been collected. 2,3,5-Tri-O-benzoyl-D-ribofuranosyl chloride [prepared from 25.0 g. (49.5 mmoles) of the corresponding acetate] dissolved in 125 ml. of xylene was added followed by removal of 130 ml. of solvent by distilling. The reaction mixture was refluxed for 5.0 hr. and then worked up and deblocked as described in the previous experiment.

The crude deblocked mixture was adjusted to 500 ml. with water, brought to pH 10.5 with concentrated ammonium hydroxide, and applied to a Dowex 1-X8 (Cl^-) column (6 × 13 cm., 200–400 mesh). The column was eluted with a water–0.1 *M* ammonium bicarbonate gradient and 400 fractions (from 70 to 85 ml./fraction) were collected. The orotidine-containing fractions as shown by the 280 mμ/260 mμ ratio (fractions 113–227) were treated as described previously. A total of 686 mg. (8.7%) of recrystallized orotidine cyclohexylammonium salt was obtained. The other main component (fractions 290–383), whose ultraviolet absorption indicated a 3-substituted orotic acid, was adsorbed onto charcoal and converted to the cyclohexylammonium salt: yield 1.34 g., $\lambda_{max}^{0.1\ N HCl}$ 284 mμ, $\lambda_{max}^{0.1\ N NaOH}$ 306 mμ. Paper chromatography using isopropyl alcohol–1 *N* ammonium hydroxide (7:3) indicated that this product was contaminated with a small amount of orotidine. This product was dissolved in 15 ml. of hot absolute ethanol, treated with Norit, and filtered. Attempted crystallization by the addition of ethyl acetate was unsuccessful. The solvents were evaporated at reduced pressure; the residue was taken up in water and chromatographed again on Dowex-1 as described above. No separation was accomplished, as shown by ultraviolet monitoring. The product was again isolated by adsorption onto acid-washed Norit: yield 0.87 g. Paper chromatography in several solvent systems indicated that this compound was still contaminated with a small amount of orotidine. The compound was dissolved in 25 ml. of hot absolute ethanol treated with a small amount of Norit and filtered. About 100 ml. of ethyl acetate was added to precipitate a syrup which was isolated by decanting the supernatant liquid after chilling: yield 571 mg. An additional 260 mg. was obtained by evaporating the supernatant liquid. The first crop was dissolved in 250 ml. of water and passed through a 2 × 6 cm. column of Dowex 50W-X8 (cyclohexylammonium form) and then evaporated to dryness *in vacuo* to afford 555 mg. of product: $[\alpha]^{25}D$ −19.7 ± 4.9° (*c* 1.015, water); R_f 0.40 with trace of slightly lower R_f material in *n*-butyl alcohol–formic acid–water (77:10:13) (solvent B).

The second crop was treated similarly: yield 240 mg.; $[\alpha]^{25}D$ −16.3 ± 4.8° (*c* 1.045, water); R_f 0.40 in solvent B. The infrared spectra of the two products were the same. These two crops correspond to a 10% yield (corrected for the recovered sodium orotate). The 240-mg. crop was dissolved in 25 ml. of water, treated with a small amount of Norit, filtered, and evaporated to an oil: yield 175 mg.

Anal. Calcd. for $C_{16}H_{25}N_3O_8$ (387): C, 49.6; H, 6.5; N, 10.9. Found: C, 49.3; H, 7.3; N, 10.8.

Acknowledgments.—We wish to thank Mr. Louis Brancone and staff for the microanalyses and Mr. William Fulmor and staff for the spectral data included in this report. Special thanks are due to Dr. T. Breitman of the Biochemical Research Section for his valuable advice on ion-exchange and charcoal-adsorption procedures.

Nucleosides. IX. The Formation of 2′,3′-Unsaturated Pyrimidine Nucleosides *via* a Novel β-Elimination Reaction[1,2]

JEROME P. HORWITZ, JONATHAN CHUA, MARGARET A. DA ROOGE, MICHAEL NOEL, AND IRWIN L. KLUNDT

Rollin H. Stevens Laboratory, Detroit Institute of Cancer Research, Detroit, Michigan 48201

Received July 15, 1965

The study reports the direct introduction of 2′,3′-unsaturation in the carbohydrate moiety of pyrimidine nucleosides *via* base-catalyzed elimination reactions. 2,3′-Anhydronucleosides (II) derived from both 2′-deoxyuridine and thymidine are converted to the corresponding 2′,3′-unsaturated nucleoside (IV) in high yield on treatment with potassium *t*-butoxide in dimethyl sulfoxide. The same base–solvent system applied to 1-(2-deoxy-3,5-epoxy-β-D-*threo*-pentosyl)pyrimidines (XIV, pyrimidines = thymine, uracil, and 4-thiouracil) also provides 2′,3′-unsaturated nucleosides (V) in excellent yields. The oxetane derivatives (XIV) and anhydro nucleosides (II) apparently both undergo β-proton abstraction (C′-2) followed by decyclization of the resulting carbanion. The close analogy of these transformations to the alkaline cleavage of related cyclic ethers is discussed. A novel double elimination reaction leading to 1-[2-(5-methylfuryl)]thymine (XVIII) is described.

Reichard, *et al.*,[3] have demonstrated the direct deoxygenation of both purine and pyrimidine ribonucleotides to corresponding 2′-deoxyribonucleotides by cell-free preparations from *E. coli* and from chick embryo. These observations have prompted the suggestion[3c,4] of 1′,2′- and 2′,3′-unsaturated nucleotides as possible intermediates in the biosynthetic pathway leading to 2′-deoxyribonucleotides. This possibility stimulated our interest in corresponding unsaturated nucleosides which to our knowledge were unknown prior to the inception of the present investigation.

It has been demonstrated that sulfonate esters of cyclic and secondary acyclic alcohols afford high yields of alkenes on treatment with potassium *t*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO)[5] at ambient temperatures. In fact, olefin formation is readily effected from a relatively wide spectrum of aliphatic functional derivatives in *t*-BuOK–DMSO.[6] The present communication describes the successful application of this base–solvent system to the synthesis of 2′,3′-unsaturated pyrimidine nucleosides from 3′-mesylates of 1-(2-deoxy-β-D-*threo*-pentosyl)pyrimidines. Moreover, the scope of base-promoted reactions in DMSO

(1) This investigation was supported in part by Public Health Service Research Grants No. CA-02903-08 and CA-02624-09 from the National Cancer Institute and in part by an institutional grant to the Detroit Institute of Cancer Research from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation.

(2) Preliminary reports: (a) J. P. Horwitz, J. Chua, I. L. Klundt, M. A. Da Rooge, and M. Noel, *J. Am. Chem. Soc.*, **86**, 1806 (1964); (b) J. P. Horwitz, J. Chua, M. A. Da Rooge, and M. Noel, *Tetrahedron Letters*, **No. 38**, 2725 (1964).

(3) (a) P. Reichard, A. Baldesten, and L. Rutberg, *J. Biol. Chem.*, **236**, 1150 (1961); (b) P. Reichard, *ibid.*, **236**, 2511 (1961); (c) P. Reichard, *ibid.*, **237**, 3513 (1962); (d) E. C. Moore and P. Reichard, *ibid.*, **238**, 2244 (1963); (e) A. Larsson, *Acta Chem. Scand.*, **17**, 891 (1963).

(4) J. P. H. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, **86**, 1236 (1964).

(5) (a) C. H. Snyder, *Chem. Ind.* (London), 121 (1963); (b) C. H. Snyder and A. R. Soto, *J. Org. Chem.*, **29**, 742 (1964).

(6) (a) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Am. Chem. Soc.*, **85**, 2739 (1963); (b) J. E. Hofmann, T. J. Wallace, and A. Schriesheim, *ibid.*, **86**, 1561 (1964).

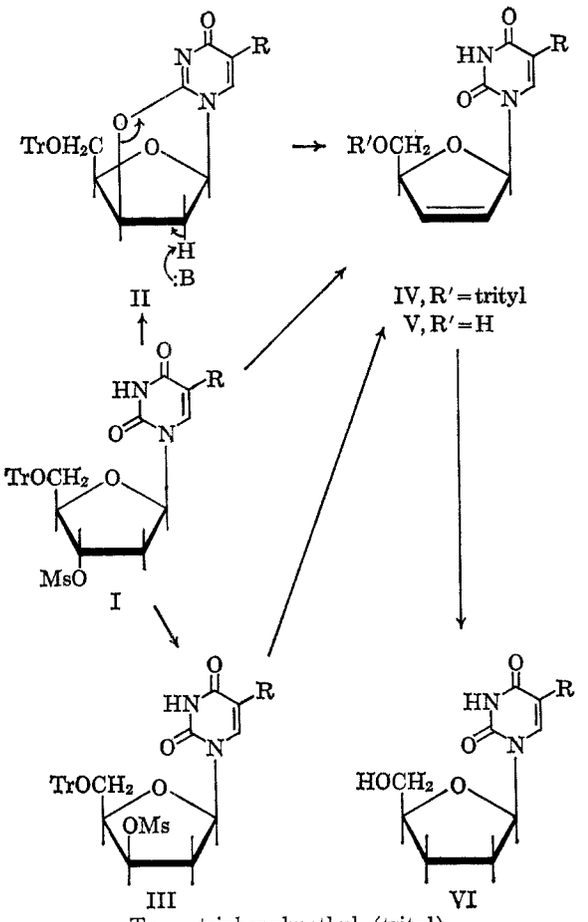
has been expanded to include the decyclization of the ether moiety in both 2,3′-anhydro- and 3′,5′-oxetano-nucleosides which provides a more practical approach to the same unsaturated products.

At the outset, the possibility of utilizing 3′-sulfonyloxy derivatives of thymidine and/or 2′-deoxyuridine as substrates for base-induced elimination reactions appeared to be remote because of the facile conversion of these esters to corresponding 2,3′-anhydronucleosides under the conditions[7] necessary to effect olefin formation. Accordingly, the initial attempt to promote β-elimination in a pyrimidine nucleoside utilized 1-(2-deoxy-3-O-mesyl-5-O-trityl-β-D-lyxosyl)uracil (IIIa) in which a *cis* relationship between the aglycon and mesyloxy moieties precludes the possibility of intramolecular nucleophilic displacement. Mesylation of 1-(2-deoxy-5-O-trityl-β-D-lyxofuranosyl)uracil[7c] provided the desired substrate (IIIa).

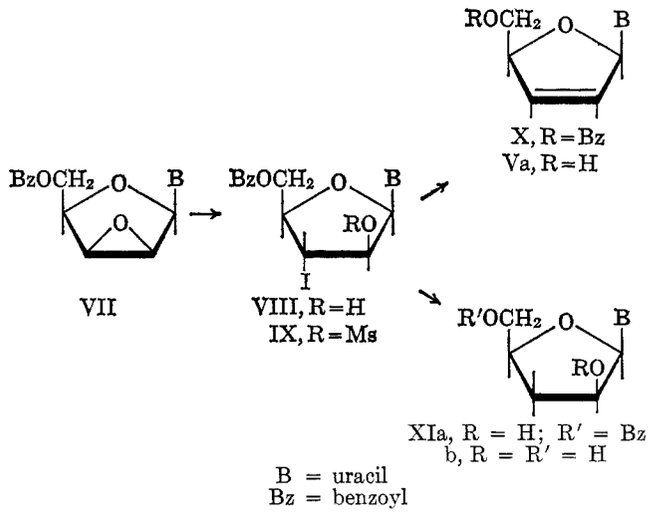
The interaction of IIIa and 2 equiv. of *t*-BuOK in DMSO at room temperature for 0.5 hr. afforded a crystalline product (77% yield) that readily absorbed bromine (chloroform) and decolorized aqueous potassium permanganate. Elementary analysis and infrared and ultraviolet spectra were all consistent with the structure 1-(5-O-trityl-2,3-dideoxy-2-ene-β-D-*glycero*-pentofuranosyl)uracil (5′-O-trityl-2′,3′-dideoxy-2′-uridinene, IVa).[8] The corresponding detritylated product (Va), which was obtained on treatment of IVa with 1 equiv. of hydrogen chloride in chloroform, readily absorbed 1 mole of hydrogen to give 2′,3′-dideoxyuridine (VIa) in good yield.

The location of the double bond in Va was established by independent synthesis which employed an approach utilized for the introduction of 2,3-unsaturation into a hexose.[9] Scission of the epoxide ring in 1-(5-O-benzoyl-2,3-epoxy-β-D-lyxosyl)uracil (VII)[10] with sodium iodide in acetone containing 1 equiv. of acetic acid gave a single iodohydrin (VIII) which was assigned the *arabino* configuration.[11] The latter was converted to a monomesylate (IX) which, in turn, was subjected to conditions of elimination with sodium iodide in acetone. Reaction occurred at 0° to give 5′-O-benzoyl-2′,3′-dideoxy-2′-uridinene (X) in 70% yield. Saponification of the benzoate ester in X gave a solid which proved to be identical in every respect with Va.

It is apparent that either of two possible *trans*-iodohydrins arising from VII would lead to X. However, had VIII possessed instead the *xylo*-configuration as a result of nucleophilic attack by iodide ion at C′-2, then hydrogenolysis of the iodohydrin, followed by ester hydrolysis should have afforded the known 1-(2-deoxy-β-D-lyxofuranosyl)uracil.[7c] Rather, this sequence of reactions produced the previously unknown 1-(3-deoxy-β-D-*threo*-pentofuranosyl)uracil (XIb) which establishes the structural identity of VIII.



Tr = triphenylmethyl (trityl)
Ms = methanesulfonyl (mesyl)
(series) a, R = H
b, R = CH_3



B = uracil
Bz = benzoyl

(7) (a) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, **28**, 942 (1963); (b) J. J. Fox and N. C. Miller, *ibid.*, **28**, 936 (1963); (c) J. P. Horwitz, J. Chua, M. Noel, and M. A. Da Rooge, *J. Med. Chem.*, **7**, 385 (1964).

(8) The unwieldy character of the systematic name prompted the adoption (in the present study) of a simplified, though less precise, form of nomenclature to designate the title compounds. The replacement of the suffix "ine" in the trivial name of the parent nucleoside by "inene" provides the desired simplification. Thus, a 2′,3′-unsaturated nucleoside derived from uridine, thymidine, adenosine, etc., becomes 2′,3′-dideoxy-2′-uridinene, 3′-deoxy-2′-thymidinene, and 2′,3′-dideoxy-2′-adenosinene.

(9) (a) N. F. Taylor and G. M. Riggs, *Chem. Ind.* (London), 209 (1963); (b) N. F. Taylor and G. M. Riggs, *J. Chem. Soc.*, 5600 (1963); (c) C. L. Stevens, N. A. Nielson, and P. Blumbergs [*J. Am. Chem. Soc.*, **86**, 1894 (1964)] employed essentially the same procedure in a synthesis of a 2′,3′-didehydro-2′,3′-dideoxy sugar nucleoside. The work appeared simultaneously with a preliminary communication (*cf.* ref. 2a) of the present study.

(10) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27**, 163 (1962).

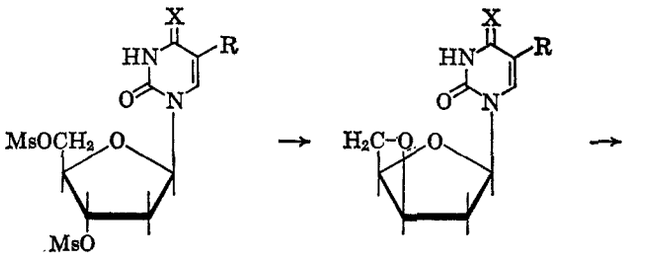
(11) This assignment is based on the normal course of opening of 2,3-anhydrofuranose derivatives: see C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 898 (1959). However, an exception to the rule of predominant C-3 opening of a 2,3-anhydrofuranoside has been reported recently by G. Casini and L. Goodman, *ibid.*, **85**, 235 (1963).

It has been demonstrated that weak acids catalyze nucleophilic attack at C′-3 of 2,3′-anhydronucleosides derived from thymidine.[7b,12] Murdock and Angier suggest[13] that this increased susceptibility toward displacement is the result of protonation of the aglycon which enables the thyminyloxy residue to behave as a leaving group comparable to sulfonyloxy or halogen functions. These observations prompted the consideration of 2,3′-anhydro-2′-deoxynucleosides as substrates for base-promoted elimination reactions. The synthesis of 2,3′-anhydro-1-(2-deoxy-5-O-trityl-β-D-lyxosyl)uracil (IIa) was essentially that described previously[7a] for the corresponding thymine derivative, IIb. Mesylation of 5′-O-trityl-2′-deoxyuridine[7c,14] provided the corresponding 3′-O-mesyl derivative (Ia) in the form of an amorphous solid, which on treatment with 1 equiv. of ethanolic sodium hydroxide gave IIa in high yield.

The interaction of IIa and 1 equiv. of *t*-BuOK in DMSO at room temperature for 0.5 hr. afforded a product (78% yield) identical in every respect with IVa. The same product, as might be expected, was obtained from the reaction of the precursory mesylate (Ia) with 2 equiv. of base. A similar set of observations was recorded for 3′-O-mesyl-5′-O-tritylthymidine (Ib). Thus Ib, on treatment with the appropriate quantity of base, gave an unsaturated nucleoside which was assigned the structure 5′-O-trityl-3′-deoxy-2′-thymidinene (IVb) on the basis of the analogy with the corresponding 2′-deoxyuridinene derivatives. Detritylation of IVb yielded 3′-deoxy-2′-thymidinene (Vb) which on catalytic hydrogenation gave the known 3′-deoxythymidine (VIb).[15]

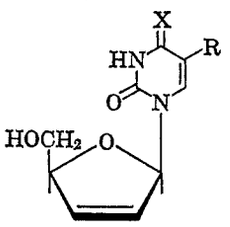
An earlier study[7a] provided access to 1-(2-deoxy-3,5-epoxy-β-D-*threo*-pentosyl)thymine (XIVb) which is readily obtained from action of aqueous sodium hydroxide on 3′,5′-di-O-mesylthymidine (XIIIb).[15] The possibility of XIVb affording a direct route to Vb *via* a base-catalyzed decyclization of the oxetane moiety was suggested by the surprising facility of the corresponding transformation in the case of the 2′-deoxy-2,3′-anhydronucleosides (II). This indeed proved to be the case. Thus, the reaction of XIVb with 2 equiv. of *t*-BuOK in DMSO gave the desired product (Vb) in 79% yield. Accordingly, 2′-deoxyuridine was transformed first to a 3′,5′-di-O-mesylate (XIIIa) and then to the corresponding oxetane derivative (XIVa). The latter, when subjected to the action of *t*-BuOK–DMSO, gave Va in excellent yield. The extension of this sequence of reactions to 1-(2-deoxy-3,5-di-O-mesyl-β-D-*erythro*-pentosyl)-5-methyl-4-thiouracil (XIVc) led to 3′-deoxy-2′-(4-thiothymidinene) (Vc) *via* XIVc.

The base-catalyzed decyclization of ethers with synchronous olefin formation has been observed in several unrelated studies. The furanose ring of 5′-sulfonium nucleosides, for example, readily undergoes decyclization in aqueous alkali with the liberation of the corresponding pyrimidine or purine base and the



XIIIa, R = H; X = O
b, R = CH_3; X = O
c, R = CH_3; X = S

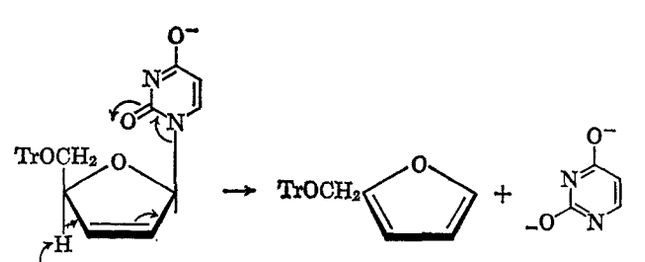
XIVa, R = H; X = O
b, R = CH_3; X = O
c, R = CH_3; X = S



Va, R = H; X = O
b, R = CH_3; X = O
c, R = CH_3; X = S

transient formation of an unsaturated sulfonium sugar.[16] In the course of the present investigation a base-catalyzed ($NaOCH_3$–$CHCl_3$) elimination of the exocyclic secondary *p*-tolylsulfonyloxy group in a D-glucofuranose structure was described which affords D-*xylo*-hexofuran-5-enoses in high yield.[17] A 3,5-oxetane derivative was suggested as the direct precursor of the unsaturated sugar which has since been confirmed.[18]

It is likely that the elimination of the sulfonyloxy group of III and the decyclization of both the anhydro bond of II and the oxetane ring of XIV are all of the E2 variety. Regardless of the precise mechanism, β-proton abstraction at C′-2[19] presents the possibility of an alternate path of elimination in which the pyrimidine moiety is the departing group. However, no evidence was obtained to indicate that this course of reaction assumes any real significance as a competitive process. In fact, the sole evidence for the elimination of the aglycon residue under these conditions was derived from the reaction of IIIa with excess (4 equiv.) *t*-BuOK which produced uracil and furfuryltriphenylmethyl ether (XV) in addition to IVa. These observations are readily explained in terms of consecutive



IVa XV

(12) N. C. Miller and J. J. Fox, *J. Org. Chem.*, **29**, 1772 (1964).

(13) K. C. Murdock and R. B. Angier [*J. Am. Chem. Soc.*, **84**, 3748 (1962)] based their conclusion on the reaction of hydrogen chloride with 2,3′-anhydro-1-(*cis*-3′-hydroxycyclopentyl)thymine.

(14) J. Smrt and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 553 (1960).

(15) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(16) J. Baddiley, W. Frank, N. A. Hughes, and J. Wieczorkowski, *ibid.*, 1999 (1962).

(17) R. E. Gramera, T. R. Ingle, and R. L. Whistler, *J. Org. Chem.*, **29**, 878, 1083 (1964).

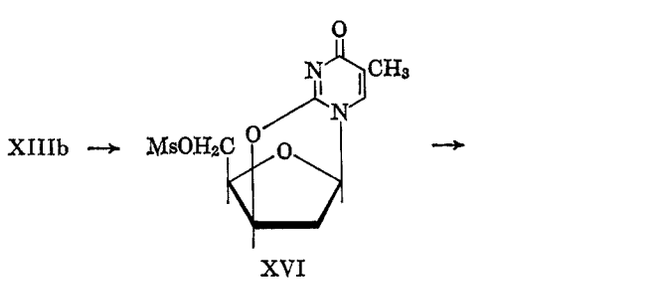
(18) J. G. Buchanan and E. M. Oakes, *Tetrahedron Letters*, **No. 30**, 2013 (1964).

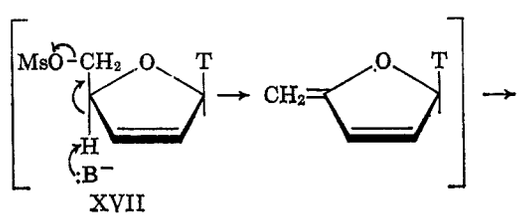
(19) The removal of a proton from the methylene carbon atom at this site rather than at C′-4 is in accord with the relative ease of carbanion formation, *i.e.*, secondary > tertiary (see ref. 6a).

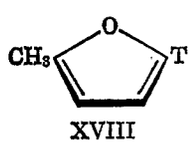
base-promoted elimination reactions, the first of which leads to IVa in the usual manner. In excess base IVa reacts further to form a β-allylic carbanion which eliminates (dianionic) uracil to form XV as represented in the preceding scheme.

An interesting double elimination reaction was observed in an attempt to extend the present studies to the conversion of 3′,5′-di-O-mesylthymidine (XIIIb) to 5′-O-mesyl-3′-deoxy-2′-thymidinene (XVII). It was anticipated that the reaction would proceed initially to 5′-O-mesyl-2,3′-anhydrothymidine (XVI) and that the latter, in turn, would undergo decyclization in the presence of excess *t*-BuOK to produce XVII. Instead, there was obtained an optically inactive, crystalline material (88% yield) with properties consistent with 1-[2-(5-methylfuryl)]thymine (XVIII). The n.m.r. spectrum of XVIII revealed the presence of two methyl groups which appear as sharp singlets at τ 8.2 and 7.75. The signals are assigned to the methyl protons of the thymine and furan moieties, respectively.

It is proposed that the 2,3′-unsaturated nucleoside (XVII) is the direct precursor of XVIII and that the latter is formed in the second of consecutive elimination reactions. Moreover, the second transformation, unlike that leading to furfuryltriphenylmethyl ether (XV) is probably the kinetically favored process.







T = thymine

This conclusion is based on the observation that the interaction of equimolar quantities of 2,3′-anhydronucleoside (XVI) and *t*-BuOK again produced the furan compound (XVIII), albeit in lower yield, as the sole reaction product. Apparently, the (concerted) process of ionization of the tertiary allylic C′-4–H bond in XVII and elimination of the 5′-sulfonyloxy group occurs more readily than the abstraction of a secondary proton from XVI and concomitant decyclization of the incipient carbanion.

A study of the addition of various electrophiles to the olefinic nucleosides IV and V is currently in progress and the results will be reported at a later date.

Experimental Section[20]

2′-Deoxy-3′-O-mesyl-5′-O-trityluridine (Ia).—Methanesulfonyl chloride (0.7 ml., 9.5 mmoles) was added slowly to a cold (0°) solution of 3.35 g. (7.13 mmoles) of 2′-deoxy-5′-O-trityluridine[7c,14] in 20 ml. of dry pyridine and the reaction mixture was stored at 5° for 24 hr. After the addition of *ca.* 1.0 ml. of water, the mixture was refrigerated for an additional 0.5 hr. and then slowly poured into 800 ml. of ice–water. The solid was collected, washed well with water, and air dried. The yellow product was dissolved in a small volume of acetone, treated with Norit, and then reprecipitated on slow addition to 1 l. of ice–water. The colorless, amorphous solid was filtered, washed with water, and dried *in vacuo* over phosphorus pentoxide, wt. 3.55 g. (88% yield). This material showed no definite melting point and gave an unsatisfactory elementary analysis.[21] *Anal.* Calcd. for $C_{29}H_{28}N_2O_7S$: C, 63.49; H, 5.14. Found: C, 62.71; H, 5.20.

2,3′-Anhydro-1-(2-deoxy-5-O-trityl-β-D-lyxosyl)uracil (IIa).—A solution of 0.549 g. (1 mmole) of Ia in 100 ml. of ethanol containing 8.85 ml. of 0.113 *N* sodium hydroxide (1 mmole) was refluxed for 2.5 hr. The solvent was evaporated and the residue was triturated with water. The solid was collected, washed with water, and air dried, wt. 0.430 g. (95% yield), m.p. indefinite (125–150°). Recrystallization of the product from ethanol afforded a colorless crystalline solid of indefinite melting point which was homogeneous by thin layer chromatography (benzene–ethanol, 7:3). *Anal.* Calcd. for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.07; H, 5.43; N, 6.21.

1-(2-Deoxy-3-O-mesyl-5-O-trityl-β-D-lyxosyl)uracil (IIIa).—Methanesulfonyl chloride (0.3 ml., 4 mmoles) was added slowly to a solution of 0.96 g. (2 mmoles) of 1-(2-deoxy-5-O-trityl-β-D-lyxosyl)uracil[7c] at 0°. After storage overnight in a refrigerator, water (1 ml.) was added and the solution was poured slowly into 250 ml. of ice–water. The solid was collected, washed well with water, and air dried. The product crystallized from ethanol (Norit) in the form of colorless needles, wt. 0.94 g. (84% yield), m.p. 133–139°. A second crystallization from the same solvent provided an analytical sample, m.p. 138.5–140°, $[\alpha]^{25}D$ −8° (*c* 0.77, acetone), λ_{max}^{EtOH} 262 mμ (ϵ 13,930) and 229 mμ (ϵ 17,030), λ_{min}^{EtOH} 245 mμ (ϵ 9290). *Anal.* Calcd. for $C_{29}H_{28}N_2O_7S \cdot C_2H_5OH$: C, 62.61; H, 5.76; N, 4.71. Found: C, 62.59; H, 5.64; N, 4.89.

2′-Deoxy-3′,5′-di-O-mesyluridine (XIIIa).—Methanesulfonyl chloride (1.8 ml., 24.5 mmoles) was added dropwise to a solution of 2.5 g. (11 mmoles) of 2′-deoxyuridine in 22 ml. of dry pyridine which had been chilled previously to −10°. After storage overnight in a refrigerator, the reaction mixture was treated with 1 ml. of water and the solution poured slowly with vigorous stirring into 1 l. of ice–water. The crystalline product was collected after 1 hr. of stirring at 0° and sucked dry, wt. 2.76 g. (66% yield), m.p. 140–142° dec. An analytical sample was obtained on recrystallization (Norit) of the crude solid from 90% ethanol, m.p. 145–146.5° dec., $[\alpha]^{25}D$ +16° (*c* 0.89, water), $\lambda_{max}^{90\%\ EtOH}$ 258 mμ (ϵ 9610), $\lambda_{min}^{90\%\ EtOH}$ 229 mμ (ϵ 2460). *Anal.* Calcd. for $C_{11}H_{16}N_2O_9S_2$: C, 34.37; H, 4.20; N, 7.30. Found: C, 34.44; H, 4.25; N, 7.22.

3′,5′-Di-O-mesyl-4-thiothymidine (XIIIc).—To a solution of 0.258 g. (1 mmole) of 4-thiothymidine[22] in 15 ml. of pyridine, chilled to 0°, was added 0.16 ml. (2.2 mmoles) of methanesulfonyl chloride and the reaction mixture was stored at 0° for 18 hr. The amber solution was poured slowly with stirring into 200 ml. of ice–water and the yellow solid was collected. The air-dried product (0.250 g.) was chromatographed on 10 g. of neutral alumina using successively petroleum ether (30–60°), benzene, chloroform, ethyl acetate, and acetone as eluents. The latter fraction, on evaporation to dryness, yielded a glass which crystallized as bright yellow needles from ethanol, wt. 0.165 g. (40% yield), m.p. 152–153° dec., $[\alpha]^{24}D$ +36° (*c* 0.78, acetone), λ_{max}^{EtOH}

(20) Potassium *t*-butoxide was obtained from M. S. A. Corp. and was used as received. J. T. Baker reagent grade dimethyl sulfoxide was distilled from calcium hydride prior to use. All melting points were taken with a Thomas–Hoover apparatus. Ultraviolet spectra were recorded by a Cary Model 11 spectrophotometer. Elementary analyses were performed by Micro-Tech Laboratories, Skokie, Ill. All evaporations were carried out *in vacuo*.

(21) K. E. Pfitzner and J. G. Moffatt, [*J. Org. Chem.*, **29**, 1508 (1964)] whose work appeared during the course of the present study, also reported an unsuccessful attempt to obtain an acceptable analysis for this compound.

(22) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, **81**, 178 (1959).

330 mμ (ε 18,120) and 247 mμ (ε 7650), λ_{min}^{EtOH} 282 mμ (ε 4590) and 225 mμ (ε 4760). *Anal.* Calcd. for $C_{12}H_{18}N_2O_8S_3$: C, 34.77; H, 4.38; N, 6.76. Found: C, 35.00; H, 4.54; N, 6.77.

1-(2-Deoxy-3,5-epoxy-β-D-*threo*-pentofuranosyl)uracil (XIVa).—A solution of 1.0 g. (2.6 mmoles) of XIIIa in 50 ml. of water containing 7.4 ml. of 1.055 *N* sodium hydroxide (7.8 mequiv.) was refluxed for 2 hr. The cooled solution was neutralized (phenolphthalein) with acetic acid and evaporated to dryness. The dry residue was triturated with several (five 25-ml.) portions of hot acetone, the salts were removed by filtration, and the acetone solution was evaporated to dryness under reduced pressure. The residue was dissolved in ethanol and treated with Norit, and the filtrate was concentrated to *ca.* 5 ml. On cooling, colorless plates were deposited, wt. 0.385 g. (71% yield), m.p. 206–210°. Recrystallization from ethyl acetate–benzene provided an analytical sample, m.p. 207–210°, $[\alpha]^{25}D$ −125° (*c* 0.62, acetone), $\lambda_{max}^{H_2O}$ 262 mμ (ε 9490), $\lambda_{min}^{H_2O}$ 230 mμ (ε 1780). *Anal.* Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.38; H, 4.70; N, 13.30.

1-(2-Deoxy-3,5-epoxy-β-D-*threo*-pentofuranosyl)-4-thiothymine (XIVc).—A solution of 0.828 g. (2 mmoles) of XIIIc in 25 ml. of hot ethanol, containing 8 ml. of 1 *N* sodium hydroxide was diluted with an equal volume of water and refluxed for 2 hr. The cooled solution was neutralized (phenolphthalein) with acetic acid and evaporated to dryness. The residue was extracted several (five 20-ml. portions) times with hot acetone, the salts were filtered, and the filtrate was evaporated to dryness. The residue crystallized from ethanol in the form of yellow prisms, wt. 0.24 g. (50% yield), m.p. 177–181°. A second recrystallization from the same solvent raised the melting point to 183–185°, $[\alpha]^{25}D$ −149° (*c* 0.56, acetone), λ_{max}^{EtOH} 332 mμ (ε 18,140) and 243 mμ (ε 3715), λ_{min}^{EtOH} 273 mμ (ε 1990) and 222 mμ (ε 1040). *Anal.* Calcd. for $C_{10}H_{12}N_2O_3S$: C, 49.98; H, 5.04; N, 11.66. Found: C, 49.93; H, 5.18; N, 11.46.

1-(5-O-Benzoyl-3-deoxy-3-iodo-β-D-arabinosyl)uracil (VIII).—A solution of 0.5 g. (1.52 mmoles) of 1-(5-O-benzoyl-2,3-epoxy-β-D-lyxosyl)uracil[10] (VII) and 0.6 g. (4 mmoles) of dry sodium iodide in 25 ml. of acetone containing 2 ml. of glacial acetic acid was heated at 90° in a pressure bottle for 24 hr. The solvent was removed at 30–35° and the residue was triturated with a small volume of water containing a few crystals of sodium thiosulfate. The solid was filtered, then dissolved in ethanol and treated with Norit. Colorless, fine needles were deposited from a small volume of alcohol, wt. 0.370 g. (63% yield), m.p. 197–200°. Recrystallization from ethanol gave analytical material, m.p. 200–202°, $[\alpha]^{25}D$ +41° (*c* 1.0, acetone), λ_{max}^{EtOH} 261 mμ (ε 8710) and 229 mμ (ε 19,640), λ_{min}^{EtOH} 248 mμ (ε 7330) and 214 mμ (ε 16,730). *Anal.* Calcd. for $C_{16}H_{15}IN_2O_6$: C, 41.94; H, 3.30; N, 6.12. Found: C, 41.68; H, 3.54; N, 6.23.

1-(5-O-Benzoyl-3-deoxy-3-iodo-2-O-mesyl-β-D-arabinosyl)uracil (IX).—To a solution of 0.510 g. (1.11 mmoles) of iodohydrin (VIII) in 10 ml. of dry pyridine at −10° was added 0.5 ml. methanesulfonyl chloride (6.58 mmoles). The mixture was held at 0° overnight, then treated with *ca.* 1.0 ml. of water and refrigerated for an additional 0.5 hr. The mixture was poured with vigorous stirring into 400 ml. of ice–water, the product was filtered, and the filter cake was washed with generous amounts of cold water. The air-dried product crystallized from ethanol, wt. 0.380 g. (65% yield), m.p. 107–112°. Recrystallization from methanol afforded an analytical sample in the form of pale yellow needles, m.p. 113.5–115.5°, $[\alpha]^{24.5}D$ +41.2° (*c* 0.8, acetone), λ_{max}^{EtOH} 260 mμ (ε 10,000) and 232 mμ (ε 14,300), λ_{min}^{EtOH} 249 mμ (ε 8760). *Anal.* Calcd. for $C_{17}H_{17}IN_2O_8S$: C, 38.07; H, 3.20; N, 5.23. Found: C, 38.20; H, 3.16; N, 5.21.

1-(5-O-Benzoyl-3-deoxy-β-D-*threo*-pentofuranosyl)uracil (XIa).[23]—A solution of 2.29 g. (5 mmoles) of VIII in 160 ml. of 95% ethanol, containing 2.0 g. of triethylamine, was shaken with 0.5 g. of 5% palladium–charcoal under 1 atm. of hydrogen for 0.5 hr. The catalyst was removed and the filtrate was concentrated to *ca.* 10 ml. whereupon crystallization occurred. The solid was collected, then recrystallized from acetone–petroleum ether (b.p. 30–60°). The product was obtained in two crops (72% yield) in the form of colorless, fine needles: wt. 0.63 g., m.p. 161–163°; 0.59 g., m.p. 156–160°. A second recrystallization from the same mixture of solvents provided an analytical sample, m.p. 163–165°, $[\alpha]^{24}D$ +103° (*c* 0.87, acetone), λ_{max}^{EtOH} 262 mμ (ε 9870) and 229 mμ (ε 13,950), λ_{min}^{EtOH} 245 mμ (ε 6740). *Anal.* Calcd. for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 58.07; H, 5.10; N, 8.00.

1-(3-Deoxy-β-D-*threo*-pentofuranosyl)uracil (XIb).—A solution of 0.632 g. (1.9 mmoles) of XIa in 25 ml. of dry methanol containing 0.1 ml. of 1 *N* sodium methoxide was refluxed for 2.5 hr. The reaction mixture was treated batchwise with 2.0 g. of IR-120 (H^+) resin and the filtrate was evaporated to dryness. The last traces of methyl benzoate were removed at 80° (5×10^{-2} mm.) and the residue was crystallized from acetone, wt. 0.361 g. (81% yield), m.p. 142–147°. A second recrystallization from the same solvent raised the melting point to 147–148°, $[\alpha]^{26}D$ +165° (*c* 0.77, water), λ_{max}^{EtOH} 262 mμ (ε 10,140), λ_{min}^{EtOH} 231 mμ (ε 1990). *Anal.* Calcd. for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.56; H, 5.47; N, 12.48.

5′-O-Trityl-2′,3′-dideoxy-2′-uridinene (IVa).[8] **From Ia.**—The following procedure is considered typical of the method by which Ia, IIa, and IIIa were converted to IVa. To a solution of 0.270 g. (2.4 mmoles) of *t*-BuOK in 10 ml. of DMSO was added 0.646 g. (1.15 mmoles) of Ia. The reaction mixture, protected from moisture, was stirred magnetically at room temperature for 0.5 hr. and then poured into 250 ml. of ice–water. Neutralization (phenolphthalein) of the solution with dilute acetic acid produced a gelatinous precipitate which was filtered, washed with water, and air dried. An ethanolic solution of the crude product was treated with Norit and then concentrated on a hot plate to *ca.* 10–15 ml. Benzene (80 ml.) was added and the volume of the solution was again reduced to 10–15 ml. Evaporation with additional benzene was continued until a slight turbidity was evident. The product crystallized at room temperature in the form of colorless needles (0.515 g.) that retained solvent of crystallization, m.p. 97–140°. A solvent-free product was obtained after drying at 100° (10^{-2} mm.) for 6 hr., wt. 0.450 g. (84% yield), m.p. 188–192°. A single recrystallization from ethanol provided an analytical sample, m.p.[24] 195–197°, $[\alpha]^{25}D$ −56° (*c* 0.4, ethanol), λ_{max}^{EtOH} 261 mμ (ε 9770), λ_{min}^{EtOH} 242 mμ (ε 6000). *Anal.* Calcd. for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.25; H, 5.29; N, 6.44.

From IIa.—The reaction of 0.234 g. (2.1 mmoles) of *t*-BuOK and 0.841 g. (2 mmoles) of IIa in 10 ml. of DMSO (0.5 hr.) gave 0.660 g. (78% yield) of product, m.p. 190–193°, which gave spectral (infrared and ultraviolet) data identical with that obtained above from Ia.

From IIIa.—The reaction of 0.112 g. (1.0 mmole) of *t*-BuOK and 0.297 g. (0.5 mmole) of IIIa in 5.0 ml. of DMSO (0.5 hr.) gave 0.185 g. (77% yield) of product, m.p. 190–192° and spectrally identical with the product obtained from Ia.

5′-O-Benzoyl-2′,3′-dideoxy-2′-uridinene (X).—To 1.1 g. (2.05 mmoles) of IX in 20 ml. of dry acetone was added, dropwise and at 0° a solution of 0.78 g. (5.2 mmoles) of dry sodium iodide in 20 ml. of dry acetone. The reaction mixture was allowed to warm to room temperature and then stirred for 1 hr. The mixture was diluted with 5 ml. of water containing a few crystals of sodium thiosulfate and evaporated to dryness at room temperature in a stream of air. The residue was triturated with several portions of chloroform and the extract was washed with water, decolorized (Norit), and dried over magnesium sulfate. The solvent was evaporated to dryness and the residue was crystallized from ether–petroleum ether (b.p. 30–60°) to give 0.453 g. (70% yield), m.p. 133–137°. The product was recrystallized from ether–petroleum ether, m.p. 138.5–139°, $[\alpha]^{25}D$ −106.8° (*c* 0.5, acetone), λ_{max}^{EtOH} 261 mμ (ε 9330) and 230 mμ (ε 14,320), λ_{min}^{EtOH} 246 mμ (ε 7300) and 217 mμ (ε 12,005). *Anal.* Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.92; Found: C, 60.99; H, 4.67; N, 8.73.

2′,3′-Dideoxy-2′-uridinene (Va). From IVa.—A chloroform solution containing 1.12 mequiv. of dry hydrogen chloride was injected slowly (0.5 hr.) through a rubber serum cap into a solution of 0.5 g. (1.1 mmoles) of IVa in 5 ml. of chloroform stirred magnetically at 0°. After an additional 0.5 hr. of stirring the solid that was deposited was collected, washed with chloroform, and crystallized from benzene–ethanol (90:10 v./v.), wt. 0.140 g. (60% yield), m.p. 150–152°. A second recrystallization from the same solvent system raised the melting point to 153–154°, $[\alpha]^{24}D$ −84° (*c* 0.3, water), $\lambda_{max}^{H_2O}$ 261 mμ (ε 10,380), $\lambda_{min}^{H_2O}$ 231

(23) Occasional difficulty was encountered in the repetition of this procedure. It is presumed that a competitive reaction leading to 2′,3′-epoxide formation is the source of the difficulty. Attempts to remedy the situation by substituting sodium acetate for triethylamine and/or palladium on barium sulfate as catalyst were unsuccessful.

(24) The unsaturated nucleosides, except where noted, resolidify above the indicated melting point range without further evidence of a change of state.

mμ (ε 2300). *Anal.* Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.39; H, 4.96; N, 13.29.

From X.—A solution of 0.2 g. (0.64 mmole) of X in 3.0 ml. of 0.5 *N* sodium hydroxide was held at 80° (external) for 1 hr.; the cooled solution was passed successively through columns of IR-120 (H^+) and IR-4B (OH^-). The columns were eluted with 50% aqueous ethanol and the eluent (*ca.* 150 ml.) was evaporated to dryness at 40–50°. The residue, after several evaporations from ethanol, crystallized from benzene–ethanol (90:10, v./v.), wt. 0.110 g. (82% yield), m.p. 152–153°, $[\alpha]^{23}D$ −88° (*c* 0.52, water). The product afforded infrared and ultraviolet spectra which were essentially superimposable with the corresponding spectra of product derived from IVa.

From XIVa.—To a solution of 0.115 g. (1.02 mmoles) of *t*-BuOK in 10 ml. of DMSO was added 0.105 g. (0.5 mmole) of XIVa. The mixture was stirred at 25° for 2 hr. and then neutralized with a dilute solution of acetic acid. The solution was evaporated to dryness at 50° (5×10^{-2} mm.), the residue was extracted with several portions (five 10-ml.) of hot acetone, and the extract was filtered from the inorganic residue. The acetone solution was evaporated to dryness and the residue was crystallized from benzene–ethyl acetate (90:10, v./v.) as a colorless solid, wt. 0.80 g. (two crops, 76%), m.p. 153–154°. This material was indistinguishable spectrally (infrared and ultraviolet) from samples of Va obtained from either IVa or X.

5′-O-Trityl-3′-deoxy-2′-thymidinene (IVb).—A solution of 1.15 g. (10 mmoles) *t*-BuOK and 2.36 g. (4.3 mmoles) of Ib in 20 ml. of DMSO, protected from moisture, was stirred magnetically at room temperature for 0.75 hr. The reaction mixture was poured into 400 ml. of ice–water, the solution was neutralized (phenolphthalein) with dilute acetic acid, and the gelatinous product was collected. The filter cake was washed thoroughly with water and air dried. The solid was dissolved in a small volume of ether and reprecipitated by slowly adding the ether solution, with stirring, to a large volume of petroleum ether (b.p. 30–60°). The product amounted to 1.8 g. (92% yield) and exhibited an indefinite m.p. 92–109°. The absence of characteristic sulfonate ester absorption in the region 8.3–8.5 μ was manifestly clear. Analytical material was obtained in the form of an amorphous solid on recrystallization from a small volume of ether, $[\alpha]^{23}D$ −32° (*c* 0.85, ethanol), λ_{max}^{EtOH} 264 m μ (ε 10,840), λ_{min}^{EtOH} 242 mμ (ε 5283). *Anal.* Calcd. for $C_{29}H_{26}N_2O_4$: C, 74.65; H, 5.61; N, 6.01. Found: C, 74.49; H, 5.64; N, 5.76.

3′-Deoxy-2′-thymidinene (Vb). From XIVb.—A solution of 0.360 g. (1.6 mmoles) of the oxetane derivative (XIVb)[7a] in 10 ml. of DMSO containing 0.360 g. (3.2 mmoles) of *t*-BuOK was stirred at room temperature for 2 hr. The reaction mixture was neutralized to *ca.* pH 7 (test paper) with ethanolic acetic acid and the solution was evaporated to dryness[25] at 50° (5×10^{-2} mm.). The residue was triturated with several portions (five 20-ml.) of hot acetone, the salts were removed by filtration, and the filtrate was evaporated to dryness. The residue was decolorized (Norit) in ethanol and the filtrate was concentrated first to *ca.* 5.0 ml. and then diluted with 25 ml. of benzene. The clear solution was again concentrated on a hot plate to *ca.* 5.0 ml. and diluted with benzene; the solution was reduced to a small volume. This process was repeated until the solution was obviously turbid. The product crystallized on standing at room temperature: first crop 0.220 g., m.p. 156–158°; second crop 0.100 g., m.p. 164–165°. The combined crops, on recrystallization from the same solvent system, gave 0.285 g. (79% yield) of a colorless, granular solid, m.p. 165–166°, $[\alpha]^{25}D$ −42° (*c* 0.69, water), $\lambda_{max}^{H_2O}$ 266 mμ (ε 9910), $\lambda_{min}^{H_2O}$ 235 mμ (ε 2460). *Anal.* Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40; N, 12.50. Found: C, 53.37; H, 5.42; N, 12.31.

From IVb.—A solution of 2.0 g. (4.28 mmoles) of IVb in 10 ml. of chloroform was treated at 0° with 0.46 mequiv. of dry hydrogen chloride in 14 ml. of chloroform for 0.5 hr. according to the procedure described above for the detritylation of IVa. The solution was decanted from a small amount of oil into 5 ml. of 2 *N* ammonium hydroxide and the residual oil, after trituration with fresh chloroform, crystallized from ethanol–benzene as described above, wt. 0.100 g., m.p. 158–162°. The chloroform–water mixture was evaporated to dryness in a stream of air, the residue was resuspended in water, and the triphenylcarbinol was removed by filtration. The aqueous filtrate was evaporated to dryness and the residue was extracted with several portions of hot acetone. The salts were removed and the acetone filtrate was evaporated to dryness. The residue crystallized from 5.0 ml. of ethanol, wt. 0.205 g. (total yield 31%), m.p. 162–163°.

3′-Deoxy-2′-(4-thiothymidinene) (Vc).—A solution of 0.240 g. (1 mmole) of XIVc in 5 ml. of DMSO containing 0.225 g. (2 mmoles) of *t*-BuOK was stirred at room temperature and in the absence of moisture for 2 hr. The reaction mixture was neutralized (test paper) with ethanolic acetic acid and then evaporated to dryness at 45–50° (10^{-2} mm.). The residue was triturated several (five 20-ml. portions) times with hot acetone, the salts were removed by filtration, and the filtrate was evaporated to dryness. The product was dissolved in ethanol and the solution was decolorized (Norit) and then concentrated on a hot plate to *ca.* 5.0 ml. Excess (25 ml.) benzene was added and the volume of the solution was reduced again to *ca.* 5.0 ml. Bright yellow prisms amounting to 0.155 g. (65% yield), m.p. 125–128°, were deposited from solution on standing. The product crystallized from ether in the form of yellow needles which were dried at 100° (10^{-2} mm.) prior to analysis, m.p. 129–130°, $[\alpha]^{25}D$ +57° (*c* 0.88, ethanol), λ_{max}^{EtOH} 332 mμ (ε 18,840) and 243 mμ (ε 3810), λ_{min}^{EtOH} 276 mμ (ε 1525) and 222 mμ (ε 220). *Anal.* Calcd. for $C_{10}H_{12}N_2O_3S$: C, 49.98; H, 5.04; N, 11.66; S, 13.34. Found: C, 49.90; H, 5.14; N, 11.73; S, 13.56.

2′,3′-Dideoxyuridine (VIa).—A solution of 90 mg. (0.55 mmole) of Va in 25 ml. of peroxide-free dioxane, containing 115 mg. of 10% palladium–charcoal catalyst was shaken with 1 atm. of hydrogen at 25°. The theoretical uptake of hydrogen was realized in 0.5 hr., the catalyst was filtered, and the filtrate was evaporated to dryness. The residue crystallized from benzene–petroleum ether in the form of colorless needles, wt. 73 mg. (81% yield), m.p. 117.5–118.5° (lit.[26] m.p. 116–117°), $[\alpha]^{25}D$ +31° (*c* 0.43, water), $\lambda_{max}^{H_2O}$ 263 mμ (ε 9820), $\lambda_{min}^{H_2O}$ 232 mμ (ε 1500). *Anal.* Calcd. for $C_9H_{12}N_2O_4$: C, 50.93; H, 5.70; N, 13.20. Found: C, 51.16; H, 5.76; N, 13.27.

3′-Deoxythymidine (VIb).—A solution of 100 mg. (0.45 mmole) of Vb in 25 ml. of dioxane containing 120 mg. of 10% palladium–charcoal was hydrogenated in the manner described above. The product crystallized from ethyl acetate as a colorless solid, wt. 70 mg. (69% yield), m.p. 149–150° (lit. m.p. 145°,[15] 147–149°[21]).

Furfuryltriphenylmethyl Ether (XV). From IIIa.—A solution of 0.8 g. (1.46 mmoles) of IIIa in 10 ml. of DMSO containing 0.360 g. (3.24 mmoles) of *t*-BuOK was stirred at room temperature for 0.75 hr. and then poured into 500 ml. of ice–water. The aqueous mixture was neutralized (phenolphthalein) with acetic acid and the gelatinous material was collected, washed with water, and sucked dry. The filter cake was triturated with 10 ml. of acetone and the insoluble material (20 mg.) was collected. The latter was identified on the basis of infrared measurements as uracil. The acetone-soluble material was chromatographed on acid-washed alumina (20 g.) using successively petroleum ether (b.p. 30–60°), ethyl acetate, and acetone as eluents. The petroleum ether fraction, on evaporation, yielded a solid which crystallized from methyl cyclohexane as colorless rectangular prisms, wt. 0.150 g. (30%), m.p. 142–143°. Mixture melting point with an authentic sample of XV was 142–143° (lit.[27] m.p. 137–139°, from ethanol). Infrared spectra derived from the two samples were essentially superimposable.

The acetone fraction, on evaporation, afforded material (0.210 g., 31%) which proved to be identical in every respect with IVa.

1-[2-(5-Methylfuryl)]thymine (XVIII). From XIIIb.—A solution of 0.275 g. (0.69 mmole) of XIIIb in 5 ml. of DMSO containing 0.250 g. (2.22 mmoles) of *t*-BuOK was stirred at room temperature for 2.5 hr. with care to exclude moisture. The reaction mixture was diluted with 5.0 ml. of water, neutralized (test paper) with dilute acetic acid, and evaporated to dryness. The residue was extracted with several portions (five 25-ml.) of acetone, the salts were removed by filtration, and the acetone was evaporated to dryness under reduced pressure. An ethanol solution of the residue was treated with Norit and the volume of the filtrate was reduced to *ca.* 5.0 ml. Excess (25 ml.) benzene was added and the solution was concentrated on a hot plate until the appearance of slight but definite turbidity. On standing, colorless, rhombic crystals were deposited from solution, wt. 0.125 g. (88% yield), m.p. 165–166.5°, λ_{max}^{EtOH} 264 mμ (ε 8240)

(25) Failure to remove the last traces of DMSO at this point leads to difficulty in the subsequent crystallization of Vb.

(26) The synthesis of VIa by an alternate route was described in the course of the present study (see ref. 22).

(27) Prepared according to the method of C. D. Hurd and C. L. Thomas [*J. Am. Chem. Soc.*, **55**, 423 (1933)], m.p. (cyclohexane) 142–143°.

and 212 mμ (ε 10,510), λ_{min}^{EtOH} 241 mμ (ε 7140); τ 8.2 (CH_3 singlet and 7.75 (CH_3 singlet) in d_6-DMSO.[28] *Anal.* Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.42; H, 4.82; N, 13.48.

From 5′-O-Mesyl-2,3′-anhydrothymidine.[15]—A solution of 0.604 g. (2 mmoles) of the anhydronucleoside and 0.224 g. (2 mmoles) of *t*-BuOK in 15 ml. of DMSO was stirred at room temperature for 1 hr. Following the procedure outlined above, there was obtained 0.120 g. (29% yield) of XVIII, m.p. and m.m.p. 162–165°. The acetone-insoluble material, when examined spectrally (ultraviolet) clearly showed the presence of unreacted starting material.[29]

(28) The authors are grateful to Dr. Robert Scott, Parke, Davis and Company, Research Laboratories, Ann Arbor, Mich., for these measurements.

(29) The use of an abbreviated reaction period was deliberate in an (unsuccessful) attempt to trap the presumed intermediate, XVII.

Nucleosides. XXXI. 3′-Amino-3′-deoxyhexopyranosyl Nucleosides. IV. Nucleoside Conversions in the 3′-Aminohexose Series[1]

KYOICHI A. WATANABE AND JACK J. FOX

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research; Sloan-Kettering Division, Cornell University Medical College, New York 21, New York

Received August 12, 1965

1-(3′-Amino-3′-deoxy-β-D-mannopyranosyl)uracil (X) was prepared from its gluco isomer II in a seven-step synthesis proceeding *via* 1-(3′-acetamido-3′-deoxy-2′-*O*-mesyl-4′,6′-*O*-benzylidene-β-D-glucosyl)uracil (V). Compound V was converted to the 2,2′-anhydro derivative VI, the first of its kind in the hexopyranosyl nucleoside area. The structure of VI was established by its conversion to 1-(3′-acetamido-3′-deoxy-4′,6′-*O*-benzylidene-β-D-mannosyl)isocytosine (VII) with liquid ammonia and to 1-(3′-acetamido-3′-deoxy-4′,6′-*O*-benzylidene-β-D-mannosyl)uracil (VIII) with alkali, the latter of which, after removal of blocking groups, yielded X. An attempted conversion of the 3′-aminogluco nucleoside II to a 4′-amino-4′-deoxygulo nucleoside XVIII *via* the aziridine XIVb was carried out. Some indication of formation of XVIII was obtained along with the formation of the crystalline hydrochloride of 1-(3′-amino-3′-deoxy-β-D-galactopyranosyl)uracil (XVI). The latter nucleoside was also obtained directly from uridine by the periodate–nitromethane procedure.

Previous papers from this laboratory[2] described the facile synthesis of 3′-amino-3′-deoxyglucosyluracil (II) by treatment of uridinedialdehyde with nitromethane followed by reduction of the nitro group. It was indicated[2] that, although the 3′-nitrogluco derivative I was obtained as the predominant isomer, other isomers were present in the mother liquors. By analogy with the work of Baer, *et al.*,[3] with glycosides, it would be expected that a maximum of four isomers would form in the course of reaction of the dialdehyde with nitromethane (though eight isomers are theoretically possible). In addition to the gluco isomer already isolated,[2] the galacto, manno, and talo isomers should also be present. (In our recent studies[4] on the application of the periodate–nitromethane procedure to the purine nucleoside, adenosine, the glucosyl-, galactosyl-, and mannosyladenine derivatives were obtained.) In the present paper we report the isolation of some of these 3′-amino isomers from uridine as well as their unequivocal synthesis from II.

The five pyrimidine nucleoside antibiotics elaborated by *Streptomyces* (amicetin, bamicetin, plicacetin, blasticidin S, and gougerotin) all contain 4-amino-4-deoxyhexosyl moieties linked to cytosine.[5] None have been synthesized chemically, although obviously such syntheses would make possible the preparation of analogs of potential biochemical interest. In this report, we also describe some preliminary attempts in the conversion of 3′-aminohexosyl nucleosides to 4′-aminohexosyl nucleoside derivatives.

The 3′-aminoglucosyl nucleoside II served as a chemical precursor for the preparation of other epimeric nucleosides. For the synthesis of the mannosyl derivative X, the *N*-acetate[2] III was converted to the 4′,6′-*O*-benzylidene derivative IV by treatment of III with benzaldehyde and zinc chloride (see Scheme I). Compound IV was very insoluble in common organic solvents and exhibited a high melting point (306–308°). Treatment of a suspension of IV in anhydrous pyridine with methanesulfonyl chloride afforded the 2′-mesylate V.

Compound V could react with alkoxide in two possible ways. The neighboring *N*-acetate could conceivably participate[6] to form an oxazoline structure VIa. Alternatively, the 2-carbonyl group of the pyrimidine moiety could participate with the formation of a 2,2′-anhydromanno nucleoside VI. If the latter course prevails, it would be the first example of an anhydro nucleoside in the hexosyl nucleoside area.

Treatment of V with sodium ethoxide in a mixture of pyridine and ethanol[7] afforded colorless needles (VI) in ~60% yield. The ultraviolet absorption

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 03190-09).

(2) (a) K. A. Watanabe and J. J. Fox, *Chem. Pharm. Bull.* (Tokyo), **12**, 975 (1964), (b) K. A. Watanabe, J. Beránek, H. A. Friedman, and J. J. Fox, *J. Org. Chem.*, **30**, 2735 (1965).

(3) H. H. Baer, *J. Am. Chem. Soc.*, **84**, 83 (1962); H. H. Baer and F. Kienzle, *Can. J. Chem.*, **41**, 1606 (1963).

(4) J. Beránek, H. A. Friedman, K. A. Watanabe, and J. J. Fox, *J. Heterocyclic Chem.*, **2**, 188 (1965).

(5) J. J. Fox, Y. Kuwada, K. A. Watanabe, T. Ueda, and E. B. Whipple, *Antimicrobial Agents Chemotherapy*, 518 (1964), and leading references therein.

(6) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1047 (1964), and leading references therein. The formation of a 2′,3′-aziridine ring by reaction of V with alkoxide is also conceivable. However, as demonstrated by Baker, *et al.*, the formation of an aziridine ring from a diequatorial arrangement of the 2′,3′ neighboring groups (as in V) in highly unlikely under these reaction conditions. The possibility of aziridine formation is discussed later (Scheme II, XIVb) with a related nucleoside.

(7) Compound V is highly insoluble in water and slightly soluble in ethanol. It is soluble in pyridine. The choice of solvent and alkoxide in this case is due to these solubility characteristics of V.