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Nucleosides. II.[1] Direct Synthesis of 5-Substituted 2′,5′-Anhydro-1-β-D-arabinofuranosyluracils from Uridine Derivatives[2]

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Reaction of 5-substituted 2′,5′-dichloro-2′,5′-dideoxyuridines (**1a**—**d**) with methanolic sodium hydroxide under reflux afforded the corresponding 5-substituted 2′,5′-anhydro-1-β-D-arabinofuranosyluracils (**3a**—**d**) in high yield. On the other hand, reaction of 5-substituted uridines (**5a**—**d**) with the Vilsmeier–Haack reagent ($POCl_3$/DMF) followed by treatment with methanolic sodium hydroxide under reflux led directly to the formation of the corresponding anhydrouridines (**3a**—**d**) in good yield.

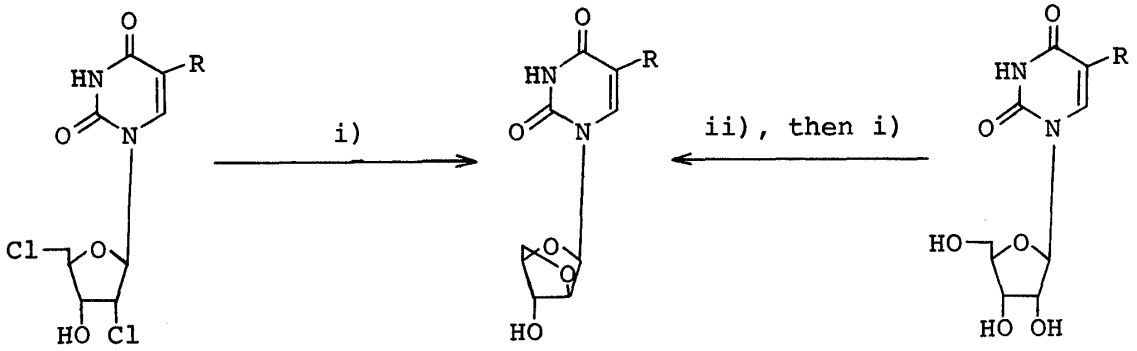
Keywords——2′,5′-anhydrouridine; 2′,5′-dichlorouridine; Vilsmeier–Haack reagent; phosphorus oxychloride; uridine chemical modification

Much work has proven that the Vilsmeier–Haack reagent is efficiently applicable to chemical modification, affording nucleosides chlorinated at the base[3] or the sugar[4] moiety. We have investigated the reaction of uridine derivatives with the Vilsmeier–Haack reagent,[5] and reported the direct synthesis of 2′,5′-dideoxy-2′,5′-dihalogenouridines from uridine derivatives by use of the reagent (POX_3/DMF).[6] These 2′,5′-dihalogenouridines are versatile intermediates for the preparation of biologically interesting 2′- and/or 5′-deoxyuridines.[7] During our investigation on the reactivities of 2′,5′-dichloro-2′,5′-dideoxyuridines (**1**) with nucleophiles, we have found a convenient synthesis of 5-substituted 2′,5′-anhydro-1-β-D-arabinofuranosyluracils (**3**) by the use of hydroxide anion as a nucleophile. 2′,5′-Anhydropyrimidine nucleosides have been synthesized by several procedures from, *e.g.*, 5′-deoxy-5′-halogeno (or 5′-methanesulfonyl)-1-β-D-arabinofuranosyluracil (or -cytosine) or 2,2′-anhydro-5′-chloro-5′-deoxy-1-β-D-arabinofuranosyluracil, but most of these syntheses involve tedious steps.[8,9] A newly devised procedure for the direct preparation of the anhydrouridines (**3**) from uridine derivatives (**5**) is also described.

Results and Discussion

Treatment of 2′,5′-dichloro-2′,5′-dideoxyuridine (**1a**)[5,6] with 1 eq of sodium methoxide under reflux for 2 h resulted in the formation of 2,2′-anhydro-5′-chloro-5′-deoxy-1-β-D-arabinofuranosyluracil (**2**), quantitatively. On the other hand, when excess sodium methoxide (10 eq) was used in the above reaction, the dichlorouridine (**1a**) was converted into the unexpected 2′,5′-anhydro-1-β-D-arabinofuranosyluracil (**3a**) in 60% yield. The structure of **3a** was supported by microanalysis and spectral data. Acetylation of **3a** with acetic anhydride in dry pyridine yielded the known 3′-*O*-acetyl derivative (**4**).[9] The structure of **3a** was ultimately confirmed by direct comparison with an authentic sample.[9]

A plausible mechanism for the formation of **3a** from **1a** is outlined in Chart 2. The base-

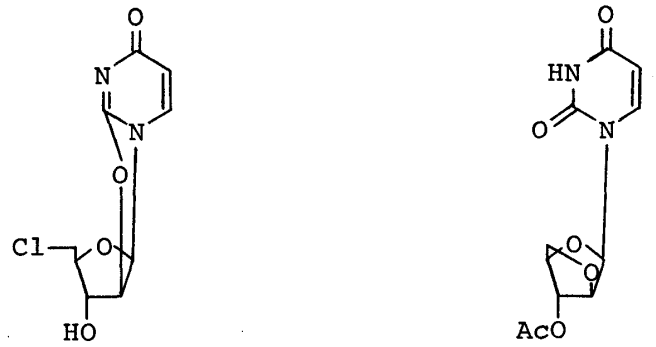


1a : R=H
1b : R=F
1c : R=Br
1d : R=CH_3

3a–d

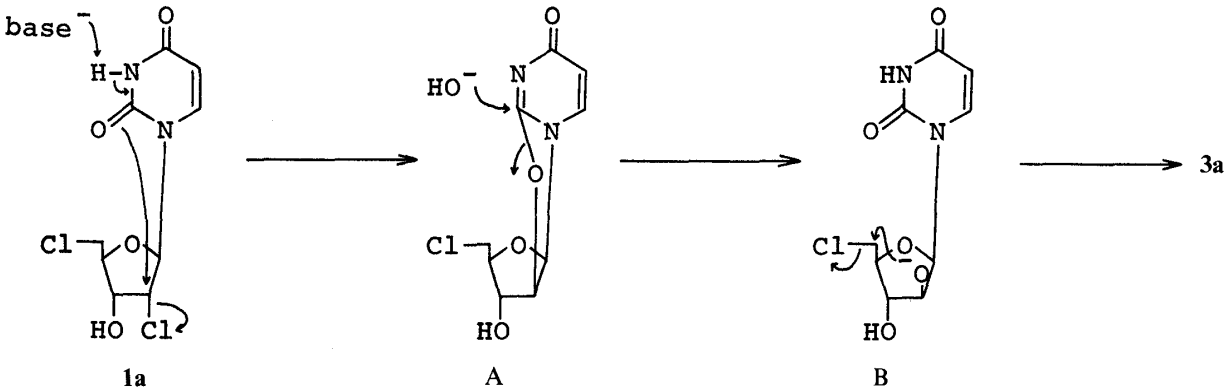
5a–d

i) aq. NaOH in CH_3OH, ii) $POCl_3$/DMF



2 4

Chart 1



1a A B

Chart 2

catalyzed cyclization of **1a** gives the 2,2′-anhydro intermediate A, which undergoes hydrolysis of the 2,2′-bond by an attack of hydroxide anion derived from water contained in the solvent on the 2-position of A to give an arabinofuranosyl intermediate B. An intramolecular cyclization between the 2′- and 5′-positions of B produces **3a**. This reaction mechanism is closely related to that of 1-(3′,5′-anhydro-2′-deoxy-β-D-threopentofuranosyl)thymine synthesis by the reaction of 3′,5′-di-*O*-mesylthymidine with sodium hydroxide.[10]

On the basis of the mechanistic considerations described above, the presence of water in the reaction mixture seems to facilitate the conversion of **1a** into **3a**. The use of aqueous

TABLE I. Preparation of 5-Substituted 2′,5′-Anhydro-1-β-D-arabinofuranosyluracils (**3a—d**)

Compd.	R	% yield		mp, °C (dec.)
		Method A (from **1**)	Method B (from **5**)	
3a	H	85	58	277 (lit.[8] 249—256)
3b	F	83	70	298
3c	Br	85	58	270
3d	CH_3	93	56	277

sodium hydroxide in place of sodium methoxide in the above conversion actually brought about a considerable increase in the yield of **3a**.Thus, treatment of **1a** with aqueous sodium hydroxide (5 eq) in methanol under reflux for 3 h smoothly afforded the expected anhydrouridine (**3a**) in an excellent yield (85%). Analogous treatment of 5-substituted 2′,5′-dichlorouridines, such as 5-fluoro- (**1b**), 5-bromo- (**1c**), and 5-methyl-2′,5′-dichloro-2′,5′-dideoxyuridine (**1d**), with methanolic sodium hydroxide similarly gave the corresponding 2′,5′-anhydrouridines (**3b**, **3c**, and **3d**, respectively) in high yields (see Table I, method A).

The anhydrouridines (**3**) were available directly from 5-substituted uridine derivatives (**5**) by a simple procedure involving the reaction with the Vilsmeier–Haack reagent and subsequent exposure to aqueous sodium hydroxide. Thus, reaction of uridine (**5a**) with phosphorus oxychloride (2.4 eq) in dimethylformamide at 60 °C for 3 h followed by treatment with aqueous sodium hydroxide in methanol under reflux for 5 h successfully gave **3a** in 58% yield. Analogous treatment of 5-substituted uridines, such as 5-fluoro- (**5b**), 5-bromo- (**5c**), and 5-methyluridine (**5d**), gave the corresponding 2′,5′-anhydrouridines (**3b**, **3c**, and **3d**, respectively) (see Table I, method B).

Although method A is slightly preferable to method B with respect to the overall yield from uridine derivatives (**5**), the preparation of starting materials, 2′,5′-dichlorouridines (**1**), from the uridines (**5**) requires a long reaction time (24 h).[6] Consequently, method B is much more practical and convenient for the preparation of 2′,5′-anhydrouridines (**3**).

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our university. Proton magnetic resonance spectra (NMR) were recorded on a JEOL JNM-PS-100 nuclear magnetic resonance spectrometer with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, br=broad). Mass spectra (MS) were taken on a JEOL JMS-D300 machine operating at 70 eV. Ultraviolet (UV) spectra were measured on a Hitachi 323 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel C-300).

2,2′-Anhydro-5′-chloro-5′-deoxy-1-β-D-arabinofuranosyluracil (2)——A mixture of **1a**[4,5] (1.0 g, 3.6 mmol) in methanolic sodium methoxide [prepared from Na (0.08 g, 3.5 mmol) in dry methanol (200 ml)] was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (20 ml). The solution was neutralized with Amberlite CG-50 (H^+) and the exchanger was washed with water. The combined solutions were evaporated to dryness *in vacuo* to give **2** (0.85 g, 98%), mp 203 °C (lit.[11] 195—196 °C). *Anal.* Calcd for $C_9H_9ClN_2O_4$: C, 44.19; H, 3.71; N, 11.45. Found: C, 43.92; H, 3.62; N, 11.34.

2′,5′-Anhydro-1-β-D-arabinofuranosyluracil (3a)——A mixture of **1a** (0.500 g, 1.78 mmol) in methanolic sodium methoxide [prepared from Na (0.400 g, 1.74 mmol) in dry methanol (100 ml)] was refluxed for 4 h. The solvent was removed under reduced pressure and the residue was dissolved in water (20 ml). The solution was neutralized with Amberlite CG-50 (H^+) and the exchanger was washed with water. The combined solutions were evaporated to dryness *in vacuo*. The resulting precipitate was recrystallized from water to give **3a** (0.242 g, 60%), mp 277 °C (lit.[8] 249—256 °C). UV λ_{max}^{EtOH} nm (ε): 265 (10360). NMR (DMSO-d_6) δ: 4.00 (2H, s), 4.17 (1H, d, J=2 Hz), 4.48 (2H, s),

5.65 (1H, d, $J=8$ Hz), 6.10 (2H, br), 7.84 (1H, d, $J=8$ Hz), 11.38 (1H, br). MS m/z: 227 ($M^+ + 1$). *Anal.* Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.59; H, 4.42; N, 12.41.

3′-*O*-Acetyl-2′,5′-anhydro-1-β-D-arabinofuranosyluracil (4)——A mixture of **3a** (0.07 g) and acetic anhydride (2 ml) in dry pyridine (2 ml) was stirred for 8 h. The solvent was removed under reduced pressure and the residue was recrystallized from 2-propanol to give **4** (0.07 g), mp 229 °C (lit.[8] 225—226 °C), which was identical with an authentic sample described in the literature.[8]

Reaction of 2,2′-Anhydro-5′-chloro-5′-deoxy-1-β-D-arabinofuranosyluracil (2) with Aqueous NaOH——A mixture of **2** (0.05 g, 0.2 mmol) and NaOH (0.024 g, 0.6 mmol) in water (3 ml) was stirred for 30 h. The solution was neutralized with Amberlite CG-50 (H^+) and the exchanger was washed with water. The combined solutions were evaporated to dryness *in vacuo* to give **3a** (0.035 g, 76%), which was identical with the compound prepared above.

5-Substituted 2′,5′-Anhydro-1-β-D-arabinofuranosyluracils (3a—d)——Method A: A mixture of **1a—d** (1 mmol), NaOH (0.2 g, 5 mmol), water (1 ml), and methanol (50 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in water (20 ml). The solution was neutralized with Amberlite CG-50 (H^+) and the exchanger was washed with water. The combined solutions were evaporated to dryness *in vacuo*. Recrystallization from water gave the corresponding product, **3a—d** (see Table I).

Method B: Phosphorus oxychloride (0.368 g, 2.4 mmol) was dissolved in dry dimethylformamide (30 ml) below 5 °C and **5a—d** (1 mmol) was added thereto. The mixture was heated at 60 °C for 3 h and the solvent was removed under reduced pressure. The residue was dissolved in water (20 ml), the solution was extracted with chloroform, and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of NaOH (0.2 g, 5 mmol), water (1 ml), and methanol (50 ml). The mixture was refluxed for 5 h and the solvent was removed under reduced pressure. The residue was dissolved in water (20 ml), the solution was neutralized with Amberlite CG-50 (H^+), and the exchanger was washed with water. The combined solutions were evaporated to dryness *in vacuo*. Recrystallization from water gave the corresponding product, **3a—d** (see Table I).

3a: Identical with an authentic sample prepared as described above.

3b: UV λ_{max}^{EtOH} nm (ε): 272 (8800). NMR (DMSO-d_6) δ: 4.01 (2H, d, $J=4$ Hz), 4.20 (1H, d, $J=2$ Hz), 4.47 (2H, d, $J=3$ Hz), 6.06 (2H, br), 8.03 (1H, d, $J=7$ Hz), 11.78 (1H, br). MS m/z: 245 ($M^+ + 1$). *Anal.* Calcd for $C_9H_9FN_2O_5$: C, 44.27; H, 3.72; N, 11.47. Found: C, 44.03; H, 3.64; N, 11.40.

3c: UV λ_{max}^{EtOH} nm (ε): 282 (9600). NMR (DMSO-d_6) δ: 3.98 (2H, s), 4.21 (1H, d, $J=2$ Hz), 4.49 (2H, s), 6.05 (2H, br), 8.08 (1H, s), 11.91 (1H, br). MS m/z: 306 ($M^+ + 1$). *Anal.* Calcd for $C_9H_9BrN_2O_5$: C, 35.43; H, 2.97; N, 9.18. Found: C, 35.17; H, 3.02; N, 9.09.

3d: UV λ_{max}^{EtOH} nm (ε): 270 (9980). NMR (DMSO-d_6) δ: 1.85 (3H, s), 3.99 (2H, d, $J=4$ Hz), 4.15 (1H, d, $J=2$ Hz), 4.46 (2H, s), 6.08 (2H, br), 7.64 (1H, d, $J=1$ Hz), 11.36 (1H, br). MS m/z: 240 (M^+). *Anal.* Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.18; H, 5.14; N, 11.62.

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References and Notes

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