-arabinofuranosyl)isocytosine (**4**). The same compound **11** was also obtained by treatment of **10** (R = Ac, R′ = H) with sodium methoxide. This experiment provided support of structure **10** for the chloro derivative. For the practical synthesis of **11**, isolation of individual intermediates was not necessary. Treatment of a crude product (a mixture of **9** and **10**) of the reaction of **2** and acyl chloride reagent (α-acetoxyisobutyryl chloride or salicyloyl chloride) with 0.5*M* sodium methoxide afforded **11** as the sole nucleosidic product in high yield.

The 4,2′-anhydro linkage of **11** was found to be very labile to acid. Treatment of **11** with a small amount of Dowex 50 (H^+) in water for 10 minutes at 50° gave 5-(β-D-arabinofuranosyl)uracil (**12**) which was isolated in crystalline form in high yield, m.p. 232-234°. The pmr spectrum of **12** showed close similarities with that of 5-(β-D-arabinofuranosyl)isocytosine (**5**). Compound **12** slowly isomerized to its α-counterpart **13** by prolonged Dowex 50 (H^+) treatment and after 16 hours at 50°, a mixture of **12** and **13** was obtained. The pmr spectrum of the mixture was superimposible with that of a mixture of **5** and **6**.

Studies on the synthesis of 2′-deoxy- and 2′-halogeno-*C*-nucleosides from the versatile intermediates **4** and **11** are now underway in our laboratory.

Acknowledgement.

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(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Grants No. CA-08748, CA-18856 and CA-17085.

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