ammonium bicarbonate, leaving crystalline arabinosyl derivative of >95% purity as established by chromatography (yield 2440 mg, 53.4%, based on unrecovered cytidine). The pure compound can be obtained by recrystallization from alcohol and alternatively, the hemisulfate can be prepared by addition of a slight excess of sulfuric acid to a 10% aqueous solution followed by precipitation with alcohol: for the hemisulfate, $[\alpha]^{25}D$ +126° (0.5%, H_2O), $\lambda_{max}^{pH\ 1}$ 280 mμ (ε 13,400) and $\lambda_{max}^{pH\ 13}$ 273.5 mμ (shoulder) (ε 10,000 and 8400); for the free nucleoside, mp 212–213°, with authentic sample mmp 211–212°, $[\alpha]^{25}D$ +151° (0.5%, H_2O). *Anal.* Calcd for $C_9H_{13}N_3O_5$: C, 44.45; H, 5.39; N, 17.28. Found: C, 44.49; H, 5.53; N, 17.18. In addition, the R_f values in several solvents and the electrophoretic mobility in saturated borax are identical with those of authentic material.

Registry No.—Arabinosylcytosine, 147-94-4; arabinosylcytosine hemisulfate, 7771-30-4.

Nucleosides. XI. 2′,3′-Dideoxycytidine

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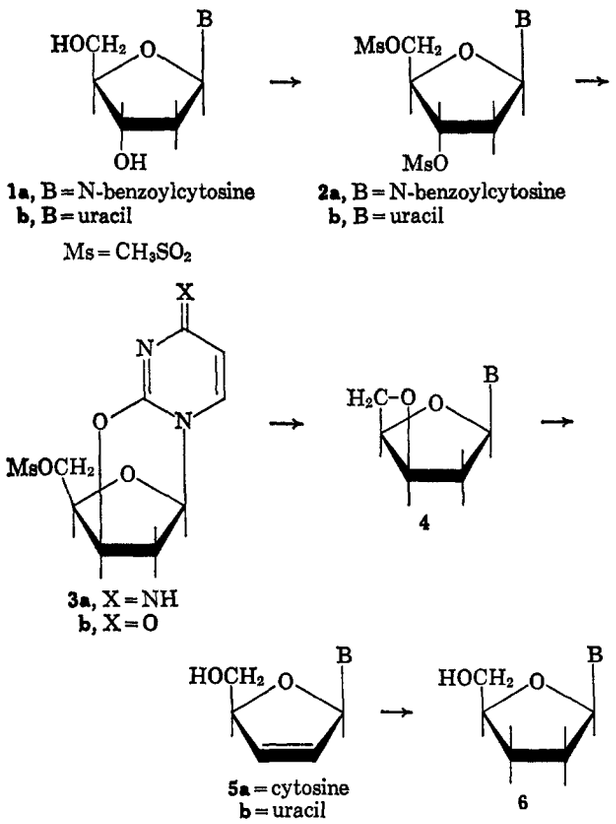
Recent reports[1] from this laboratory described the direct introduction of 2′,3′ unsaturation into the carbohydrate moieties of several pyrimidine and purine nucleosides *via* novel base-catalyzed elimination reactions.[2] A rationale for the synthesis of olefinic nucleosides was provided in an earlier communication.[1] The elucidation of the structure of the antibiotic blasticidin S, which has been shown to be a derivative of the 2′,3′-unsaturated nucleoside, cytosinine,[3] has attracted additional attention to this class of compounds. Apart from these considerations, the 2′,3′-olefinic derivatives afford a direct approach to 2′,3′-dideoxynucleosides of which 2′,3′-dideoxyadenosine and 3′-deoxythymidine are of particular interest as possible chain terminators of deoxyribonucleic acid (DNA) biosynthesis.[4] 2′,3′-Dideoxycytidine (**6a**) would be of interest for similar reasons[5] and the present communication describes the application of methods developed in our previous studies to the synthesis of **6a** *via* the corresponding 2′,3′-unsaturated derivative (**5a**). (See Scheme I.)

It has been demonstrated[1b,c] that the decyclization of the oxetane ring in, for example, 1-(2-deoxy-3,5-epoxy-β-D-*threo*-pentofuranosyl)uracil (**4b**) is readily effected by potassium *t*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO), affording 1-(2,3-dideoxy-2-ene-β-D-*glycero*-pentofuranosyl)uracil (**5b**, 2′,3′-dideoxy-2′-uridinene[6]) in good yield. The requisite 3′,5′-oxetane derivatives are readily obtained by the action of aqueous sodium hydroxide on 3′,5′-di-O-methylsulfonate esters of pyrimidine 2′-deoxynucleosides (**2**).[1c,7]

SCHEME I



The reaction of N-benzoyl-2′-deoxycytidine (**1a**)[5a] with 2 equiv of methanesulfonyl chloride gave the 3′,5′-di-O-mesyl derivative (**2a**) in near quantitative yield. The latter, on treatment with excess aqueous sodium hydroxide, yielded a crystalline product (58% yield) with properties consistent with the 3′,5′-epoxy nucleoside (**4a**). The chemical shifts of the carbohydrate protons in **4a** are readily assigned by analogy with the nmr spectra of other members of this series of nucleosides (Table I). Moreover, the specific rotation of the product is in accord both in sign and magnitude with optical rotatory values of all the 3′,5′-epoxynucleosides prepared to date (*cf.* Table I) in this laboratory.

It is now firmly established[1c,7] that the conversion of, for example, 3′,5′-di-O-mesyl-2′-deoxyuridine (**2b**) to **4b** involves the intermediate formation of the 2,3′-anhydronucleoside (**3b**). Rupture of the anhydro bond occurs at C-2 of the aglycon and intramolecular displacement of the 5′-O-mesyloxy function follows to effect formation of the oxetane ring. On this basis, then, it seems reasonable to conclude that the conversion of **2a** to **4a** involves the corresponding intermediate, 5′-O-mesyl-2,3′-anhydro-2′-deoxycytidine (**3a**). This conclusion is noteworthy in view of the fact that,

(1) (a) J. P. Horwitz, J. Chua, I. L. Klundt, M. A. Da Rooge, and M. Noel, *J. Am. Chem. Soc.*, **86**, 1896 (1964); (b) J. P. Horwitz, J. Chua, M. A. Da Rooge, and M. Noel, *Tetrahedron Letters*, 2725 (1964); (c) J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, **31**, 205 (1966); (d) J. P. Horwitz, J. Chua, and M. Noel, *Tetrahedron Letters*, 1343 (1966).

(2) A synthesis of 2′,3′-dideoxy-2′,3′-didehydroadenosine, which is essentially the same as that described in **1d**, has also been reported by J. R. McCarthy, Jr., M. J. Robins, L. B. Townsend, and R. K. Robins, *J. Am. Chem. Soc.*, **88**, 1549 (1966).

(3) For key references to this subject, see H. Yonehara and N. Otake, *Tetrahedron Letters*, 3785 (1966).

(4) (a) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 3585 (1964); (b) M. J. Robins, J. R. McCarthy, Jr., and R. K. Robins, *Biochemistry*, **5**, 224 (1966).

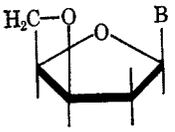
(5) (a) An unsuccessful attempt to prepare **6a** by an alternate route has been described by E. Benz, N. F. Elmore, and L. Goldman, *J. Org. Chem.*, **30**, 3067 (1965). (b) After the completion of the present study, one of us (J. P. H.) learned (personal communication) that **6a** had been prepared by an alternate though undisclosed route, by Dr. James H. Hunter of The Upjohn Co.

(6) See ref 1c for the basis of this nomenclature.

(7) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, **28**, 942 (1963).

TABLE I

PHYSICAL CONSTANTS OF SOME 1-(2-DEOXY-3,5-EPOXY-β-D-*threo*-PENTOSYL)PYRIMIDINES



B	$[\alpha]^{24}D$, deg (c, H_2O)	Nmr[a] H-1′	H-2′	H-3′	H-4′	H-5′
Cytosine	−118 (0.535)	6.56	2.63	5.72	4.29	4.94
Uracil	−125 (0.62)	6.58	2.65	5.68	4.23	4.98
Thymine	−127 (1.03)	6.60	2.68	5.75	4.28	5.03
4-Thiothymine[b]	−149 (0.555 acetone)	6.50	...[c]	5.56	4.10	4.87

[a] Spectra were determined at 60 Mc with a Varian A-60A spectrometer. Proton chemical shifts (ppm) were measured from DSS as internal reference in D_2O except as noted. The shifts were measured to multiplet centers with an accuracy ±0.05 ppm. [b] Spectrum was measured in dimethyl sulfoxide-d_6. [c] Obscured by solvent.

prior to the present study, evidence in support of the existence of 2,3′- (or 2,5′-) anhydronucleosides derived from 2′-deoxycytidine has been inconclusive.[8] Thus, transformations that would have been expected to involve such intermediates have afforded instead products corresponding to the cleavage of the N-glycosidic bond.[5a]

The interaction of **4a** and *t*-BuOK in DMSO gave 2′,3′-dideoxy-2′-cytidinene (**5a**) in 61% yield. The nmr spectrum of the product showed, in accord with the structural assignment, two adjacent vinyl protons centered at δ 6.5 and 6.02. Moreover, the catalytic hydrogenation of the 2′,3′ double bond in **5a** was readily effected affording 2′,3′-dideoxycytidine (**6a**) in good yield. The detection, in addition, of a small quantity of cytosine in hydrogenation mixture indicates the relatively facile hydrogenolysis of the glycosidic nitrogen bond in **5b**.

The biological properties of **4a** and **5b** will be described elsewhere.

Experimental Section[9]

N-Benzoyl-2′-deoxy-3′,5′-di-O-mesylcytidine (2a).—To a solution of 2.11 g (6.4 mmoles) of **1a**[5a] in 20 ml of dry pyridine cooled to −5° was added 1.0 ml (13.6 mmoles) of methanesulfonyl chloride and the reaction mixture was stored at 0° for 18 hr. The pale yellow solution was poured slowly with vigorous stirring into 200 ml of ice water and, after 0.5 hr of additional stirring, the product was collected and air dried (2.8 g 91% yield), mp 152–154° dec. An analytical sample of the same melting point was obtained in the form of colorless needles on recrystallization for 95% ethanol, $[\alpha]^{27}D$ +47° (*c* 0.61, DMF).

Anal. Calcd for $C_{18}H_{21}N_3O_9S_2$: C, 44.34; H, 4.34; N, 8.62. Found: C, 44.56; H, 4.64; N, 8.38.

1-(2-Deoxy-3,5-epoxy-β-D-*threo*-pentofuranosyl)cytosine (4a).—A solution of 2.2 g (4.52 mmoles) of **2a** in a mixture of 150 ml of ethanol and 35 ml of water containing 15 ml of 1 *N* sodium hydroxide was refluxed for 2 hr during which time the color of the reaction mixture changed from deep rose to yellow. The cooled solution was adjusted to pH 9 (test paper) with dilute acetic acid and then evaporated to dryness. The residue was triturated with several (five 50-ml portions) portions of hot acetone and the filtered solution was evaporated to dryness. The residue was suspended in *ca.* 5 ml of cold ethanol and the crystalline product was collected, 0.485 g, mp 223–226°. A second crop (0.065 g, total yield 58%, mp 210–215°) was obtained after concentration of the filtrate. The combined material on recrystallization (Norit) from ethanol formed colorless, rhombic crystals (0.5 g): mp 228–229°, with some prior discoloration at 215°; ultraviolet spectrum (H_2O) λ_{max} 271 mμ (ε 9100), λ_{min} 250 mμ (ε 6500).

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.50; H, 5.36; N, 19.87.

2′-3′-Dideoxy-2′-cytidinene (5a).—To a solution of 0.530 g (4.7 mmoles) of *t*-BuOK in 15 ml of dry DMSO was added 0.480 g of **4a** and the mixture, protected from moisture, was stirred magnetically at room temperature for 2 hr. The reaction mixture was evaporated to dryness at 40–50° (10^{-3} mm) and the residue was dissolved in *ca.* 2.0 ml of water, neutralized by passage through a 20 × 1 cm column of IRC-50 (H^+). The eluent was evaporated to dryness; the residue was dissolved in 5 ml of 30% methanol and chromatographed on a (18 × 1 cm) column of Dowex-1 (OH^-).[10] Elution of the column with 30% methanol and spectrophotometric examination of the effluent (7.5-ml samples) at 270 mμ revealed the product to be concentrated in fractions 6–9. The latter were combined and evaporated to dryness. The residue, on trituration with cold ethanol, crystallized (0.12 g): mp 168–169°.[11] A second crop (0.17 g, total yield 61%, mp 160–162°) was obtained on concentration of the alcohol filtrate to *ca.* 2 ml. Recrystallization of the first from ethanol did not raise the melting point, $[\alpha]^{27}D$ +52° (*c* 0.97, ethanol), $\lambda_{max}^{0.1\ N\ HCl}$ 275 mμ (ε 10,100), 215 mμ (ε 11,900), $\lambda_{min}^{0.1\ N\ HCl}$ 240 mμ (ε 605), $\lambda_{max}^{H_2O}$ 271 mμ (ε 8710), $\lambda_{min}^{H_2O}$ 247 mμ (ε 6010), $\lambda_{max}^{0.1\ N\ NaOH}$ 271 mμ (ε 8890), 231 mμ (ε 7710), $\lambda_{min}^{0.1\ N\ NaOH}$ 247 mμ 247 mμ (ε 6100). Nmr spectral data (D_2O) showed a sharp doublet at δ 3.80 owing to H′5 protons, a complex multiplet at δ 5.0 assigned H′4, two vinyl protons centered at 6.5 (H′3) and 6.02 (H′2), a multiplet centered at 6.98 for the anomeric proton, and a sharp doublet centered at δ 7.76 assigned to the pyrimidine C5 proton.

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.78; H, 5.38; N, 19.96.

2′,3′-Dideoxycytidine (6a).—A solution of 0.11 g (0.53 mmole) of **5a** in 50 ml of absolute ethanol containing 0.03 g of 10% palladium–charcoal catalyst was shaken under 1 atm of hydrogen at 25°. The theoretical uptake was realized in 20 min. The catalyst was filtered and the filtrate was evaporated to dryness. The residue on thin layer chromatography (silica gel, benzene–ethanol 7:3) failed to indicate any unreduced **5a**. However, the product appeared to be contaminated with a small amount of cytosine. The mixture was chromatographed on a 5 × 1 cm column of Dowex-1 (OH^-) in the manner described above for **5a**. Fractions 1–3, which were judged on the basis of tlc to contain only **6a**, were combined and evaporated to dryness. The residue crystallized from an ethanol–benzene mixture to give 80 mg (72% yield) of product: mp 215–217°, $[\alpha]^{25}D$ +81° (*c* 0.635, H_2O); ultraviolet spectral data[12] $\lambda_{max}^{0.1\ N\ HCl}$ 281 mμ (ε 13,700), $\lambda_{min}^{0.1\ N\ HCl}$ 242 mμ (ε 665), $\lambda_{max}^{H_2O}$ 272 mμ (ε 9650), $\lambda_{min}^{H_2O}$ 239 mμ (ε 5320), $\lambda_{max}^{0.1\ N\ NaOH}$ 272 mμ (ε 9150), $\lambda_{max}^{0.1\ N\ NaOH}$ 247 mμ (ε 4990).

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.11; H, 6.32; N, 19.90.

Registry No.—**2a**, 7481-86-9; **4a**, 7481-87-0; **5a**, 7481-88-1; **6a**, 7481-89-2; uracil derivative, 3056-16-4; thymine derivative, 7481-90-5; 4-thiothymine derivative, 6166-40-1.

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(8) See ref 5a for a summary of the literature on this subject.

(9) Elementary analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Melting points were taken with a Thomas–Hoover apparatus. Ultraviolet spectra were recorded by a Cary Model 11 spectrophotometer. All evaporations were carried out *in vacuo*.

(10) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).

(11) The product, in accord with the behavior noted[1c] with other 2′,3′-unsaturated nucleosides, resolidifies above the indicated melting point range (*ca.* 173–174°) without further evidence of a change of state.

(12) Dr. Hunter (*cf.* ref 5b) was kind enough to provide the following data on **6a** which he isolated in the form of a hydrochloric salt of indefinite melting point: $[\alpha]D^{23}$ +70° (*c* 1.017, H_2O), $\lambda_{max}^{0.1\ N\ HCl}$ 280 mμ (ε 13,300), $\lambda_{max}^{H_2O}$ 274 mμ (ε 10,050), $\lambda_{max}^{0.1\ N\ NaOH}$ 271 mμ (ε 9000).